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WILEY Haemophilia

POSTER PRESENTATIONS

P001 | Patient and treatment related factors and inhibitor development after 50 exposure days in patients with non-severe hemophilia A—preliminary data of a nested case-control study

A. Abdi[1,*]; C. Eckhardt[1]; M. Coppens[2]; M. Cnossen[3]; R. Schutgens[4]; B. Laros-van Gorkom[5]; E. Santagostino[6]; A. Tagliaferri[7]; M. Mazzucconi[8]; J. Astermark[9]; M. Holmström[10]; J. Oldenburg[11]; C. Ettingshausen[12]; V. Jimenez-Yuste[13]; S. Haya[14]; J. van der Bom[15]; S. Gouw[1]; K. Fijnvandraat[1]; on behalf of INSIGHT Study Group

[1]Department of Pediatric Hematology, Immunology and Infectious Diseases, Emma Children's Hospital, Amsterdam UMC, location AMC; [2]Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, location AMC, Amsterdam; [3]Department of Paediatric Haematology, Erasmus Medical Center—Sophia Children's hospital, Rotterdam; [4]Van Creveldkliniek, University Medical Center Utrecht, Utrecht; [5]Department of Hematology, Radboud University Medical Center, Radboud University, Nijmegen, Netherlands; [6]Fondazione IRCCS Ca' Granda Foundation, Ospedale Maggiore Policlinico, Milan; [7]Regional Reference Center for Inherited Bleeding Disorders, University Hospital of Parma, Parma; [8]Universita' Roma La Sapienza, Policlinico Umberto I, Rome, Italy; [9]Department of Hematology and Vascular Diseases, Skåne University Hospital, Malmö; [10]Coagulation Unit, Haematology Centre, Karolinska University Hospital, Stockholm, Sweden; [11]Department of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn; [12]HZRM—Haemophilia Centre Rhein Main, Frankfurt-Mörfelden, Germany; [13]Department of Hematology, La Paz University Hospital-IdiPaz, Madrid; [14]University Hospital la Fe, Valencia, Spain; [15]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands

Introduction: Inhibitor development is a major complication of factor VIII (FVIII) treatment in non-severe hemophilia A (NSHA). In contrast to severe patients, in whom the risk to develop an inhibitor decreases after 50 exposure days (EDs), NSHA patients have a lifelong inhibitor risk. The aim of this study is to identify patient and treatment related factors associated with late onset inhibitor development in NSHA patients with more than 50 EDs.

Methods: In this nested case-control study, we selected all patients with inhibitor development after 50 EDs (cases) and matched inhibitor-negative patients (controls) from the INSIGHT cohort, including 2709 NSHA patients (FVIII level 2-40 IU/dL). Matching was based on date of birth, number of EDs and center/country. Clinical data of the first ED and the last 30 EDs were collected until inhibitor development in cases and up to the same number of EDs in controls. Patient and treatment related factors were compared between cases and controls. We performed conditional logistic regression on the matched groups to analyze the association between patient and treatment related determinants and inhibitor development, adjusted for predefined confounders.

Results: In total, 31 cases and 84 controls were included. Of all patients, patient related factors were available. Treatment related factors were available in 24 cases and 73 controls. Arg2150His was the most prevalent F8 mutation in cases (19%) and controls (7%). Median FVIII baseline level was comparable for cases (6.0, IQR 4.0-10.0) and controls (6.0, IQR 3.0-12.0). At first treatment, cases were older (35 years, IQR 12-49) than controls (18 years, IQR 8.5-37). At last treatment, plasma-derived FVIII was the most used product type in both groups: 63% in cases and 55% in controls. In the last 10 EDs, mean FVIII dose was higher in cases (35 IU/kg, IQR 20-45) than in controls (25 IU/kg, IQR 18-35). Furthermore, the time interval in which the last 10 EDs were received was shorter in cases (30 days, IQR 9-384) than in controls (202 days, IQR 23-620). The multivariable analyses are currently being performed and the results will be presented at the conference.

Discussion/Conclusion: Our preliminary findings suggest that patient and treatment related factors are associated with inhibitor development after 50 EDs in patients with NSHA.

Disclosure of Interest: None declared.

P002 | Ways to fight against pain related to hemophilic Arthropathy: Experiment in Strasbourg hospital

A. Raissi[1,*]; L. Sattler[2]; C. Madignier[3]; A. C. Gerout[4]; E. Salvat[5]; D. Desprez[3]

[1]Laboratory of Hematology, Emile Muller Hospital, Mulhouse; [2]Laboratory of Hematology; [3]CRTH Strasbourg; [4]Hospital Pharmacy; [5]Pain Assessment and Treatment Center, Strasbourg Hospital, Strasbourg, France

Introduction: Hemophilic arthropathy, leading to a disabling chronic pain, is a complication occurring in the majority of patients with severe haemophilia and type 3 von Willebrand disease (VWD). Orthopedic interventions are usually indicated and represent a definitive remedy. However patients are often not in favor.

Methods: In 50 patients with severe hemorrhagic disorders, followed in the Hemophilia Treatment Center of the Strasbourg Hospital, we report the pain management associated with hemophilic arthropathy.

Results: Out of these 50 patients, 82% have a severe haemophilia and 4% a type 3 VWD. Moreover, 95% of the patients have one target joint or more. 86% are feeling the pain at least once per day, a pain which is evaluated at an average of 4.9 [3-10] (mean, min–max) on a graduated scale from 1% to 10.32% patients have a physical

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activity, known to be beneficial for the joint health, while only 10% are sedentary.

94% of patients are regularly using analgesic drugs. The consumption is even daily for some of them and 30% combine at least two pain killers. Regarding molecules, 40% are using paracetamol, 20% paracetamol + codeine, 11% nefopam, 11% tramadol, and 5% morphine. Moreover, 40% of patients have recourse to NSAIDs despite their adverse events, celecoxib being however the most frequently used. Homeopathy associated with the use of essential oils is an option chosen by only one patient.

30% of patients benefit regularly from physiotherapy sessions, including massages, cryotherapy and transcutaneous electrical nerve stimulation (TENS). 14% are trying alternative medicine such as acupuncture, moxibustion, relaxation or hypnosis. Besides, 9% are frequently using cannabis as medicine.

Discussion/Conclusion: Finally, 32% of our patients complain about having no effective solution to ease their pain, despite a large therapeutic arsenal and a good knowledge of their pathology. This is comforting our idea to develop medical consultations with a pain treatment specialist.

Disclosure of Interest: None declared.

P003 | Almadinah protocol for menstrual cycle control among GT patients: Report of first three patients

A. Tarawah

Pediatrics Hematology, King Abdullah Medical City, Madinah, Saudi Arabia

Introduction: Though Glanzmann Thrombasthenia (GT) is a rare inherited bleeding disorder, it is more common among Middle Easters. In AlMadinah, Saudi Arabia, it has been reported as high as 1:40 000.

Menorrhagia is a common manifestation among GT patients. Due to rarity of the condition, there are little data experience in management of this issue. Many experts believe to cease menstrual cycle in these patients. This principle was not accepted by our patients' culture. It was necessary to develop a protocol to satisfy patients culture and not to have serious bleeds. Seven girls enrolled to the protocol to date. We are reporting the first 3 girls as they completed more than 3 years on protocol.

Methods: AlMadinah protocol for menstrual cycle control among GT patients has developed in 2014 to control menorrhagia in GT patients and may extend to other bleeding disorders. GT females who manifest menorrhagia enrolled in this protocol. The protocol calls for Hormonal therapy (progesterone or combined progesterone and estrogen) to be continue on a daily basis. At proposed time of menstruation (assigned by patient and physician), hormonal therapy will be stopped, Antifibrinolytic drugs will be started. With the first bleed, one dose rFVIIa will be given. If a massive bleed occurs, rFVIIa will be initiated, and platelet transfusions will be avoided unless needed. Hormonal therapy will re-start between days three and five. Antifibrinolytic drugs will continue until there are no more bleeds. Women of child-bearing age who want to conceive will be discharged from the protocol.

Results: The first 3 girls admitted to the protocol have had heavy first menstrual cycle enough to need 14 red blood cells transfusion over 14 days for the first patient. All of them started protocol after the first menstrual cycle by age 14, 13 and 13 years respectively. They have completed 54, 46 and 38 months respectively. They had 49, 41 and 28 menstrual cycle. Two patients needed farther management of 3 menstrual cycles in form of platelets transfusion and rFVIIa. All other menstrual cycles where within the acceptable amount.

Discussion/Conclusion: AlMadinah protocol for menstrual cycle control among GT patients is a promising protocol for GT girls among cultures where menstrual cycle cannot be ceased. This protocol needs to have more investigation in a larger group of patients in a multicenter trial.

Disclosure of Interest: None declared.

P004 | Report of seventeen Glanzmann thrombasthenia patients in one family

A. Tarawah

Pediatrics Hematology, King Abdullah Medical City, Madinah, Saudi Arabia

Introduction: Glanzmann Thrombasthenia (GT) is a rare inherited bleeding disorder, first described by Dr. Edward Glanzmann in 1918. GT is a quantitative or qualitative deficiency of platelet glycoprotein complex IIb–IIIa. Thought GT is rare, it has been reported more frequent in the middle east countries. In Madinah, Saudi Arabia GT rate was 1:40 000 population.

In this work we are reporting a family with 17 GT patients.

Methods: Direct interview with GT cases, both parents and senior relatives. For cases medical record of each patient has reviewed.

Diagnosis of GT made through screening tests (PT, aPTT, TT and PFA200), flow cytometry is diagnosis confirmatory. Molecular genetics made for selected cases.

Results: Six siblings with bleeding diathesis has confirmed with GT. Four males aged 18, 15, 13 and 12 years. Two females aged 10 and 3 years. Parents are first degree cousins. Father is Confirmed GT. Uncle has been confirmed to be GT. Ante who married to her first degree cousin have seven children with confirmed GT, 5 males and two females. A father uncle and father grandfather had characteristically muco-cutaneous frequent bleeds where diagnosis of GT was not established at that era. Genetics characterization was Homozygous ITGA2BNM_000419:exon13:c.1210 + 5G>A, This rare mutation may cause Missense Phenotype.

Discussion/Conclusion: GT though is a rare bleeding disorder, but it is commoner among our nations in the middle east probably due to consanguine marriages such as the current family

Disclosure of Interest: None declared.

P005 | Five years of tailored low dose prophylaxis in a small cohort of kids with severe hemophilia a using solvent detergent (SD-F) cryoprecipitate

A. El Ekiaby; M. El Ekiaby

Blood Transfusion and Hemophilia Treatment Center, Shabrawishi Hospital, Giza, Egypt

Introduction: Prophylaxis with clotting factor concentrates in patients with severe hemophilia is now considered the standard of care. In our center we have adopted the production of Solvent Detergent Treated and microbial filtered (SD-F) cryoprecipitate.

Methods: Aim of the study: Study the safety and the efficacy of tailored lower dose prophylaxis program using SD-F cryoprecipitate in young kids with severe hemophilia A.

10 kids with severe hemophilia A were sequentially enrolled in this program starting from January 2011 till February 2014. Age of enrollment was 2-4 years. All kids were negative for inhibitors to FVIII. IRB and patient family consent was obtained. Kids were infused with 20 iu FVIII/kg once weekly. If one joint experienced more than one breakthrough bleed, the same dose was increased to twice weekly and if still there were more breakthrough bleeds the frequency of the same dose was increased to 3 times per week. Breakthrough bleeds were treated by infusion of 25 iu FVIII/kg once or more according to the severity of the bleed. The short-term evaluation of this program was based on the annual bleeding rate (ABR) and Hemophilia Joint Health Score (HJHS)

Results: 10 kids were followed on prophylaxis for a mean period of 41 months (15-60 months). The mean age at start was 33.36 months (24-51 months). The average FVIII consumption/kg/year was 1028.9 iu (545-1684 iu). Out of the 10 kids 7 are on SD-F cryoprecipitate infusion once weekly, two twice weekly and one three times weekly. ABR was 2 (0-4), HJHS of the 9 kids was zero. One kid developed target knee joint. None of them developed FVIII inhibitors or experienced adverse events from the infusion of SD cryoprecipitate. There was no transmission of HBV, HCV or HIV.

Discussion/Conclusion: This study demonstrates efficacy and safety of SD-F cryoprecipitate as well as feasibility of low dose prophylaxis.

Disclosure of Interest: None declared.

P006 | Gait analysis to evaluate patients with moderate haemophilia: A research protocol

A. Fouasson-Chailloux[1,*]; M. Trossaert[2]; C. Vinatier[3]; F. Rannou[4]; M. Dauty[1]; J. Guicheux[3]; Y. Maugars[5]

[1]*MPR Locomotrice;* [2]*Centre de Traitement – Hémophilie, CHU de Nantes;* [3]*Inserm UMR 1229, RMeS, université de Nantes, Nantes;* [4]*Service de Rééducation et Réadaptation de l'appareil Locomoteur, Hôpital Cochin, Paris;* [5]*Rhumatologie, CHU de Nantes, Nantes, France*

Introduction: Patients with moderate form of the disease represent 15% of all patients. Their management is still not well codified concerning the use or not of prophylaxis to prevent haemarthrosis. Currently, Gait Analysis appears as an innovative clinical research tool and has previously shown its interest in haemophilia, especially with its capacity to show early walking anomalies in asymptomatic patients with severe haemophilia. Nowadays, this tool has never been use specifically in moderate haemophilia.

Methods: This project aims to evaluate walking functional consequences of moderate haemophilia. Gait Analysis corresponds to an objective measure of the human gait with force sensors that measure the ground reaction forces when walking while patients' motions are recorded thanks to reflective markers positioned on the skin to define body segments. Electromyography is also used to assess muscular function.

Results: Data from the Gait Analysis are:

Spatio-temporal outcomes such as speed, cadence, step length, support, swing time…).

Kinematics outcomes (motion capture) presented as curves of joints displacements according to time.

Kinetics outcomes which correspond to the ground reaction forces measured with force platforms when the patients walk on them. The association of these data with the kinematics ones allows calculating joint power.

We will analyze different clinical parameters (range of motion, quality of life scores, …), radiological parameters (x-rays, US imaging), biological parameters (clotting factors rate) in order to draw a complete picture of the articular situation in these patients with moderate haemophilia.

Discussion/Conclusion: With this project, we expect to have a better knowledge of walking impairment in patients with moderate haemophilia. We aim to determine potential prognostic factors of disability, such as: age, Pettersson score, US data, level of clotting factors, which could explain, at least partially, walking deterioration. We also aim to show walking modifications including asymptomatic ones at early stages of the disease.

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P007 | UK EHL outcomes registry: First report on baseline pain and quality of life

A. Miners[1,*]; M. Phillips[2]; D. Beech[3]; P. Collins[4]; N. Curry[5]; C. Grimley[6]; C. Hay[7]; J. Hanley[8]; M. Makris[9]; S. Mangles[10]; M. Mathias[11]; B. Myers[12]; C. Tait[13]; P. Chowdary[2]

[1]*The London School of Hygiene & Tropical Medicine, University College London;* [2]*Katherine Dormandy Haemophilia and Thrombosis Centre, Royal Free London NHS Foundation Trust, London;* [3]*Royal Cornwall Hospital, Treliske;* [4]*Arthur Bloom Haemophilia Centre, University Hospital of Wales, Cardiff;* [5]*Oxford University Hospital, Oxford;* [6]*Nottingham University Hospital, Nottingham;* [7]*Manchester Haemophilia Centre, Manchester Royal Infirmary, Manchester;* [8]*Royal Victoria Hospital, Newcastle;* [9]*University of Sheffield, Sheffield;* [10]*Hampshire Hospitals NHS Foundation Trust, Basingstoke;* [11]*Great Ormond Street Hospital, London;* [12]*Lincoln County Hospital, Lincoln;* [13]*Glasgow Royal Infirmary, Glasgow, United Kingdom*

Introduction: The current UK standard of care for patients with severe haemophilia A and B is regular prophylaxis with either factor VIII or IX between 2 to 4 times a week to maintain a trough level of 1%, affording protection against spontaneous bleeding events and resultant joint damage. New extended half-life coagulation factor concentrates (EHL-CFC) have been introduced into routine clinical care with the potential aim of optimising prophylaxis through decreased infusion frequency and higher trough levels.

Thus far, data on patients switched to EHL-CFCs have mainly been collected through participants in clinical trials who may not be representative of the UK population.

Methods: The UK EHL Outcomes Registry was established to systematically collect data on all patients being switched across the UK in the 2 years post-switch. The principal goals of the registry are to collect data on quality of life (QOL), physical activity, factor consumption and treatment information to identify the relationships between patient, treatment characteristics and outcomes as these new products become available.

Results: Until 11 Oct 2018, 96 adult patients and 49 children have been enrolled into the registry. The data on QOL and pain for adults only are reported in this abstract. 14 UK sites contributed to the adult cohort and they completed the EQ5DL.

The average score of these patients was very good at 0.80, with no differences seen across the age groups. 75% of adults completed the Brief Pain Inventory, seven-day recall (BPI_7d) at study entry. BPI_7d is a validated tool that is used to assess the presence and severity of pain and pain-related functional impairment. 77% of the respondents at study entry reported pain that was interfering with activities in the preceding week. The severity of pain and interference with activities in around half the patients reporting pain was minimal to mild. Patients reported the use of a variety of analgesics including paracetamol, non-steroidal agents, opiates and factor concentrate.

Discussion/Conclusion: Our data suggests that pain is widely prevalent but the severity and interference seem to be minimal in around half the patients. Further understanding of the severity and management of pain requires correlation with joint damage and bleed prevention.

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P008 | Accelerating access for Emicizumab- the first early access to medicines scheme (EAMS) for a bleeding disorder in the UK

G. Tobaruela[1]; A. Marshall[2,*]; M. Rijkeboer[1]; F. Rowley[1]; J. DiCapite[1]; S. Srinivasan[2]

[1]*Roche Products Limited, Welwyn Garden City;* [2]*Chugai Pharma UK Ltd, London, United Kingdom*

Introduction: The EAMS was launched by the UK government in 2014. It aims to give people with life-threatening or seriously debilitating conditions access to promising unlicensed and off-label medicines, where unmet medical needs are high. The Medicines and Healthcare products Regulatory Agency (MHRA) give a scientific opinion on benefit/risk balance, based on current available data. Roche/Chugai applied for an EAMS scientific opinion for emicizumab in September 2017, for people with haemophilia A with factor VIII (FVIII) inhibitors.

Methods: We applied via the MHRA process for promising innovative medicine designation and EAMS scientific opinion. Following positive opinion, healthcare professionals identified potential participants to enrol. Applications were assessed and approved by a haematologist at Roche to ensure patient eligibility. Free-of-charge emicizumab was supplied until reimbursement was approved. We have analysed application forms for enrolment and participant characteristics data.

Results: Positive opinion was issued on 29 December 2017 (EAMS number 00031/0004). Eligibility criteria were diagnosis of haemophilia A (any severity) with FVIII inhibitors, and aged 1 year and over. People with high risk of thrombotic microangiopathy were not eligible. The EAMS closed to new applications after 61 days, once EU marketing authorisation was granted. Roche/Chugai received and approved 32 applications from 16 Comprehensive Care Centres, including 1 shared care arrangement with a Haemophilia Centre. Twenty participants were adults, 12 were <18 years old. Most had severe haemophilia A (n = 27). Thirty participants were initiated on

emicizumab, two did not start emicizumab treatment before reimbursement was available. One non-related adverse event was reported during the EAMS. Effectiveness data were not collected by Roche/Chugai.

Discussion/Conclusion: This was the first UK EAMS for a bleeding disorder and the first broad emicizumab early access programme in Europe. Collaboration between the MHRA, National Health Service, treatment centres and Roche/Chugai provided eligible people an opportunity to receive emicizumab ahead of marketing authorisation and reimbursement, outside a clinical trial or compassionate use setting. Companies investigating new medicines should consider early access schemes during their development programmes.

Disclosure of Interest: G. Tobaruela Employee of: Roche Products Limited, A. Marshall Employee of: Chugai Pharma UK Ltd, M. Rijkeboer Employee of: Roche Products Limited, F. Rowley Employee of: Roche Products Limited, J. DiCapite Employee of: Roche Products Limited, S. Srinivasan Employee of: Chugai Pharma UK Ltd.

P009 | Long-term efficacy and safety of prophylactic treatment with recombinant factor IX FC fusion protein (rFIXFc) in subjects with severe or moderate haemophilia B: final longitudinal analysis of B-LONG/kids B-LONG and B-YOND

A. D. Shapiro[1,*]; R. Kulkarni[2]; M. V. Ragni[3]; J. Mahlangu[4]; J. Oldenburg[5]; B. Nolan[6]; M. C. Ozelo[7]; A. Willemze[8]; J. Feng[9]; C. Barnowski[9]; C. Barnes[10]

[1]*Indiana Hemophilia & Thrombosis Center, Indianapolis, IN;* [2]*Michigan State University, East Lansing, MI;* [3]*Hemophilia Center of Western Pennsylvania, University of Pittsburgh, Pittsburgh, PA, United States;* [4]*Haemophilia Comprehensive Care Center, Faculty of Health Sciences, University of Witwatersrand and NHLS, Johannesburg, South Africa;* [5]*Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany;* [6]*Our Lady's Children's Hospital, Dublin, Ireland;* [7]*Hemocentro UNICAMP, University of Campinas, São Paulo, Brazil;* [8]*Sobi, Stockholm, Sweden;* [9]*Bioverativ, a Sanofi Company, Waltham, MA, United States;* [10]*Royal Children's Hospital, Melbourne, Australia*

Introduction: rFIXFc is an extended half-life therapy that demonstrated safety and efficacy in previously treated subjects with haemophilia B in the Phase 3 B-LONG/Kids B-LONG trials (NCT01027364/NCT01440946) and B-YOND extension (NCT01425723). Herein is a post hoc analysis of final longitudinal data (focusing on prophylactic regimens) from these studies.

Methods: Subjects ≥12 years of age in B-LONG received one of the following: weekly dose-adjusted prophylaxis (WP; starting dose 50 IU/kg), individualized interval-adjusted prophylaxis (IP; 100 IU/kg every 10 days initially), or on-demand dosing. Subjects <12 years of age in Kids B-LONG received 50-60 IU/kg every 7 days, with adjustments in dose/interval as needed. In B-YOND, subjects received WP (20-100 IU/kg every 7 days), IP (100 IU/kg every 8-16 days), modified prophylaxis, or on-demand dosing. Subjects in B-YOND could switch treatment groups at any time. Data from B-LONG/Kids B-LONG start to B-YOND end were pooled. Median and interquartile range are presented.

Results: A total of 123 subjects from B-LONG and 30 from Kids B-LONG were included. Cumulative duration was 3.63 (1.27-5.93) years in B-LONG/B-YOND and 2.88 (1.86-4.30) years in Kids B-LONG/B-YOND. No inhibitor development was reported and rFIXFc was generally well tolerated. Annualized bleeding rates (ABR) were low. In subjects who started treatment in B-LONG, overall ABRs on WP were 2.13 (1.00-4.39) at Year 1 (n = 67) and 1.50 (0.00-4.00) at Year 5 (n = 22); on IP ABRs were 2.07 (0.00-5.71) at Year 1 (n = 34) and 1.00 (0.00-2.00) at Year 5 (n = 19); for those who started in Kids B-LONG, ABRs were 2.00 (1.00-3.12) at Year 1 (n = 29) and 0.00 (0.00-2.18) at Year 4 (n = 10). Annualized rFIXFc consumption was stable over time. Dose and interval compliance rates were 99.3% (96.2%-100.0%) and 97.7% (95.7%-99.7%), respectively, in B-LONG/B-YOND and 99.1% (98.5%-100.0%) and 97.4% (92.9%-99.0%), respectively, in Kids B-LONG/B-YOND.

Discussion/Conclusion: This longitudinal analysis represents the longest duration of exposure to extended half-life rFIXFc to date (median 3.6 years in adults/adolescents, 2.9 years in children), with results that demonstrate consistent and favourable efficacy and safety, stable consumption, extended prophylactic dosing intervals, and high adherence, over time.

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P010 | 25 years of intracranial haemorrhage in haemophilia: Risk factors, management and outcomes in a Portuguese haemophilia center

F. Rodrigues; A. Palricas Costa*; A. Pereira; C. Catarino

Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisboa, Portugal

Introduction: Intracranial hemorrhage (ICH) is the most severe hemorrhage in patients with haemophilia and often the first clinical manifestation of the disease. ICH may be life threatening and often causes long term disabling neurological sequelae. A prompt diagnosis and intensive therapy are essential in the prevention of these complications. Recurrence of ICH is frequent and prophylaxis certainly plays an important role in its prevention.

Methods: In this retrospective study, we evaluated risk factors, management and outcomes of ICH in patients with haemophilia registered at our Centre in a period of 25 years (1993-2018).

Results: During this period, 183 patients with hemophilia were registered in our Centre, 81 of them with severe haemophilia. Fifteen episodes of ICH were confirmed in 12 severe patients, 3 of whom experienced recurrence of the ICH. Six of these events were observed in patients with inhibitors. Eight episodes occurred in the first year of life and in 6 it was the first clinical manifestation of haemophilia. Episodes were diagnosed between 3 days of life and 31 years (median age of 9 months). A history of recent trauma was documented in 8 episodes (53%). All patients were submitted to replacement therapy, with a median duration of 27 days (10-60). Inhibitors developed in 6 (50%) patients during the period of intensive treatment. Surgical procedures were performed in 8 (53%) episodes of ICH. Despite treatment, 2 patients (16.7%) died in the sequence of a second episode of ICH, and 2 other patients presented permanent neurological sequelae. Nine patients received prophylactic treatment after the initial ICH episode and, in these patients, no new episodes of ICH were observed.

Discussion/Conclusion: In haemophilia patients ICH remains a severe complication, and early and intensive replacement therapy is essential in preventing serious complications. However, in our patients, intensive treatment was associated with a high rate of inhibitor development. In our case series previous ICH, trauma and the presence of inhibitors were identified as the most important risk factors for ICH. On the other hand, prophylaxis has, in our view, demonstrated to play an important role in prevention of the devastating complications of ICH.

Disclosure of Interest: None declared.

P011 | Evaluating thrombin generation profiles based on FVIII levels in patients with haemophilia A

A. Marco Rico[1,*]; L. Tomas Menor[1]; P. Marco Vera[1,2]

[1]Haemostasis and Thrombosis, General University Hospital; [2]Clinical Medicine, Miguel Hernandez University, Alicante, Spain

Introduction: The thrombin generation assay (TGA) enables global assessment of the haemostasis measuring thrombin concentration before and after the clot is formed. Few data evaluate the information obtained from the TGA to adjust the dose and duration of the factor replacement therapy in patients with haemophilia. TGA may emerge as a useful tool to assess prophylaxis depending on FVIII levels measuring global clotting parameters. The aim of this study was to evaluate the relationship between thrombin generation parameters and FVIII activity.

Methods: Subjects were recruited at our Haemophilia Clinic from July 2018 onwards. They were patients with severe haemophilia A without inhibitors. This is an observational prospective study and samples were obtained previous to factor infusion (trough level) or 30 minutes after (peak level). We applied for the Pearson or Spearman correlation test based on parametric or non-parametric data respectively.

Results: 16 samples of patients with severe haemophilia without inhibitors with a median age of 9.6 (2-41) have been enrolled. The median through level was <1% while the FVIII activity 30 minutes after infusion was 42.6 (8.4-89.1). We observed a positive correlation between the thrombin generation parameters and FVIII:C both pre and post infusion of factor therapy: Endogenous thrombin potential (ETP) vs FVIII:C: r:0.946 previous to infusion whilst r:0.8153 post-infusion; Peak of thrombin vs FVIII:C: r:0.5973 previous to infusion while r:0.7701 post-infusion).

Discussion/Conclusion: The TGA could be a useful test to monitor effectiveness in haemophilic patients receiving factor concentrates. Further studies evaluating the replacement therapy in patients with haemophilia including a higher number of patients in collaboration with other Haemophilia Centres are required

Disclosure of Interest: None declared.

P012 | Efficacy and PK of turoctocog alfa pegol in patients with severe haemophilia A: Results from 4 clinical trials

A. Tiede[1,*]; S. Meunier[2]; P. Chowdary[3]; S. R. Lentz[4]; K. Kavakli[5]; K. Hampton[6]; J. Oldenburg[7]; F. Driessler[8]; E. Santagostino[9]; W. Clausen[10]

[1]*Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School (MHH), Hannover, Germany;* [2]*Unité d'Hémostase Clinique, Groupement Hospitalier Est, Hospices Civils de Lyon, Lyon, France;* [3]*The Katherine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free Hospital, London, United Kingdom;* [4]*Division of Hematology, Oncology, and Blood & Marrow Transplantation, Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, United States;* [5]*Department of Hematology, Ege University Children's Hospital, Izmir, Turkey;* [6]*Department of Cardiovascular Science, University of Sheffield, Sheffield, United Kingdom;* [7]*Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany;* [8]*Global Medical Affairs Biopharma, Novo Nordisk Health Care AG, Zürich, Switzerland;* [9]*Angelo Bianchi Bonomi Centre for Haemophilia and Thrombosis, IRCCS Cà Granda Foundation, Maggiore Hospital Polyclinic, Milan, Italy;* [10]*Novo Nordisk A/S, Søborg, Denmark*

Introduction: Turoctocog alfa pegol (N8-GP) is an extended half-life recombinant glycoPEGylated FVIII product. Data are presented from 4 clinical trials in severe haemophilia A (HA) patients (pts) of all ages.

Methods: Males with severe HA (FVIII activity <1%), no previous FVIII inhibitors, enrolled and were treated with N8-GP: pathfinder 1 (phase 1), ≥18 years, 25, 50, 75 IU/kg, single dose; pathfinder 2 main (phase 3), ≥12 years, 50 IU/kg every 4 days (50Q4D); pathfinder 2 extension (extn), pts with ≤2 bleeds in last 6 mo of the main phase were eligible for randomisation to receive 50Q4D or 75 IU/kg once weekly (75Q7D); pathfinder 3 (phase 3 surgery), ≥12 years, 50 IU/kg single dose before surgery and 20-75 IU/kg after; pathfinder 5 main (phase 3 with a *post-hoc* minor surgery analysis), <12 years, 60 IU/kg twice weekly (BIW). PK, ABR, surgery, haemostatic success rate, *post-hoc* analysis of target joints (TJ), safety and HRQoL were analysed.

Results: 270 pts were exposed, ~77 000 exposure days were reported in >882 pt/y. Data showed: mean terminal half-life ($t_{½}$) in pathfinder 1/2/5 was 19.0/18.3/14.7 hours, respectively; $t_{½}$ ratio between N8-GP and previous FVIII was 1.6/1.85-fold increased in adults/children, respectively. Mean estimated trough levels (95% CI) were 3.0% (2.6-3.4, pathfinder 2 main), 3.1% (2.2-4.5, 50Q4D extn), 1.2% (0.8-1.7, 75Q7D extn), 1.5% (1.2-1.9, pathfinder 5). PK predictions modelled FVIII activity levels >5% for 90% (adults/adolescents) and 72.3% (children) of the respective Q4D/BIW dosing intervals. Overall median ABRs were 1.18 (pathfinder 2 main); 0.0 (50Q4D extn and 75Q7D extn) and 1.95 (pathfinder 5). For surgery, N8-GP successfully managed 95.6% of 45 major surgeries (pathfinder 3) and all minor surgeries in children (pathfinder 5). Haemostatic success rate for treatment of bleeds was 87.5% (adults/adolescents) and 78.6% (children). Of 13 paediatric pts with TJ at baseline, 10 with 17 TJ had no bleeds in 14 TJ after 1 year of N8-GP treatment. No safety concerns were identified; an inhibitor was detected in 1 pt (pathfinder 2). Sustained/improved HRQoL was reported.

Discussion/Conclusion: N8-GP treatment was well tolerated and provided reliable prophylaxis with a choice of Q4D, BIW and (for selected pts) Q7D dosing regimens. These simple, predictable dosing regimens can improve pts' FVIII activity levels from severe to moderate and even mild levels, with low ABRs.

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P013 | Prophylaxis with factor VII activated in patients with severe hemophilia and inhibitors in Colombia

A. F. Escobar-Gonzalez[1,2,*]; N. Duque-Zapata[2,3]; M. Vásquez[2,3]; C. Orozco[2,3]; J. Donado[2,3]

[1]*Hematology;* [2]*Research Group Medicarte;* [3]*Epidemiology, Medicarte S.A., Medellín, Colombia*

Introduction: The development of inhibitors in patients with severe Hemophilia A occurs in up to 20%-30% and Hemophilia B in up to 3%-6%. Recent studies have shown that prophylaxis with bypass agents

can reduce bleeding episodes by approximately 50%-80%. Our objective was to compare the number of bleeding at baseline and after treatment with activated Factor VII (rFVIIa), in pediatric patients with hemophilia complicated by inhibitors.

Methods: Cross-sectional study of a cohort of patients under 18 years of age with hemophilia treated with rFVIIa for the management of inhibitors, from 2011 to 2018 in a specialized center in Colombia. A description of the general and clinical characteristics was made. The analysis of spontaneous bleeding was made using the paired Student t-test.

Results: Thirteen patients were included, with a median and IQR: age 9 years (IQR 6-11), time of evolution of the disease 10 years (IQR 5-10); 84.6% (11) of the patients with Hemophilia A, 7.69% (1) of the patients were indigenous.

A median and IQR were presented for the initial factor level of 0.10% (IQR 0.01-0.30); level of factor to the development of inhibitors was 0.30% (IQR 0.10-0.90); level of basal inhibitors was 25 Units Bethesda (UB)/mL (IQR 2.70-70.50); time with the presence of inhibitors was 3 years (IQR 1.35-3.78); maximum peak was 128 UB/mL (IQR 58.5-256.0). The drug associated with the development of inhibitors in 53.8% (7) was recombinant factor VIII, in 7.7% (1) factor VIII plasma-derived, in 15.4% (2) factor IX plasma-derived, and in 23% (3) there was no information.

The 15.4% (2) of patients treated with rFVIIa received previous treatment with activated prothrombin complex, 61.5% (8) had immunotolerance, with a median treatment of 10 months (IQR 3-28). Regarding the treatment with rFVIIa, the median time of treatment was 12 months (IQR 12-20), the median frequency of treatment was 3 times per week (IQR 3-3), with a median of 91 mcg/kg/per dose (IQR 76-110).

A statistically significant difference was found between the number of bleeding at baseline and after treatment, the difference bleeding was 2.9 (IC 95% 0.6-5.2), *P*-value 0.01.

Discussion/Conclusion: The experience of the cohort, showed a clinically and statistically significant reduction of 61% in the number of bleeding episodes, that matches what is reported in the literature (50%-80% reduction), decreasing the overall rate of bleeding in these patients and improving their quality of life.

Disclosure of Interest: A. Escobar-Gonzalez Speaker Bureau of: declares to be Advisor for Bayer, Novo, Pfizer, Biomarin, Shire and Speaker for Bayer, Novo, Pfizer, Shire, N. Duque-Zapata: None declared., M. Vásquez: None declared., C. Orozco: None declared., J. Donado: None declared.

P014 | Risk factors for development cardiovascular disease in patients with hemophilia in a population of North of Spain

A. Bernardo Gutierrez; L. F. Avila Idrovo; A. Caro Gómez; A. Solé Magdalena; D. Martinez Carballeira; J. R. Corte; I. Soto Ortega

Hematology, Hospital Universitario Central de Asturias, Oviedo, Spain

Introduction: The management of cardiovascular diseases in patients with a history of haemophilia is a challenge given the need to find an appropriate balance between the bleeding and ischemic risk, which requires close coordination between cardiologists and specialists in hemophilia

Methods: We do a retrospective study of patients diagnosed with Hemophilia A and B at the Central University Hospital of Asturias. In this study, 55 men with hemophilia were included, of which 52 (94.5%) presented hemophilia A (HA) and 3 (5.5%) hemophilia B (HB). The disease was severe in 54.5% (19 patients with HA and 3 with HB), moderate in 10.9% and mild in 49%. Data collection was obtained from the clinical history of patients in all its formats (digital, electronic, laboratory information system ...)

Results: We describe a median age was 37 years (minimum = 8, maximum = 82). Regarding the level of factor at the time of diagnosis, the median level of factor VIII: Cro was 4.40% (0%-38.20%), levels of factor VIII: C was 5.50% (0%-40.60%), and factor IX levels were 1% (0.81%-1.40%).

When analyzing the cardiovascular risk factors it was evidenced an important number of patients presented dyslipidemia in a percentage of 23.6% and smoking in 20%, similar to those reported by other international studies. We find that the prevalence of arterial hypertension was 9%, obesity 9%, much less than what is estimated in recent published studies, probably due to the small number of patients included. Likewise, 2 thrombotic episodes were detected, one in a patient with mild hemophilia (acute myocardial infarction and stroke) and another in a patient with severe hemophilia (stroke), in this case an incidence of 5.4 / 1000 inhabitants.

Discussion/Conclusion: Patients with hemophilia have the same risk factors as patients in the general population. Given that patients with hemophilia have life expectancies almost similar to those of the general population at this time due to advances in the treatment of this entity, they present typical cardiovascular affections of population aging. The best options for the management of these patients should be based on the individualization of the few existing protocols for the management of thrombotic pathology in the hemophilic population.

Disclosure of Interest: None declared.

P015 | Thrombotic and hemorrhagic complications of patients with hemophilia belonging to the central university hospital of Asturias

A. Bernardo Gutierrez*; L. F. Avila Idrovo; A. Caro Gomez; A. Solé Magdalena; D. Martinez Carballeira; J. R. Corte; I. Soto Ortega

Hematology, Hospital Universitario Central de Asturias, Oviedo, Spain

Introduction: With the advances in the treatment of hemophilia, serious hemorrhagic complications have decreased and the life expectancy of patients with hemophilia has increased significantly, which

now approaches life expectancy in the male population in general, this translates that these patients are susceptible to thrombotic complications similar to the general population, if they do not modify the risk factors triggers

Methods: A retrospective study of 55 patients diagnosed with hemophilia was carried out, of which 52 (94.5%) presented hemophilia A (HA) and 3 (5.5%) hemophilia B (HB). The disease was severe in 54.5% (19 patients with HA and 3 with HB), moderate in 10.9% and mild in 49%. The median age was 37 years (minimum = 8, maximum = 82). Major and minor hemorrhagic complications and thrombotic phenomena were identified during the last two years of follow-up.

Results: in this study it was demonstrated that the majority of the hemorrhagic episodes were hemarthrosis and muscular hematomas (25.4% and 18.1%, respectively). Within the hemorrhagic complications, 13 patients (23.6%), had severe HA, 5 (9%) moderate HA, 9 (16.3%) mild HA and 2 (3.6%), severe HB. Of the patients who presented hemorrhagic complications, 62% (18) were under treatment on demand and 31% (9) under prophylactic treatment.

Regarding thrombotic complications, 3 patients (5.4%) presented episodes of thrombosis, 2 patients with mild HA (stroke and acute myocardial infarction), and 1 patient with severe HA development of ischemic stroke, this constitutes an incidence of 5.4 / 1000 inhabitants.

Discussion/Conclusion: The increase in life expectancy of patients with hemophilia has led to the appearance of thrombotic events in this population with an incidence of 5.41/1000 inhabitants, lower than that reported in different studies, probably a decrease in our population. due to the small size of patients, in terms of hemorrhagic episodes, they are comparable with the rest of the population, being more frequent the muscular bleeds and hemarthrosis especially in patients who are not in a prophylaxis regimen

Disclosure of Interest: None declared.

P016 | Osteoarticular disease in patients with diagnosis of hemophilia in Asturias

A. Bernardo Gutierrez; A. Caro Gómez; L. F. Avila Idrovo; A. Solé Magdalena; D. Martinez Carballeira; J. R. Corte Buelga; I. Soto Ortega

Hematology, Hospital Universitario Central de Asturias, Oviedo, Spain

Introduction: Hemarthrosis is an important hemophilia complication. These hemorrhages represent 80% of the total and beginning in childhood. Arthropathy is a chronic disease caused by repetitive hemarthrosis that leads to the development of synovitis that causes and intense pain.

The treatment of hemarthrosis is on the one hand hematological, mediating replenishment of the deficit factor of coagulation and on the other rehabilitation to try to recover mobility prior to joint bleeding.

Methods: The objective of the current study was to assess the joint status of patients with hemophilia with imaging and monitoring techniques by specialists in Rehabilitation at the Central University Hospital of Asturias. Various imaging tests were used, including radiography. in 34 patients (61.8%), soft tissue ultrasound in 16 (29%), CT in 4 (7.2%), NMR in 8 (14.5%) and bone densitometry in 1 patient (1.8%).

Results: Of the 55 haemophilic patients in total, 32.7% (18 patients) had a Rehabilitation assessment periodically on a biannual, annual or biannual basis and 67.2% (37 patients) were not assessed by this specialty or were given high. Of the patients who had follow-up, 27% (10 patients) had had some joint or muscular haemorrhagic complication, most of them receiving substitution treatment under demand regimen. Regarding the total of surgeries performed on hemophiliac patients, 7.2% were trauma-type surgeries.

Discussion/Conclusion: We identified two important limitations in the care of our patients with hemophilia. While it is true that most of our patients have radiological studies to assess the degree of involvement of arthropathy or involvement of the locomotor system, we do not have a systematized radiological study protocol and repeat them according to the periodicity required for each patient. Secondly, the follow-up of patients with hemophilia by the Rehabilitation Service in our center is extremely irregular so that 67.2% of patients do not have regular follow-up and do not follow the guidelines indicated by the different scientific societies of Hemophilia.

Disclosure of Interest: None declared.

P017 | Prevalence of infectious diseases in patients diagnosed with hemophilia in Asturias

A. Bernardo Gutierrez; A. Solé Magadalena; L. F. Avila Idrovo; A. Caro Gómez; D. Martinez Carballeira; J. R. Corte Buelga; I. Soto Ortega

Hematology, Hospital Universitario Central de Asturias, Oviedo, Spain

Introduction: One of the major complications that patients with hemophilia was the transmission of infectious diseases, through the plasma derivatives used for their treatment because there were not screening systems for the detection of them.

Methods: he objective was to determine the rate of infectious diseases in patients diagnosed with Hemophilia in our autonomous community (Asturias). A retrospective study was conducted with 55 patients diagnosed with hemophilia, of which 52 (94.5%) presented haemophilia A (HA) and 3 (5.5%) hemophilia B (HB), with the serious disease in 54%, 5% (19 patients with HA and 3 with HB), moderate in 10.9% and mild in 49% of patients.

An information document on human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV) was published together with a review of the treatment schemes in our environment, as well as the therapeutic success

Results: In our population of hemophiliacs HIV infection rates of 14.5% are reported, for HBV 23.6% and 43.6% for HCV. All patients with HIV are being controlled by the Infectious Diseases Unit of the Internal Medicine Service and antiretroviral treatment (72% of the results, with

undetectable viral load). 78.26% of patients with HCV have eradicated the disease. All patients with a history of HBV are currently free of disease. 30.3% of patients with a history of HCV or HBV developed cirrhosis. A patient with hepatocarcinoma within the development cirrhosis has been documented, currently in palliative treatment for his neoplasia, but with a longer survival since the diagnosis (8 years).

Discussion/Conclusion: In our population, the prevalence of HCV and HBV infection is similar to that of communication in different international studies, while HIV infection is clearly lower. Currently, most patients with HCV have eradicated the disease and all patients with antiretroviral treatment. The new antiviral treatments have meant an improvement in the quality of life of our patients and an increase in their survival.

Disclosure of Interest: None declared.

P018 | Autologous stem cell in amyloidosis with factor X deficiency: Prophylactic management

A. Rodriguez*; N. Bermejo; S. Caceres; B. Moriano; M. Espina; M. J. Arcos; H. Bañas; F. Carnicero; S. Suarez-Varela; R. Cardesa; O. Ferre; F. Ibañez; C. Cabrera; J. Bergua

Hematology, Hospital San Pedro de Alcantara, Caceres, Spain

Introduction: Amyloidosis may cause factor X deficiency, which may lead to an increase in hemorrhagic morbidity, mainly in risky procedures, such as a stem cell transplant. Scientific articles reference the prophylactic use of factor IX/X plasma derived (pdFIX/X) concentrate in allogeneic stem cell transplant, but there is currently no data regarding autologous transplant.

Methods: A 53-year-old man, diagnosed with multiple myeloma and amyloidosis (renal and cardiac), in complete response after 8 cycles of Bortezomib-Dexamethasone, was referred to our hospital in 2014 for autologous stem cell transplant evaluation. Clotting results, previously normal, showed prolonged aPTT due to a deficiency in factor X (FX:C: 35%) associated to amyloidosis, without hemorrhagic manifestation.

Results: Before the transplant a single dose of 15 IU/Kg of pdFIX/X (Factor X P Behring) was administered to evaluate the pharmacokinetic, getting a good response with FX:C: 48.7% at 30 minutes after, 41.8% at 12 hours after, and 41.8% at 24 hours after. Due the high hemorrhagic risk in transplant, was decided to maintain platelet above 40 000/mm^3.

Autologous stem cell transplant and subsequent post-transplant control were performed without hemorrhagic complications, pdFIX/X was not necessary, however 14 pool of platelets were transfused in total during the 21 days of hospitalization to maintain the platelet count goal. Analytical follow-up showed progressive improvement of the aPTT until it was back to a normal range in August 2015, where it is staying 4 years after transplant.

Discussion/Conclusion: The most frequent deficiency of clotting factors secondary to amyloidosis is factor X, which occur due to the adsorption of the factor in the amyloid fibrils, shortening its plasma half-life. The treatment of amyloidosis with chemotherapy and stem cell transplant represents the best long-term option for the correction and even normalization of factor X. However, in the acute phase of chemotherapy and transplant, it presents a high hemorrhagic risk, so hemostatic prophylaxis is recommended.

In conclusion, maintaining platelet count above 40 000/mm^3 appears to be effective for hemostatic prophylaxis in factor X deficiency associated with amyloidosis, in case of bleeding can be used pdFIX/X for fast recovery of factor X.

Disclosure of Interest: None declared.

P019 | Comorbidities in aging persons with haemophilia A (PwHA)

A. Patel*; E. Yang; K. Raimundo; R. H. Ko

Genentech Inc., South San Francisco, United States

Introduction: Improvements in disease management for persons with haemophilia A (HA) have resulted in increased life expectancy of PwHA. As PwHA age, it is important to understand their comorbidity profile. We examined the prevalence of comorbidities in aging PwHA.

Methods: A retrospective, cross-sectional analysis was performed using the MarketScan® Medicare Supplemental and Coordination of Benefits Database, from 1/1/2006 to 30/9/2015 (study period). PwHA were patients with ≥2 HA diagnoses within 12 months; the first HA diagnosis was assigned as the index date. Males aged ≥65 years with ≥1 year of continuous insurance enrolment following the index date were included in the study. Comorbidities were identified using ICD-9 codes including cardiovascular disease (myocardial infarction, hypertension, hyperlipidemia and others), blood infections (hepatitis, HIV/AIDS), chronic liver or kidney disease, pain (chronic pain and joint pain), mental health conditions (depression, anxiety, dementia), diabetes, cancer, joint or musculoskeletal conditions (including osteoarthritis and arthropathy), and others (anaemia, sexual dysfunction and others), during the 1 year post-index period. Comorbidities were described and compared across PwHA aged 65-74 years and ≥75 years.

Results: In total, 375 PwHA (65-74 years, n = 164; ≥75 years, n = 211) were identified. Mean age was 76.6 (median: 72.0). The most prevalent comorbidity in PwHA was cardiovascular disease (65-74 years: 87.8%; ≥75 years: 93.8%), followed by diabetes (34.2%; 37.9%), anaemia (34.2%; 51.7%), joint or musculoskeletal conditions (26.8%; 23.2%), pain (28.7%; 27.5%), cancer (20.7%; 29.4%), and chronic renal disease (14.0%; 23.2%). Less frequent comorbidities included mental health issues (9.8%; 13.7%), blood infections (9.2%; 3.8%), and chronic liver disease (3.1%; 5.2%). The prevalence of these comorbidities increased with age.

Of the cardiovascular diseases, hypertension (65-74 years: 67.1%; ≥75 years 72.0%), hyperlipidaemia/dyslipidaemia (51.8%; 49.3%), ischaemic heart disease (43.9%; 49.8%), and atrial fibrillation (36.0%; 48.8%) were the most common.

Discussion/Conclusion: Older adults with haemophilia A have a high prevalence of aging-related comorbidities. The majority of PwHA had evidence of cardiovascular disease. Disease management should include a comprehensive assessment of health status to best support patient care.

Disclosure of Interest: A. Patel Shareholder of: Genentech, Employee of: Genentech, E. Yang Shareholder of: Roche, Employee of: Roche, K. Raimundo Shareholder of: Genentech, Employee of: Genentech, R. Ko Shareholder of: Genentech, Employee of: Genentech.

P020 | BAY 94-9027 and recombinant factor VIII Fc fusion protein: A head-to-head, randomized, crossover, pharmacokinetic study in patients with severe haemophilia A

A. Shah[1,*]; A. Solms[2]; S. Wiegmann[2]; M. Ahsman[3]; E. Berntorp[4]; T. Zhivkov[5]; T. Lissitchkov[5]

[1]Bayer, Whippany, United States; [2]Bayer, Wuppertal, Germany; [3]LAP&P Consultants BV, Leiden, Netherlands; [4]Centre for Thrombosis and Haemostasis, Lund University, Skåne University Hospital, Malmö, Sweden; [5]Specialized Hospital for Active Treatment, Sofia, Bulgaria

Introduction: BAY 94-9027 is a B-domain-deleted recombinant factor VIII (FVIII) site-specifically PEGylated with a 60-kDa (2 × 30-kDa) polyethylene glycol (PEG) to extend half-life, with efficacy at dosing intervals up to every 7 days shown in clinical trials. The pharmacokinetic (PK) profile of BAY 94-9027 was compared with that of recombinant FVIII Fc fusion protein (rFVIIIFc; Eloctate®).

Methods: This phase 1, open-label, crossover study included patients aged 18-65 years with severe hemophilia A and ≥150 FVIII exposure days. Patients were randomized to receive a single 60 IU/kg i.v. infusion of BAY 94-9027 or rFVIIIFc followed by the other treatment, with a washout of ≥7 days between treatments. PK samples were collected predose and up to 120 hours postinfusion. Primary PK endpoint was area under the curve from time 0 (predose) to last data point [$AUC_{0\text{-Tlast}}$] by one-stage assay. As the data were not normally distributed because of a single outlier patient, parametric statistical analysis was not an optimal analysis method, therefore statistical comparisons were made using nonparametric (Wilcoxon rank sum test) methods. Population PK models were developed to simulate times to 1, 3, 5, and 10 IU/dL FVIII.

Results: For the 18 study patients, geometric mean (% coefficient of variation) $AUC_{0\text{-Tlast}}$ for BAY 94-9027 and rFVIIIFc was 2659 (60.6) and 2408 (32.1) IU•h/dL, respectively. Median (min; max) $AUC_{0\text{-Tlast}}$ was 3100 (470; 5300) for BAY 94-9027 and 2500 (1410; 4170) for rFVIIIFc. Median (Q1; Q3) intra-individual ratio of BAY 94-9027:rFVIIIFc $AUC_{0\text{-Tlast}}$ was 1.24 (1.11; 1.36), with a Wilcoxon 2-sided *P*-value of 0.011. Modelling predicted that for these 18 patients time to 1, 3, 5, and 10 IU/dL FVIII thresholds is increased by is 16, 19, 21 and 25% (median) for BAY 94-9027 versus rFVIIIFc.

Discussion/Conclusion: The data indicate that BAY 94-9027 has improved $AUC_{0\text{-Tlast}}$ compared with rFVIIIFc. A longer time above FVIII threshold is expected with BAY 94-9027 than with an equivalent dose of rFVIIIFc. BAY 94-9027 can offer patients an improved PK profile vs rFVIIIFc; this improvement could translate into clinically meaningful outcomes in the management of patients with haemophilia A.

Disclosure of Interest: A. Shah Shareholder of: Bayer, Employee of: Bayer, A. Solms Employee of: Bayer, S. Wiegmann Employee of: Bayer, M. Ahsman Consultant for: Bayer, E. Berntorp Grant/Research support from: Bayer, CSL Behring, Shire, SOBI/Bioverativ, Consultant for: Bayer, LFB, Octapharma, Roche, Shire, Speaker Bureau of: Bayer, T. Zhivkov: None declared., T. Lissitchkov Shareholder of: Bayer, SOBI, Octapharma, Roche, Sanofi, Shire, Grant/Research support from: Bayer, Octapharma, Sanofi, Consultant for: Bayer, SOBI, Roche, Shire, Speaker Bureau of: Roche, Shire.

P021 | Pharmacokinetics and biomarkers in persons with haemophilia a (PwHA) receiving emicizumab every 2 or 4 weeks

A. Kiialainen[1,*]; C. Schmitt[1]; J. I. Adamkewicz[2]; C. Petry[1]; S. Pipe[3]; G. Young[4]; J. Mahlangu[5]; M. Lehle[1]; T. Chang[2]; C. Dhalluin[1]; V. Jimenez-Yuste[6]; S. Meeks[7]; J. Oldenburg[8]; M. Shima[9]; S. Chebon[1]; M. Niggli[1]; C. Negrier[10]; G. G. Levy[2]

[1]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [2]Genentech Inc., South San Francisco; [3]University of Michigan, Ann Arbor; [4]Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, United States; [5]University of the Witwatersrand and NHLS, Johannesburg, South Africa; [6]La Paz University Hospital, Madrid, Spain; [7]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University, Atlanta, United States; [8]University of Bonn, Bonn, Germany; [9]Nara Medical University, Kashihara, Japan; [10]Louis Pradel University Hospital, Lyon, France

Introduction: Emicizumab, a recombinant, humanized, bispecific monoclonal antibody, demonstrated clinically meaningful bleed prevention and a favourable safety profile in PwHA with or without inhibitors in HAVEN 2 (NCT02795767), HAVEN 3 (NCT02847637), and HAVEN 4 (NCT03020160) when given every 2 (Q2W) or 4 weeks (Q4W). We report pharmacokinetic (PK) and pharmacodynamic (PD) data for these dosing regimens.

Methods: Eligible patients of all ages with or without FVIII inhibitors received emicizumab prophylaxis: 4 weekly loading doses of 3 mg/kg, then 3 mg/kg Q2W (n = 10 HAVEN 2; n = 48 HAVEN 3) or 6 mg/kg Q4W (n = 10 HAVEN 2; n = 41 HAVEN 4). PD effects were assessed via a FVIII chromogenic activity assay with human reagents (FVIII:C) and FXIa-triggered thrombin generation (TG). Changes from baseline in activated partial thromboplastin time (aPTT), prothrombin time (PT), antigen levels of FIX and FX, D-dimer and prothrombin fragment 1 and 2 (F1.2) were determined. Emicizumab concentrations and FVIII inhibitor titres were measured via validated ELISA and a Chromogenic Bethesda Assay with bovine reagents, respectively.

Results: Emicizumab trough plasma concentrations and reported FVIII:C activity increased during the loading doses to reach means

of ~50 μg/mL and ~20 U/dL at Week 5, and were maintained at ~40-47 μg/mL and ~17-20 U/dL, respectively, thereafter. As expected, mean trough concentrations were generally lower in PwHA given emicizumab Q4W vs Q2W. Similarly, TG peak height (HAVEN 3 and 4) increased until Week 5 (>100 nM) with levels sustained thereafter. aPTT was normalised after the first emicizumab dose. In general, PK/PD relationships were similar regardless of dosing regimen; reported FVIII:C and TG peak height correlated with emicizumab concentration. Emicizumab did not significantly affect FIX and FX plasma antigen levels, or concentrations of safety markers of activated coagulation (PT, D-dimer and F1.2). Patients' FVIII inhibitor titre (HAVEN 2 and 4) remained stable or declined slightly over time. No *de novo* FVIII inhibitors developed.

Discussion/Conclusion: PD markers demonstrated on-target activity of emicizumab irrespective of FVIII inhibitor status or dosing regimen. Emicizumab dosing Q2W or Q4W demonstrated sustained PK and PD, and comparable PK/PD characteristics to the once-weekly dosing regimen (Schmitt et al. EAHAD, 2018) in PwHA with or without FVIII inhibitors.

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P022 | Pharmacokinetics and biomarkers in persons with haemophilia a (PwHA) without FVIII inhibitors receiving emicizumab once weekly in the phase 3 HAVEN 3 study

A. Kiialainen[1,*]; C. Schmitt[1]; J. Oldenburg[2]; M. Callaghan[3]; M. Niggli[1]; C. Petry[1]; G. Castaman[4]; M. Shima[5]; J. Mahlangu[6]; I. Paz-Priel[7]; G. G. Levy[7]; J. I. Adamkewicz[7]

[1]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [2]University Clinic Bonn, Bonn, Germany; [3]Children's Hospital of Michigan, Detroit, United States; [4]Careggi University Hospital, Florence, Italy; [5]Nara Medical University, Kashihara, Japan; [6]University of the Witwatersrand and NHLS, Johannesburg, South Africa; [7]Genentech, Inc., South San Francisco, United States

Introduction: Emicizumab, a recombinant, humanized, bispecific monoclonal antibody, restores the function of missing FVIIIa in PwHA by bridging FIXa and FX. It showed significant bleed reduction and a favourable safety profile in PwHA without inhibitors in the HAVEN 3 study (NCT02847637; Mahlangu et al. NEJM, 2018). We present the pharmacokinetics (PK) and pharmacodynamics (PD) of emicizumab prophylaxis once weekly (QW) in PwHA without inhibitors in HAVEN 3 (Arms A and D).

Methods: In HAVEN 3, PwHA without FVIII inhibitors aged ≥12 years received emicizumab 3 mg/kg QW for four wks followed by 1.5 mg/kg QW maintenance (cut-off 15 Sep 2017; N = 96). PK and PD were assessed through 48 wks of emicizumab exposure. Emicizumab levels were measured with a validated ELISA assay. PD was assessed using a chromogenic FVIII activity assay (FVIII:C) containing human reagents and by FXIa-triggered thrombin generation (TG). Changes from baseline in activated partial thromboplastin time (aPTT), prothrombin time (PT), antigen levels of FIX and FX, D-dimer and prothrombin fragment 1 and 2 (F1.2) were determined. FVIII inhibitor titres were measured using a Chromogenic Bethesda Assay containing bovine reagents.

Results: Mean steady-state emicizumab trough plasma concentrations reached >50 μg/mL by Wk 5 and were sustained throughout emicizumab maintenance dosing, consistent with a half-life of ~30 days. PD markers demonstrated on-target activity of emicizumab. Mean reported FVIII:C activity increased to ~25 U/dL by Wk 5 and was maintained >20 U/dL throughout the study. Mean TG peak height was maintained at ~110 nM from Wk 5 onwards. Reported FVIII:C activity and TG peak height correlated with emicizumab concentration. aPTT normalised after the first emicizumab dose and subsequently remained at or just below the normal range. Use of FVIII at study entry was reflected by normal aPTT, measurable FVIII activity and TG in some PwHA at baseline. Emicizumab did not significantly affect FIX and FX plasma antigen levels, or concentrations

of safety markers of activated coagulation (PT, D-dimer and F1.2). No *de novo* FVIII inhibitors developed.

Discussion/Conclusion: The PK and PD profiles, and PK/PD relationship, of emicizumab QW in PwHA without inhibitors were consistent with those from PwHA with inhibitors in HAVEN 1 (Adamkewicz et al. ISTH, 2017).

Disclosure of Interest: A. Kiialainen Shareholder of: Roche, Employee of: Roche, C. Schmitt Shareholder of: Roche, Employee of: Roche, J. Oldenburg Shareholder of: Shire, Baxter, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Consultant for: Baxter, Bayer, Biogen Idec, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire, Swedish Orphan Biovitrum, Speaker Bureau of: Baxter, Bayer, Biogen Idec, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire, Swedish Orphan Biovitrum, M. Callaghan Shareholder of: Alnylam, Grant/Research support from: Shire, Pfizer, Consultant for: Shire, Octapharma, Grifols, Pfizer, Bayer, Roche, Bioverativ, HEMA Biologics, Paid Instructor at: Pfizer, Roche/Genentech, Novo Nordisk, Global Blood Therapeutics, Sancilio, Amgen, Speaker Bureau of: Shire, Roche/Genentech, Bayer, Novo Nordisk, M. Niggli Employee of: Genentech, C. Petry Shareholder of: Roche, Employee of: Roche, G. Castaman Grant/Research support from: CSL Behring, Pfizer, Sobi, Consultant for: Roche, Speaker Bureau of: CSL Behring, Novo Nordisk, Kedrion, Uniqure, Bayer, Sobi, Shire, Werfen, M. Shima Grant/Research support from: Chugai, Bayer, Novo Nordisk, Shire, Consultant for: Chugai, Speaker Bureau of: Roche, Chugai, Shire, CSL Behring, Bayer, Novo Nordisk, Bioverativ, J. Mahlangu Grant/Research support from: Bayer, Biogen, Biomarin, CSL, Novo Nordisk, Pfizer, Sobi, Roche, Unique, Consultant for: Alnylam, Bayer, Biotest, Biogen, Baxalta, CSL Behring, Catalyst Biosciences, Novo Nordisk, Roche and Spark, Speaker Bureau of: Alnylam, Bayer, Biotest, Biogen, Novo Nordisk, Pfizer, Sobi, Shire, Roche, ISTH and WFH, I. Paz-Priel Employee of: Genentech, G. Levy Shareholder of: Roche, Employee of: Genentech, J. Adamkewicz Shareholder of: Roche, Employee of: Genentech.

P023 | Prospective, observational, 2-cohort study of adult patients with severe haemophilia A in Greece. Cost, clinical outcomes and quality of life comparison between on demand and secondary prophylaxis treatment strategies (HAMLET)

A. Kouramba[1,*]; P. Kotsi[1]; V. Akianidis[2]; A. Varaklioti[1]; O. Katsarou[1]

[1]*National Reference Centre For Congenital Bleeding Disorders, Laiko General Hospital;* [2]*Bayer Hellas A.G., Athens, Greece*

Introduction: Prophylaxis treatment in haemophilia has been shown to be beneficial over on demand treatment in reducing bleeding frequency, prevention of arthropathy and improvement of Health-Related Quality of Life (HRQoL). However it is associated with higher cost. We present the results of HAMLET study which has been designed to compare cost, clinical outcomes and quality of life between on demand (OD) and secondary prophylaxis (SP) treatment in adult patients with severe haemophilia A.

Methods: HAMLET collects detailed clinical and health economic data from a pre-specified cohort of 72 adults with severe Haemophilia A, without inhibitors, 47 treated on demand and 25 on secondary prophylaxis during a follow up period of 18 months. Quality of life is assessed using Haem-A-QoL and EQ-5D instruments completed by patients during visits according to the study.

Results: The average annual direct medical cost per patient of management by specialist was €51851.5 (SD: 44717.8, 95% CI: 37 916-65 787) for OD and €160181.0 (SD: 60995.4, 95% CI: 135003-185359) for SP adult patients with severe Hemophilia A ($P < 0.001$). The difference in the medical cost was driven by the cost of medication treatments for haemophilia which was in average €44665.0 for the OD and €156960.6 for the SP patients ($P < 0.001$). On the contrary, the cost of laboratory tests and the cost of specialist visits and physiotherapies was significantly higher in OD than SP group (234.1 vs 141.4, $P = 0.026$ and 48.9 vs 42.0, $P = 0.019$ respectively). Patients in OD treatment experienced higher number of joint bleeds (24.6, SD: 14.2) compared to SP treatment (4.2, SD: 4.8) ($P < 0.001$). In all visits, except visit 5, SP patients exhibited better HRQoL as assessed by Haem-A-QoL. There was no difference in HRQoL measured using EQ-5D.

Discussion/Conclusion: In Greece, the medical per-patient cost of management, by specialist, of adult patients with severe haemophilia A was three times higher for SP treatment compared to OD treatment. The observed cost difference was counterbalanced with a better HRQoL in the SP treated patients compared with the OD treated patients and better clinical outcomes.

Disclosure of Interest: None declared.

P024 | Benefits of prophylaxis with recombinant FIX albumin fusion protein: Real-life experience in 9 patients

A. Tagliaferri[1,*]; G. Quintavalle[1]; G. F. Rivolta[1]; F. Riccardi[1]; A. Matichecchia[1]; A. Benegiamo[2]; R. Rossi[2]; A. Coppola[1]

[1]*Regional Reference Centre for Inherited Bleeding Disorders - University Hospital of Parma;* [2]*Laboratory of Clinical Chemistry and Hematology - University Hospital of Parma, Parma, Italy*

Introduction: Few real-life data are available on prophylaxis with albutrepenonacog alfa, a recombinant Factor IX (FIX) fusion protein with albumin (rIX-FP), showing in clinical trials significant reduction of infusion burden and concentrate consumption in patients with hemophilia B. We here report our single-centre experience over 16 mo.

Methods: Pharmacokinetic (PK) studies (50 IU/Kg rFIX-FP, ≥96 hours wash-out) were carried out measuring FIX:C at baseline

and 1, 6, 24, 48, 72, 120, 168 and 240 hours after infusion. Based on PK and clinical needs rIX-FP prophylaxis was prescribed and then adjusted according to clinical and laboratory follow-up (bleeding and infusion report, trough FIX:C), monthly for 3 mo, then every 3 mo over 1 yr.

Results: Nine patients (FIX<1%, n = 8; age, mean ± 1SD, 34.8 ± 14.2 years) with negative inhibitor history received rIX-FP. All but one were on secondary/tertiary prophylaxis with standard products (2/wk, n = 7; every 3-days, n = 2). A 60-year old patient with history of 3 intracranial bleeds started prophylaxis with rIX-FP, previously unfeasible due to venous access problems. Mean follow-up was 10 ± 5 mo, but a patient participating in the rIX-FP clinical trial program was treated for 75 months. Mean rIX-FP in vivo recovery and half-life were 1.25 ± 0.2 and 80.2 ± 14.2 hrs, respectively. Mean prophylactic dose was 46 ± 7 IU/Kg. High 240-hours FIX levels (6.4-9.6%) led to prescribe every 10 d-regimens in 3 patients. Three started every 7 d-regimens, then prolonged every 10 (n = 2) or 14 d (n = 1). The patient in the rIX-FP trial passed from lower-dose weekly to 75 IU/Kg every 14-days. Due to several target-joint bleeds occurring ≥10 d after infusion, he resumed a 10-days interval, then reducing rIX-FP 50 IU/Kg. The youngest (13-years old) patient and one with severe arthropathy, experiencing traumatic bleeds, remained on 7-days regimens. High satisfaction to treatment due to the reduction of venipunctures (mean −65%, −71/years) was reported, together with mean 64% lower FIX consumption, calculated according to the last rIX-FP regimen, compared to the last year on standard products. No adverse events or inhibitor development occurred.

Discussion/Conclusion: This real-life experience clearly shows benefits of prophylaxis with rIX-FP, providing prolonged protection and improved quality of life. Individual PK data and careful patients' follow-up allow to optimize prophylaxis regimens and cost-benefit ratios.

Disclosure of Interest: None declared.

P025 | Stability of turoctocog alfa, a recombinant factor VIII product, during continuous infusion in vitro

K. Kawasugi[1]; D. Pollard[2]; A. M. Nøhr[3,*]; D. K. Normann Rasmussen[3]; J. Taaftegaard Jensen[3]; M. Takeyama[4]

[1]Teikyo University School of Medicine, Tokyo, Japan; [2]Katharine Dormandy Haemophilia & Thrombosis Centre, Royal Free London NHS Foundation Trust, London, United Kingdom; [3]Novo Nordisk A/S, Gentofte, Denmark; [4]Nara Medical University, Kashihara, Japan

Introduction: Turoctocog alfa (NovoEight®) is a recombinant factor VIII (rFVIII) product used for prophylaxis against and treatment of bleeding in patients with haemophilia A, including those undergoing surgery and invasive medical procedures. This *in vitro* study evaluated the physical and chemical stability of turoctocog alfa during continuous infusion (CI) over 24 hours at 30°C.

Methods: The study was performed at 30°C (± 2°C). Three strengths of turoctocog alfa (500, 1000 and 3000 IU) were reconstituted to 4.3 ml in NaCl solution, according to the manufacturer's recommendations. The CI system comprised a B Braun Perfusor® Space automatic infusion pump, a BD™ Plastipak™ syringe and an Original-Perfusor® Line infusion tube, with pump speed set at either 0.6 or 1.5 ml/h. Turoctocog alfa concentrations equating to doses of 1.1–16.1 IU/h/kg body weight were assessed. The following parameters were evaluated at selected time points between 0-24 hours: appearance of solution, clarity, pH, potency, content, total high molecular weight proteins (HMWPs), purity, and oxidised rFVIII. FVIII activity was measured using both the one-stage clotting and chromogenic assays.

Results: The potency of turoctocog alfa was maintained within the acceptance criteria during CI for both pump speeds with all three strengths at 6, 12 or 24 hours (500 IU: ≥476 IU/vial; 1000 IU: ≥1005 IU/vial; 3000 IU: ≥2980 IU/vial). Purity was within the acceptance criteria at 6, 12 or 24 hours for both pump speeds (500 IU: ≥94.4%; 1000 IU: ≥94.6%; 3000 IU: ≥92.4%). There tended to be a small increase in oxidised forms (500 IU: ≤3.1%; 1000 IU: ≤2.7%; 3000 IU: ≤3.1%), but these were all within acceptance criteria limits. Minor increases in total HMWP (all within the acceptance criteria), was observed with all three strengths (highest value: 2.8% at 24 hours for 3000 IU). Content, appearance, clarity and pH all remained within acceptance criteria.

Discussion/Conclusion: Chemical and physical stability of turoctocog alfa was maintained during CI over 24 hours. There was no degradation or change in any of the parameters tested. Potency was within the pre-specified shelf-life specification range throughout 24 hours of infusion. These findings confirm the suitability of turoctocog alfa for CI for clinical use, such as in the surgical setting.

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P026 | The effect of anti-von Willebrand factor immunoglobulin on assays of von Willebrand factor: A case report

A. Bowyer[1,*]; P. Brown[1]; B. Hopkins[2]; A. Lowe[1]; S. Kitchen[1]; J. van Veen[1]; P. Mensah[2]; R. Maclean[1]

[1]Coagulation, Sheffield Teaching Hospitals NHSFT, Sheffield; [2]Coagulation, University Hospitals of Leicester, Leicester, United Kingdom

Introduction: Caplacizumab is an anti-von Willebrand factor (VWF) immunoglobulin which targets the A1 domain of VWF to inhibit binding of ultra-large molecular weight multimers to platelet glycoprotein

(GP) 1b-IX-V receptors. Caplacizumab has been reported to induce quicker resolution of an acute TTP episode compared to placebo. Clinical studies have reported greatly reduced VWF ristocetin cofactor activity (VWF:RCo) in patients following treatment with caplacizumab. We present two cases (P1 and P2), with reduced platelet count and ADAMTS13 activity, that were treated daily with 10 mg subcutaneous caplacizumab together with daily plasma exchange and immunosuppressive therapy. VWF assays were performed prior to and following drug administration on days (D) 1, 2 and 6 (P2) or 9 (P1).

Methods: Hyphen Biomed chromogenic FVIII (France), VWF:Ag, BC von Willebrand reagent and Innovance VWF Ac (Siemens, Germany) were performed on Sysmex CS5100i. VWF:Ag, VWF:RCo and VWF Activity were performed on ACL TOP and a second VWF:RCo was performed on Acustar (Werfen, USA). Manual VWF:RCo was tested by visual agglutination of fixed platelets.

Results: Chromogenic FVIII activity, both VWF:Ag and Werfen VWF activity assay remained within reference ranges at each time point. From D2, manual VWF:RCo, Innovance and BC VWF activities were undetectable in both patients. Werfen VWF:RCo was abnormal in P1 from D1 (29 IU/dL) and in P2 from D2 (16.8 IU/dL). Acustar VWF:RCo was reduced in P1 at D9 (36 IU/dL) and in P2 from D2 (26 IU/dL). Percentage (%) difference was calculated against the pre dose levels. For VWF activity assays, the median % difference ranged from 47.9% (P2 using Werfen VWF Act) to 98.9% (P1 using BC VWF).

Discussion/Conclusion: In the presence of caplacizumab, reduction of VWF activity was observed with each assay however the degree of loss was variable. Most activity assays based on VWF binding via Ristocetin and either platelets or fragments of platelet GP1b receptors demonstrated significant reduction of activity after day 2 of treatment. The results of the monoclonal antibody-based Werfen VWF Activity remained within the normal reference range throughout. It is important that haemostasis laboratories understand how their VWF activity assays perform in the presence of caplacizumab since a haemostatically challenged patient may have apparently normal or slightly reduced VWF parameters with some reagents.

Disclosure of Interest: None declared.

P027 | The effect of emicizumab on assays of factor VIII activity in severe haemophilia A patients and artificially spiked plasma

A. Bowyer*; S. Kitchen; R. Maclean

Coagulation, Sheffield Teaching Hospitals NHSFT, Sheffield, United Kingdom

Introduction: Emicizumab (Hemlibra, Roche Chugai) is a bispecific antibody to activated factor IX (FIXa) and factor X (FX). It is currently licensed in the UK for treatment of haemophilia A (HA) with inhibitors. Emicizumab interferes with standard one-stage factor VIII activity (FVIII:C) assays (sOSA), resulting in very high FVIII:C, and with chromogenic FVIII assays (CSA) that use bovine-sourced reagents resulting in no activity. CSA using human-sourced reagents or a modified OSA (mOSA), which uses a higher plasma dilution and emicizumab-specific calibrator (r2 Diagnostics), can measure the presence of emicizumab. This study investigated the measurement of in-vitro spiked plasma (IVSP) and SHA patients prophylactically treated with emicizumab by OSA and CSA of FVIII:C.

Methods: Normal plasma, spiked with emicizumab from 2.5-400 μg/mL, and 7 samples from 4 SHA patients treated once weekly with emicizumab were tested by sOSA using Actin, Actin FS, Actin FSL, Pathromtin SL, Synthasil, APTT SP and Synthafax and plasma calibrators. A mOSA was also performed using a 1/80 initial dilution and r2 emicizumab calibrator for each APTT reagent. CSA were performed with Hyphen Biophen (human sourced reagents) and the bovine-sourced reagents Siemens, Rossix, Coamatic, SP4 VIII and Technoclone.

Results: sOSA median percentage difference (% diff) from the expected target with IVSP ranged from 623% (Synthasil) to 2200% (Actin FS); Hyphen CSA was −12%. Using r2 calibrator, the median % diff mOSA ranged from 3% (Actin FSL) to 12% (APTT SP); Hyphen CSA was 11%. For SHA patients, median sOSA VIII:C ranged from 356 IU/dL (Pathromtin SL) to 1691 IU/dL (Synthafax); Hyphen CSA was 31 IU/dL. mOSA FVIII:C ranged from 45.7-51.8 μg/mL (Actin FSL and Synthafax). Results for the bovine CSA with IVSP or SHA were undetectable.

Discussion/Conclusion: Standard one-stage FVIII:C assays significantly overestimated the FVIII activity of in vitro-spiked plasma and severe HA patients; a wide variation in FVIII:C was observed with the different APTT reagents. The bovine-based chromogenic FVIII:C assays did not detect emicizumab activity when calibrated against either plasma or emicizumab-specific reference plasmas. The human-based Hyphen chromogenic assay or mOSA calibrated against r2 emicizumab reference plasma could be used in the quantification of emicizumab in both IVSP and SHA patients.

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P028 | The socioeconomic burden of moderate and severe haemophilia in China: A feasibility study

A. Martin*; T. Burke; G. Pedra; J. O'Hara

HCD Economics, Warrington, United Kingdom

Introduction: The psychosocial and economic burden of haemophilia for patients, caregivers, and wider health care system has remained understudied in China. The feasibility of conducting a comprehensive burden of illness (BOI) in adult patients with moderate and

severe haemophilia in China has not previously been explored. The objective of this study were to explore the socioeconomic burden of moderate and severe haemophilia and impact on health-related quality of life.

Methods: A retrospective, cross-sectional, 'bottom-up' BOI study was piloted. A societal perspective was adopted to consider direct medical, non-medical and indirect cost information, including employment and out-of-pocket expenses, as well as quality of life and adherence.

Results: Clinical reports for 20 patients were received with high rate of full form completion (19/20). Patients had a mean age of 26 (SD 13.8) and of which, 5 had moderate and 15 had severe haemophilia. Patients self-rated their health with a mean score of 71.6 (SD 15.1) ranging 40 to 100 and 3/20 respondents indicated that they suffer anxiety or depression related to their haemophilia. Responses appeared clinically plausible as respondents indicated that they experienced a mean of 18.8 bleeds (SD 17.8) in the last 12 months and 13 respondents had a major bleed in the past 12 months. Of 20 respondents, 17 had a target joint and 16 reported they had joints with chronic damage due to haemophilia. Respondents had diverse care history and their treatment profiles varied between on-demand and prophylaxis factor replacement and use of cryoprecipitate. Notably, some respondents indicated that out-of-pocket payments were extensive as only 77% (SD 10.8) of care was covered by insurance.

Discussion/Conclusion: The findings of the pilot study indicate that socioeconomic and health burden of haemophilia is considerable. The study demonstrates feasibility of data collection and results indicated that there exists an important unmet clinical need in haemophilia patients in China.

Disclosure of Interest: None declared.

P029 | Von Willebrand disease caused by homozygous C.421G>T (p.Asp141Tyr) mutation is associated with a bleeding phenotype and fatal outcome in most patients

A. Ruiz-Sáez[1,*]; R. Marchi[2]; A. Boadas[1]; M. Echenagucia[1]; T. Obser[3]; R. Schneppenheim[3]

[1]Centro Nacional de Hemofilia, Banco Municipal de Sangre, DC.; [2]Centro de Medicina Experimental, Instituto Venezolano de Investigaciones Científicas, Caracas, Venezuela, Bolivarian Republic Of; [3]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Introduction: Von Willebrand disease (VWD) is a heterogeneous bleeding disorder, due to deficiency or defect of VW factor, a multifunctional protein. Type 3 VWD is the most severe form of this entity; it is usually inherited in an autosomal recessive pattern and characterized by a variable life-long mucocutaneous bleeding tendency and propensity to develop vascular malformations. We describe clinical and genetic findings of two unrelated type 3 VWD families with a severe bleeding phenotype that was causing early death of most patients.

Methods: Family 1: 43-year-old female, with severe bleeding since 4 months old including massive hemoperitoneum during ovulation, late postpartum bleeding, hematuria, hemarthrosis, hematoma and bilateral preretinal bleeding, ISTH BAT score 41. There was no history of consanguinity; however, parents are from the same town. Three brothers and 2 sisters died during the first bleeding episode at very young age. FVIII:C was 0.03 $IUmL^{-1}$, VWF:Ag and VWF:RCo unmeasurable. Family 2: 3-month-old girl with bleeding tendency since 15-days after birth: prolonged bleeding after venipuncture, severe petechial rash and some edema in arms after venipuncture but also occasionally in legs. Skin vascular malformation of the neck. She died at first episode of epistaxis and probably respiratory tract bleeding unresponsive to FVIII + VWF concentrates and blood transfusions. Her parents are third degree cousins. An older sister died at 12-months, during first epistaxis, unresponsive to treatment. FVIII:C was 0.019 UmL^{-1}, VWF:Ag and VWF:RCo unmeasurable. Mutation analyses were performed by direct sequencing of the 52 VWF exons. Possible large deletions or insertions were investigated by multiplex ligation-dependent probe amplification (MLPA) analysis.

Results: Both patients were diagnosed with Type 3 VWD. A new homozygous mutation, 421G>T (p.Asp141Tyr), localized in the propeptide D1 domain was found in both proposita. Furthermore, both families shared the homozygous von Willebrand factor variant p.Phe2561Tyr. Both families were from the Venezuelan Andes.

Discussion/Conclusion: The mutation p.Asp141Tyr was associated with fatal outcome in most of the descendent of both families. It would be interesting to investigate what genetic markers make the difference in the survivors.

Disclosure of Interest: None declared.

P030 | Use of extended half-life rFVIII-Fc or rFIX-Fc in previously treated patients with hemophilia A or B. A single center experience

A. Ruiz-Sáez*; A. Boadas; M. Echenagucia

Centro Nacional de Hemofilia, Banco Municipal de Sangre, DC., Caracas, Venezuela, Bolivarian

Introduction: As part of the WFH Humanitarian Aid Program, since 2015, previously treated Venezuelan patients (PTP) were treated with FVIIIFc or rFIXFc in different therapeutic modalities.

Methods: We evaluated efficacy and safety in 221 PTP with hemophilia A(HA) and 78 with hemophilia B(HB) treated with rFVIIIFc or rFIXFc. Doses used as recommendations of WFH[1], adjustments according to clinic if necessary. In 50 patients, FVIII/FIX was measured by one-stage factor assay at different times to estimate the PK using the WAPPS-HEMO[2] system.

Results: I. *HA:* 150 severe, 32 moderate, 12 mild, 27 patients (p) with high response inhibitor (HRI), mean age: 25 years, range: 1-82 years. Treatment: A. Some form of prophylaxis in 153p (69.2%), age: 2-68 years. Mean dose 30 IU FVIII/kg (10-60); weekly

dose 46 IU/kg (12-123). Dosing: 34% 1/weekly; 32% 2/weekly; 6.4% 3/weekly; 27.6% 1/5d B. Surgery 18 in 17p, age: 7-82 years, 10 major/8 minor, good evolution. C. Episodic: 155/95p, mean age 30 years (1-70); 107 hemarthrosis, 24 muscles, 6 gastric, 4 pseudotumor, 4 oral, 4 hematuria, 3 post-surgical, 2 polytraumatisms, 1 ocular. D. Immune Tolerance Induction: Dose: 50 IU/kg, 3/weekly, age 8 years (1-32). Outcome: Success 5, on-going 15, not-evaluable 7. II. *HB*: 58 severe, 12 moderate, 7 mild and 1 HB carrier. Mean age: 28 years (1-79). A. Some form of prophylaxis 37 (47.4%), mean dose: 37 IU/kg (16-71), weekly dose: 34 IU/kg (16-71). Dosing: 1/weekly 83% and 1/10 days 17%. B. Surgery: 10 procedures (5 major) in 9p, good evolution. C. Episodic: 78 events, 66 hemarthrosis, 5 muscles, 2 pseudotumor, 2 oral, 1 gastric, 1 hematuria and 1 CNS. No adverse effects have been observed with the use of both products. PK: Using on average only 3 determinations it was possible to estimate PK in an individualized way. rFVIIIFc: mean half-life 21.3 hours (h), mean dose: 40.4 IU/kg, time to 0.01 IU/mL 125.1 h. For rFIXFc mean half-life 81.7 h, mean dose 21 IU/kg, time to 0.01 IU/mL 208.7 h.

Discussion/Conclusion: The use of rFVIIIFc and rFIXFc has shown efficacy and safety in our patients. Use of PK estimation was a tool that helps us to optimize and individualize prophylaxis. rFVIIIFc and rFIXFc use has been of great benefit for our patients, especially for patients with HB, who have been able to reduce the frequency of infusions even using doses lower than those used in phase III clinical studies. 1.FMH. Fact Sheet: www.wfh.org 2. www.wapps-hemo.org

Disclosure of Interest: None declared.

P031 | Results from a prospective, randomised, controlled phase 2 study of fibrinogen concentrate vs cryoprecipitate in pseudomyxoma peritonei surgery

A. Roy[1,*]; N. Sargant[1]; S. Rangarajan[1]; S. Alves[1]; J. Bell[1]; S. Stanford[1]; C. Solomon[2]; I. Kruzhkova[2]; S. Knaub[2]; F. Mohamed[1]

[1]*Basingstoke and North Hampshire Hospital, Hampshire, United Kingdom;* [2]*Octapharma AG, Lachen, Switzerland*

Introduction: Maintaining adequate plasma fibrinogen levels during cytoreductive surgery for pseudomyxoma peritonei (PMP) may help control haemostasis. FORMA-05 compared the efficacy and safety of cryoprecipitate with a new highly purified, double virus-inactivated human fibrinogen concentrate (HFC; *Octafibrin*; Octapharma) in patients with acquired fibrinogen deficiency undergoing surgery for PMP.

Methods: FORMA-05 is a prospective, single centre, randomised, controlled phase 2 study. Patients undergoing surgery for PMP with predicted intraoperative blood loss ≥2 L without fibrinogen supplementation pre-emptively received HFC (4 g) or cryoprecipitate (2 pools of 5 U). The composite primary endpoint was intraoperative (assessed by surgeon and anaesthesiologist) and postoperative efficacy (assessed by haematologist), graded using objective 4-point scales and adjudicated by an Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC).

Results: The interim analysis per-protocol set included 24 patients (HFC, n = 11; cryoprecipitate, n = 13). The mean intraoperative dose of HFC was 6.4 g vs a mean of 3.9 pools of cryoprecipitate, containing approximately 7.7-8.9 g fibrinogen. Median duration of surgery was 7.7 h. Intraoperative haemostatic efficacy was rated excellent/good for 90.0% and 76.9% of patients receiving HFC and cryoprecipitate, respectively (IDMEAC: 90.0% v 61.6%), with similar blood loss. Postoperative haemostatic efficacy was rated excellent for all 24 patients. Infusions were initiated 0.5 hours earlier with HFC than cryoprecipitate due to faster product availability. Intraoperative HFC led to a greater mean increase in FIBTEM A20 v cryoprecipitate (3.1 v 0.6 mm; $P < 0.01$) and higher mean increase in plasma fibrinogen (0.7 v 0.3 g/L; $P = 0.01$).

There were 2 serious adverse events (SAEs) in the HFC group and 9 in the cryoprecipitate group, including 4 thromboembolic events (TEEs) (2 deep vein thromboses, 2 pulmonary embolisms). No AEs or SAEs were deemed related to the HFC by the investigator.

By study completion 48 patients were enrolled; results were comparable with the interim analysis. Full study results are expected late 2018.

Discussion/Conclusion: In this interim analysis HFC was at least as efficacious as cryoprecipitate for the treatment of bleeding in patients undergoing surgery for PMP. No related AEs and no TEEs occurred in the patients treated with HFC.

Disclosure of Interest: A. Roy Grant/Research support from: Octapharma, N. Sargant: None declared., S. Rangarajan: None declared., S. Alves: None declared., J. Bell: None declared., S. Stanford: None declared., C. Solomon Employee of: Octapharma, I. Kruzhkova Employee of: Octapharma, S. Knaub Employee of: Octapharma, F. Mohamed Grant/Research support from: Octapharma.

P032 | Emicizumab therapy for infants and young pediatric patients—a single center experience

A. Barg*; E. Avishai; R. Leiba Fisher; D. Bashari; S. Levy-Mendelovich; O. Cohen; T. Barazni-Brutman; L. Stencel; T. Livnat; G. Kenet

The Israeli National Hemophilia Center, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

Introduction: The Israeli National hemophilia center treats over 660 hemophilia patients, including about 150 pediatric patients with hemophilia A (HA). Emicizumab is a bispecific antibody that bridges activated factor IX and factor X to restore the function of activated factor VIII, which is deficient in persons with HA.

Methods: Children with HA and inhibitors were eligible for the study provided their guardians signed informed consent. Therapy was initiated at the hemophilia treatment center. Emicizumab treatment was initiated at a loading dose of 3 mg/kg once weekly for 4 weeks, followed by 1.5 mg/kg once weekly. Clinical follow up was conducted every 1-2 weeks during the loading period and maintained via telephone conference talks with patients' families weekly. Any bleeding or other adverse event was recorded.

Lab follow up comprised global coagulation assays including rotational thromboelastometry (ROTEM) and thrombin generation, obtained prior and during treatment with Emicizumab.

Results: Eleven children were included in this study. Age at commencement of Emicizumab was 2 to 80 months. Historical peak inhibitor range was 4-420 Bethesda units (BU). Since the initiation of treatment with Emicizumab 8/11 children did not require any additional treatment. None of the patients experienced hemarthrosis or any other spontaneous bleeds following treatment with Emicizumab. Two patients required treatment with rFVIIa due to facial trauma. One patient required additional treatment with rFVIIa and FVIII due to major bleeding following circumcision. All ROTEM parameters normalized following loading period treatment. Thrombin generation analysis demonstrated elevation of mean endogenous thrombin potential (ETP) following Emicizumab treatment. Mean thrombin peak height increased from about 17 to 50 nM prior and post Emicizumab loading respectively.

Discussion/Conclusion: This study demonstrates the effectiveness of Emicizumab in reducing bleeds in HA patients with inhibitors including infants and toddlers. Our experience suggest that treatment with Emicizumab may not be sufficient for surgical procedures. Thrombin generation may reflect more accurately the hemostasis than ROTEM in patients treated with Emicizumab.

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P033 | Intermediate dose prophylaxis in adults with haemophilia A: A clinical audit from a resource limited setting

A. Ashok[1]; R. Sudevan[2]; G. Vidyadharan[3]; A. C. Jacob[3]; R. Prabhu[1]; M. Unni[1]; R. G[1]; A. A[1]; N. Sidharthan[1,*]

[1]Department of Medical Oncology and Haematology; [2]Department of Health System Research; [3]Department of Pathology, Amrita Institute of Medical Sciences and Research centre, Kochi, India

Introduction: Prophylaxis is considered to be the standard of care for patients with hemophilia(PWH) of any age group worldwide. The majority of PWH in India is not under any prophylaxis treatment. Generally developing world is in shortage of evidence based data regarding prophylaxis in adult PWH. To address this challenge we initiated a short term secondary/tertiary intermediate dose prophylaxis in adult PWH with moderate/severe haemophilia A. The objectives were to compare the effect of prophylaxis v/s on-demand therapy in terms of bleed rate, days of work lost and number of hospital visits.

Methods: PWH aged >18 years with moderate/severe haemophilia A who consented to participate in the prophylaxis were enrolled. Those PWH with Factor VIII(FVIII) inhibitor were excluded. A total of eight patients (7 with severe haemophilia and one with moderate haemophilia) received an average dose of 23 IU/kg recombinant FVIII (rFVIII) concentrate twice weekly for 2 months. Inhibitor screening was performed at the end of prophylaxis. Measurement of FVIII trough level was done in all patients. The number of days of work lost and that of hospital visits during 2 months of two types of treatments were also documented. Statistical analysis was done in SPSS-21. The continuous variables were expressed in mean with standard deviation and categorical variables as frequency with percentage.

Results: The mean age of the participants was 31.63 years (SD±6.98). The mean bleed rate during two months of on demand V/s intermediate dose prophylactic regimen was 5.125 V/s 0.625 (P = 0.01). The mean of FVIII consumed by a PWH during prophylaxis was 13500 IU/month (ie, 23 IU/kg/dose). The median time gap between prophylactic infusion to trough level was 67.50 hrs (60-74 hours) and the median trough level observed was 2.50% (range 1-5%). The mean work days lost and hospital visits for hemophilia care during 2 months of on demand therapy was 30.63 days (SD±24.59) and 20.63 days (SD±24.51). During prophylaxis period the work days lost and hospital visits were zero. The FVIII inhibitors were reported as absent at the end of prophylactic treatment.

Discussion/Conclusion: The results of our clinical audit show that Intermediate dose prophylaxis with rFVIII concentrates in young adult patients with moderate/severe haemophilia A appears to be effective in reducing the frequency of all type of bleeds as well as help to save their productive work days.

Disclosure of Interest: None declared.

P034 | Correlating joint bleeding rates and head us score in haemophilia A patients treated by late/secondary prophylaxis

A. Banchev[1,*]; D. Stoyanova[1]; D. Konstantinov[1]; I. Ignatova[2]; E. Peteva[2]; V. Kaleva[2]; S. Kostova[3]; A. Pavlova[4]

[1]Department of Paediatric Haematology and Oncology, University Hospital Tsaritza Giovanna - ISUL, Sofia; [2]Department of Paediatric Haematology and Oncology, University Hospital Sv. Marina, Varna; [3]Department of Paediatrics, University Hospital G. Stranski, Pleven, Bulgaria; [4]Institute of Experimental Haematology and Transfusion Medicine, Bonn, Germany

Introduction: Primary prophylaxis stands for "gold standard" in Haemophilia treatment. However, secondary/late prophylaxis is still the mainstay treatment modality for children and young adults in

various countries. Aim: To evaluate the joint health using ultrasound examination along with analysis of the reported bleeding events in a cohort receiving late/secondary prophylaxis.

Methods: The study comprises 42 patients with Haemophilia A (HA) (6-28 years old) treated in 3 haemophilia centres in Bulgaria. Ankles, knees and elbows were evaluated using HEAD-US ultrasound protocol and 3-year-joint bleeding rates (jBR) for the respected joints retrospectively collected.

Results: Assessed were 252 joints of 38 children and young adults with severe HA and 4 children with moderate HA. In 183 joints none bleedings were reported. Ultrasound identified defects in 54.7% ankles, 47.8% knees and 19.5% elbows. Moderate to strong correlations were found between HEAD US score in different joints and jBR.

Discussion/Conclusion: HEAD US score effectively evaluates arthropathic abnormalities in patients on late/secondary prophylaxis. The good correlation between ultrasound findings with jBR provides evidence for the relationship between the abnormalities observed sonographically and the underlying coagulation disorder.

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2. Corte-Rodriguez H De, et al. The value of HEAD-US system in detecting subclinical abnormalities in joints of patients in hemophilia. Expert Review of Hematology 2018;4086.

Disclosure of Interest: None declared.

P035 | Measuring rFIX-Fc with 17 different combinations coagulometers - reagents: A single center study

T. Sinegre; A. Trayaud; M. Tardieu; L. Talon; A. Vaissade; A. Lebreton*

CHU Clermont-Ferrand Hématologie, Clermont Ferrand, France

Introduction: rFIX-Fc is an extended half-life (EHL) recombinant FIX concentrate approved for the prophylaxis and treatment of bleeding events in haemophilia B. A high laboratory and reagent-specific variability is described for rFIX-Fc activity measurements.

The aim of this single-center study was to evaluate the intra-laboratory variability of 17 different combinations coagulometers/reagents with a focus on lower concentrations.

Methods: Human FIX deficient plasma was spiked with rFIX-Fc at 150%, 100%, 80%, 20%, 5%, 2% and 1% based on label potency. We evaluated the spikes recovery with 3 coagulometers (STAR MAX, ACL TOP700 and Cs2100) using for each instrument captive silica based and non-silica based aPTT reagents. Three reagents (STA-Cephascreen, Synthafax and Actin FS) were evaluated on all coagulometers. The 2 available chromogenic assays (ROS FIXa and Biophen FIX:C were evaluated on all coagulometer. All experiments were performed by the same staff, in a single room, in triplicates with 3 dilutions.

Results: We confirmed that kaolin based OSC assays underestimate rFIX-Fc. Acceptable recoveries were found for PTT-A on Stago coagulometer and an underestimation was found for low concentrations. Pathromtin and Actin FS performed on Cs2100 display acceptable recoveries on all the range of target values. Synthasil performed on ACL TOP700 have acceptable recoveries from 150% to 20% and an overestimation was found for low concentrations. STA-Cephascreen has acceptable recoveries, except for low concentrations on ACL TOP coagulometer, overestimating rFIX-FC measurements. Synthafax has acceptable recoveries with ACL TOP700 coagulometer for all the range of concentrations. This reagent adapted on STAR MAX shows an overall overestimation and when adapted on a Cs2100, it displays acceptable recoveries except for low concentrations that are overestimated. The two chromogenic assays have acceptable recoveries for rFIX-Fc on all coagulometers from 150% to 50% concentrations. ROS FIXa underestimated rFIX-Fc recovery for the lower concentrations on STAR MAX and ACL TOP700 coagulometers. Biophen FIX:C underestimated rFIX-Fc recoveries for concentrations below 50% with all coagulometers.

Discussion/Conclusion: This study provides the pattern of several combinations coagulometers—reagents for rFIX-Fc measurements and confirms a high variability for several reagents for low concentrations.

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P036 | Coagulation defects in young females with heavy menstrual bleeding

A. Ayhan*; S. Yılmaz; A. Baysal; A. Akçakaya; A. Atuğ

Medeniyet University, İstanbul, Turkey

Introduction: Congenital bleeding disorders frequently manifest during childhood but sometimes especially in the presence of mild deficiencies the diagnosis may be difficult in early childhood. In young females heavy menstrual bleeding can be the only sign of a presence of an underlying coagulation defect. The aim of this study is to evaluate the frequency of coagulation defects in patients without a known disorder but with history of excessive menstrual bleeding.

Methods: The medical records of 46 female patients aged between 12.5 - 18 years were analyzed retrospectively. All of them had a history of heavy menstrual bleeding and were referred to our pediatric hematology department for detection of hematologic pathology.

Results: Of these 46 patients, 17 (40%) patients were diagnosed with a bleeding disorder. These were: von Willebrand factor deficiency in four (8.7%) patients; factor VIII deficiency in two (4.4%) patients;

factor VII deficiency in two (4.4%) patients; hypofibrinogenemia in three (6.5%) patients; factor V deficiency in one (2.2%) patient, factor X deficiency in three (6.5%) patients; Glanzmann thrombasthenia in two (4.4%) patients.

Discussion/Conclusion: Our results suggest that sometimes congenital coagulation defects may not be diagnosed in early childhood and excessive menstrual bleeding may be the first finding in these young females. These disorders must be evaluated as the underlying disorders in young females with unexplained heavy menstrual bleeding.

Disclosure of Interest: None declared.

P037 | Evaluation of patients with prolonged coagulation tests

A. C. Ayhan*; A. Akçakaya; A. Baysal; S. Yılmaz; A. Atuğ

Medeniyet University, İstanbul, Turkey

Introduction: The aim of our study is to document the major causes of prolonged prothrombin time (PT) and /or activated partial thromboplastin time (APTT) in patients referred to our department for their abnormal test results.

Methods: The medical records of 316 patients were analyzed retrospectively. 153 patients were female, 163 were male. They were aged between 25 days - 18 years. PT and APTT tests of all patients were repeated once again at our department before they were evaluated further for coagulation defects.

Results: When the coagulation tests were repeated 273 (86%) patients had test results between normal limits. 43 (14%) displayed abnormal results again for the second time. 14 of these patients received oral or im vitamin K replacement therapy; 11 of them had normal results after vitamin K replacement and 3 of them still had abnormal results. Finally 32 (10%) patients (19 female, 13 male) were further evaluated for factor deficiencies and presence of circulating anticoagulants. Results of 15 (4.7%) patients indicated factor deficiencies (mild, moderate or severe). Results these patients were: von Willebrand Factor deficiency mild-moderate in 4 patients, severe in 1 patient; Factor IX deficiency: 1 patient; Factor VIII deficiency severe in 1 patient, mild-moderate in 2 patients; Factor VII deficiency: severe in 1 patient, mild in 1 patient; hypofibrinogenemia: mild in 3 patients; Factor XII deficiency: 1 patient.

Discussion/Conclusion: Our results suggest that only a small number of patients with prolonged PT and APTT results are really diagnosed with factor deficiencies. Repeating the coagulation tests before deciding to study factor levels in patients especially who don't have a history of bleeding helps us to prevent unnecessary detections.

Disclosure of Interest: None declared.

P038 | An unusual association of severe hemophilia A and recurrent henoch-schönlein purpura in a child

A. Unuvar[1,*]; R. Tuna[1]; S. Ocak[1]; D. Tugcu[1]; O. Koker[2]; R. Omeroglu[2]; Z. Karakas[1]; S. Karaman[1]

[1]Istanbul University, Istanbul School of Medicine, Division of Pediatric Hematology & Oncology; [2]Istanbul University, Istanbul School of Medicine, Division of Pediatric Rheumatology, Istanbul, Turkey

Introduction: Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis of childhood with unknown etiology characterized by inflammation of small blood vessels with leukocytoclastic infiltration of tissue. HSP is characterized by palpable purpura, arthritis, and less frequently gastrointestinal or renal vasculitis.

Methods: Herein, we report a 10-year-old child with severe hemophilia A and recurrent HSP.

Results: The patient was diagnosed as severe hemophilia A (FVIII level: 0.88%) when he was 10 months old. However, he was on episodic therapy due to the non-compliant family. Fortunately, he had a few bleeding history (9 different bleedings in 8 years) with normal physical examination of musculoskeletal system during his irregular follow-up. But, he was diagnosed as HSP two years ago. He had extensive palpable purpura, arthritis, gastrointestinal involvement (severe abdominal pain, abdominal distention, severe free fluid collection, and positive fecal occult blood test), microscopic hematuria, and scrotal edema. After the skin biopsy, corticosteroid therapy (2 mg/kg/day) was started, and factor concentrate was given once a day for 5 days. The diagnosis of HSP was confirmed by the skin biopsy at that time. The patient was closely followed-up by the Department of Pediatric Surgery for possible urgent intervention of intussusception or abdominal perforation, also. All clinical symptoms and findings resolved completely and the patient was discharged at the 10th day of admission, and prednisone was stopped after a taper schedule beginning at the 14th day of therapy. The patient was lost to follow-up after this period, and he was admitted with iliopsoas hemorrhage one year later. After the successful initial therapy of iliopsoas hemorrhage, the regular secondary prophylaxis was started. However, the patient was diagnosed as HSP two weeks ago, again. The patient had palpable purpura, arthritis, and severe abdominal pain at this admission, and there was no renal involvement. Corticosteroid therapy was started again, and the secondary prophylaxis of hemophilia (three days in a week) was continued. All symptoms and findings weaned, again.

Discussion/Conclusion: In conclusion, recurrent HSP can be diagnosed in a child with severe hemophilia A. The close follow-up and well-designed management is mandatory for this unusual association.

Disclosure of Interest: None declared.

P039 | Long-term efficacy and safety of prophylactic treatment with recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with severe haemophilia A: Final longitudinal analysis of A-LONG/kids A-LONG and ASPIRE

B. Konkle[1,*]; G. Young[2]; R. Liesner[3]; J. Mahlangu[4]; S. A. Brown[5]; B. Nolan[6]; N. Tripkovic[7]; J. Feng[8]; C. Barnowski[8]

[1]*Bloodworks Northwest, Seattle, WA;* [2]*Children's Hospital, Los Angeles, CA, United States;* [3]*Great Ormond Street Hospital for Children, London, United Kingdom;* [4]*Haemophilia Comprehensive Care Center, Faculty of Health Sciences, University of Witwatersrand and NHLS, Johannesburg, South Africa;* [5]*Royal Children's Hospital, Queensland Haemophilia Centre, Brisbane, Australia;* [6]*Our Lady's Children's Hospital, Dublin, Ireland;* [7]*Sobi, Stockholm, Sweden;* [8]*Bioverativ, a Sanofi Company, Waltham, MA, United States*

Introduction: Recombinant factor VIII Fc fusion protein (rFVIIIFc) is an extended half-life therapy that demonstrated long-term safety and efficacy in previously treated subjects with severe haemophilia A in the Phase 3 A-LONG/Kids A-LONG trials and ASPIRE extension. Here we report final longitudinal data for prophylactic regimens from these studies.

Methods: In this longitudinal post-hoc analysis, subjects aged ≥12 years who enrolled in A-LONG and continued in ASPIRE received one of four rFVIIIFc regimens: individualized prophylaxis (IP; 25–65 IU/kg every 3-5 days, or twice weekly), weekly prophylaxis (WP; 65 IU/kg every 7 days), modified prophylaxis (MP), or episodic dosing. Subjects aged <12 years from Kids A-LONG received IP or MP. Subjects could switch treatment groups any time during ASPIRE. Data from start of A-LONG/Kids A-LONG to end of ASPIRE were pooled. Median and interquartile range are presented (25th and 75th percentile).

Results: 164 subjects from A-LONG and 69 from Kids A-LONG were included. Cumulative rFVIIIFc duration was 4.2 (2.8-5.3) years in A-LONG/ASPIRE and 3.4 (1.5-4.2) years in Kids A-LONG/ASPIRE. No inhibitor development was reported; rFVIIIFc was generally well tolerated. Annualised bleeding rate (ABR) remained low: in subjects who started treatment in A-LONG, overall ABR on IP was 1.2 (0-4.0) at Year 1 (n = 122) and 0.5 (0-2.0) at Year 5 (n = 46), while ABR on WP was 2.0 (1.0-5.0) at Year 1 (n = 38) and 1.7 (0-5.1) at Year 5 (n = 13); in subjects who started treatment in Kids A-LONG, overall ABR on IP was 1.8 (1.0-3.0) at Year 1 (n = 61) and 1.3 (0-2.0) at Year 4 (n = 31). Annualised rFVIIIFc consumption was stable over time. Dose and interval compliance was 99.1 (97.9-99.7) and 98.0 (95.0-100.1), respectively, in A-LONG/ASPIRE and 96.4 (86.1-99.4) and 95.9 (91.9-99.2), respectively, in Kids A-LONG/ASPIRE. Small cohort numbers limit these analyses.

Discussion/Conclusion: This longitudinal analysis represents the longest duration of exposure to extended half-life rFVIIIFc to date (median 4.2 years in adults/adolescents, 3.4 years in children), with results that demonstrate consistent and favourable efficacy and safety, stable consumption, flexible prophylactic dosing, and high adherence, over time.

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P040 | Long term realworld health care comparison of expenditures and international units dispensed of extended and standard half-life recombinant factor IX products in hemophilia B patients

B. J. Tortella[1,*]; A. Chhabra[2]; P. Fogarty[1]; E. Rubinstein[2]; L. J. Young[3]; J. Alvir[2]

[1]*Pfizer, Inc., Collegeville;* [2]*Pfizer, Inc., New York, United States;* [3]*Pfizer, Inc., Pfizer Limited, United Kingdom*

Introduction: Intravenous factor IX (FIX) infusions to replace missing coagulation factor are required for hemophilia B treatment. Extended half-life (EHL) FIX replacement products were introduced, with fewer infusions required compared with standard half-life (SHL) FIX products. Previous reports demonstrated high costs associated with EHL product use but were short-term in nature.

Methods: The USA IQVIA™ Health Plan Claims Database was queried for SHL and EHL FIX IUs dispensed and for expenditures over 47 months (Population-Level Study), with a second query to include only data 1 yr before and after the SHL FIX to EHL (FIX-Fc, FIX-Alb) switching (Switch Analysis) from May 2014—Mar 2018. Descriptive statistics were calculated, with medians used to accommodate for skewed distributions.

Results: Population-Level Study: 102 FIX, 52 FIX-Fc, and 8 FIX-Alb patients were identified. Over the 47-month period, quarterly median IUs dispensed were 40 513 FIX, 46 638 FIX-Fc, and 35 814 FIX-Alb, while quarterly median clotting factor expenditures were $50 619 FIX, $118 883 FIX-Fc, and $147 743 FIX-Alb. Annualized, this would be $202 476 FIX, $475 532 FIX-Fc, and $590 972 FIX-Alb. Switch Analysis: Fourteen patients had data 1 yr before and 1 yr after switching from FIX to FIX-Fc. Pre-switch FIX quarterly median IUs vs post-switch FIX-Fc were 46 408 FIX and 49 181 FIX-Fc. Pre-switch FIX quarterly median expenditures vs post-switch FIX-Fc were $71 481 FIX to $127 624 FIX-Fc. Annualized, these would be $285 924 for FIX and $510 496 for FIX-Fc.

Discussion/Conclusion: This 47-month population-level analysis is the longest real-world data review reported to date, albeit unadjusted for treatment regimen or disease severity. It shows that total FIX expenditures were 135% higher with FIX-Fc and 192% higher with FIX-Alb while IUs dispensed were 15% higher for FIX-Fc and 12% lower for FIX-Alb compared with SHL FIX in US hemophilia B patients. The Switch Analysis indicated a 6% increase in IUs dispensed after switching from FIX to FIX-Fc and a 79% increase in expenditures in the 1-year period before and after the FIX to FIX-Fc switch. Further analyses, incorporating essential clinical characteristics, should be explored.

Disclosure of Interest: B. Tortella Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc, A. Chhabra Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc, P. Fogarty Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc, E. Rubinstein Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc, L. Young Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc, J. Alvir Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc.

P041 | Long-term real-world health care comparison of expenditures and international units dispensed for haemophilia A patients switching to extended from standard half-life recombinant factor VIII products

B. J. Tortella[1,*]; A. Chhabra[2]; P. Fogarty[1]; E. Rubinstein[2]; L. Young[3]; J. Alvir[2]

[1]Pfizer Inc, Collegeville; [2]Pfizer Inc, New York, United States; [3]Pfizer Limited, Surrey, United Kingdom

Introduction: Haemophilia A can be treated with intravenous (IV) factor VIII infusions that replace the missing coagulation factor. Recently, extended half-life (EHL) FVIII products were approved, necessitating fewer IV injections compared with standard half-life (SHL) FVIII products. High costs with EHL products (eg, FVIII-Fc) have been demonstrated, albeit with short-term data.

Methods: The IQVIA™ Health Plan Claims Database was queried for SHL and EHL FVIII IUs dispensed and expenditures for 1 year before and after the SHL to EHL switch, from January 2007—March 2018. Descriptive statistics were calculated, with medians used to accommodate skewed distributions.

Results: Fourteen patients had data for 1 year before and 1 year after switching from SHL FVIII to EHL products (FVIII-Fc). Patients had to have 6 months of enrolment pre- and post-switch in the claims database. Pre-switch quarterly median SHL FVIII IUs vs post-switch EHL FVIII-Fc IUs were 45 209 for SHL FVIII and 82 738 for EHL FVIII-Fc. Pre-switch FVIII quarterly median clotting factor expenditures vs post-switch were $49 713 for SHL FVIII and $154 252 for EHL FVIII-Fc. Annualised, this would be $198 852 for SHL FVIII and $617 008 for EHL FVIII-Fc.

Discussion/Conclusion: This switch analysis indicated an 83% increase in SHL FVIII vs FVIII-Fc IUs dispensed, and a 210% increase in expenditures in the 1-year period before and after switching from SHL FVIII to EHL FVIII-Fc. Further analyses incorporating essential clinical characteristics and looking at long-term utilization on SHL and EHL FVIII products should be explored.

Disclosure of Interest: B. Tortella Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc, A. Chhabra Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc, P. Fogarty Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc, E. Rubinstein Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc, L. Young Shareholder of: Pfizer, Inc, Employee of: Pfizer Limited, J. Alvir Shareholder of: Pfizer, Inc, Employee of: Pfizer, Inc.

P042 | Factor VII deficiency acquired through liver transplantation: Two clinical cases

B. Ferro*; A. Ribeiro; T. Araújo; R. Pardal; F. Rincón; F. Bargado; J. Lopes; I. Borges

Immunohematology Department, Hospital Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal

Introduction: The transmission of coagulation factor deficiencies through liver transplantation (LT) is rare. There is only one published report about factor VII deficiency acquired by LT and we present two cases.

Methods: Case reports based on retrospective medical record analysis.

Results:

Clinical Case 1: A 28-year-old man with cryptogenic liver cirrhosis, portal hypertension and splenomegaly, with no bleeding history and normal coagulation tests in 2013.

In November/2015 he underwent ABO-matched LT. In post-operative day (POD) 2, activated partial thromboplastin time (aPTT) and factor V (fV) were both normal. The patient was found to have an isolated prolonged prothrombin time (PT)=24.3 sec, which persisted throughout the hospitalization, despite administration of vitamin K.

In POD 47, he presented normalization of liver enzymes and a PT = 17 seconds. Due to persistent prolongation of PT, the patient was referred to our coagulopathy department. Extrinsic/common pathway factors were measured: fVII = 20.6%; fII, fV and fX were normal.

Clinical Case 2: A 59-year-old man with ethanolic cirrhosis, hepatitis C and hepatocellular carcinoma; without bleeding history.

In April/2017 he was admitted to our Center for LT. He underwent ABO-matched LT. 24 hours post-LT, coagulation evaluation revealed PT prolongation (20.8 sec), fV = 52.7% and aPTT = 19 seconds.

In POD 10, the patient presented normalization of hepatic enzymes and fV = 93.9%, maintaining PT prolongation, despite vitamin K administration.

In POD 25, due to persistently abnormal PT, coagulations factors were measured: fVII = 33.2%; fII, fV, fIX and fX within normal ranges.

In POD 27, the patient was submitted to surgical removal of abdominal drains, with previous administration of 2 mg of fVIIr (fVII = 14% and hemorrhagic risk).

He maintains fVII deficiency (33.2%) 6 months after LT.

Discussion/Conclusion:: In both clinical cases, the absence of hemorrhagic history, the evidence of a normal PT in the past and the persistence of an isolated deficiency of factor VII post-LT were suggestive of an acquired factor VII deficiency trough LT.
In this context, diagnosing fVII deficiency is a challenge. Usually PT prolongation post-LT is due to transient graft dysfunction or vitamin K deficiency. When PT prolongation persists, despite normalization of liver function and administration of vitamin K, an acquired fVII deficiency should be suspected. The diagnosis is relevant because of its therapeutic implications.
Disclosure of Interest: None declared.

P043 | Surgical prophylaxis in patients with factor VII deficiency: Experience in our center

B. Díaz Roldán*; J. F. Dominguez Rodríguez; R. Zapata Bautista; F. Fernández Moreno; P. Verlarde López de Ayala
Hospital Juan Ramón Jiménez, Huelva, Spain

Introduction: Factor VII deficiency is the most frequent alteration among uncommon congenital disorders of coagulation. It is an entity with a very variable phenotype. Patients with an activity lower than 2% present severe hemorrhagic symptoms while above 20% are usually asymptomatic. The most frequent manifestations are epistaxis and menorrhagia. Substitute treatment for surgical intervention is recommended in patients with a severe phenotype. In general for surgical intervention, it is recommended to maintain factor VII levels above 15-20%. Our objective is to present our experience regarding prophylaxis in patients with factor VII deficiency in the face of surgical intervention.
Methods: We selected patients with factor VII deficiency who were going to undergo surgery at our center from January 2016 to September 2018. A total of 15 patients were studied, of which 46.67% (7 patients) were women. Patients were separated into two groups based on their factor VII levels. The first group, the patients with factor VII levels above 20% were 13 patients (86.6%). Two patients (13.4%) had factor VII levels below 20%. Only one patient (with factor VII levels below 10%) had mild bleeding phenotype (repeat epistaxis). Only prophylaxis was applied for surgical interventions in patients with factor VII levels below 20% with rFVIIa and with tranexamic acid.
Results: Both patients who received prophylaxis and those who did not receive it did not have bleeding greater than usual in the surgical interventions. In addition, patients who received treatment with rFVIIa did not have thrombotic complications.
Discussion/Conclusion: - Factor VII deficiency is an entity with a highly variable phenotype, although in general patients usually present bleeding phenotypes with factor VII levels below 20%.
- In surgical interventions, it is recommended to maintain factor levels above 20%, which is why we consider it necessary to apply prophylaxis before surgery in patients with factor levels below 20%.
- In our sample of patients, patients with factor levels above 20% who did not receive prophylaxis did not have bleeding greater than usual, so their factor VII levels were in the hemostatic range.
- The patients who received prophylaxis with rVIIa did not have thrombotic events, even though the thrombotic risk is a factor to consider, so each patient should be evaluated individually.
Disclosure of Interest: None declared.

P044 | Oral anticoagulation as a confusion factor in the diagnosis of acquired hemophilia

B. Díaz Roldán*; J. F. Domínguez Rodríguez; F. Fernández Moreno; R. Zapata Bautista; M. A. Ruíz Cobo
Hospital Juan Ramón Jiménez, Huelva, Spain

Introduction: Acquired hemophilia is a rare coagulation disorder characterized by the production of autoantibodies that neutralize factor VIII. It is typical of adults being the most affected pregnant women and the elderly. The typical clinic is characterized by cutaneous hemorrhages, although joint bleeding is not characteristic. The diagnosis is based on low factor VIII levels and the identification of the autoantibody (inhibitor). Due to it is a common entity in elderly people, differential diagnosis is often complicated due to associated comorbidities and the use of drugs such as oral anticoagulants.
Methods: We present the clinical case of an 82-year-old man who was anticoagulated with sintrom due to permanent atrial fibrillation and a history of cardioembolic ischemic stroke. The patient went to the emergency department due to an extensive hematoma in the left thigh. In the analysis he had an activated thromboplastin time (aPTT) of 2.66 ratio [0.7-1.2], which it corrected when mixed with normal plasma. The hematoma was related to the oral anticoagulant, so it was suspended. The evolution of the patient was satisfactory so despite presenting an aPTT of 1.96, the anticoagulant treatment was reintroduced with low molecular weight heparin. The patient went to the emergency department again for a new hematoma on the lateral side of the neck and right shoulder of spontaneous appearance. In the analytical study an aPTT of 2.83 was observed. In that context, we made a dosage of factors, in which a factor VIII of 4.7% stood out. The inhibitor study was performed, which was positive with 7.5 Bethesda units.
Results: The patient was diagnosed of acquired hemophilia, the anticoagulation was stopped and we initiated treatment with steroids and recombinant factor VII due to the significant mass effect of the supraclavicular hematoma. The evolution of the patient was positive and the patient was discharged with steroid treatment. At discharge, the patient had factor VIII levels of 363.7 and a negative inhibitor study.
Discussion/Conclusion: In elderly patients under treatment with oral anticoagulants in the presence of spontaneous hematomas and after discontinuation of anticoagulation it is important to check the normalization of aPTT since anticoagulation can act as a confounding factor in the diagnosis of acquired hemophilia.
Disclosure of Interest: None declared.

P045 | Over two decades of orthopaedic surgery in patients with inhibitors—quantifying the complication of bleeding

B. Guevel*; G. Erturan; N. Goddard

Trauma & Orthopaedic Surgery, Royal Free Hospital, London, United Kingdom

Introduction: Haemophilia patients undergoing orthopaedic procedures will often require exogenous factor VIII or IX therapy to prevent haemorrhage. A particular subset of these patients, however, develop antibodies (inhibitors) against these replacement factors. Agents that bypass the inhibitors, such as recombinant factor VIIa and activated prothrombin complex concentrate, have been utilised for several decades, with overall positive reports of their use historically. There is growing concern amongst orthopaedic surgeons, however, regarding the associated high complication rate of bleeding. To explore and quantify this concern, we conducted a literature review spanning the last two decades on haemophilia patients with inhibitors undergoing orthopaedic surgery.

Methods: Medline, Google Scholar, Biosis, Current Contents and EMBASE databases were searched between January 1996 and December 2017 using the terms 'inhibitor' AND/OR 'orthopaedic' AND/OR 'surgery' AND/OR 'haemophilia'. Review articles, non-English language articles and papers on non-orthopaedic surgery were excluded. We used 25 different outcome descriptors to describe bleeding complications and applied them to each individual study's intra-operative and post-operative period to ensure an exhaustive capture.

Results: 42 publications were included. There were 308 cases of major orthopaedic surgery performed in 229 patients with a total of 125 individual bleeding complications, giving a bleeding complication rate of 40.6%. 31.3% of procedures had a bleeding complication in the current decade compared to 28.4% in the previous decade, with arthroplasty and arthroscopy having the highest complication rate.

Discussion/Conclusion: This review highlights the need to be cautious when using bypassing agents in the inhibitor population as there is a measurable risk of bleeding associated with their use in major orthopaedic surgery. The benefits in quality of life against this risk should be considered and thoroughly discussed with the patient pre-operatively. Recent advances in the monitoring of haemostatic efficiency have proved valuable in improving the safety profile of these agents and further advances of this nature should be sought.

Disclosure of Interest: None declared.

P046 | Identification of effective factor VIII thresholds for bleeding risk reduction in patients with haemophilia A receiving rVIII-SingleChain

W. McKeand[1]; C. Fosser[2]; J. Roberts[1]; B. Goldstein[1,*]; Y. Li[1]; M. Tortorici[1]

[1]*CSL Behring, King of Prussia;* [2]*Cytel, Cambridge, United States*

Introduction: High trough levels during prophylaxis treatment have been difficult to maintain due to the relatively short half-lives of standard-acting factor VIII (FVIII) products. With the introduction of longer-acting products, different regimens may allow higher trough levels to be achieved. The aim of this study was to assess the threshold levels of FVIII associated with significant reduction of bleeding risk, evaluate pharmacokinetic (PK) determinants of efficacy, and quantify the relative risk of bleeding episodes based on FVIII activity levels.

Methods: rVIII-SingleChain is a single-chain recombinant FVIII. Data for up to 2 years from a Phase III study were utilized in the analysis, including all recorded bleeding episodes after the first infusion of rVIII-SingleChain. FVIII activity levels for each 12 hour time interval were simulated using a previously published population PK model. Bleeding risk reduction was estimated using an exposure-response analysis via a Cox proportional hazard model that related the time to a bleeding episode with exposure and dosing regimen. Direct time-matched FVIII activity at the time of a bleed, and cumulative FVIII exposure as related to bleeding risk reduction were assessed.

Results: In the 147 patients included in this analysis, 715 bleeding events were reported. Patients with FVIII levels >1% had a 74% reduction in bleeding risk compared to patients with FVIII levels <1%. Patients who maintained FVIII activity level >1% for 6 months or 1 year decreased the relative bleeding risk by 71% and 92%, respectively. Longer intervals maintained above threshold provided increasing protection against the risk of a bleed. The prophylaxis regimen showed a 91% reduction in relative risk compared with the on-demand regimen.

Discussion/Conclusion: This analysis quantitatively supports the rationale for optimized treatment regimens in adult haemophilia A patients by maintaining FVIII levels above 1%. Prophylaxis regimens provide lower bleeding rates than an on-demand regimen.

Disclosure of Interest: W. McKeand Employee of: CSL Behring, C. Fosser Consultant for: CSL Behring, J. Roberts Employee of: CSL Behring, B. Goldstein Employee of: CSL Behring, Y. Li Employee of: CSL Behring, M. Tortorici Employee of: CSL Behring.

P047 | ICHEC: Refining the pediatric bleeding assessment tool

B. Peters[1,*]; E. Stokhuijzen[1]; M. Cnossen[2]; T. Biss[3]; M. Peters[1]; M. Suijker[1]; V. Blanchette[4]; P. James[5]; M. Rand[6]; K. Fijnvandraat[1]

[1]*Pediatric hematology, Emma Children's Hospital, Amsterdam UMC, Amsterdam;* [2]*Pediatric hematology, Sophia Children's Hospital, Erasmus Medical Centre, Rotterdam, Netherlands;* [3]*Clinical hematology, Royal Victoria Hospital, Newcastle, United Kingdom;* [4]*Pediatric Haematology/Oncology, Hospital for Sick Children, Toronto;* [5]*Department of Medicine, Kingston, Queen's University, Kingston;* [6]*Pediatric Haematology/Oncology, Hospital of Sick Children, Toronto, Canada*

Introduction: The evaluation of bleeding symptoms in children may be challenging, as symptoms can be subtle and children face less hemostatic challenges compared to adults. The existing bleeding assessment tools (BATs) for children (ISTH-BAT and Pediatric Bleeding

Questionnaire (PBQ)) have their limitations as scoring is based on the most severe episode and therefore they might lack sensitivity to pick up subtle cues and are inflexible to intercurrent changes in the bleeding phenotype. This study aims to develop a refined BAT with higher sensitivity and flexibility. Currently we present preliminary results comparing the diagnostic accuracy of both BATs for the first 60 subjects.

Methods: In this observational, multicenter cohort study, we aim to include 200 pediatric subjects presenting with signs and symptoms of bleeding, and/or a positive family history of a bleeding disorder. We developed a comprehensive bleeding questionnaire (iCHEC for Identifying Children with HEreditary Coagulation disorders), including the ISTH-BAT and PBQ, to be completed by the subjects. Uniform diagnostic laboratory work-up is performed afterwards. In the presented preliminary analysis, total bleeding scores (TBS) are compared between children with and without a hemorrhagic disorder. A TBS cutoff ≥ 3 for ISTH-BAT and ≥ 2 of the PBQ is considered as positive test outcome. Differences between the two groups are analyzed statistically by Mann-Whitney U test.

Results: Preliminary results for 60 subjects are presented. Most were female (n = 36, 60%); median age was 5.0 years (IQR 2-13). Eight (13%) were diagnosed with a bleeding disorder. Neither TBS of the ISTH-BAT (Median 3.5 (IQR 0.25-4.75) and 2.0 (IQR 0-4) respectively, in subjects with and without a bleeding disorder) nor PBQ (Median 3.5 (IQR 0.75-6.75) and 2.0 (IQR 1-5), respectively in subjects with and without a bleeding disorder) demonstrated a statistically significant difference between both groups.

Both, ISTH-BAT and PBQ, had a low positive predictive value (21% and 15%) and a high negative predictive value (92% and 90%). Sensitivity (ISTH-BAT: 63%, PBQ: 75%) and specificity (ISTH-BAT: 63%, PBQ: 37%) were low.

Discussion/Conclusion: These results confirm that the ISTH-BAT and PBQ might lack discriminative power in children. This underlies the clinical need of a refined BAT that can take a fingerprint of a child's bleeding history and thereby discriminates between children with and without an inherited bleeding disorder.

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P048 | Continued characterization of the immune response in a phase-1/2 clinical study of valoctocogene roxaparvovec, an AAV5 mediated gene therapy for hemophilia A

B. Long[1,*]; B. Kim[1]; W. Y. Wong[1]; K. Yang[1]; C. Vettermann[1]; K. Yu[1]; K. Lau[1]; R. Hardet[2,3]; K. Kuranda[2,3]; P. Veron[2]; F. Mingozzi[2,3]; G. F. Pierce[4]; B. Schweighardt[1]

[1]BioMarin Pharmaceutical Inc., Novato, United States; [2]University Pierre and Marie Curie and INSERM U974, Paris; [3]Genethon and INSERM U951, Evry, France; [4]Consultant, La Jolla, United States

Introduction: For gene therapies, immunogenicity toward the vector delivery system or the expressed transgene product is one of many factors that may play a role in limiting therapeutic efficacy. This report describes up to two years of immunogenicity data following administration of Valoctocogene roxaparvovec (Valrox), an investigational AAV5-mediated gene therapy encoding human FVIII (hFVIII-SQ) for the treatment of Hemophilia A.

Methods: In study BMN 270-201, patients with severe Hemophilia A were screened for both pre-existing antibodies directed against the AAV5 vector and inhibitors of transduction using a cell-based *in vitro* transduction inhibition (TI) assay. Patients testing positive in either assay or who had a history of FVIII inhibitors were excluded from the trial. Post-infusion plasma was analyzed for total antibody (TAb) responses specific for the AAV5 capsid and against hFVIII using bridging ECLA immunoassays. Development of FVIII inhibitors was monitored using the Nijmegen-modified Bethesda assay. Peripheral blood mononuclear cells were analyzed by IFN-γ ELISpot assay for detection of capsid-specific and hFVIII-SQ-specific cellular immune responses. In a separate exploratory analysis, inflammatory biomarkers were assessed in plasma at weekly intervals in a multiplexed bead array assay.

Results: All patients remained negative in the Nijmegen-modified Bethesda assay for FVIII inhibitors. One patient tested positive at a single time point for anti-FVIII TAb, but was negative at all subsequent time points. Cellular immune responses against peptides spanning AAV5 capsid and hFVIII-SQ were largely negative. A limited number of transient positive responses were detected sporadically at single time points, but were generally not associated with elevations of alanine aminotransferase or loss of FVIII expression. Post infusion samples were AAV5 TAb positive by Week 8 and remained positive at all subsequent time points.

Discussion/Conclusion: The predominant immune response elicited by Valrox administration appears to be largely limited to the development of antibodies against the AAV5 vector capsid. No FVIII inhibitor responses have developed following Valrox administration. Cellular immune responses have not been associated with worsened safety or efficacy outcomes.

Disclosure of Interest: B. Long Employee of: BioMarin, B. Kim Employee of: BioMarin, W. Y. Wong Employee of: BioMarin, K. Yang Employee of: BioMarin, C. Vettermann Employee of: BioMarin, K. Yu Employee of: BioMarin, K. Lau Employee of: BioMarin, R. Hardet Grant/Research support from: ERC, K. Kuranda Grant/Research support from: ERC, P. Veron Grant/Research support from: ERC, F. Mingozzi Grant/Research support from: ERC, G. Pierce Consultant for: BioMarin, B. Schweighardt Employee of: BioMarin.

P049 | Revised pharmacokinetics of Benefix

B. Tardy[1,2,*]; T. Lambert[3]; P. Chamouni[4]; A. Montmartin[2]; M. Trossaert[5]; S. Claeyssens[6]; C. Berger[1]; L. Ardillon[7]; V. Gay[8]; A. Harroche[9]; X. Delavenne[2]

[1]*Haemophilia Treatment Centre, CHU Saint-Etienne, Hôpital Nord;* [2]*Sainbiose, INSERM U1059, Université Lyon, Saint-Etienne;* [3]*Haemophilia Treatment Centre, CHU Paris Sud-Hôpital de Bicêtre, Le Kremlin Bicêtre;* [4]*Laboratoire d'Hématologie, Institut de Biologie Clinique, CHU de Rouen, Rouen;* [5]*Haemophilia Treatment Centre, Nantes University Hospital, Nantes;* [6]*Haemophilia Treatment Centre, CHU Toulouse-Hôpital Purpan, Toulouse;* [7]*Haemophilia Treatment Centre, CHU Tours-Hôpital Trousseau, Tours;* [8]*Service hémostase clinique, hémophilie, hémovigilance, Centre hospitalier Métropole Savoie, Chambéry;* [9]*Service D'hématologie clinique, Hôpital Necker Enfants-Malades, Université Paris Descartes, Paris, France*

Introduction: Pharmacokinetic (PK) studies performed during product development defined the half-life of Benefix as being 16 and 24 hours in pediatric and adult patients respectively. However, in these studies, sampling stopped 72 hours after Benefix infusion. In a study in which the PK of Benefix was compared to that of factor IX concentrate (IX-Fc), sampling was unfortunately stopped at 96 hours in patients receiving Benefix; at that time, factor IX (fIX) level differed by only 2.5% between patients treated with Benefix and IX-Fc, respectively (1). Moreover, in our clinical practice, we observed residual fIX levels above 2% even 170 hours after Benefix infusion in some patients. We therefore suspected that the half-life of Benefix had been largely underestimated.

Ref 1: Powell and al. N Engl J Med 2013; 369: 2313-2323.

Methods: We evaluated 430 values (short PK evaluations or residual fIX levels measured at a routine visit) in 63 haemophilic patients treated with Benefix in 6 haemophilic centres. FIX activities were analysed using a non-linear mixed model and Monolix software. A covariate analysis including body weight, age, dose (IU/kg), and infusion frequency was performed to identify factors implicated in inter-patient PK variability. Differences in reagent/instrument use between the six centres were taken into account. Individual PK parameters were estimated using a Bayesian approach.

Results: Clearance was found to be 2 times lower (at least) than previously reported values. Among 35 residual fIX levels measured 72 hours after Benefix infusion, 34 was above 1% (4 centres, 12 patients, mean dose = 54 [25-96] IU/kg; mean fIX level = 6% [1.2-17%]). Among 18 residual fIX levels measured 96 hours after Benefix infusion, 17 was above 1% (3 centres, 11 patients, mean dose = 52 [23-75] IU/kg; mean fIX level = 2.9% [1.6-5%]). Among 21 residual fIX levels measured 168 hours after Benefix infusion, 15 was above 1% (3 centres, 5 patients, mean dose = 51 [42-58] IU/kg; mean fIX level = 1.8% [1.1-2.4%]).

Discussion/Conclusion: The high residual level of Benefix could be related to an extravascular storage of this product. These results are particularly interesting from a financial point of view considering that Benefix is 30% cheaper than IX-Fc, at least in France. A PK study comparing Benefix and IX-Fc, with the same late sampling points, is warranted to evaluate differences in PK between these two products.

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P050 | On-demand treatment with fibrinogen concentrate for acute bleeding and surgical prophylaxis in patients with congenital fibrinogen deficiency—results from a phase 3 study

F. Peyvandi[1,2]; B. A. Schwartz[3,*]; C. Solomon[4]; B. Madan[5]; T. Lissitchkov[6]; A. Almomen[7]; C. Khayat[8]; C. Ross[9]; N. Zozulya[10]; on behalf of FORMA-02 clinical investigators

[1]*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Fondazione Luigi Villa;* [2]*Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy;* [3]*Octapharma US, Hoboken, NJ, United States;* [4]*Octapharma AG, Lachen, Switzerland;* [5]*Centre for Haemostasis & Thrombosis, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom;* [6]*SHAT "Joan Pavel" PLC, Sofia, Bulgaria;* [7]*Centre of Excellence in Thrombosis & Hemostasis, College of Medicine and KKUH, King Saud University, Riyadh, Saudi Arabia;* [8]*Hotel Dieu De France, Beirut, Lebanon;* [9]*St John's Medical College Hospital, Bangalore, India;* [10]*Federal State Budgetary Institution "Hematological Scientific Center" of Ministry of Healthcare of the Russian Federation, Moscow, Russian Federation*

Introduction: Patients with congenital fibrinogen deficiency experience severe and/or frequent bleeding episodes (BEs). Human fibrinogen concentrate (HFC) can help to arrest such bleeding. FORMA-02 examined the efficacy of a new plasma-derived, double virus-inactivated HFC (*Octafibrin;* Octapharma) for treatment of BEs and surgical prophylaxis in patients with a- and hypofibrinogenaemia.

Methods: FORMA-02 was a prospective, open-label, multinational study in a- or hypofibrinogenaemic patients (≥12 years). The efficacy of HFC in treating the 1st BE per patient was assessed using an objective 4-point scale by the investigator and adjudicated by an Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC). Secondary endpoints included efficacy in surgical prophylaxis and maximum clot firmness (MCF), measured using ROTEM in plasma, as a surrogate marker of efficacy.

Results: Patients (N = 24) received HFC for treatment of 89 BEs. The median (range) dose of HFC administered for treatment of BEs was 59.4 mg/kg (32.1-273.8) per BE. Haemostatic efficacy for the first BE per patient was rated as a success (rating of excellent or good) for 100% (90% CI 0.89-1.00) of patients by both the investigator and IDMEAC. The first HFC infusion for treatment of the first BE per patient led to a mean increase in plasma fibrinogen of 111.75 ± 28.74 mg/dL 1 hour post-infusion and a mean increase in MCF of 6.48 ± 3.07 mm. Haemostatic efficacy for all BEs was 96.6% (90% CI 0.92-0.99) as assessed by the investigator and 98.9% (90% CI 0.95-0.999) by the IDMEAC.

Nine patients received HFC as prophylaxis for 12 surgeries (1 major). Intraoperative and postoperative efficacy were rated by the surgeon and IDMEAC as a success in 100% (90% CI 0.82-1.00) of cases. The 1st HFC infusion per surgery led to a mean increase in plasma fibrinogen of 104.55 ± 43.64 mg/dL 1 hour post-infusion.

Fifteen serious adverse events occurred in 5 patients; 1 deemed possibly related to the HFC (digital ischaemia of moderate severity that resolved without sequelae). No inhibitory anti-fibrinogen antibodies were detected. There were no severe allergic or hypersensitivity reactions.

Discussion/Conclusion: The new HFC was efficacious for on-demand treatment of acute bleeding and for surgical prophylaxis and demonstrated a favourable safety profile in patients with congenital fibrinogen deficiency.

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P051 | Post-marketing observational study of the safety and efficacy of fibrinogen concentrate in congenital fibrinogen deficiency

F. Peyvandi[1,2]; B. A. Schwartz[3,*]; C. Solomon[4]; S. Knaub[4]; B. Toth[5]

[1]*Department of Pathophysiology and Transplantation, Università degli Studi di Milano;* [2]*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Fondazione Luigi Villa, Milan, Italy;* [3]*Octapharma US, Hoboken, NJ, United States;* [4]*Octapharma AG, Lachen, Switzerland;* [5]*Octapharma Pharmazeutika Produktionsgesellschaft m.b.H, Vienna, Austria*

Introduction: Congenital fibrinogen deficiency is associated with severe and/or frequent bleeding episodes (BEs). In clinical studies, human fibrinogen concentrate (HFC) has been shown to rapidly restore haemostasis in the event of such bleeding. The FORMA-07 study will collect real-world information from clinical practice concerning the safety and efficacy of a new HFC (*Fibryga*; Octapharma), a highly purified, plasma-derived, lyophilised HFC, which undergoes two dedicated virus inactivation/removal steps during production.

Methods: FORMA-07 is a post-marketing, multicentre observational study in adults and adolescents (≥12 years) with congenital a- or hypofibrinogenaemia who are expected to require on-demand treatment with HFC for BEs. Exclusion criteria include: other bleeding disorders; acquired fibrinogen deficiency; dysfibrinogenemia; anti-fibrinogen inhibitor; participation in concurrent clinical studies. HFC will be individually dosed to achieve a target fibrinogen level, as per the locally approved package insert.

The primary endpoint is the incidence of thromboembolic adverse drug reactions (ADRs) in patients receiving HFC for on-demand treatment of BEs (with focus on major BEs). Secondary endpoints include the haemostatic efficacy of HFC for treatment of all BEs recorded in the study, assessed by the investigator using a 4-point objective scale within 2-24 hours following treatment. Safety endpoints include ADRs, serious ADRs, and ADRs of special interest (i.e., thromboembolic events and allergic reactions, including anaphylaxis).

The planned study duration is up to 6 years and the study aims to enrol a minimum of 25 patients treated with HFC, to describe 105 BEs, including a minimum of 10 major BEs in 10 patients. The study will be considered completed when a minimum of 10 patients have at least one documented major BE. During the observation period, enrolled patients may be treated for any BEs. All BEs treated in-hospital with HFC throughout the study will be documented and followed up for up to 28 days after treatment.

Results: Results are expected Q2 2025.

Discussion/Conclusion: Real-world evidence from routine clinical use will further support clinical study data on the use of this HFC for the treatment of bleeding in patients with congenital fibrinogen deficiency.

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P052 | The experience of major orthopedic surgeries in patients with severe hemophilia

B. Antmen[1,*]; I. Sasmaz[1,2]; B. S. Karagun[1]; G. Leblebisatan[2]; C. Ozkan[3]; Y. Sarpel[4]

[1]*Pediatric Bone Marrow Transplantation Unit, Department of Pediatric Hematology, Adana Acibadem Hospital;* [2]*Pediatric Hematology;* [3]*Orthopedia, Cukurova University;* [4]*Orthopedia, Orthopedia Hospital, Adana, Turkey*

Introduction: Hemophilia is an X-linked inherited bleeding disorder characterized by a deficiency of clotting factor VIII or IX. Although medical management with replacement factor is often effective, patients with severe hemophilia may develop chronic synovitis and arthropathy best treated with more invasive means. Total joint replacement and other surgeries is needed for these severe patients with haemophilia. In this retrospective study, we evaluated our hemophiliac patients who needed orthopedic surgeries.

Methods: In this study, we retrospectively presented a series of 21 orthopaedic surgical procedures in 12 patients with hemophilia A and 6 patients with hemophilia B, age ranging from 3 to 38 years with an average of 16 years in Çukurova region, southern part of Turkey. Elective surgical procedures were performed 7 total knee arthroplasty, 3 arthrodesis (2 of them knee, 1 of them ankle), 2

corrective osteotomies in the knee, 1 excision of giant cell tumor of tendon sheath and 1 open flexor tenotomy for hammer toes. Urgent fasciotomy was performed in 4 hemophilia patients after developed acute compartment syndrome. Internal fixation was performed in two patients with hemophilia A because of fractures after trauma. Gradual reduction and external fixation was performed in one patient for pathological dislocation of the wrist.

Results: Blood transfusion was given to all patients performing knee arthroplasty. Postoperative functional evolution after knee arthroplasty was good in all patients. Skin grafting was needed and performed for all patients developing compartment syndrome. No patients suffered from deep infection. There were no thromboembolic complications. No patients died during or after all surgical procedures.

Discussion/Conclusion: Total knee replacement in patients with chronic arthropathic hemophiliac patients resulted in improvement in range of movement and function. The management of acute compartment syndrome in patients with hemophilia requires replacement of clotting factors, and urgent fasciotomies. In these retrospective study showed that a multidisciplinary approach need for these hemophiliac patients who need vary orthopedic surgeries by the hematologists, surgeons and physiotherapists in the comprehensive hemophilia treatment centers.

Disclosure of Interest: None declared.

P053 | Survival analysis of radiosynovectomy in the hemophilia with inhibitors: An 18-year retrospective review

B. Zulfikar[1,*]; C. Turkmen[2]; B. Koc[3]; O. Kılıcoglu[4]

[1]*Department of Pediatric Hematology/Oncology, Istanbul University, Cerrahpasa Medical Faculty and Oncology Institute;* [2]*Department of Nuclear Medicine, Istanbul University, Istanbul Medical Faculty;* [3]*Department of Pediatric Hematology/Oncology, Istanbul University, Oncology Institute;* [4]*Department of Orthopedics and Traumatology, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey*

Introduction: Hemophilia is an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) or factor IX (FIX). Recurrent bleedings cause haemophilic synovitis. Additionally, the development of an inhibitor is the most common and most serious complication in patients with haemophilia (PwH) and standard treatments are insufficient in bleeding control. Radiosynovectomy has been effective in reducing the frequency of hemarthroses and resolving vicious cycle of bleeding-synovitis-bleeding in PwH and also PwH with inhibitors. We retrospectively reviewed our 18-year experience with radiosynovectomy to determine the outcome in the joints of PwH with inhibitors.

Methods: Radiosynovectomy was performed in 64 joints of 21 PwH with inhibitors between February 2000 and October 2018. The mean age was 14.1 ± 9.8 years. All patients were boys and hemophilia A (HA). Hemostasis was applied according to our institutional protocol. Y-90 was used for knee, hip and shoulder joints and Re-186 for ankle and elbows. Clinical evaluation was focused on bleeding tendency and function of treated joints. Data are presented as mean standard deviation. Two patients had been lost to follow-up. Repeated radiosynovectomy was analysed as the first one.

Results: The follow–up time was 80.16 ± 57.60 months. The mean bleeding frequency of the joints was 13.17 ± 16.29 within the last 6 months in the pretreatment evaluation. After the treatment, the mean bleeding frequency of the joints decreased to 2.25 ± 11.73 for 6 months. Arnold/Hilgartner score at the time of radiosynovectomy was 1.89 ± 0.95. An assessment of joint mobility by means of range of motion (ROM) measurements revealed that, of the 64 treated joints of which 30 had restriction before treatment; ROM had no change in 58 (90%) and improved in 1 (1.5) joint after synovectomy. There were 5 (7.8%) joints that had decreased ROM during follow-up. In the follow-up period bleeding frequency decreased 60 (93%) of 64 joints. Radiosynovectomy did not work only 2 joints. No side-effects were recorded.

Discussion/Conclusion: The treatment of bleedings in PwH with inhibitors is still challenging. Radioactive synovectomy is a choice of treatment for chronic hemophilic synovitis in our institution for more than 20 years for PwH. These findings support the use of radiosynovectomy as the efficient and safe treatment of choice in hemophilic synovitis with PwH with inhibitors.

Disclosure of Interest: None declared.

P054 | Transition from Benefix to Alprolix and the effect on paediatric patients with haemophilia B in Ireland

C. Ferry[1,*]; B. Nolan[2]; B. brady[1]; I. kelly[1]; M. Kavanagh[1]

[1]*Haemophilia;* [2]*OLCHC, Dublin, Dublin, Ireland*

Introduction and objective: The standard prophylaxis for all paediatric patients with severe Haemophilia B was Benefix. Since June 2017, Alprolix has been offered to children with severe haemophilia B fulfilling the following criteria: no history of FVIII inhibitor, >50 exposure days to factor FIX concentrate one to two infusions of factor FIX concentrate weekly.

The aim of this study was to compare bleeding history of those patients while on Benefix and Alprolix. The specific objectives were to identify if patients developed inhibitors, the weekly consumption of factor dose/kg and if bleeds were spontaneous or traumatic joint or non-joint bleeds.

Methods: Method: Seven children met the criteria to switch and were offered the option to switch. Data was collected one year pre and post commencement of Alprolix. This data was collected from the patient Electronic Health Care Record System (Clintech). Bleeding episodes included both traumatic and spontaneous injury. All were reported by the parents to the nursing/medical staff and required treatment with Alprolix.

Results:

Results: Seven patients aged between 7-15 years agreed to change their treatment of choice from Benefix to Alprolix. On review of the year pre commencement of Alprolix, 4 children had a total of 8 bleeding episodes. Of these bleeds, 1 was spontaneous and 7 were traumatic. 5 were joint bleeds and 3 non-joint bleeds. The year post

commencing Alprolix identified 3 children having a total of 5 bleeding episodes. 0 were spontaneous and 5 were traumatic. 1 was a non-joint bleed and 4 were joint bleeds. Bringing down the annual bleed rate. The overall median usage of Benefix was 81 IU/kg, for children aged 7-15 the median usage and frequency was 43 IU/kg twice per week. The overall median usage of Alprolix was 50 IU/kg, for children aged 7-15 years the median usage was 50 IU/kg once per week.

Discussion/Conclusion: Conclusion: Overall this study found that there were no reactions to Alprolix, no patients developed inhibitors, no patients requested to switch back, overall average usage decreased to 54.6 IU/kg/week, and less bleeding episodes on the longer acting factor. With fewer IV administrations, the quality of life has improved for these patients and their families.

Disclosure of Interest: None declared.

P055 | Pharmacokinetic-guided prophylaxis based on bayesian model with myPKFiT® in hemophilia A: Turkish experience

C. Balkan[1,*]; C. Albayrak[2]; N. Y. Ozbek[3]; Z. Kaya[4]; I. Sasmaz[5]; T. Celkan[6]; M. Yagci[7]; S. Karaman[8]; E. Erduran[9]; F. Sahin[10]; G. N. Ozdemir[11]; on behalf of myPKFiT Study Group: T. Patiroglu, Y. Oymak, E. Turkkan, M.S. Evim, H. Gulen, Y. Ay, V. Okan, S. Aksu, T. Ileri, Z. Salcioglu, N. Andic, B. Yilmaz, B. Antmen, D. Albayrak, H. Oren, A. Kupesiz, E. Zengin, M. Soker, C. Ar, K. Kavakli

[1]Pediatric Hematology, Ege University Children's Hospital, Izmir; [2]Pediatric Hematology, 19 Mayıs University, Samsun; [3]Pediatric Hematology, Diskapi Yildirim Beyazit Hospital; [4]Pediatric Hematology, Gazi University, Ankara; [5]Pediatric Hematology, Cukurova University, Adana; [6]Pediatric Hematology, Istanbul Cerrahpasa University, Istanbul; [7]Hematology, Gazi University Hospital, Ankara; [8]Hematology, Istanbul University, Istanbul; [9]Pediatric Hematology, Karadeniz Teknik University, Trabzon; [10]Hematology, Ege University Hospital, Izmir; [11]Pediatric Hematology, Kanuni Sultan Suleyman Hospital, Istanbul, Turkey

Introduction: Plasma levels of replacement factors are influenced by the patient's age, weight and metabolic characteristics. myPKFiT® is a web-based application that was developed by Baxalta (Shire) as a pharmacokinetics (PK) and dosing calculator for Advate®. This device helps to personalise dosing with only 2 blood samples, compared to 11 with standard PK sampling. In this study we planned to evaluate whether PK-tailored prophylaxis is an effective option which reduces bleeding rates in HA.

Methods: 135 patients with HA from 28 centers were recruited in this study. All patients were on prophylaxis with Advate. The age of the patients were 17.5 ± 9.9 years. 29 patients received primary prophylaxis, whereas 106 received secondary prophylaxis. PK analysis was performed with myPKFiT in all patients. Treatment adjustments were made based on PK results, joint status and physical activity level of the patient and bleeding phenotype. ABR before and after adjustments were obtained using the patient's clinical history data.

Results: The mean weight of the patients was 47.9 ± 24.2 kg. All patients received prophylaxis with Advate at a dose of 25.9 ± 6.8 IU/kg for 1-3 days per week. PK evaluation was performed in all patients with Advate at a dose of 25.7 ± 7.3 IU/kg. Half-life of FVIII was found as 10.0 ± 1.9 (6.0-17.8) hours. The time spent until FVIII levels below 1% was found as 51.1 ± 11.3 (27.0-110.0) hours. After PK evaluation, prophylaxis regimen was rearranged in 51 patients (38%). In 21 patients, only the treatment dose was increased. In 9 patients, both the dose and the frequency of the treatment were increased. In 8 patients, only the treatment frequency was increased. In 7 patients, the frequency was decreased whereas the dose was increased. In 4 patients, the treatment dose was decreased. In 2 patients, the treatment schedule was rearranged based on the activity level. While the ABR before PK evaluation was 6.0 ± 4.2 (0-36.0), it decreased to 1.4 ± 1.6 (0-5.0) after the treatment rearrangement ($P = 0.025$).

Discussion/Conclusion: PK-guided dosing allows for FVIII level prediction at any time during treatment. The need for only 2 samples to estimate PK parameters facilitates its use in routine clinical practice with little inconvenience for patients and caregivers. Our results suggest that PK-tailored prophylaxis could be an effective option for children and adults with HA reducing bleeding rates.

Disclosure of Interest: None declared.

P056 | Haemophilia A genotype-phenotype analysis in Turkey

C. Albayrak[1,*]; K. Kavakli[2]; C. Ar[3]; D. Albayrak[4]; Y. Kılınç[5]; Z. Başlar[3]; C. Balkan[2]; Ç. Timur[6]; T. Celkan[7]; Y. Oymak[8]; Z. Kaya[9]; H. Çağlayan[10]; on behalf of Turkish Hemophilia Federation Research Group

[1]Pediatric Hematology Department, Ondokuz Mayıs University Medical Faculty, Samsun; [2]Pediatric Hematology Department, Ege University, Izmir; [3]Hematology Department, Istanbul University, Istanbul; [4]Pediatric Hematology Department, Samsun Medicalpark Hospital, Samsun; [5]Pediatric Hematology Department, Çukurova University, Adana; [6]Pediatric Hematology Department, Yeditepe university; [7]Pediatric Hematology Department, Istanbul University, Istanbul; [8]Pediatric Hematology Department, Dr. Behçet Uz Training Hospital, Izmir; [9]Pediatric Hematology Department, Gazi University, Ankara; [10]Molecular Biology and Genetic, Boğaziçi University, Istanbul, Turkey

Introduction: The genotype distribution in hemophilia A patients in Turkey and there is no comprehensive studies showing the relationship between phenotype. The aim of this study was to collect retrospective clinical information of hemophilia A patients who had been mutated and to evaluate the relationship between genotype and phenotype.

Methods: The study was planned as a study project of Hemophilia Federation Research Group 2018-01. In the scope of the project, the results of the Hemophilia A mutations previously studied at Boğaziçi University were requested. The results were written with the patient name, the result of the mutation, the sending center and the name of the physician. Physicians who sent the mutation study were sent short forms containing questions about their patients' results and clinical information. The data were evaluated statistically.

Results: The mutation of 250 patients with hemophilia A was studied at Boğaziçi University until today. Here, the findings of 101 patients

from seven different centers were filled in and their information forms were filled. The age distribution of the patients was between 1 month and 65 years. The mean age at diagnosis was 3.7 years (SD 8.8). 85% of the patients were severe hemophilia. The most common mutation was intron 22 inversion and 62 (61%) of the cases were detected. Missense mutations were detected in 25 (25%) patients, nonsense mutations in 6 (6%) and other rare mutations in 7 (7%) patients.

Seventy-eight percent of the patients had a family history of hemophilia. There were only two patients who were used for prenatal diagnosis as a result of mutation. Seventy-eight percent of the patients were receiving prophylaxis treatment and 62% were using a plasma source factor. Eighteen patients (18%) had inhibitors. Three of them were nonsense mutations and fifteen patients with intron 22 inversion mutations. Two patients with inhibitor died due to cerebral hemorrhage and bleeding into the abdomen.

Discussion/Conclusion: It is very important that countries know their hemophilia genotype distribution. Despite advances in hemophilia care in Turkey is inadequate information about the genotype distribution. Long-term follow-up of patients to determine the relationship between the phenotype and new mutations should be followed. However, there are some difficulties in collecting retrospective clinical information; the centers and physicians where the patients were followed may have changed.

Disclosure of Interest: None declared.

P057 | Recombinant factor VIII half life using a bayesian model in patients with severe haemophilia A on prophylaxis in Turkey

C. Albayrak[1,*]; D. Albayrak[2]

[1]*Pediatric Hematology Department, Ondokuz Mayis University Medical Faculty;* [2]*Pediatric Hematology Department, Samsun Medicalpark Hospital, Samsun, Turkey*

Introduction: FVIII half life (FVIII T/2) in patients with haemophilia A (HA) on prophylaxis are usually determined by using numerous blood samples. This procedure has practical difficulties to be implemented in patients. Nevertheless, estimation of individual FVIII T/2 is required, since it varies widely and it could affect the effectiveness of prophylaxis. The aim of this study was to identify PK parameters with two blood samples in patients with HA on prophylaxis.

Methods: FVIII T/2 was estimated in seventeen patients with HA aged 3.6-32 years. Only one patient had a positive history of FVIII inhibitor with low titre. All HA were on regular prophylaxis with rFVIII (Advate, Shire) with three infusions per week, 500 or 1000 or 1500 IU according to weight (maximum 4500 IU/week). After 72 hours of washout period, blood samples were collected at 3 and 24 hours after factor infusion. FVIII activities were determined by one-stage assay. FVIII T/2 was calculated based on a Bayesian model (myPKFIT). Nonparametric statistics were used.

Results: Twenty one severe HA patients were analyzed. Mean age was 14.6 years (SD: 7.0) median age was 15 years (range 3.6-32) and mean weight was 50.7 kg (SD 22.5), median weight was 55 kg (range 15-82). In patients, mean dose was 25.6 IU/kg (SD: 5.6; median 23.1 range 18.3-37.5). Mean FVIII T/2 was 10.04 hours (SD: 1.25; median 9.9 range 8.0-12.4). Our patients were divided into those who were 17 years old and older (eight patients) and those who were below 17 years old (thirteen patients). Mean FVIII T/2 was found significantly shorter in young people (9.6-11) ($P = 0.01$). Factor VIII clearance was significantly increased in all young people (<17 years old) (0.044-0.037) ($P = 0.012$).

Discussion/Conclusion: It is useful to calculate factor half-life using practical methods such as Bayesian model in patients with hemophilia. For explain the concept of FVIII T/2, we can show the graph prepared with own blood samples. In this way, we can apply individualized treatment. In our country, the social security institution pays maximum of 4500 IU factor per week prophylactically for severe hemophilia. Effective use of the limited factor is necessary.

Disclosure of Interest: None declared.

P058 | Modern treatment of inhibitor-positive patients with haemophilia A (motivate)—an international observational study

C. Escuriola-Ettingshausen[1,*]; R. F. Sidonio Jr[2]

[1]*HZRM Hämophilie Zentrum Rhein Main GmbH, Mörfelden-Walldorf, Germany;* [2]*Aflac Cancer and Blood Disorders Center, Emory University, Atlanta, United States*

Introduction: Immune tolerance induction (ITI) with replacement factor VIII (FVIII) is the only clinically-proven strategy for eradicating FVIII inhibitors, the most serious complication of haemophilia A management. Recently, the bispecific FIX and FX monoclonal antibody emicizumab was approved for bleeding prevention in people with haemophilia A and inhibitors, offering a new approach to treatment. The MOTIVATE study will capture different management approaches for people with haemophilia A and high-titre inhibitors in routine clinical practice by evaluating the efficacy and safety of ITI, including ITI in combination with emicizumab prophylaxis.

Methods: MOTIVATE is an international observational study, planned to be initiated in 30 centres worldwide. Around 120 people with haemophilia A and inhibitors are planned to be enrolled. One group will be treated with current ITI protocols using human cell line-derived recombinant FVIII (Nuwiq®) or plasma-derived FVIII containing von Willebrand factor (octanate® or wilate®). The second group will combine ITI regimens using any of these products with emicizumab prophylaxis. The third group will use routine prophylaxis with emicizumab or bypassing agents (BPAs), without ITI. BPAs may be used in case of bleeding episodes and for prophylaxis during traditional ITI. All treatment will be at the investigator's discretion and details of the therapeutic regimen will be documented over a 5 year observation period. Optional sub-studies will include *F8* gene mutation analysis, FVIII inhibitor epitope mapping, thrombin generation assay, batch selection and joint health analysis.

Results: The primary objectives of the MOTIVATE study are ITI outcomes with and without emicizumab and annualised bleeding rates across all treatment groups. Secondary objectives include time to ITI outcome, rate of ITI relapse, frequency and severity of bleeding events, use of BPAs and overall treatment costs. Safety will be assessed by monitoring adverse drug reactions, in particular the incidence of thrombotic events.

Discussion/Conclusion: MOTIVATE will collect real-world clinical experience of current practice and new approaches for the management of haemophilia A with inhibitors. These data are expected to facilitate important discussions on evolving the standard of care for people with haemophilia A and inhibitors, in the context of new therapeutic developments.

Disclosure of Interest: C. Escuriola-Ettingshausen Grant/Research support from: Bayer Healthcare, Biotest, CSL Behring, Grifols, Octapharma, NovoNordisk, Shire, Sobi, Roche, Alnylam, LFB, Consultant for: Bayer Healthcare, Biotest, CSL Behring, Grifols, Octapharma, NovoNordisk, Shire, Sobi, Roche, Alnylam, LFB, Speaker Bureau of: Bayer Healthcare, Biotest, CSL Behring, Grifols, Octapharma, NovoNordisk, Shire, Sobi, Roche, Alnylam, LFB, R. Sidonio, Jr. Grant/Research support from: Bayer, Bioverativ, CSL Behring, Octapharma, Genentech/Roche, Shire, Novo Nordisk, Uniqure, Grifols, Kedrion, Spark, Consultant for: Bayer, Bioverativ, CSL Behring, Octapharma, Genentech/Roche, Shire, Novo Nordisk, Uniqure, Grifols, Kedrion, Spark.

P059 | Assessment of clotting activity of recombinant FIX-Fc fusion protein in French haemostasis laboratories

C. Pouplard[1]; C. Ternisien[2]; A. Sadeghi-Khomami[3]; C. Martinez[4,*]

[1]*Hemophilia Care Center, University Hospital of Tours, Tours;* [2]*Hemophilia Care Center, University Hospital of Nantes, Nantes, France;* [3]*Precision BioLogic Inc., Dartmouth, Nova Scotia, Canada;* [4]*Swedish Orphan Biovitrum, Levallois, France*

Introduction: As extended-half-life factor replacement therapies become available, such as recombinant FIX-Fc fusion protein (rFIX-Fc), it is important to ensure the reliability of their therapeutic monitoring. The European field study assessed agreement between European haemostasis laboratories in measuring FIX activity in plasma samples containing various concentrations of rFIXFc. In contrast to other European laboratories, French centers widely used an APTT reagent containing kaolin as activator to measure FIX activity. In this context we performed a subanalysis of the European field study.

Methods: Human FIX immunodepleted plasma was spiked with rFIXFc (Alprolix®) at three nominal levels (based on manufacturer's labelled potency). Samples were shipped frozen to laboratories in France and tested for FIX activity by the labs' own aPTT-based one-stage clotting assay or chromogenic assay.

Results: Forty sets of results were received from 34 centres: C.K. Prest® (n = 22); SynthASil® (n = 7); Actin FS®, Pathromtin SL®, PTT-Automat® (each n = 2); APTT-SP®, Cephascreen®, Triniclot APTT HS® (each n = 1); and the chromogenic assay Biophen FIX® (n = 2). Overall mean FIX clotting activities of 0.80, 0.20 and 0.05 IU/mL plasma samples measured by one-stage assay (n = 38), were 0.68 IU/mL (CV = 19%, range 0.49-1.02), 0.20 IU/mL (CV = 23%, range 0.12-0.30) and 0.06 IU/mL (CV = 27%, range 0.04-0.10), respectively. Results for aPTT reagents reported by more than 5 labs were further evaluated. Mean recovered activity using SynthASil® (n = 7; silica-based) was close to target values with best recovery at the high level: 0.83 IU/mL (CV = 6%, range 0.76-0.90), 0.26 IU/mL (CV = 7%, range 0.24-0.30) and 0.08 IU/mL (CV = 12%, range 0.07-0.10). Mean FIX clotting activities measured by C.K. Prest® (n = 22; kaolin-based) were 0.59 IU/mL (CV = 10%, range 0.49-0.71), 0.16 IU/mL (CV = 11%, range 0.12-0.19) and 0.05 IU/mL (CV = 18%, range 0.04-0.07). Recovery of FIX activity of samples by the chromogenic assay was in the range of 74-110% of target values.

Discussion/Conclusion: rFIXFc activity was well recovered by SynthASil® aPTT reagent as indicated in previous studies. On average, the measured rFIXFc activity by C.K. Prest® at 0.05 IU/mL level was good, but at the higher levels noticeably underestimated. Preliminary data indicates that the chromogenic assay is promising for rFIXFc measurement.

Disclosure of Interest: C. Pouplard Consultant for: Bayer, CSL Behring, Novo Nordisk, Octapharma, Roche/Chugai, Shire and Swedish Orphan Biovitrum, C. Ternisien Consultant for: Bayer, CSL Behring, Novo Nordisk, Octapharma, Roche/Chugai, Shire and Swedish Orphan Biovitrum, A. Sadeghi-Khomami Employee of: Precision BioLogic Inc., C. Martinez Employee of: Sobi.

P060 | Improved recovery of rVIII-singleChain and rIX-FP spiked plasma samples in the one-stage clotting assay

J. Schiebel; C. Horn*; C. Mengel; H. Metzner

Recombinant Product Development, CSL Behring, Marburg, Germany

Introduction: Plasma standards diluted in NaCl solution are typically used in current practice to calibrate the one-stage (OS) clotting assay for monitoring of recombinant FVIII or FIX levels in patient plasma. We hypothesize that the use of NaCl solution for dilution of the plasma standard results in a suboptimal measurement accuracy of post-infusion levels. This study aimed to determine whether the use of immuno-depleted factor deficient plasma (iDPL) instead of NaCl solution for dilution of the plasma standard would result in an improved recovery for rVIII-SingleChain and rIX-FP containing samples.

Methods: To mimic post-infusion plasma samples, rIX-FP, rIXFc and rFIX were spiked into FIX iDPL at different concentrations. Similarly, rVIII-SingleChain was spiked into FVIII iDPL. Normal human plasma was used as clotting factor standard and was either diluted in NaCl solution or iDPL. Several aPTT activator reagents were tested.

Results: The calibration curves obtained from application of the two different procedures for standard dilution deviated significantly from each other, resulting in different measured OS clotting activities. For the conventional dilution using NaCl solution, poor linearity over the investigated spike concentrations and overestimation at lower spike concentrations was generally observed. When applying the iDPL dilution, linearity was considerably improved. Particularly at low spike concentrations the iDPL dilution procedure resulted in a more accurate recovery. These effects were present for the majority of the 14 tested activator reagents in the case of rIX-FP, as well as for rFIXFc and rFIX. Importantly, similar trends were also found for rVIII-SingleChain.

Discussion/Conclusion: Dilution of the plasma standard in iDPL resulted in more accurate recoveries in the OS clotting assay over the range of investigated spike concentrations. On the basis of these in vitro data, the choice of the plasma-standard diluent may impact the accuracy of FVIII and FIX post-infusion clinical monitoring.

Disclosure of Interest: J. Schiebel Employee of: CSL Behring, C. Horn Employee of: CSL Behring, C. Mengel Employee of: CSL Behring, H. Metzner Employee of: CSL Behring.

P061 | Successful use of EHL-FIX in hemophilia B carriers with FIX deficiency: A single center experience

C. R. Hermans[1,*]; S. Eeckhoudt[2]; A. Van Damme[3]; C. Lambert[1]

[1]*Division of Adult Haematology;* [2]*Biological Chemistry;* [3]*Paediatric Haematology, Cliniques universitaires Saint-Luc, Brussels, Belgium*

Introduction: Several extended half-life FIX (EHL-FIX) concentrates have been developed using various technologies (PEGylation, fusion with albumin or Fc Fragment of immunoglobulins) with the aim of decreasing the frequency of infusions in patients with severe/moderate HB. Although EHL-FIX concentrates have mainly been studied in patients treated prophylactically and undergoing surgery, they can potentially be used in patients with mild hemophilia B presenting with bleeds or requiring invasive procedures. They could also be used in HB carriers although very little experience of EHL-FIX use in this setting has been reported so far.

Methods: We here describe the successful use of EHL-FIX in three HB carriers with FIX deficiency.

Results: The first patient is a 57-year-old carrier with a FIX at 0.3 IU/mL who received a unique bolus of 6000 units of Fc-FIX before partial breast resection for breast cancer. FIX reached 1.42 IU/mL and was at 0.6 IU/mL 3 days post-surgery. The second is a 31 year-old-lady with a FIX at 0.16 IU/mL who received 6000 bolus Alb-FIX before vaginal delivery under epidural analgesia. FIX reached 1.04 IU/mL post-bolus and was 0.35 IU/dL on day 4 when a new bolus of 6000 units was repeated. None of these patients presented with delayed bleeding complications and no additional bolus were required. The third patient is a 15-year-old girl with severe FIX deficiency previously treated with standard FIX 2/week who was started on prophylaxis with Alb-FIX 3000 units every two weeks with an ABR of 0 and a very positive impact on the treatment burden and quality of life.

Discussion/Conclusion: These cases illustrate that EHL-FIX can also be used to prevent peri-operative and post-operative hemorrhagic complications in HB carriers with FIX deficiency requiring major invasive procedures with several advantages including reduced frequency of administration, easier venous access, decreased treatment burden and prolonged hemostatic control with maintenance of high FIX levels several days post-infusion. As expected, in our HB carrier with severe FIX deficiency, prophylaxis with EHL-FIX was as effective as reported in male patients. Although larger studies are needed, these limited observations emphasize that symptomatic female HB carriers should benefit from innovations and have access to the major advantages provided by EHL-FIX.

Disclosure of Interest: None declared.

P062 | Using patient-level simulation to model patient-centric outcomes in the advent of gene therapy in severe haemophilia A

J. O'Hara[1,2]; M. Jain[3]; M. Stevenson[4]; T. Burke[2]; C. Camp[3,*]

[1]*Faculty of Health and Social Care, University of Chester, Chester;* [2]*HCD Economics, Daresbury;* [3]*BioMarin Europe Ltd, London;* [4]*School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom*

Introduction: Haemophilia is a rare congenital blood disorder characterised by a deficiency of coagulation factor. Severe haemophilia A (HA) (<1% normal factor VIII level) is associated with significant morbidity and lifelong treatment requiring regular intravenous injections of factor replacement therapy. Furthermore, persons with severe HA are highly heterogeneous in terms of patient characteristics, current and previous treatment regimens, and pathophysiology, which is reflected in idiosyncratic bleeding patterns and diverse trajectories of joint progression. Gene therapy for the treatment of severe HA has the potential to provide lifelong benefits to patients. To date, there are currently few published models estimating the incremental health gains and costs associated with the advent of gene therapy. The aim of this research is to establish patient-level simulation modelling as an appropriate framework to capture the complex and heterogeneous burden experienced by persons with severe HA to inform decision making from a UK perspective.

Methods: The proposed modelling framework will compare the advent of a gene therapy for severe HA to current standard of care in UK clinical practice, notably, prophylactic factor VIII replacement. Clinical evidence available from published literature sources will be supplemented by expert elicitation where evidence is limited. The 'Cost of Haemophilia across Europe—a Socioeconomic Survey' (CHESS) dataset, a cost-of-illness assessment in severe HA and B

conducted in 2015 in five European countries, will be utilised to predict costs (treatment and non-treatment), health-related quality of life, and workforce participation.

Results: Outputs from the model include quality adjusted life years (QALYs); total, treatment-related, and non-treatment-related costs; life years; and work force participation. Treatment strategies will be compared using incremental cost-effectiveness ratios (ICER). In addition, probabilistic sensitivity analysis and a wide range of scenario analyses will be undertaken to explore uncertainty.

Discussion/Conclusion: A patient-level simulation modelling framework should facilitate a more precise representation of the burden and potential unmet need experienced by persons with severe HA in current UK clinical practice and capture how the advent of gene therapy could change the treatment landscape.

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P063 | Interest of combination of two assays in diagnosis and follow-up of haemophilia A

C. Fauconnier*; M.-A. Van Dievoet; C. Marlière; C. Lambert; C. Fillée; J.-P. Defour; S. Eeckhoudt; C. Hermans

Cliniques universitaires Saint-Luc, Bruxelles, Belgium

Introduction: Two different types of assays are generally used for the measurement of FVIII activity: a one-stage assay (OSA), based on the activated partial thromboplastin time (aPTT) and a two-stage or chromogenic substrate assay (CSA). However, discrepancies between these assays are frequently reported. At Cliniques Universitaires Saint-Luc Brussels, we follow a population of 250 haemophilic patients. In this respect, we monitor the patients by using both assays since no specific consensus has been implemented yet.

Methods: We analysed retrospectively 882 laboratory prescriptions for which both tests were executed in diagnosis as well as treatment setting. OSA is realized with the HemosIL Werfen kit, whereas Biophen FVIII:C from HYPHEN BioMed is used for CSA. Clinical discrepancy was defined as a difference in the classification of haemophilia A which is based on the percentage of FVIII: <1% (severe haemophilia), 1%-5% (moderated haemophilia), 6%-40% (minor haemophilia), >40% (normal value). Two patients receiving emicizumab (17 samples) were excluded due to extreme discrepancies between assays.

Results: Of the 865 samples, 12% were clinically discordant. Among these, 67% and 33% presented higher and lower results respectively with OSA in comparison to CSA.

Discussion/Conclusion: Discrepancies between assays measuring FVIII are frequent, particularly at low values. Even if some authors affirm that CSA improves diagnosis of haemophilia A, in view of our results, we prefer to continue using both tests in our center. Yet, some haemophilia centers only use OSA. Consensus between haemophilia centers should standardise the management of haemophilia patients. In this study, we emphasize the need to combine both approaches.

Disclosure of Interest: None declared.

P064 | The ADVANCE Study: A longitudinal study of age-related comorbidities in people with haemophilia—baseline interim results after completed inclusion

C. Qvigstad[1,2,*]; P. A. Holme[1]; C. Tait[3]; P. de Moerloose[4]; G. Dolan[5]; on behalf of the ADVANCE Working Group

[1]Department of Haematology, Oslo University Hospital Rikshospitalet; [2]Institute of Clinical Medicine University of Oslo, Oslo, Norway; [3]Department of Haematology, Royal Infirmary, Glasgow, United Kingdom; [4]University Hospital and Faculty of Medicine of Geneva, Geneva, Switzerland; [5]Centre for Haemostasis and Thrombosis, St Thomas' Hospital, London, United Kingdom

Introduction: The ADVANCE Working Group, a collaboration of more than 20 haemophilia centres across Europe, conducted a cross-sectional study of Haematuria and Hypertension in Haemophilia A and B in people with haemophilia (PWH) 40 years and older. Building on this existing dataset to collect prospective data in 800 PWH on the incidence and management of cardiovascular disease (CVD), the ADVANCE Study will compare the baseline observed fatal and non-fatal CVD events against expected numbers based on CVD risk prediction scores (SCORE & QRISK2).

Methods: This prospective, non-interventional, multi-centre, observational study collected data from PWH with mild (5%-40%), moderate (1%-5%) and severe (<1%) haemophilia A (HA) and B (HB) under routine treatment. Disease status and comorbidities in the recruited age cohorts are monitored annually and intended for up to 10 years. The development of cardiovascular comorbidities and their management in the aging PWH is the primary research focus. Secondary outcomes will include other co-morbidities and haemophilia status/treatment. Interim analysis four years after study inclusion has been performed on disease characteristics and comorbidities.

Results: Baseline data for 791 patients and accumulated data from approximately 2400 years follow-up. Of the 791 (mean age 54, range 40-88), 85% have HA (33% mild, 11% moderate, 56% severe) and 15% have HB. 38% of PWH were treated prophylactically and 59% receiving on-demand treatment. 38% had a history of hypertension, 88% of which are treated, 5 PWH had a history of acute coronary syndrome (ACS) and a further 3 suffered an ACS during follow-up. Diabetes, mostly type 2, in 8% of the patients. Of the 16% of PWH with HIV, 86% are on antiretroviral therapy, almost 90% have severe haemophilia and approximately 60% are aged 40-49. 39% of PWH have never been infected with hepatitis C (HCV) or have had natural clearance of HCV, with 3% currently receiving antiviral therapy. HCV is more common in severe haemophilia. Nearly one in four have chronic liver disease, 90% due to hepatitis and only five patients reported with hepatocellular carcinoma.

Discussion/Conclusion: Recruitment for the study is on target to achieve approximately 5000 follow-up years from the participants. The final analysis should enable the development of guidelines specific to the management of older PWH and comorbidities.

Disclosure of Interest: None declared.

P065 | Clinical efficacy of different treatment options for haemophilia: Pitfalls of comparing annual bleeding rates

C. Keipert; M. Mueller-Olling; F. Gauly; C. Arras-Reiter; A. Hilger

Haematology, Paul-Ehrlich-Institut, Langen, Germany

Introduction: A wide range of emerging treatment options for haemophilia A and B are in development or on their way to market authorization comprising gene therapy, bispecific monoclonal antibodies, anti-TFPI antibodies or other non-replacement therapies such as RNAi therapeutics. To demonstrate efficacy of treatment, Annual Bleeding Rates (ABR), are often used as primary or secondary endpoint in clinical trials.

Methods: Definitions of ABR and bleeding episodes from clinical trial protocols and literature have been reviewed and compared. In addition, data from the confidential PEI clinical trial database have been assessed e.g. regarding factor concentrate administration, treatment regimen and reason for treatment. Anonymized data from 31 clinical trials have been analyzed.

Results: No consensus in minimum standards of ABR assessment is available. Supported by PEI database analyses, distinct pitfalls in the assessment of the ABR have been identified. The definition and assessment methods of ABR, in particular the classification and distinction of bleeding events used in clinical trials and in the literature varies considerably. Moreover, factors such as assessment period, sample heterogeneity, therapeutic regimens and consumption of coagulation products, can constitute a substantial methodological bias and have to be considered in the interpretation of ABR measures. Due to the numerous difficulties in the ABR measurement, a direct comparison of efficacy following different treatment scenarios and products may be severely compromised.

Discussion/Conclusion: Clear definition of parameters and characteristics and awareness of the important pitfalls when using ABR as measure for the efficacy of treatment, is prerequisite for enabling conclusions on different treatment regimens and products including non-replacement therapies.

Disclosure of Interest: None declared.

P066 | Real-world clinical experience of switching to rVIII-SingleChain in adults/adolescents and paediatric patients with haemophilia A

G. Goldmann[1]; M. Olivieri[2]; J. Oldenburg[1]; K. Kurnik[2]; C. Bidlingmaier[2,*]

[1]*Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn;* [2]*Pediatric Hemophilia Center, Department of Pediatrics, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-Universität München, Munich, Germany*

Introduction: rVIII-SingleChain is a novel B-domain truncated recombinant factor VIII in which heavy and light chains are covalently linked, resulting in an increased stability and a high binding affinity for von Willebrand factor. Clinical studies in patients with haemophilia A, have shown rVIII-SingleChain to be efficacious for the treatment and prevention of bleeds, and to have a favourable safety profile. Data on the physician and patient experience of using rVIII-SingleChain for the treatment of haemophilia A patients in a real-world clinical setting is needed. Here we summarize our experience when switching adults/adolescents (Bonn Centre) and children (Munich Centre) to rVIII-SingleChain.

Methods: Adults/adolescents from the Bonn Centre (n = 11) and children from the Munich Centre (n = 12) with severe haemophilia A were switched to rVIII-SingleChain and their clinical response and tolerability to treatment was reported.

Results: In both adults/adolescents and children, the transition to rVIII-SingleChain proceeded without any problems. rVIII-SingleChain was shown to be effective for prophylaxis and in the treatment of bleeding episodes. A reduction in injection frequency was possible in the majority of adult/adolescent patients (91%), and most (73%) were able to reduce or maintain their weekly factor consumption of rVIII-SingleChain. In children, 83% maintained their injection frequency and a dose reduction has thus far been initiated in four of the twelve children. rVIII-SingleChain was well tolerated; there were no safety events and no patients developed inhibitors.

Discussion/Conclusion: Within our two centres, the transition to rVIII-SingleChain was straightforward; effective bleed control was achieved across all age groups. rVIII-SingleChain provided the opportunity for reductions in both injection frequency and dose in adult/adolescent patients, thereby reducing their treatment burden. In children it offered the possibility for dose reduction in some patients.

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Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum, Speaker Bureau of: Baxter, Bayer, Biogen Idec, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer and Swedish Orphan Biovitrum, K. Kurnik Grant/Research support from: Bayer, Biotest, CSL Behring, Roche and Shire, Consultant for: CSL Behring and Shire, C. Bidlingmaier Grant/Research support from: Bayer, Biotest, CSL Behring, Intersero, Novo Nordisk, Octapharma, Pfizer, Roche, Shire and Swedish Orphan Biovitrum, Consultant for: Bayer, Biotest, CSL Behring, Pfizer, Roche and Swedish Orphan Biovitrum.

P067 | Pharmacokinetic parameters, FVIII consumption and cost evaluation in 13 patients with severe haemophilia who switched from conventional therapy to efmoroctocog alfa: Experience of a French haemophilia center

C. Flaujac[1,*]; R. Favre[1]; S. Le Dore[2]; E. Ferre[2]; A. Rafowicz[2]; N. De Gunzburg[2]; F. Samdjee[3]; E. De Raucourt[2]

[1]*Service Hématologie Biologique;* [2]*CRTH;* [3]*Pharmacie, CH André Mignot, Le Chesnay, France*

Introduction: Efmoroctocog alfa (Elocta®) is a recombinant human FVIII bound to the Fc fragment of a human immunoglobulin which enhances half-life. The goal of this study was to evaluate pharmacokinetic (PK) parameters in patients switch from conventional FVIII to Elocta®, and to determine if tailored PK-driven prophylaxis with Elocta® reduce injection frequency, cost and improve QoL.

Methods: Thirteen patients with severe HA previously treated with conventional FVIII concentrates were switched to Elocta®. All patients were older than 15 years, treated either on demand (n = 4) or on prophylaxis (n = 9). Using the WAPPS-Hemo database, PK were evaluated for each patient with Elocta®, tailored PK-driven prophylaxis was then assessed, in order to obtain a through level of FVIII >1%. FVIII half-lives calculated with Elocta® and the mean number of UI/kg per week injected with Elocta® were compared to those with regular products. After 1 to 14 months, patients were asked about their QoL with Elocta®.

Results: FVIII half-live with Elocta® increased for all patients with a mean half-life of 17 hours (h) with Elocta® compared to 10.7 hours with regular concentrates, with a mean gain of 62%. The 13 patients were satisfied or very satisfied of the switch, either because of lower frequency of injections or because their articular pain was reduced. A decrease global FVIII consumption (99.3 UI/kg/w with conventional products to 82.9 UI/kg/w) was observed. No adverse effect was noticed. All the patients except one remained on prophylaxis with 1 to 2 injections per week. Only one patient «on demand» has reduced his FVIII consumption, but not his frequency of infusion because of hip pain. Considering price market of these products in our institution, the switch to Elocta® has permitted significant saving, decreasing from 62.24 euros /kg/week to 53.73 euros /kg/week.

Discussion/Conclusion: Tailored PK driven prophylaxis with Elocta®, in 13 HA patients, allows to reduce injections frequency in comparison to usual conventional FVIII therapy. All patients have a positive feeling with Elocta®. A global decrease in FVIII consumption was observed and cost evaluation was in favour of Elocta®. These preliminary results have to be confirmed on larger and prolonged study.

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P068 | A simple functional mobility assessment tool for use in clinical practice or real-life studies with hemophilia patients: Step 1, development of the questionnaire (French version)

C. Négrier[1,*]; V. Barbay[2]; A. Harroche[3]; C. Gandossi[4]

[1]*Hemophilia Care Center, Lyon;* [2]*Hemophilia Care Center, Rouen;* [3]*Hemophilia Care Center, Paris;* [4]*Swedish Orphan Biovitrum, Levallois-Perret, France*

Introduction: Most mobility assessment tools in haemophilia, used in clinical trials, are considered too long and/or complex to be implemented in clinical practice. As new drugs become available, there is an increasing need for a fast and simple scoring system to rate in persons joint function with Haemophilia.

Methods: To develop a valid patient-reported outcome measure, the method described by Rothrock (Clinical Pharmacology & Therapeutics (2011) was used, starting with a conceptual model development. Questionnaires of functional scores were collected through a comprehensive literature review by an external clinical expert, searching for available functional tools in haemophilia as well as rheumatoid arthritis and multiple sclerosis. After minor adaptations, the final questionnaire was scored with the aim to obtain a final score of 0 to 100. At the end of the process, a beta-test on 23 patients was performed by 3 physicians to verify comprehension by patients and feasibility in daily clinical practice.

Results: Hundred and one (of 221 abstracts) full text publications were selected in haemophilia, 394 (of 683 abstracts) in rheumatoid arthritis and 5 (of 320 abstracts) in multiple sclerosis. After a selection based on validated tools, royalty-free and relevance to joints' damage, a total of 190 questionnaires were submitted to an item improvement, which allowed us to narrow down the number of questionnaires. In the end, 17 questionnaires were selected, constituting a bank of 128 questions. Using a weighted model a total score between 0 and 100 was constructed, with 100 being the maximum severity. The beta test demonstrated that the questionnaire was easy to fill in by patients, with an average of 8 minutes duration and 0 to 1 missing data. The questionnaire was filled in during a consultation by 17 patients and before a consultation by 6 patients.

Discussion/Conclusion: The existing composite scales in rheumatoid arthritis seem to be an appropriate model for the construction of this functional mobility questionnaire. Multiple sclerosis was less applicable, as the questionnaires found did not add any dimension to other pathologies. Results of beta-testing clearly demonstrated that the questionnaire is well understood and manageable in clinical practice. Step 2 will be to perform the psychometric validation.

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P069 | 25 years of induction of immune tolerance in a Portuguese hemophilia center

S. Campanico; C. Catarino*; F. Rodrigues; A. Pereira; C. Jacinto Correia

Hospital Santa Maria, Lisboa, Portugal

Introduction: The development of inhibitors for FVIII/FIX continues to be one of the most serious complications in the treatment of hemophilia. Immune tolerance induction (ITI) still remains as the most effective approach in the management of this complication.

Methods: In this retrospective study we evaluated the characteristics, treatment and outcome of patients with haemophilia and inhibitors who have undergone ITI at our Center over the past 25 years (1993 - 2018).

Results: A total of 15 boys with severe hemophilia A and 1 with severe hemophilia B, underwent 18 courses of ITI during this period.

The age at which patients developed an inhibitor ranged from 11 months to 41 years and all patients had high responding inhibitors.

The time between inhibitor development and initiation of ITI ranged from 2 to 70 months. ITI was started after 1 month to 9 years after the first detection of inhibitors and titer of inhibitors at the start of ITI was less than 10 UB in 14 patients.

Five patients were given plasma-derived and 11 patients were given recombinant products. Dose and schedules varied, with daily doses of 100 U/kg being used in most patients (range 50-200 IU/Kg/day).

In the 13 patients (86.7%) that became tolerized to FVIII, the time to achieve an inhibitor titre of <0.6 UB ranged from 1 to 30 months. In the patient with hemophilia B, ITI was successful and no complications were observed. The 2 non-caucasian patients submitted to ITI achieved tolerance.

In 2 cases of ITI failure, the first attempt was interrupted because of complications related to CVC, leading to the recurrence of inhibitors. Change from recombinant product to plasma derived was tried in 1 patient with no success.

In cases of ITI success, and after a follow-up period between 4 months and 24 years, there was no recurrence of inhibitors.

Discussion/Conclusion: In ITI the optimal agent, dose and infusion schedule for each patient have not been determined. In our patients the interval between inhibitor detection and initiation of ITI as well as the type of product used, and ethnicity did not appear to influence the outcome. In patients with higher titers of inhibitors, a longer period of ITI was required. Although the number of patients does not allow us to draw conclusions we find that the results obtained in our patients are similar to those reported in other registries.

Disclosure of Interest: None declared.

P070 | 5 patients, 4 products, 5 inhibitors—what are the odds?

C. Jacinto Correia; C. Catarino*; S. Campaniço; F. Rodrigues; A. Pereira

CHLN – Hospital de Santa Maria, Lisboa, Portugal

Introduction: Inhibitor development is a major complication of haemophilia therapy being described in about 1/3 of severe Hemophilia A patients.

Methods: The aim of this study is to evaluate inhibitor development in 5 consecutive previously untreated patients (PUPs) with severe haemophilia A and analyze factors associated with its development.

Results: In a 2 year period (Oct 2016-Sept 2018), 5 boys with severe haemophilia A were diagnosed in our center at a median age of 8 M (0.1-18). Diagnosis was always made in the context of a bleeding episode that was, in all 5 patients, the first manifestation of the disease. Two of the bleeding episodes were considered severe (an intracranial (ICH) and a paravertebral hemorrhage).

Median age at first exposure to FVIII concentrate was 12 M (0.1-18), and treatment was initiated with 4 different recombinant FVIII products. Primary prophylaxis was started in just 1 patient, at the age of 12 M, weekly, at a low dose. Bleeding was the reason for first treatment on the other 4 cases, although intensive treatment was performed in just 1 patient (ICH).

All these 5 patients developed a high titer inhibitor in median number of 20 ED (6-31). Initial inhibitor titer ranged between 1.9 and 30 BU, and maximal titer between 26 and 143 BU. The median age of the inhibitor detection was 15 M (3-26).

None of the patients had a family history of inhibitors. Genetic study was performed in all patients but results are only available for 2 of them. In both cases a high risk mutation was identified.

All patients were treated with recombinant products (1 Refacto AF; 1 Novo Eight; 1 Elocta; 2 Advate). One of the patients on Advate was the one submitted to an intensive treatment related to the ICH.

Immune tolerance induction was adopted with success in 2 patients.

Discussion/Conclusion: The incidence of inhibitors we here report is higher than any other we are aware of. Our study is limited by small sample size and therefore we cannot draw any conclusion about risk factors for inhibitor development. We look at it as just a question of bad luck and do not pretend to find any statistical significance in this.

We just wanted to share our recent experience that we think demonstrates that we know little about inhibitors. It is essential to continue gathering data to help us all understand the risk factors behind this serious complication of haemophilia treatment.

Disclosure of Interest: None declared.

P071 | It`s still need for pain assessment in patients with hemophilia?

C. E. Ursu[1,*]; S. T. Arghirescu[2]; E. Boeriu[2]; J. M. Patrascu[3]; A. Traila[4]; D. Mihailov[5]; C. Jinca[2]; C. M. Toma[6]; R. Oltean[6]; M. Serban[7]

[1]Pediatric Hematology, European Treatment Center for Hemophilia, Children Emergency Hospital Louis Turcanu; [2]Pediatric Onco-hematology; [3]Orthopedics, European Treatment Center for Hemophilia, University of Medicine and Pharmacy "V.Babes", Timisoara; [4]Hematology, Medical Rehabilitation Center for Children and Adolescents "Cristian Serban", Buzias; [5]Pediatric Intensive Care Unit, University of Medicine and Pharmacy "V.Babes"; [6]Pediatrics; [7]Pediatric Onco-hematology, European Treatment Center for Hemophilia, Children Emergency Hospital Louis Turcanu, Timisoara, Romania

Introduction: Pain, as an expression of joint or tissue bleeding, is a common symptom of patients with hemophilia (PwH), unfortunately sometimes accompanying them throughout life with devastating consequences. Objective. We aimed the analysis of pain perception in the context of a comprehensive assessment based on age, severity of the disease, joint affection, and therapeutic regimen.

Methods: The study was conducted on a total of 80 PwH: 37 children and 43 young adults with hemophilia, 4 of them complicated with inhibitors. A multidisciplinary team assessed the pain using the joint pain score from Haemophilia Joint Health Score (HJHS), pain domain, visual analogue scale from quality of life questionnaire, EuroQol 5 Domains (EQ5D)/EuroQol VAS (EQ-VAS) and, also, evaluated the health status according to International Classification of Functioning (ICF). The results were statistically analyzed by IBM SPSS Statistics 14.0 software.

Results: The predominant pain pattern was joint pain (92, 1%), with significant differences in frequency and intensity, in both the HJHS score and the EQ5D domain ($P < 0.001$). Comparison of the VAS-EQ mean value between children and adults revealed significant differences ($P < 0.001$), lower values being found in the group of adult patients (63.5 ± 14.1 vs 82.3 ± 20.9). Pain perception was not directly proportional with disease severity, it was more an expression of the patient's expectation and perception. Pain correlated significantly with age (r = 0.44, $P = 0.003$) and with HJHS score (r = 0.61, $P < 0.001$). An explanation could be the annual joint bleeding rate (AJBR) and the favourable impact of a regular or intermittent prophylactic substitution. Regarding the ICF status only 21.62% of children vs 100% adults, had a restriction of these parameters. In our study, all patients used non-opioid medication; stage II opioids were administered in 24.2% and stage III in 9.1% of adults for a short period of time.

Discussion/Conclusion: The present study supports with current data the decisive importance of an optimal therapeutic substitution, which besides the definite advantages for the joints health, is indispensable for prevention or relief of pain, a symptom that could accompany PwH a whole lifetime. Pain should be addressed by a multidisciplinary team, started earlier and applied properly to avoid intoxication by overdose and suicide cases.

Disclosure of Interest: None declared.

P072 | Determinants of prophylaxis regimen choice for patients with haemophilia A switching to BAY 81-8973: Real-world findings from the TAURUS non-interventional study

C. Santoro[1,*]; B. Fuh[2]; P. Maes[3]; M. E. Mingot Castellano[4]; R. Berrueco Moreno[5]; P. Q. Lê[6]; S. Rauchensteiner[7]; M. Wang[8]

[1]Department of Cellular Biotechnology and Hematology, University of Rome, Rome, Italy; [2]Department of Pediatrics, East Carolina University, Greenville, United States; [3]Department of Pediatrics, Antwerp University Hospital, Antwerp, Belgium; [4]Department of Hematology, Hospital Regional Universitario de Málaga, Málaga; [5]Department of Pediatric Hematology, Hospital Sant Joan de Déu, Barcelona, Spain; [6]Department of Hematology Oncology, Queen Fabiola Children's University Hospital, Brussels, Belgium; [7]Bayer, Basel, Switzerland; [8]Hemophilia and Thrombosis Center, University of Colorado, Aurora, United States

Introduction: BAY 81-8973 (Kovaltry®) is an unmodified, full-length recombinant factor VIII (FVIII) indicated for prophylaxis and the treatment of bleeds in patients with haemophilia A (HA); its safety and efficacy were established in the LEOPOLD clinical trials. Launched in 2016, BAY 81-8973 has accumulated 8031 patient-years of exposure to 31 Aug 2018. The TAURUS study (NCT02830477) looks at BAY 81-8973 prophylaxis in routine clinical practice. Here, we report the reasons for less frequent (≤2 times per week [×W]) vs more frequent (≥3 × W) dose regimens upon switching to BAY 81-8973.

Methods: TAURUS is an international, open-label, prospective, non-interventional, single-arm study of patients with moderate or severe HA (FVIII ≤5% or ≤1%) and ≥50 exposure days to any FVIII (target recruitment N = 350). At baseline, physicians documented the reason for regimen choice. A scheduled interim analysis (30% of patients recruited) was conducted with data collected to 2 Jul 2018.

Results: At the cut-off date, 160 patients were enrolled. BAY 81-8973 regimens for patients receiving ≥3 × W dosing at baseline (n = 94, 59%) were: daily, n = 2; every other day, n = 26; 3 × W, n = 66. For patients on ≤2 × W dosing at baseline (n = 52, 33%), regimens were: 2 × W, n = 41; every fourth day, n = 1; 1.5 × W, n = 1; 1 × W, n = 7. Pre-study, most patients had been on prophylaxis (97%; 83% on rFVIII-FS). At baseline, ≥3 × W patients were younger than ≤2 × W patients (21.5 vs 27.0 years) and had received prophylaxis for longer pre-study (13 vs 9 years); more ≥3 × W vs ≤2 × W patients had severe HA (88% vs 79%) and a history of inhibitors (7% vs 4%). The most common reasons for regimen selection were: current treatment regimen (57%), bleeding history (36%), 'patient/caregiver preference' (34%) and adherence/compliance history (24%). 'Adherence/compliance history'

was cited more frequently in the ≤2 × W group than the ≥3 × W group (31% v 23%, respectively). No patients developed inhibitors.

Discussion/Conclusion: BAY 81-8973 treatment can be successfully individualised according to patient need/disease. Patients receiving BAY 81-8973 ≥ 3 × W were younger and had a longer history of prophylaxis than those treated ≤2 × W. Current regimen and bleeding history were the most common determinants of BAY 81-8973 regimen choice.

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P073 | TAURUS real-world study: Straightforward transition to BAY 81-8973 prophylaxis in patients with haemophilia A with maintained or reduced dosing frequency

C. Santoro[1,*]; M. Wang[2]; B. Fuh[3]; P. Maes[4]; M. E. Mingot Castellano[5]; R. Berrueco Moreno[6]; S. Rauchensteiner[7]; P. Q. Lê[8]

[1]Department of Cellular Biotechnology and Hematology, University of Rome, Rome, Italy; [2]Hemophilia and Thrombosis Center, University of Colorado, Aurora; [3]Department of Pediatrics, East Carolina University, Greenville, United States; [4]Department of Pediatrics, Antwerp University Hospital, Antwerp, Belgium; [5]Department of Hematology, Hospital Regional Universitario de Málaga, Málaga; [6]Department of Pediatric Hematology, Hospital Sant Joan de Déu, Barcelona, Spain; [7]Bayer, Basel, Switzerland; [8]Department of Hematology Oncology, Queen Fabiola Children's University Hospital, Brussels, Belgium

Introduction: BAY 81-8973 (Kovaltry®) is an unmodified, full-length recombinant FVIII indicated for prophylaxis and treatment of bleeds in patients with haemophilia A (HA); its safety and efficacy were established in the LEOPOLD clinical trials. Launched in 2016, BAY 81-8973 has accumulated 8031 patient-years of exposure as of 31 Aug 2018. The TAURUS study (NCT02830477) assesses BAY 81-8973 use in routine clinical practice.

Methods: TAURUS is an international, open-label, prospective, non-interventional, single-arm study of patients with moderate or severe HA (FVIII ≤5% or ≤1%) and ≥50 exposure days to any FVIII product (target recruitment N = 350). Investigators record patient and disease characteristics at baseline and for 1 year of treatment; patients complete bleed diaries and report treatment satisfaction (HEMO-SAT) and adherence (VERITAS-PRO). A scheduled interim analysis (30% patients recruited) was conducted with data collected to 2 Jul 2018.

Results: At cut-off, 89 patients had ≥6 months of follow-up data (median observation period 201 days); 33% (n = 29) had completed 1 year of study. Most patients had severe HA (85%). Pre-study, all were treated with prophylaxis, with 67% treated ≥3 times per week (×W). The majority of patients (91%) remained on their previous regimen (7% reduced frequency, 1% increased frequency). The proportion of patients on ≤2 × W increased from 27% (n = 24) pre-study to 33% (n = 29) at baseline and 38% (n = 34) at last follow-up. Median weekly dose on study was 52 IU/kg (65 IU/kg for ≥3 × W and 43 IU/kg for ≤2 × W) vs 56 IU/kg (64 IU/kg and 50 IU/kg, respectively) with previous treatment. Median (quartile [Q] 1; Q3) patient-reported annualised joint bleed rates on study were 1.4 (0.0; 6.1), 1.1 (0.0; 5.3) and 1.1 (0.0; 5.3) for ≤2 × W, ≥3 × W and all patients, respectively. HEMO-SAT (range 0-100; 0 = highest satisfaction) and VERITAS-PRO (range 24-120; 24 = highest adherence) median total scores at baseline/1 year were 13/13 and 36/36 (both n = 80). No patients developed inhibitors.

Discussion/Conclusion: These real-world data show that most patients switching to BAY 81-8973 remain on the same individualised treatment regimen for a year post-switch. The finding of low joint bleeding rates confirms and extends clinical trial results, demonstrating effective prophylaxis with BAY 81-8973 in a real-world setting.

Disclosure of Interest: C. Santoro Consultant for: Bayer, Shire, Pfizer, Novo Nordisk, Roche, CSL Behring, SOBI, Novartis, Speaker Bureau of: Bayer, Shire, Pfizer, Novartis, M. Wang Grant/Research support from: Biomarin, uniQure, Pfizer, Shire, CSL Behring, Genentech, Bayer, Novo Nordisk, Consultant for: Bayer, Shire, CSL Behring, Genentech, Novo Nordisk, Octapharma, B. Fuh Consultant for: Bayer, Pfizer, Novartis, Micelle Biopharma, P. Maes Grant/Research support from: Bayer, Consultant for: Advisory Board, Bayer, M. Mingot Castellano Consultant for: Shire, Pfizer, Bayer, Sobi, Amgen, Novartis, Alexion, Leo Pharma, Grifols, Roche, Novo Nordisk, R. Berrueco Moreno Grant/Research support from: Sobi, Consultant for: Advisory Board, Bayer, S. Rauchensteiner Employee of: Bayer, P. Q. Lê: None declared.

P074 | The impact of public transport in hemophilia care in Kenya

C. Njuguna[1,*]; F. Njuguna[2]; A. Greist[1]; C. Asirwa[3]

[1]Hematology, IHTC, Indianapolis, United States; [2]Paediatrics, Moi University/MTRH; [3]Hemat-Oncology, AMPATH/MTRH, Eldoret, Kenya

Introduction: In healthcare, public transport is one of the pillars to accessing important services and activities that improve public health by providing access to such services like health care appointments and emergencies. It has played a big role in aiding healthcare delivery by offering alternative courier services that are affordable, easily accessible and well networked significantly enhancing care for people living with hemophilia by ensuring treatment is attainable.

Objectives: -To provide support in management and care for People Living With Hemophilia (PLWH).

-To maximize on the use of the existing resources in improving hemophilia care in Kenya.

-To promote better referrals and consultations among healthcare providers from different levels of health care system in Kenya.

Methods: Currently, there are estimated 700 diagnosed cases of hemophilia in Kenya with a population of around 49 million. Most of them are not able to access treatment on time due to the long distances to the main HTCs, social and economic limitations. As a result, our HTC has given out contacts through which communications and consultations related to hemophilia issues are done. Treatment plans are discussed over the phone where necessary, medications packed in a well labeled parcel together with instructions for use and delivered to the relevant transport provider's office. The applicable fee is well subsidized as compared to conventional courier services that exist in the country. Upon delivery which takes at most 24 hrs, the recipient is notified through an SMS and collects the package but from a more convenient location.

Results: In the year 2016, 88250 IU of factor VIII for 33 PLWH and 4000 IU of factor IX for 2 PLWH was delivered to various destinations at a cost of Ksh7, 000($70). In 2017, 260250 IU of factor VIII for 48 PLWH and 118250 IU of factor IX for 11 PLWH was sent at a cost of Ksh11, 800($118). Up to date in 2018, 130500 IU of factor VIII for 23 PLWH and 25500 IU of factor IX for 9 PLWH has been dispatched at a cost of Ksh5200 ($52). These costs are half what it would take when using the regular courier services.

Discussion/Conclusion: Accessing hemophilia care in a resource limited setting is a challenge but it can be alleviated by making good use of the available options. This complements the mentorship efforts by the main HTCs to the lower facilities.

Disclosure of Interest: None declared.

P075 | The top 10 research priorities in bleeding disorders: A James Lind Alliance priority setting partnership

M. Laffan[1]; D. Stephensen[2,3,*]; C. Camp[4]; L. Carroll[5]; P. Collins[6]; D. Eleston[7]; P. Gallagher[8]; K. Khair[9]; W. McKeown[10]; J. O'Hara[11]; S. Shapiro[12]; S. Stanworth[13]; A. Waterman[14]; L. Woollard[15]; S. Upadhyaya[16]; on behalf of James Lind Alliance Bleeding Disorder Priority Setting Partnership

[1]Department of Haematology, Imperial College London, London; [2]Haemophilia Centre, Kent and Canterbury Hospital, Canterbury; [3]Haemophilia Centre, Royal London Hospital, London; [4]HCD Economics, Daresbury; [5]Haemophilia Society, London; [6]Arthur Bloom Haemophilia Centre, University Hospital of Wales, Cardiff; [7]ITP Patient Support Association, Bedfordshire; [8]City Sprint Group; [9]Haemophilia Comprehensive Care Centre, Great Ormond Street Hospital for Children NHS Trust, London; [10]Antrim Area Hospital, Antrim; [11]Faculty of Health and Social Care, University of Chester, Chester; [12]Oxford Haemophilia and Thrombosis Centre; [13]NHS Blood and Transplant, Oxford University Hospitals NHS Foundation Trust, Oxford; [14]National Childbirth Trust; [15]On the Pulse Consultancy, London; [16]The James Lind Alliance, Southampton, United Kingdom

Introduction: The James Lind Alliance (JLA) Bleeding Disorder Priority Setting Partnership (PSP) is an independent, evidence-based project of patients, carers and health care professionals (HCP) with the purpose of identifying the TOP 10 uncertainties around diagnosis and management of inherited and acquired bleeding disorders.

Methods: 478 uncertainties were submitted by patients, carers and HCP in an initial paper and online survey. Following removal of duplicate and out of scope questions and consolidation of related uncertainties, 66 unanswered questions remained. Patients, carers and HCP were invited to rank their TOP 10 priorities from the 66 consolidated unanswered questions in a second online survey. This identified the top 25 uncertainties and these were prioritised at a final workshop of patients, carers and HCP using open discussion and consensus ranking facilitated by JLA advisors.

Results: The TOP 10 priorities

What is the role and cost effectiveness of blood clotting tests that give immediate results at the bedside (point of care) in managing medical, surgical or obstetric haemorrhage?

How can we balance the risk and benefit of antithrombotic treatment for cardiovascular disease in patients with bleeding disorders?

What is the best haematological approach to management of severe haemorrhage after delivery?

How should heavy periods be managed in women with bleeding disorders?

What is the relationship between immune thrombocytopenic purpura (ITP) and fatigue?

What are the most effective treatments for acute and chronic pain in people with haemophilia?

What are the benefits of psychological and psychosocial strategies for support of individuals or families affected by bleeding disorders?

What are the genetic and environmental factors that predispose people to ITP?

What is the best way to prevent or treat bleeds in people with bleeding disorders who have developed an inhibitor?

What is the best way to tell the difference between pain from acute bleeds, non-bleeding muscle/ligament injury and long term joint damage?

Discussion/Conclusion: People with bleeding disorders, their families and HCP have collectively decided questions they want to see answered by research. The final TOP 10 list of questions will be an invaluable resource to inform prioritisation and funding of future research into bleeding disorders.

Disclosure of Interest: None declared.

P076 | Development of a haemophilia physiotherapy intervention for optimum musculoskeletal health (Dolphin trial)

D. Stephensen[1,2,*]; M. Bladen[3]; L. Carroll[4]; W. Drechsler[5]; D. Lowery[6]; T. Pellatt-Higgins[6]; E. Saloniki[6]; F. Hashem[6]

[1]*Kent Haemophilia Centre, Canterbury;* [2]*Haemophilia Centre, Royal London Hospital;* [3]*Haemophilia Centre, Great Ormond Street Hospital NHS Trust;* [4]*Haemophilia Society;* [5]*Faculty of Life Sciences and Medicine, Kings College London, London;* [6]*Centre for Health Service Studies, University of Kent, Canterbury, United Kingdom*

Introduction: Haemophilic arthropathy is associated with muscle weakness and may be reduced prior to the onset of clinical arthropathy. Muscle weakness is strongly correlated to reduced walking distances, slower ascent and descent of stairs, and altered joint motion and forces during weight bearing activities. Our aim was to develop a muscle strengthening exercise intervention for children that could be tested in a randomised clinical trial.

Methods: We conducted modified Nominal Group Technique focus groups with academic experts and specialist physiotherapists, and most importantly in consultation with patients. The exercise programme was demonstrated to five boys with haemophilia and their parents. Children and parents were asked; what they thought about the exercises and whether they could undertake them on a regular basis, where they thought the best place was for undertaking them, and how they would like to receive information on the exercise programme. They were also asked questions about how they would feel about taking part in a study testing the benefits of the exercises, issues around being allocated randomly into study groups, and what would encourage the children to continue on the exercise programme.

Results: Strong consensus from physiotherapists indicated the exercise programme should include exercises focused on strength, balance, proprioception, flexibility and mobility, and a motor learning component. Families noted the best place for the intervention being carried out was at home and that twice per week would be achievable. Parents felt that in order to sustain interest and motivation, it was important to build in an incentive that would be valued by the child. They also said that in order to find out whether or not the exercise programme worked, they would not have a problem with their child being allocated into an intervention or usual care groups.

Discussion/Conclusion: Engaging clinicians and patients in partnership as part of the research process enhanced the design of an exercise intervention ensuring it is acceptable and potentially beneficial for children with chronic disorders. The efficacy of a 24-session progressive exercise programme of stretching, strengthening, balance, proprioceptive and mobility using functional movement patterns is currently being tested in a randomised controlled trial.

Disclosure of Interest: None declared.

P077 | Sacrococcygeal pilonidal sinus surgery in two patients with haemophilia

D. Albayrak*; C. Albayrak

Pediatric Hematology Department, Samsun Ondokuz Mayis University Faculty Of Medicine, Samsun, Turkey

Introduction: Sacrococcygeal pilonidal sinus disease (PSD) is a common chronic inflammation of the natal cleft and presents as an abscess or a chronically discharging, painful sinus tract. It has an incidence of 1.2-2.5/1000 in children. Onset is around puberty. Symptoms of recurrent abscess and chronic suppuration may interfere with education and social integration. Treatments should cause minimal disruption while having good cure and recurrence rates. The management of chronic PSD is variable, contentious, and problematic. Although many surgical procedures have been tried, the best surgical method remains controversial.

We presented two haemophilia patients undergoing pilonidal sinus surgery in our hospital.

Methods: We presented two haemophilia patients undergoing pilonidal sinus surgery in our hospital.

Results: Case 1. Sixteen-year-old boy with severe haemophilia B was unresponsive to two-year medical treatment. Excision surgery planned for pilonidal sinus disease. Inhibitory test was negative. His weight was 50 kg. Presurgery 1800 IU plasma derived factor IX was given Presurgery factor IX level was 64%. Tranexamic acid was started. He was removed from the hospital at four days after the surgery.

Case 2. Nineteen-year-old boy with severe haemophilia A was unresponsive to four-year medical treatment. He has family history for haemophilia and has intron 22 inversion mutation. Excision surgery planned for pilonidal sinus disease. Inhibitory test was negative. His weight was 90 kg. Presurgery 2000 IU recombinant factor VIII was given then factor level was 52%. Tranexamic acid was started. We give 2000 unit factor VIII was given every 24 hours, total three doses. He was removed from the hospital at two days after the surgery. Surgical procedure completed with a total of 67 IU / kg factor VIII

After then, 2000 IU prophylaxis was continued for two days a week. Two weeks later, there was no bleeding or discharge. Wound healing was completed. For four months after surgery, the disease was not repeated.

Discussion/Conclusion: There is no case series related to sacrococcygeal pilonidal sinus disease surgery in hemophilia patients. However, if surgical surgeons and hematologists cooperate and communicate closely, these surgical procedures can be performed successfully.

Disclosure of Interest: None declared.

P078 | Haemnet horizons: Enhancing patient care by fostering a growing haemophilia nurse community

S. Dodgson[1]; M. Holland[1]; D. Pollard[2,*]

[1]*Haemnet;* [2]*Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London, United Kingdom*

Introduction: Haemnet Horizons is an action-based programme that brings together nurses from across Europe to share knowledge and experience. Participants have applied learning from the literature on Appreciative Inquiry and Communities of Practice and together are exploring the future shape of haemophilia nursing in the context of innovative therapies and the need to deliver care to a diversifying population.

Methods: Nurses working in haemophilia centres across Europe were invited to participate in an ongoing series of workshops, each designed to build on the agenda identified by members of the group. The process is designed to encourage and support haemophilia nurses to engage in research and service development activities and to review progress as a group; it also aims to build capacity and confidence around the four tenets of the Advanced Nurse Practitioner role: research, leadership, clinical practice and education.

Results: In the four Haemnet Horizons workshops held so far, 19 haemophilia nurses from 13 countries agreed three areas for action as an initial focus:

For nursing research to become the 'norm' and to find ways of making it possible and practical for all haemophilia nurses to engage in it.

For the development of patient-focused care based on equal collaboration between all healthcare professional.

Ready access to haemophilia-related education developed and delivered by haemophilia nurses.

Subsequently, research projects have been developed focusing on product switching and the frequency of follow-up assessments for patients with mild haemophilia. The group have also undertaken a pan-European survey of nurse educational needs that sits alongside the EAHAD curriculum, and are collaborating on translating video resources for patients from English into Spanish.

Discussion/Conclusion: The participants in this evolving series have valued the opportunity to meet, to share their knowledge and experience of nursing, and to share perspectives. Nursing practice varies across Europe, although most participants share common challenges: the feeling of "not being alone" was valued. The workshops have reinforced that supporting the development of haemophilia nurse practice across Europe will require exchange of ideas and experience both within and between countries. In the medium to longer term, the group envisage this sharing of knowledge and experience will maximise benefit for people with bleeding disorders.

Disclosure of Interest: S. Dodgson: None declared., M. Holland Employee of: Haemnet, D. Pollard: None declared.

P079 | Impact of acute and chronic pain on the EQ-5D: Insights from the PROBE study

D. Noone[1,2,*]; C. Chai-Adisaksopha[3]; R. Curtis[4]; N. Frick[5]; M. Nichol[6]; B. O'Mahony[7,8]; D. Page[9]; A. Pastarnak[5]; J. Stonebraker[10]; A. Iorio[3]; M. Skinner[11,12]

[1]Health Decision Consultants, Dublin, Ireland; [2]European Haemophilia Consortium, Brussels, Belgium; [3]Dept. of Medicine, McMaster University, Hamilton, Canada; [4]Factor VIII Computing, Berkeley, California; [5]National Hemophilia Foundation, New York City; [6]Sol Price School of Public Policy, University of Southern California, Los Angeles, United States; [7]Irish Haemophilia Society; [8]Trinity College Dublin, Dublin, Ireland; [9]Canadian Hemophilia Society, Montreal, Canada; [10]Poole College of Management, North Carolina State University, Raleigh, United States; [11]Department of Health Research Methods, McMaster University, Hamilton, Canada; [12]Institute for Policy Advancement Ltd., Washington, United States

Introduction: Acute and chronic pain as well as the potential access to medications, including haemophilia specific products, significantly impact the quality of life of people with haemophilia (PWH). Generic questionnaires such as the EQ-5D are used to measure the impact of the condition on life experience. EQ-5D in particular is designed to record the individual experience on the day of completion. There is little information on how the response to the pain domain in EQ-5D is driven by acute or chronic pain. The Patient Reported Outcomes, Burdens and Experiences (PROBE) is a questionnaire developed by patients to measure what matters to them in a way that allows comparison with people without bleeding disorders.

Methods: We hypothesized that joint analysis of EQ-5D and PROBE measures would allow deeper understanding of the impact of acute and chronic pain on the respective scores. Descriptive and correlation analysis were performed.

Results: Of 1287 respondents, 686 have severe haemophilia and were examined in this article. We identified 4 subgroups based on responses to PROBE questions asking about acute and chronic pain: no pain (NP, 12.46%), acute pain (AP, 16.13%), chronic pain (CP, 16.23%) and both chronic and acute pain (A/CP, 55.13%). The mean (SD) ages for NP, AP, CP and A/CP were 27.5 (18.3), 24.8 (15.0), 39.2 (15.57) and 37.6 (16.0), respectively. There was a weak correlation ($r = 0.21$, Pearson) between chronic and acute pain. The mean (SD) EQ-5D utility values for NP, AP, CP and A/CP were 0.91 (0.12), 0.82 (0.21), 0.75 (0.17) and 0.65 (0.28), respectively. Standard t-tests indicated that all groups were statistically different from each other. A similar trend was seen in VAS score.

Discussion/Conclusion: Acute pain has a significant impact on the quality of life of PWH. This is further exacerbated by the presence of chronic pain and the combination of both leads to the greatest decrease in quality of life. The EQ-5D does discern a difference between both types of pain. However, if chronic pain only is present at the time the EQ-5D is administered, the result may mask the full extent of the impact on the utility value unless the context and timing of using these generic tools are understood. This may lead to a misrepresentation of the true nature of pain within the severe haemophilia population.

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P080 | Predictors for acute and chronic pain in patients with severe haemophilia in the PROBE cohort

D. Noone[1,2,*]; C. Chai-Adisaksopha[3]; R. Curtis[4]; N. Frick[5]; M. Nichol[6]; B. O'Mahony[7,8]; D. Page[9]; A. Pastarnak[5]; J. Stonebraker[10]; A. Iorio[3]; M. Skinner[11,12]

[1]Health Decision Consultants, Dublin, Ireland; [2]European Haemophilia Consortium, Brussels, Belgium; [3]Dept. of Medicine, McMaster University, Hamilton, Canada; [4]Factor VIII Computing, Berkeley, California; [5]National Hemophilia Foundation, New York City; [6]Sol Price School of Public Policy, University of Southern California, Los Angeles, United States; [7]Irish Haemophilia Society; [8]Trinity College Dublin, Dublin, Ireland; [9]Canadian Hemophilia Society, Montreal, Canada; [10]Poole College of Management, North Carolina State University, Raleigh, United States; [11]Department of Health Research Methods, McMaster University, Hamilton, Canada; [12]Institute for Policy Advancement Ltd., Washington, United States

Introduction: For people with severe haemophilia, acute and chronic pain is often part of their daily reality. We looked at the extent to which this pain was influenced by annual bleed rate, presence of target joints or joints with reduced range of motion.

Methods: A binary regression analysis was performed to measure the association of acute and chronic pain with selected predictors from the PROBE Phase 2 data. The dependent variable (outcome) was the likelihood of reporting chronic and acute pain. The 5 predictor variables included in the model were: age, reported annual bleeding rate (ABR), current treatment, presence of a target joint and range of motion (ROM) in a joint.

Results: There were 1287 respondents from 21 countries in total, 658 of whom had severe haemophilia and information for the predictor variables. For acute pain, the univariate logistic regression analysis showed a significant association for ABR (all bleeds) with patients reporting 2-3 bleeds/year being 2.9 times more likely to report acute pain compared to those with 0-1 bleeds/year, and those reporting more than 15 bleeds/year being 10.3 times more likely. Those reporting the presence of a target joint were 2.0 times more likely to report acute pain than those without a target joint. In the full model (all 5 predictors) the impact of ABR is reduced but remains significant. Overall, the full model only predicts 13% of the variation in those who report acute pain. For chronic pain models, the univariate model predicts that those with 2-3 bleeds/year and >15 bleeds/year are 2.2 and 5.5 times more likely to report chronic pain compared to those with 0-1 bleeds/year, explaining 14% of the variance in chronic pain. In the full model however, the most responsible predictor was the presence of a joint with reduced ROM, with those reporting a limitation being 5 times more likely to report chronic pain than those with full range of motion, which explains 23% of the variance.

Discussion/Conclusion: Our predictors were found to correlate with acute and chronic pain. While acute pain is primarily driven by the frequency of bleeding and the presence of a target joint, chronic pain is primarily driven by the presence of a joint with reduced range of motion. Therefore, it would be worth exploring whether treatment regimens targeted to reduce annual bleeding rates or those aimed at improving the range of motion would be more effective in reducing chronic pain.

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P081 | Syrian hemophilia guests living in Southern and Southeastern Anatolia

D. A. Tuncel[1,*]; C. Acıpayam[2]; H. Erdem[3]; E. Unal[4]; A. Akdeniz[5]; S. Akbayram[6]

[1]Department of Pediatrics, Division of Pediatric Hematology and Oncology, Adana Health Research and Training Center, Sağlık Bilimleri University, Adana, Turkey, ADANA; [2]Department of Pediatrics, Division of Pediatric Hematology and Oncology, Faculty of Medicine, Sutcu Imam University, Kahramanmaraş; [3]Department of Internal Medicine, Division of Hematology, TC SBU Sanlıurfa Mehmet Akif İnan Health Research and Training Center, Sanlıurfa; [4]Department of Pediatrics, Division of Pediatric Hematology and Oncology, Erciyes University, Kayseri; [5]Department of Internal Medicine, Division of Hematology, Mersin University, Mersin; [6]Department of Pediatrics, Division of Pediatric Hematology and Oncology, Gaziantep University, Gaziantep, Turkey

Introduction: The war started in Syria in 2011 and continues. Syrians settled in our country, hemophilia patients are followed up and treated.

Methods: 17 pediatric hemophilia patients and 5 adult hemophilia patients were included. 17 children (17 patients, 17%) were male and 17 (% 11.7) were female. The mean age of the patients was 108.29 ± 59.64 months (9-192 months), with a mean age of 26.00 ± 31.19 months (6 days-87 months).

Results: Thirteen patients were hemophilia A, 1 type 3 von Willebrand, 3 had factor XIII deficiency. Seven patients with hemophilia A, only 14 were treated with prophylaxis, and 3 patients were on-demand therapy. One prophylaxis treated patient had recurrent genital tract, severe gastrointestinal bleeding. All patients inhibitor negative. 5 patients had target joint (4 knees, one elbow joint). Iliopsoas bleeding, severe tonsil hemorrhage, severe gastrointestinal bleeding has been diagnosed. Patients were diagnosed in Syria but had not received any prophylaxis treatment, only 1-2 factors could be given in hemorrhages in

their countries. It was learned that they were diagnosed as late and hemorrhages were severe. A 3-year-old patient with a diagnosis of type 3 von Willebrand disease was admitted to our clinic for the first time with posttraumatic subdural hematoma. Factor VIII was 0.9% and von Willebrand antigen was 10%. Gastrointestinal bleeding was followed by prophylaxis. Factor XIII deficiency 3 patients; 6-day-old infant Factor XIII level was 3%, 1 year old male patient Factor XIII level was under 4%, 7 years old patient Factor XIII level was 2%. Bleedings were massive umbilicus hemorrhage, nosebleeds, iliopsoas and intracranial hemorrhage. Three of the patients with intracranial hemorrhage had died. All parents were relatives. Genetic counseling were given to parents.

5 Adult patients have severe haemophilia, 1 is moderate, 1 is mild hemophilia, they have diagnosed in Syria and they do not receive regular treatment. The mean age was 34.4 years (20-55 years). Inhibitors were negative. A patient has a history of iliopsoas hemorrhage. The patient had a knee prosthesis. 4 patients are under treatment of prophylaxis.

Discussion/Conclusion: Patients with hemophilia present with severe bleeding. It was learned that they could not have regular controls, treatment could not be performed in their countries. Syrian guests of hemophilia diagnose and treatments are provided in our country.

Disclosure of Interest: None declared.

P082 | Perioperative care of the patient with hemophilia undergoing urgent appendectomy

D. Tugcu[1,*]; A. Unuvar[1]; R. Tuna[1]; S. Karaman[1]; A. Karadag[2]; Z. Bayramoglu[3]; S. Ocak[1]; F. Basar[2]; Z. Karakas[1]

[1]*Pediatric Hematology-Oncology*; [2]*Pediatric Surgery*; [3]*Radiology, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey*

Introduction: Surgery may be required for hemophilia-related complications or unrelated disease in hemophilia A patients. Prevention of bleeding at the time of major surgery in patients with Hemophilia A requires careful planning. A major surgical procedure is defined as one that requires hemostatic support for periods exceeding 5 consecutive days.

Methods: We report the presentation of acute appendicitis in a 4 6/12-year-old child with severe hemophilia A.

Results: A 4 6/12 years old male patient presented to our emergency department with complaints of abdominal pain and vomiting. Because his mother and aunt are known to be carriers of hemophilia, the patient was diagnosed as severe hemophilia A when he was 1 month old (Factor VIII level % 0.4). To patient who had joint bleeding, intramuscular hematomas, soft tissue traumas and head traumas within the first year, primary prophylaxis was started, 250 unit per week, when he was 1 years old. Prophylaxis doses were increased to 250u, two times a week, at the age of 2 years; 500 u, two times a week, at the age of 3 years; 500u, three times a week, at the age of 3 ^{6} /12 years. After the patient was 4 years of age, the dose of prophylaxis was increased to 750 units, three times per week, according to the pharmacokinetic profile and daily activities. He was diagnosed as acute appendicitis clinically and radiologically during this period. Inhibitor screening was negative. Factor replacement was performed 50 u/kg before the operation, 40 u/kg, post-op 1-3rd days, 30 u/kg 4-6th days, 20 u/kg 7-14th days according to guidelines. Factor VIII level was measured as 74 IU/dL preoperatively, 65 IU/dL post-op 1st day, 53 IU/dL post-op 2nd day, 63 IU/dL post-op 3rd day, 39 IU/dL post-op 4th day. There wasn't any bleeding in the post-operative period.

Discussion/Conclusion: In cases of severe hemophilia, requiring urgent surgery such as acute appendicitis, additional planning, close monitoring and interaction with the healthcare team were requirement to provide adequate hemostasis

Disclosure of Interest: None declared.

P083 | Efficacy of biosimilar recombinant factor VIIa severe bleeding complicated by platelet transfusion refractoriness

D. Johns

Abhilash Clinic, Trikakara, Kochi, India

Introduction: Severe bleeding combined with platelet transfusion refractoriness is a relatively common adverse effect of many hematological disorders. Recombinant activated factor VIIa aids in hemostasis in coagulopathy.

The study aimed to assess the effectiveness of biosimilar recombinant activated factor VIIa.

Methods: A descriptive cross sectional study was conducted between December 2017—September 2018. Sixty patients were enrolled in the study. Demographic data, age and other baseline data were similar in all the groups. The adverse events were also recorded in the questionnaire.

The patients were divided into three groups (20 each)

Group 1-Biosimilar recombinant activated factor VIIa

Group 2- recombinant activated factor VIIa

Group 3- Conventional hemostatic treatment. (Control group)

Results: Among the patients the mean age was 45.76 years. There were equal distribution of males and females in each group. The frequency of distribution were Factor VIIa deficiency>factor V deficiency> Glanzmann thrombasthenia>Hemophilia A with inhibitor>acquired hemophilia> Hemophilia B with inhibitor.

The responses were assessed at 24 hr, 48 hr and at 72 hr. The responses of patients in group 1 and group 2 were comparable and did not have a significant difference. However both were significantly better than group 3 as measured by the bleeding score, control of bleeding and activated partial thromboplastin time.

Adverse events were seen mostly as bleeding in joints which were similar in all groups.

Discussion/Conclusion: Biosimilar recombinant activated factor VIIa and recombinant activated factor VIIa may be used with better efficacy compared to the conventional hemostatic treatment
Disclosure of Interest: None declared.

P084 | Physical activity in persons with hemophilia (PwH) from France (FR), Italy (ITA), and United States (US) from the hemactive patient survey

D. Nugent[1,*]; J. O'Hara[2,3]; G. LeCleir[4]; M. Skinner[5,6]

[1]*Children's Hospital of Orange County, University of California at Irvine, Irvine, United States;* [2]*HCD Economics, Daresbury;* [3]*University of Chester, Chester, United Kingdom;* [4]*Bayer Consumer Care AG, Basel, Switzerland;* [5]*Institute for Policy Advancement, Ltd., Washington, D.C., United States;* [6]*McMaster University, Hamilton, Canada*

Introduction: PwH benefit from prophylaxis but are limited in physical activity due to comorbidities, treatment burden and psychosocial issues. The HemACTIVE study sought to understand and evaluate the impact of these influences on physical activity, with the aim of improving clinical care.
Methods: Persons with moderate/severe hemophilia A, aged 2-65 years (caregivers for PwH <18 y), were given a 25-minute, IRB-approved, web-based questionnaire. Findings from FR, ITA, and US are presented.
Results: 209 PwH enrolled (n = 39 FR, 60 ITA, 110 US). Most had severe hemophilia (76%), were >18 y (72%), and were on prophylaxis (82%), with varying proportions between countries. Overall, 69% of participants reported being currently active or highly active (54% FR, 77% ITA, 70% US). The proportion of US PwH who considered daily activities to be extremely/very important was greater than the proportion who actually participated in activities (~90% vs 81%), while the reverse was found in FR (~50% vs >79%) and ITA (~72% vs >85%). More PwH reported adjusting activities due to hemophilia (79% FR, 95% ITA, 73% US) than stopping activities due to hemophilia (69% FR, 63% ITA, 35% US), with issues of pain, joint damage, and anxiety reported as top reasons for either. Overall, ~90% from each country wished to be more active, believing that increased activity could be enabled by greater bleed protection (76%>80%) and less pain (73%>78%). Compliance to prescribed treatment was reported by 33% of US PwH vs 56%, and 58% of FR and ITA PwH, respectively. In FR and ITA, the top reasons for noncompliance were belief that treatment was not necessary (50%) and managing treatment around activities (40%), respectively, whereas forgetfulness was the top reason (55%) in the US. More than half of PwH (59% FR, 54% ITA, 63% US) considered changing treatments, but only 7% from ITA actually did so (vs 38% from FR and 25% from US). The top reason for considering a switch was consistent across countries: wanting to infuse less often (48-56%).
Discussion/Conclusion: While study participants differed in self-reported activity levels, aspirations, and treatment perspectives, all were aligned in the desire for greater activity, better bleed protection and pain relief, and less frequent infusions. In order to better understand the patient perspective, both positive and negative influencers need to be more fully investigated.
Disclosure of Interest: D. Nugent Consultant for: Bayer, Shire, Novo Nordisk, J. O'Hara Consultant for: Alnylam, Pfizer, Roche, Bayer, Shire, SOBI, Novo Nordisk, G. LeCleir Employee of: Bayer, M. Skinner Grant/Research support from: Baxalta, Bayer, Bioverativ, CSL Behring, Novo Nordisk, Roche, Sobi, Consultant for: Bayer, BioMarin, Pfizer, Roche, Spark, Novo Nordisk.

P085 | Characterisation of haemophilia randomised clinical trials registered on clinicaltrials.gov

D. A. Gómez[1,*]; J. Ramirez[2]; H. Martinez[1]

[1]*Centro de Atención Integral en Hemofilia, Centro Médico Imbanaco;* [2]*Physiological Sciences, Universidad del Valle, Cali, Colombia*

Introduction: The international committee of Medical Journal Editors (ICMJE) demands mandatory registration of randomised clinical trials (RCT) before the recruitment of patients, as a condition to consider any individual article for publication. International legislation regarding the approval of drugs into the market entails not only publication of trial results but making data available in the same record in which the trial was originally disclosed. In this study, we present a characterisation of ClinicalTrials.gov haemophilia registries.
Methods: A systematic review was carried out among clinical trial registries (ClinicalTrials.gov) and further repositories (PubMed). Records compatible with haemophilia were represented into numerical, dichotomous, and categorical variables. Data mining across PubMed and ClinicalTrials.gov was performed by expert search queries. Databases are available.(1)
Results: There are 540 registries matching haemophilia in ClinicalTrials.gov [n = 349 (clinical trials); n = 191 (observational studies)]. Over half (57%; 198 out of 349) of clinical trials were completed by the date of the search query (October 23, 2018); about one-quarter of closed trials were published on biomedical journals indexed by PubMed (25.8%; 52 out of 198) and one-third (34.8%; 69 out 198) of these studies successfully disclosed their results on ClinicalTrials.gov. The most common types of studies were phase III (n = 66; 33.3%), phase I (n = 47; 23.7%), and phase IV (n = 34; 17.2%).
Discussion/Conclusion: Clinical trial registries allow the characterization of human studies according to treatment type (e.g., rFVIIa), disease (eg. haemophilia), locations (e.g., United States), recruitment status (i.e., completed, terminated, not yet recruiting, and unknown). The evidence of haemophilia treatments gathered across clinical trial registries might serve to guide novel approaches, aimed to translate scientific evidence into clinical practice guidelines. It is imperative to promote the disclosure of haemophilia clinical trial results as a pragmatic way to guide decision-making by physicians and to improve the processes of patient informed consent.
References: ClinicalTrials.gov haemophilia records - Oct. 16 / 2018

https://docs.google.com/spreadsheets/d/1hIxA56FZUMsu1gtm1AO5MeFPmnU4dzEXHW6K9oY_YiU/edit#gid = 597755131

Disclosure of Interest: None declared.

P086 | The WFH world bleeding disorders registry

M. Naccache[1]; D. Coffin[1,*]; A. Iorio[2]; G. F. Pierce[1]; J. O'Hara[3]; S. Diop[4]; H. van den Berg[5]; V. Byams[6]; C. Hermans[7]; D. Noone[8]; B. Konkle[9]

[1]*World Federation of Hemophilia, Montréal;* [2]*McMaster University, Hamilton, Canada;* [3]*HCD Economics, Manchester, United Kingdom;* [4]*Cheikh Anta Diop University, Dakar, Senegal;* [5]*University Medical Center, Utrecht, Netherlands;* [6]*Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, United States;* [7]*Haemophilia Clinic, Division of Haematology, St-Luc University Hospital;* [8]*European Hemophilia Consortium, Brussels, Belgium;* [9]*Bloodworks Northwest, Seattle, United States*

Introduction: Registries, with international collaboration between centres and countries, are an effective way to pool data to achieve the required sample size to conduct clinical research on rare disorders, such as hemophilia. The World Federation of Hemophilia (WFH) launched the World Bleeding Disorders Registry (WBDR) in 2017. The WBDR provides a global platform for hemophilia treatment centres (HTCs) to collect standardized data on the patient clinical experience, which can be used to address important clinical questions and support advocacy initiatives.

Methods: The WBDR is a prospective, longitudinal, observational registry of patients diagnosed with hemophilia A and B. It is a privacy-protected online web-based data entry system. Hemophilia treatment centres are first invited to register to indicate their interest to participate. Following their registration, HTCs need to obtain ethics approval from their institution prior to being able to enrol patients in the registry. The goals of the WBDR are to enrol 200 HTCs from more than 50 countries, and at least 10 000 people with haemophilia during the first five years, aiming for representation of patients from around the world and from all levels of access to care.

Results: Currently, 119 HTCs from 68 countries have registered with the WBDR. Of these, a leading group of 36 HTCs from 25 countries have received ethics approval (Figure 1) and have enrolled a total of 790 patients (Figure 2). The majority of patients are male (n = 732, 95%), with haemophilia A (82%, n = 630) and diagnosed prior to 5 years of age (70%). The age of first bleed occurred before age 12 months for 70% of patients, and the age of first joint bleed occurred after age 36 months for 53% of patients.

Discussion/Conclusion: The WBDR is establishing itself as the only global registry collecting standardized clinical data on people with hemophilia from around the world. Within the first year of its implementation, the registry has representation from all regions worldwide. Steady patient enrolment since launch will allow us to reach 1000 patients within the first year. This is an exciting first step towards a global database, which will support research and advocacy for enhanced patient care worldwide. The WFH thanks our Visionary Partners: Shire and SOBI, and our Collaborating Partners: Bayer, Grifols, Pfizer, Roche and Sanofi.

Disclosure of Interest: None declared.

P087 | Effective modulation of antiaggregants and replacement therapies with simoctocog-alfa in a severe haemophilia a patient undergoing a metallic stent implant for acute myocardial infarction

D. Cultrera[1,*]; S. Cabibbo[2]; A. Cipolla[1]

[1]*UOC Ematologia, Az. Ospedaliera-Universitaria "Policlinico - V. Emanuele" Catania, Catania;* [2]*U.O.S. di Ematologia, Servizio di Immunoematologia e Medicina Trasfusionale, ASP 7, Ragusa, Ragusa, Italy*

Introduction: Severe haemophilia A (HA) 56 years old patient, without inhibitors, with HCV and HIV seroconversion, undergoing plasma derived replacement therapy and then rFVIII (octocog-alpha). The patient moved to our centre in Catania in 2016.

Methods: The infectious pathology was treated with Dolutegravir and Darunavir with negativization of viral load and good compensation of liver function indices.

Despite replacement therapy given every other day with 3000 IU of rFVIII, the patient kept showing recurrent hemarthroses, mainly in knees and elbows, and a poor control of bleeding events (approximately 3 per month).

In April 2017 an inferior acute myocardial infarction (AMI) occurred and a coronary angiography was performed with implant of a metallic stent, followed by a double antiaggregant therapy with Aminosalicylic acid and Clopidogrel.

However, in spite of the replacement treatment with rFVIII, an increase in hemorrhagic manifestations occurred and, on the other hand, suspension of the cardiological therapy would have led to a new ischemic episode.

So the patient was offered to switch to Simoctocog alfa (Nuwiq), thinking that this drug could be more effective and, as manufactured in human embryonic kidney cell lines, also less immunogenic.

From September 2017 the patient started with Nuwiq 3000 IU every other day.

Due to the permanence of hemarthroses, related to the concomitant therapy with antiaggregants to treat the ischemic pathology, the dosage was reduced to 3000 IU three times a week (i.e. Monday, Thursday, Sunday), in order to avoid the occlusion of the stent, and to perform a pharmacokinetic test, which showed 3% FVIII activity level at 96 hours from the last infusion.

Results: Such values allowed us to modulate both the replacement and the cardiological therapies attaining a good hemodynamic balance and a clear reduction of bleeding episodes (about one a month).

Discussion/Conclusion: With this case-report we intend to show that it's possible to effectively modulate replacement therapy and another

apparently contraindicated treatment in a patient with severe HA that underwent the implant of a metallic stent following an AMI.
Nuwiq appears to be well tolerated, effective in the control of bleeds and characterized by a satisfactory pharmacokinetic profile.
Disclosure of Interest: None declared.

P088 | Aesthetic surgical operations in a patient with actor VII deficiency

D. Ozatli*; O. Meletli

Haematology Department, Ondokuz Mayis University, Samsun, Turkey

Introduction: Factor VII deficiency is a rare genetic bleeding disorder characterized by a deficiency or reduced activity of clotting factor VII. This presents with a wide spectrum of clinical severity that correlates poorly with plasma factor 7 levels. The symptoms and severity of factor VII deficiency are highly variable; no consistent correlation between the amount of factor VII in the blood and overall severity is seen. Some individuals may not develop any symptom including individuals with relatively low levels of factor VII. Other individuals may have mild cases that are only apparent after trauma or surgery.
When we look at the literature we see that there are many publications or case reports about surgical operations and bleeding in patients with factor VII deficiency
A retrospective series of administration of Factor VII reported marked reduction in bleeding or cessation of bleeding. Indications included elective surgery, emergency surgery, spontaneous hemorrhage, childbirth, menorrhagia, and hematuria. Dose and schedule of administration varied.
If we look at the literature, we do not see much of the publication about aesthetic surgical operations at factor VII deficiency. Herein we present a patient with F VII deficiency who had 2 aesthetic operations without complication in 3 years interval.
Methods: Our patient was diagnosed at 10 years old female patient, the patient's factor VII level was measured as 6%, and there was no serious bleeding in the patient's history.
Two operations were performed for aesthetic purposes during the patient's follow-up, breast and nose operations were performed for 3 years apart. 30 mcg/kg of FVII was given half an hour before each operation, the same dose repeated 2 hours after the operations and until bleeding control was achieved 30 mcg / kg every 4 hours factor VII replacement was performed.
Results: No major bleeding was seen during those operations.
Discussion/Conclusion: As a result, aesthetic surgical procedures can be performed in those patients with appropriate prophylaxis and follow-up
Disclosure of Interest: None declared.

P089 | Mutation spectrum of factor VII gene (F7)

E. Demidova*; V. Salomashkina; E. Yakovleva; N. Zozulya; V. Surin

National Research Center for Hematology, Moscow, Russian Federation (Russia), Moscow, Russian Federation

Introduction: Blood coagulation is the most important part of the hemostasis system, which is responsible for stopping bleeding when the body's vascular system is damaged. The main role of factor VII (FVII) is to initiate the process of coagulation. Factor VII deficiency (congenital proconvertin deficiency) is rare and inherited recessively. It presents as a hemophilia-like bleeding disorder. The study of the mutation spectrum for given population is important for the development of genetic diagnostics of this disease.
This research is focused on the description of factor VII gene mutation spectrum in Russian population.
Methods: We analyzed all functionally important regions including promotor region and exons of factor VII gene using Sanger sequencing and revealed mutations for 18 patients with deficiency of the factor VII (FVII) activity.
Results: We found altogether 16 genetic defects with two of them being prevailing. The most frequently observed mutation was deletion CD464 del C (HGMD, Acc. CD941675) found in 7 patients. For the Russian population, this mutation probably has a monophyletic origin and is linked to polymorphism CD354 GCC>GTC (Ala354Val). We found the mutation at position -122 from ATG C>T, that is known to significantly reduce promoter activity (Sabater-Lleal et al., 2007), in 5 patients in heterozygous state, combined with other mutations, and in a single patient with 62% of FVII activity it was the only mutation found, presented in homozygous state. Two patients had -1 (-55 from ATG) C>T mutation. Other mutations were found in individual patients. Two mutations: IVS4 -1 G> A and CD 22 GGC> GAC (Gly22Asp), from the described spectrum were new and were not previously described. The status of substitution in intron 8 (IVS8 + 7 G> A) is unclear. In a patient that carried no other substitutions and was homozygous for this variant the FVII activity was 50%. Nine patients with low activity factor (1-6%) had mutations in the homozygous state or were compounds of two mutations. For seven patients with medium factor activity (33-62%), single mutations were detected in the heterozygous state.
Discussion/Conclusion: For the Russian patient population, it is advisable to start the search for mutations from the 9th exon, since it contains the major mutation CD464 del C, and from the promoter region (mutations are in the positions -55 and -122).
Disclosure of Interest: None declared.

P090 | Long-term safety and efficacy of recombinant factor ix fusion protein (rIX-FP) in patients with haemophilia B: Interim results from an ongoing phase 3b extension study

E. Santagostino[1,*]; I. Pabinger[2]; A. Brainsky[3]; Y. Li[3]; W. Seifert[4]

[1]Foundation IRCCS Ca'Granda, Maggiore Hospital Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy; [2]Department of Haematology and Haemostaseology, Medical University of Vienna, Vienna, Austria; [3]CSL Behring, King of Prussia, United States; [4]CSL Behring, Marburg, Germany

Introduction: rIX-FP is a recombinant human coagulation factor IX (FIX) genetically fused to recombinant human albumin by a cleavable linker. In the PROLONG-9FP clinical trial programme, rIX-FP showed an improved pharmacokinetic profile compared with standard FIX products, allowing a prolonged dosing interval in patients with haemophilia B. A phase 3b extension study is evaluating the long-term safety and efficacy of rIX-FP; interim results are available after approximately 3 years of treatment.

Methods: Patients received prophylaxis with rIX-FP on a 7- (25-50 IU/kg), 10- or 14-day (50-75 IU/kg) dosing regimen; dosing interval could be changed at any 6-month follow-up. Patients ≥18 years old could switch to a 21-day regimen at a dose of 100 IU/kg if well controlled on a 14-day regimen. The primary outcome was the number of patients who developed FIX inhibitors. Secondary outcomes included annualised spontaneous bleeding rate (AsBR) and adverse events.

Results: At the data cut (March 2017), 59 previously treated adult/adolescent patients (≥12 years) and 24 paediatric patients (<12 years) had enrolled in the study (mean time on study: 29.8 months). In total, 79% of patients ≥12 years switched from a 7-day interval to a 10- (n = 12), 14- (n = 26) or 21-day interval (n = 11). Two patients starting 21-day dosing switched back to a 14-day interval to reduce their bleeding frequency. At the data cut, 25% of paediatric patients had an extended dosing interval of 10 (n = 1) or 14 days (n = 5). Four paediatric patients who started dosing intervals of 10 or 14 days switched back to shorter intervals to maintain lower bleeding rates. In adults, the median (Q1, Q3) AsBR for 7-, 10-, 14- and 21-day regimens was 0.33 (0.00, 2.39), 0 (0.00, 0.68), 0.26 (0.00, 1.54) and 0 (0.00, 0.45), respectively. In paediatric patients, the median AsBR for 7-, 10- and 14-day regimens was 0 (0.00, 0.59), 0 (0.00, 3.06) and 0.75 (0.00, 2.86), respectively. Seventy-seven (92.8%) patients had at least 100 exposure days (EDs) to rIX-FP (median EDs: 165). No patient had developed inhibitors or antibodies to rIX-FP.

Discussion/Conclusion: These results demonstrate the long-term efficacy and tolerability of prophylaxis with rIX-FP. For selected patients, rIX-FP allows extended treatment intervals of 21 days in adults and 10 and 14 days in children.

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P091 | Medical care for patients with congenital factor VII deficiency

E. Yakovleva[1,*]; N. Konyashina[2]; L. Gorgidze[2]; M. Kumskova[1]; O. Dimitrieva[1]; E. Likhacheva[1]; M. Protasov[3]; G. Mishin[4]; N. Sadykova[4]; N. Zozulya[1]

[1]Department of coagulation disorders; [2]Express laboratory; [3]Department of surgery; [4]Department of reconstructive orthopedic surgery for hemophiliac patients, National Research Center for Hematology, Moscow, Russian Federation

Introduction: Congenital FVII deficiency is a rare bleeding disorder with an estimated incidence of 1 in 500000. There is a variable spectrum of bleeding manifestations ranging from epistaxis to life-threatening hemorrhages. Comorbidities in patients with congenital FVII deficiency are an issue. Treatment of these patients is a complex task and requires following the strategy of hemostatic therapy and cooperation with other professionals.

The aim: to describe the medical care for patients with congenital FVII deficiency at the National Research Center for Hematology.

Methods: We followed up 72 patients with congenital FVII deficiency. There are two options to manage patients with FVII deficiency in our Center. The outpatient care in the Department of coagulation disorders includes diagnosis, consultation, follow-up, and hemostatic therapy. The inpatient care is carried out in the Surgery and Orthopedic/Traumatology departments. Gynecological, urological and dental assistance is also available.

Results: Since 2017, 23 patients have been referred. Seventeen of them were referred for the first time. According to the lab results and clinical manifestations, 3 patients have a severe clinical phenotype (FVII 1%>7%), 15 patients have moderate to mild clinical phenotypes (FVII 2-62%) and 5 patients are asymptomatic (FVII 4-52%). The range of medical care performed is as follows: teeth extraction, gynecologic surgery, left hip joint arthroplasty, osteosynthesis of tibia, hemorrhoidectomy, pregnancy care. To manage or prevent the hemorrhagic syndrome we used the recombinant activated factor VII in different doses and regimens.

Discussion/Conclusion: Patients with congenital FVII deficiency need lifelong observation by hematologist for control of hemorrhagic syndrome. Moreover, comorbidities in patients with congenital FVII deficiency demand the cooperative work with other specialists (in cases of surgery, extraction of teeth, pregnancy or delivery) and the individualized hemostatic therapy.

Disclosure of Interest: None declared.

P092 | Functional outcome measures in pediatric patients with haemophilia: Prospective observational study

E. Forneris*; on behalf of Dr. Mauro Pagliarino, Dr. Irene Ricca, Dr. Berardino Pollio

Regional Reference for Inherited Bleeding and Thrombotic Disorders in Pediatric Age, Città Della Salute e Della Scienza, Turin, Italy

Introduction: Identification of clinical outcome measures is necessary in order to allow clinicians to analyse in detail the global status of musculoskeletal system and, subsequently, to design a personalized therapeutic-rehabilitative program. Nowadays, there is no validated functional assessment so it emerges the need to create an assessment tool able to define the clinical functional status of the musculoskeletal system that can be used in everyday clinical practice.

Methods: a prospective observational study of 12 months was defined, according with these two inclusion criteria: haemophilia

diagnosis and age between 6 to 18 years old. Overall, 43 patients afferent to the "Regional Reference Centre for Haemorrhagic and Thrombotic Hereditary Diseases in the Pediatric Age" (Turin- Italy) were included.

Each patient is given the following protocol performed by experienced physiotherapist. Baseline data include general characteristics (age), disease profile (severe, moderate, mild haemophilia), treatment (primary prophylaxis, on-demand, immune tolerance induction), compliance (yes or no), joint history (target joint/Annual Bleeding Rate -ABR), anthropometric data (weight, height, BMI index), musculoskeletal system clinical (Haemophilia Joint Health Score –HJHS-, joint test (°) and Manual Muscle Testing of hip, knee, ankle, elbow) and functional assessment (G-sensor, Free walk system by BTS): walk, time up & go and six minutes walking test analysing temporo-spatial parameters; PedHal (%).

Results: processing of the results obtained from the study and data statistical analysis (Nonorm test). Results show a statistically significant correlation between the following data: age starting prophylaxis and walking test (*P* value 0.009), six minutes walking test (*P* value 0.013), ABR (*P* value 0.023) and HJHS (*P* value 0.001); residual activity of factor (%) and HJHS (*P* value 0.005); compliance and ABR (*P* value 0.001) and HJHS (*P* value 0.001).

Discussion/Conclusion: Our data suggest that a systematic clinical functional assessment could be a valid tool to improve the quality of patient clinical management, even in those subjects whose ABR and HJHS are zero, preventing the main complication of musculoskeletal system, as to monitor the clinical-functional status over the time.

Disclosure of Interest: None declared.

P093 | Hemostatic profile in people with moderate to severe hemophilia A

E. Sueldo[1,*]; A. Baques[2]; P. Donascimento[2]; M. Arias[1]

[1]*Hematology Laboratory;* [2]*Hemophilia, UNIDAD ASISTENCIAL POR MAS SALUD DR. CESAR MILSTEIN, Ciudad Autonoma de Buenos Aires, Argentina*

Introduction: Hemophilia is a rare disorder in which your blood doesn't clot normally because it lacks sufficient blood-clotting proteins (clotting factors).

Objective: To compare the hemostatic profile of people with moderate or severe hemophilia A (MHA and SHA respectively) and to assess whether the presence of reactive hepatitis C markers affects the hemorrhagic behaviour of people with SAH.

Methods: 307 samples of people with Hemophilia (PWH): 116 MHA samples; 46 ± 14 years of age, 191 SHA samples; 48 ± 15 years of age.

Hemostasis parameters evaluated: TP (PT-Fibrinogen HS Plus), APTT (APTT-SP), parameters of the APTT-SP waveform (MAX1: maximum peak of the first derivative: velocity of clot formation,MAX2: maximum peak of the second derivative: acceleration), Fibrinogen (FIB), FVIII:C and other coagulation factors, vWF:Ag, D dimer (DD), Protein C (PC), Free PS (PSL), Antithrombin (AT).

In addition, SHA patients were discriminated: with and without reactive markers for Hepatitis C

ACL TOP 300 Instrumentation Laboratory.

Results: SHA: APTT (sec) 98 ± 9, FVIII:C (%) 0.5 ± 0.4, MAX1 (dAbs/dt) 53 ± 37, MAX2 (dAbs2/dt) 44 ± 21, FIB (mg/dL) 319 ± 99, vWF:Ag (%) 151 ± 80, DD (μg/mL) 0.9 ± 1.6, AT (%) 97 ± 21, PC (%) 93 ± 29, PSL (%) 91 ± 22. MHA: APTT 65 ± 12, FVIII:C 2.8 ± 1.2, MAX1 115 ± 45, MAX2 126 ± 63, FIB 327 ± 147, vWF:Ag 156 ± 77, DD 0.5 ± 0.8, AT 100 ± 17, PC 100 ± 29, PSL 88 ± 23. SHAR: APTT 102 ± 19, FVIII:C 0.5 ± 0.4, MAX1 47 ± 36, MAX2 39 ± 19, FIB 316 ± 105, AT 95 ± 23, PC 90 ± 32, PSL 85 ± 20. SHANR: APTT 89 ± 18, FVIII:C 0.6 ± 0.4, MAX1 68 ± 37, MAX2 54 ± 21, FIB 325 ± 86, AT 103 ± 14, PC 99 ± 23, PSL 102 ± 22. TP and other coagulation factors were normal or border-line without significant differences between SHA and MHA

Discussion/Conclusion: There were differences between SHA and MHA in APTT, FVIII: C, MAX1, MAX2, but there were no in PC, PSL, AT, vWF: Ag, Fibrinogen, DD, which means that the studied PWH's hemorrhagic pattern and their velocity and acceleration values are only due to the factor VIII deficiency, the latter are lower as the deficit of the factor VIII increases. There were significant differences in AT and PSL levels but no differences in PC levels between SHAR and SHANR. SHAR had lower levels of AT and PSL and significant differences in velocity and acceleration than SHANR, probably by slight deficiencies of the other coagulation factors associated with this comorbidity

Disclosure of Interest: None declared.

P094 | Intracranial hemorrhage in four infants with different congenital factor deficiencies

E. Turkkan

Pediatric Hematology, Okmeydani Egitim ve Arastirma Hastanesi, Istanbul, Turkey

Introduction: Intracranial hemorrhage (ICH), is a rare but a life-threatening manifestation of inherited deficiencies of coagulation factors (DCF). In this article, we report 4 young patients presenting with ICH who were subsequently diagnosed with hereditary DCF.

Methods: The patients were 1 day, 3 months, 2 months and 14 days old, respectively. All patients were full-term infants, 3 with caesarean section and one with vaginal deliveries. No family history of bleeding disorders were reported by the all of the parents. In first two cases, Prothrombin time (PT) assays were severely prolonged, but partial thromboplastin time (PTT), platelet count, and bleeding times were normal. FVII assays showed that FVII levels of 24 and 0.3%, respectively. The third case, two months old girl infant, presented with recurrent seizures. At admission, her coagulation parameters were as follows: activated partial thromboplastin time was 173.9 seconds (control 33 seconds), prothrombin time 65.6 seconds (control 14 seconds) with international normalized

ratio of 5.6, platelet count was normal. Subsequent coagulation assays revealed a plasma factor V activity of 9% with all other coagulation factors in the normal range. And in the fourth case, 14 days old male newborn who presented with prolonged PTT, ICH and hydrocephalus, coagulation factor assays revealed a plasma factor VIII activity 0.4%.

Results: Computed tomography scans showed subdural hemorrhage in three of them and a parenchymal hematoma at the right superior fronto-parietal region in one case. We started rFVIIa therapy in two infants with factor FVII deficiency. The factor V deficient infant was managed conservatively with fresh frozen plasma (FFP) and supportive management. Transfusions of FFP and platelet concentrate caused a temporary normalization of coagulation profile and then the hematoma was drained. The patient with factor VIII deficiency (hemophilia A) was treated with factor VIII replacement therapy

Discussion/Conclusion: In our cases, the patients were delivered by caesarean except one case born in vaginal delivery without any perinatal problem. The hemorrhages differed in origin and responded quickly to replacement therapy. Pediatricians should be aware that ICH can be life threatening in hereditary CFD and some cases will have no family history

Disclosure of Interest: None declared.

P095 | Design of a phase 3, prospective, multicenter, open-label study of safety and hemostatic efficacy of rurioctocog alfa pegol in previously untreated patients <6 years of age with severe hemophilia A

E. Mullins[1,*]; C. Kefurt[2]; W. Engl[2]; S. Tangada[3]

[1]University of Cincinnati College of Medicine and Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States; [2]Shire, Vienna, Austria; [3]Shire, Lexington, MA, United States

Introduction: This ongoing study will investigate the safety, immunogenicity, and hemostatic efficacy of PEGylated recombinant factor VIII (FVIII), rurioctocog alfa pegol (SHP660, BAX 855; ADYNOVI™; Baxalta [part of Shire, Lexington, MA, USA]), for prophylaxis and control of bleeding episodes in previously untreated patients (PUPs) <6 years of age with severe hemophilia A (HA), providing information currently lacking for this population.

Methods: Patients eligible for this phase 3, prospective, open-label, multicenter study (NCT02615691): <6 years old; severe HA (FVIII <1%); <3 exposure days to antihemophilic factor (recombinant), SHP660, or plasma transfusion. Exclusion criteria: FVIII inhibitor history or presence at screening (titer ≥0.6 BU/mL using the Nijmegen modification of the Bethesda assay); diagnosis of hemostatic defect other than HA; history of treatment with any other FVIII concentrates; body weight <5 kg at baseline; platelet count <100 000/mL; severe renal impairment; or severe chronic hepatic dysfunction. Patients receive SHP660 treatment either on-demand at 10-80 IU/kg if <3 years of age with <2 joint bleeds at any time, or prophylactically at 25-80 IU/kg ≥1/week. Prophylaxis can be initiated at any time but must be initiated before the age of 3 years or once the patient has had 2 joint bleeds, whichever occurs first.

Results: The study has a planned completion date in 2023. Primary endpoint: incidence of FVIII inhibitor development. Secondary endpoints include: occurrence of adverse events and serious AEs; development of binding IgG and IgM antibodies to FVIII, PEG-FVIII, and PEG; annualized bleeding rate; number of infusions required per bleeding episode; weight-adjusted consumption of SHP660; overall hemostatic efficacy for prophylaxis at 24 hours after initiation of bleed treatment and at resolution; and the incremental recovery of SHP660 at baseline and over time. Exploratory endpoints include epigenetic analysis of immune cell populations (T cells, NK cells etc.), to understand the influence of these cells on FVIII inhibitor development.

Discussion/Conclusion: Results from this study will provide clinical data on the safety and efficacy of SHP660 in PUPs, adding to evidence from previously treated children and older patients with severe HA.

Disclosure of Interest: E. Mullins Consultant for: Shire, Speaker Bureau of: Shire, C. Kefurt Shareholder of: Shire, Employee of: Shire, W. Engl Shareholder of: Shire, Employee of: Shire, S. Tangada Shareholder of: Shire, Employee of: Shire.

P096 | Treatment of severe haemophilia A and clinical outcome: 2 years evaluation from a Portuguese centre

E. Cruz*; M. Coutinho; F. Leite; M. Pereira; S. Morais

Clinical Haematology, Santo António University Hospital, Porto, Portugal

Introduction: Haemophilia treatment varies significantly across countries in Europe and inside each country between different centres. Data about different treatment regimens, effectiveness of treatment and clinical outcomes are only reported by few centres and data are frequently variable between studies. Therefore, information is difficult to compare and may not reflect the real-world of haemophilia care.

The objective of this work was to evaluate treatment regimens and clinical outcomes in severe haemophilia A in a single Portuguese centre, in the last two years (2016/2017). This may contribute to increase knowledge about haemophilia treatment in Portugal.

Methods: Only persons with severe haemophilia A were included (44 in 2016 and 45 in 2017). Patients with inhibitors were excluded (2 in 2016 and 3 in 2017). Parameters evaluated were treatment regimens (prophylaxis, on demand and regular prophylaxis), amount of FVIII (IU/Kg/person) and clinical outcomes (ABR-annual bleeding rate and AJBR-annual joint bleeding rate).

Results: Prophylactic treatment increased in 2016 from 50% to 63% of patients in 2017. This was reflected in the FVIII amount used, that was in average 91679 IU/person (1627 IU/Kg) in 2016 and

114506 IU/person (1918 IU/Kg) in 2017. The mean (min-max) prescribed treatment in all forms of prophylaxis (n = 17) was 2407 IU/Kg (1083-5813), in regular prophylaxis (n = 12) 3019 IU/Kg (1808-5813) and 934 (33-2325) in on demand (n = 17), in 2016; these values were 2586 IU/Kg (1068-6476) in prophylaxis (n = 25), 2961 IU/Kg (1355-6476) on regular prophylaxis (n = 17) and 490 (31-2316) in on demand (n = 16), in 2017, respectively. In 2016, medians ABR and AJBR were 8 and 4 to any prophylaxis, 6.5 and 2.5 in regular prophylaxis and 9.5 and 7 in on demand treatment; in 2017 medians ABR and AJBR were 5 and 4 to all prophylaxis, 3 and 1 in regular prophylaxis and 7 and 3 in on demand.

Discussion/Conclusion: From 2016 to 2017 there was an increase of 25% in FVIII use to treat severe haemophilia A and there was also an increase in the number of patients under prophylaxis. Not only more adult patients were on prophylaxis, but that was more regular, with impact in the clinical outcomes, with decreased in ABR and AJBR, and median values similar to those reported by other European centres. These results may contribute to increasing knowledge about haemophilia care in Portugal and in real-world.

Disclosure of Interest: None declared.

P097 | Evaluation of hemorrhagic variability in congenital coagulopathies using the ISTH-BAT score

S. Ferreira; M. Dias; M. Carneiro; F. Leite; S. Morais; E. Cruz*

Clinical Haematology, Santo António University Hospital, Porto, Portugal

Introduction: Bleeding manifestations in congenital bleeding disorders are variable and difficult to evaluate. The ISTH-BAT (International Society on Thrombosis and Haemostasis - Bleeding Assessment Tool) is a bleeding score (BS) that aims to standardize haemorrhagic symptoms.

The objective of this work was to determine the bleeding variability in people with congenital coagulopathies (PWCC) using the questionnaire ISTH–BAT.

Methods: 109 PWCC were included: 43 with von Willebrand disease (vWD), 42 with platelet disorders (PD), 5 with factor deficiencies and 9 with fibrinolysis defects (FD). The average age was 35 ± 18 (minimum-maximum 1-81), with predominance of adults (>18 years) (n = 87, 80%) and women (n = 78, 72%).

Results: Overall mean of BS was low but with great variability (6.1, minimum-maximum 0-30) with women presenting higher BS in relation to men (6.8 vs 4.4) and adults towards children (6.6 vs 4.2). No significant differences were found in mean BS according to different pathologies. Regarding the type of bleeding, and considering the two more numerous pathologies (vWD and PD), the most frequent bleedings were from the oral cavity (74% and 66%) and ecchymosis (71% and 63%), followed by menorrhagia (56% and 58% of women) and epistaxis (44% and 63%); with different frequencies between these 2 subgroups are the post-surgical bleedings (32% and 13%) and postpartum hemorrhage (28% and 12% of women). In terms of severity, the epistaxis and postpartum bleeding appear more severe in vWD (59% and 71%) than in PD (25% and 33%, respectively). In FD bleeding, the profile is slightly different, with bruises (88%), menorrhagia (88%) and post-surgical bleeding (63%), being the most prevalent; curiously, these ones were all severe.

Discussion/Conclusion: This study confirms that women and adults have higher BS than men and children, respectively, as expected. The most prevalent haemorrhagic symptoms were mucocutaneous (oral cavity bleeding, bruising and epistaxis), however, in comparison with PD, vWD is associated with a higher frequency and more severe post-surgical and postpartum bleedings. Despite the limited number of people with FD to allow definitive conclusions, the results point to an increased frequency and severity of post-surgical bleedings. The BS is easily applicable in clinical practice and allows classification of patients regarding bleeding manifestations.

Disclosure of Interest: None declared.

P098 | Successful immune tolerance induction rescue (ITI-R) with simoctocog alfa (rHFVIII) in hemophilia A patients and high-titer inhibitors: Three case reports

E. Zanon[1,*]; S. Pasca[1]; R. Marino[2]; I. Ricca[3]; B. Pollio[3]

[1]Hemophilia Center, University Hospital of Padua, Padua; [2]Hemophilia and Thrombosis Center, University Hospital of Bari, Bari; [3]Pediatric Hemophilia Center, Città della salute e della scienza di Torino, Turin, Italy

Introduction: The appearance of inhibitors (INH) is the most serious complication in hemophilia A (HA). The primary objective is their eradication. When the primary ITI fails, another ITI-R is often started

Methods:

We report three successful cases of ITI-R with simoctocog alfa:

Results: Case-1: Adult with moderate HA who developed INH after surgery and concomitant switch to another concentrate. First ITI was started with pdFVIII/vWF at 200 IU/kg/day, INH progressively decreased, reaching 15 BU, but without ever disappearing. This ITI was stopped after 19 months. A second ITI was then tried with high dose regimen of moroctocog-alfa, but also in this case the mean INH remained steadily high (21 BU) and this treatment was considered a failure after 15 months. A third ITI-R was then started with simoctocog-alfa, at 200 IU/kg/day. INH progressively decreased and 7 months later disappeared Case-2: Child, with severe HA, initially treated on demand, developed a transient low titer INH (3 BU), which quickly disappeared. At the age of 42 months he was put on prophylaxis with moroctocog-alfa, and one year later developed a new low titer INH. A first ITI was then started with this rFVIII 100 IU/kg/day, reduced to 50 IU/kg three times a week when the INH seemed to disappear. Subsequently the ITI was reported to 200 IU/kg/day again, due to INH recurrence. INH reached 103 BU, and the ITI was considered failed 57 months later. An ITI-R was then started with simoctocog-alfa

200 IU/kg/day, INH progressively decreased and disappeared 22 months from the ITI-R onset. Case-3: Child with severe HA put on prophylaxis with octocog-alfa at 16 months after two serious haemorrhagic events. He developed a high titer INH after 10 ED (32 BU). A first ITI with octocog-alfa 200 UI/kg/day was started when the INH decreased <5 BU, reduced to 100 IU/kg/day and subsequently every other day when the INH seemed to disappear, but it increased again, and this ITI was considered failed after 36 months. An ITI-R with simoctocog-alfa 200 IU/kg/day was then started. The INH disappeared 6 months later

Discussion/Conclusion: Simoctocog-alfa could be an important option in treating patients with HA and high-titer INH particularly in those who underwent one or more failed ITI previously. More data is requested to confirm these results

Disclosure of Interest: None declared.

P099 | Coronary artery bypass surgery in three patients with haemophilia

F. Sahin[1,*]; F. D. Atilla[1]; Z. Demirci[2]; P. Ozturk[3]; M. Ozbaran[3]

[1]Hematology; [2]Internal Medicine; [3]Cardiothoracic Surgery, Ege University, Izmir, Turkey

Introduction: Life expectancy in haemophilia is same comparing to general population. The aging patient with haemophilia faces many challenges particularly atherosclerosis. Cardiovascular causes of mortality occur at a similar frequency as in the general population, but the contributing risk factors in haemophilia are incompletely understood. Existing literature on this issue is lacking, and there is not a guided way of appropriate treatment of these complications.

Methods: Here we present three cases with haemophilia treated with the same protocol by a multidisciplinary team which facilitated successful coronary artery bypass grafting (CABG) surgery. One patient with mild haemophilia A (47 years old), one with mild haemophilia B (45 years old) and one with severe hemophilia A (49 years old) who have known coronary artery disease and identified multivessel disease, CABG was considered by multidisciplinary team.

Results: All the patients were treated with bolus factor concentrates due to pharmaco-kinetic analyses could not be performed. Inhibitory antibody testing of factor 8 or 9 assessed at least 1 day prior to operation. Patients with haemophilia A and B received a factor concentrates bolus of 50 IU and 100 IU per kg, respectively within 1 hour of induction as a preoperative care plan. During operation for another bolus was given which consisted of 500 IU and 1000 IU per liter of intraoperative blood loss for haemophilia A and B respectively. Additional post-operative factor administration was performed according to 4th hour factor level for maintaining the target factor level. Bolus infusion of 500 mg tranexamic acid were administered every 8 hours for the first five days. Target FVIII activity level was 100-120 IU/dL mL for the first 48 h, followed by 80-100 IU/dL for post-operative days 2-5 and 60-80 IU/dL for post-operative days 6-10. APTT was monitored every 4 times for the operation day and then every 12 hours thereafter. No patients developed postoperative thrombotic, hemorrhagic of infective complications.

Discussion/Conclusion: In this case series, CABG surgeries was managed by a protocol which quoted by Bhave P et al. (J Card. Surg. 2015;30:61-69) established to optimize perioperative management. We did not observe any adverse events during and after CABG surgeries. With attentive monitoring and appropriate follow-up patients with haemophilia can safely undergo invasive cardiac procedures.

Disclosure of Interest: None declared.

P100 | Molecular analysis and detection of relationship between genotype and phenotype in patients with hemophilia B in Iran

F. Zaker*; M. shakori; A. dorgalaleh

Iran University of Medical Sciences, Tehran, Iran, Islamic Republic Of

Introduction: Hemophilia B is one of the common bleeding disorders that more than 1000 people in Iran are affected. Mutation in factor IX gene result in bleeding symptoms. According to FIX activity level in plasma, disorder classified to 3 levels. In Sistan and Baluchestan province due to high prevalence of family marriage, probability of birth of patient is higher and identification of common regional mutations can prevent such an event. The aim of study is to investigate phenotype and genotype of patient in this province.

Methods: This study has done on 20 hemophilic male patients range age between 1- 16 years old. Informed consent was obtained from all patients and normal controls. Over 90% patients had consanguineous marriage. Disease had established in hemophilia center of Sistan and Baluchestan province according to laboratory tests such as high PT, PTT and factor assay. DNA samples extracted according to standard protocols and all exons and promoter amplified with PCR and sequenced with direct method. Data analysis was performed using Chromas and CLC software.

Results: These mutations accompanied with severe clinical manifestation including epistaxis, haematoma, haemarthrosis etc. Factor IX level was measured less than 1% of normal. In 18 patients mutations were detected and all had point mutations without deletion. 10 mutations were missense and 8 were nonsense. 18 mutations (90%) had occurred in exons and 2 (10%) likely in intron that not identified. The sequence data showed 12 mutations in exon 8 (892 C>T, 1007 T>A, 880 C>T, 1113 C>A), 4 in exon 4 (304 T>C), and 2 in exon 2 (191 G>A).

Discussion/Conclusion: Different mutations can cause hemophilia B disease. There is a correlation between the type of mutation and phenotype of the disease. These findings can be used to create a national database.

Disclosure of Interest: None declared.

P101 | The constitutional deficit in factor VII hematology department experience Annaba Chu

F. Grifi*; A. Djenouni

Hematology -medical department- Badji Mokhtar University -Annaba Algeria, Annaba Algeria, Algeria

Introduction: Factor VII deficiency was described for the first time in 1952 by Dr. B. Alexander. It is an abnormality of coagulation that can be qualitative and / or quantitative, with autosomal recessive inheritance. It is characterized by phenotypic and genotypic heterogeneity. The clinical expression is very variable and the severity of the hemorrhagic syndrome is not correlated with the plasma level of the factor.

Methods: The objective of our work is to specify the epidemiological, clinico-biological and evolutionary characteristics of patients followed at our level. This is a retrospective descriptive study, spanning from September 2008 to September 2018 and covering a series of 32 cases of congenital factor VII deficiency. The studied parameters include: Epidemiological data, hereditary character, clinical, biological, therapeutic and evolutionary data.

Results: The average age of discovery of our cohort was 23 years with extremes of [06-75 years], the current average age is 32 years with extremes of [15-80 years]. The sex ratio is 1.12. The notion of second degree consanguinity is found only in 03 families. Similar cases are found in 06 families with an average of 2 cases per family.

The circumstances of discovery are variable:

Incidental discovery during a preoperative assessment.

During a family survey.

Cutaneous and mucous haemorrhagic syndrome.

The clinical symptomatology is variable:

Complete absence of clinical signs in 10 patients.

A hemorrhagic syndrome:

Epistaxis and gingivorrhagia of low abundance with repetition: at 04 patients.

Hematuria: 02 patients.

Haemarthrosis: 01 patient.

Menorrhagia of great abundance: 01 patient.

From a biological point of view, the factor VII level is variable [<10%-52%]. The therapeutic management, based on the recombinant factor VII (Novo Seven), the administered dose is variable of 15-30 µg / kg. The indications of this substitution are: dental extractions, surgical procedures, menorrhagia, haemarthrosis.

Discussion/Conclusion: Factor VII deficiency of coagulation is a heterogeneous group both clinically and biologically, the symptomatology is often uncorrelated with the level of residual coagulant activity, its discovery is often fortuitous and the preventive treatment is difficult in asymptomatic patients.

Disclosure of Interest: None declared.

P102 | Assessment of patients with von Willebrand disease with ISTH-BAT and PBQ scores

F. B. Belen[1]; E. G. Umit[2,*]; Y. Zengin[3]; M. S. Evim[4]; E. Unal[5]; H. M. Ozbas[6]; C. Acipayam[7]; on behalf of Turkish Hematology Association-Hemophilia Masterclass Working Group

[1]Department of Pediatric Hematology and Oncology, Baskent University Faculty of Medicine, Ankara; [2]Department of Hematology, Trakya University Medical Faculty, Edirne; [3]Department of Biostatistics, Baskent University Faculty Medical Faculty, Ankara; [4]Department of Pediatric Hematology and Oncology, Uludag University Medical Faculty, Bursa; [5]Department of Pediatric Hematology and Oncology, Erciyes University Medical Faculty, Kayseri; [6]Department of Hematology, Giresun University Medical Faculty, Giresun; [7]Department of Pediatric Hematology and Oncology, Kahramanmaras Sutcuimam University Medical Faculty, Kahramanmaraş, Turkey

Introduction: The evaluation of bleeding symptoms is the crucial step in diagnosis of bleeding disorders. Bleeding scores in both adults (ISTH-Bleeding Assessment Tool) and children (Pediatric Bleeding Questionnaire-PBQ) are developed in order to standardize the bleeding symptoms and guide the diagnosis. We aimed to evaluate the bleeding phenotype of patients with Von Willebrand Disease (VWD) patients with ISTH-BAT and PBQ scores and investigate the correlation of Von Willebrand Factor levels and bleeding scores of the patients.

Methods: A total of 62 patients aged between 3-61 ages with the diagnosis of VWD (54 VWD Type 1 and 8 VWD Type 3 patients) were included in the study. ISTH-BAT score was administered to patients ≥18 years old, and PBQ was administered to pediatric (3-18 years) patients face to face or via phone calls. The von Willebrand factor (VWF) levels and ristocetin cofactor activity (VWF:Ricof), FVIII levels were reviewed retrospectively from hospital records. Cut off point for positive score was accepted as ≥2. The data were analysed in SPSS v17.0 programme.

Results: Fifty two of the patients (83.9%) were female, and 10 (16.1%) were male patients. The median age of Type 1 VWD patients was 28 (3-61 ages, minimum-maximum), 17 (6-30 ages, minimum-maximum). The median bleeding score in Type 1 VWD and Type 3 VWD was 3 (0-19) and 16 (9-27) respectively ($P < 0.05$). The median Von Willebrand factor (VWF) level was found to be 22.3 IU/dL (2-50 IU/dL) in Type 1 VWD and 2.5 IU/dL (0-10 IU/dL) in Type 3 VWD. Epistaxis, superficial bleedings, bleeding from minor wounds, oral bleeding, umbilical bleeding, muscle hematoma and hemarthrosis were found to be statistically significant in showing dependence between diagnosis status (whether VWD Type 1-3) and bleeding symptoms ($P < 0.05$). Rate of positive scores for bleeding after tooth extraction, postsurgical bleeding, menorrhagia and CNS bleeding were not found to be different in the two groups ($P > 0.05$). A negative statistically significant correlation was found between VWF and VWF:Ricof levels and total score positivity in both groups ($P < 0.05$).

Discussion/Conclusion: Both bleeding score assessments, ISTH-BAT for adult patients and PBQ for pediatric patients are found to be

useful in evaluation of bleeding symptoms of our patients. The total bleeding score is negatively correlated with VWF and VWF:Ricof levels.

Disclosure of Interest: None declared.

P103 | Von Willebrand factor inhibitors developed in type 3 von Willebrand disease

F. Megdiche[1,*]; O. Kassar[2]; S. Hdiji[2]; L. Mbarek[1]; M. Charfi[2]; M. Elloumi[2]; C. Kallel[1]

[1]*Laboratory of Hematology, Hospital University Habib Bourguiba, Sfax-Tunisia, Hospital University Habib Bourguiba, Sfax-Tunisia;* [2]*Department of clinical Hematology, Hospital University Hedi Chaker, Sfax-Tunisia, Hospital University Hedi Chaker, Sfax-Tunisia, Sfax, Tunisia*

Introduction: The development of von Willebrand alloantibodies (anti-VWF) is an uncommon complication that is possibly noticed in 5%-10% of patients with von Willebrand disease type 3 (VWD3), after receiving a plasmatic substitution therapy. We describe the case of a young VWD3 woman, in whom an anti-VWF was strongly suspected and we discuss the corresponding diagnostic procedure, the therapeutic approach chosen and the reported clinical course.

Methods: A 32-year-old woman affected by VWD3 was diagnosed at the age of two years old. During her childhood, she suffered from repeated epistaxis and as she grew older, she started suffering from menometrorrhagia. She was then undergoing a substitution therapy, upon request, starting with cryoprecipitates and then with plasmatic (FVIII / FvW) (Immunate®) since 2012.

Results: In 2018, she complained of a sudden onset of an ankle's hemarthrosis and of a persistent pain in the elbow, five days after receiving plasmatic concentrates (FVIII/ FvW) testifying to an inefficiency of the treatment. An anti-VWF was then suspected. The inhibitor screening test was positive (using the bethesda Nijmegen method) with an absence of both anti-Factor VIII antibody and lupus anticoagulant (LA). The anti-VWF titration was about 5.8 Bethesda Unit (BU). In addition, a recovery test of injected plasmatic concentrates (20 IU / kg FvW and 40 IU / kg FVIII) was carried out with a FVIII recovery rate of 1.8%/U/kg and a total absence of recovery for the FvW was noticed. The patient had then received a bypassing agent (rFVIIa-Novoseven®) at a dose of 5 mg (twice a day) to treat the bleeding episodes and an immunosuppressor (Azathioprine-Imurel®) to eradicate the inhibitors. Eight months later, inhibitor testing showed a decrease of the anti-VWF titer to 0.7 BU.

Discussion/Conclusion: The development of inhibitors in patients with VWD3 is really underestimated. In the case of an ineffective treatment, the presence of alloantibodies should be suspected. Many technical difficulties could be encountered during the screening and titration of these inhibitors. As a consequence, the diagnostic protocol is still not well defined for these patients. Besides, no consensus exists up to this moment to standardize this research. It would be, then, interesting to search for inhibitors using two different methods which are the bethesda Nijmegen method and the Enzyme Linked ImmunoSorbent *Assay* (ELISA).

Disclosure of Interest: None declared.

P104 | Single centre experience in acquired haemophilia A over five years

F. D. Atilla*; Z. Demirci; F. Sahin

Internal Medicine/Hematology, Ege University, IZMIR, Turkey

Introduction: Acquired haemophilia A (AHA) is a rare, autoimmune disease which presents suddenly started hemorrhages without any personal or family history. Approximately 50% of reported cases are still idiopathic and the rest is associated with other conditions, mainly underlying malignancies, autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus, drug administration and postpartum period.

Methods: Here we report five cases of AHA which have been diagnosed in the last five years.

Results: The mean follow-up was 26 months (range 8-40). Underlying etiologies included followings; idiopathic in one case, postpartum in two cases, infection in one case and malignancy in the rest one. The median age was 37 years (24-84). Four patients had bleeding at diagnosis. The sites of bleeding were; muscular 20%, urinary and gastrointestinal tract 20%, post-partum bleeding 40%. Recombinant activated factor VII (rFVIIa) was used in one patient and activated prothrombin complex concentrate (aPCC) was used in two patients. The median APTT was 58 seconds (46-62) and hemoglobin was 8.5 g/dL (5.7-10.8). Median FVIII was detected 1.5% (0.7-12). Inhibitor activity was titrated by Bethesda method at diagnosis and median value for inhibitor titer was 53.7 BU/mL (8-117.7). All patients received initial therapeutic of glucocorticoids as a monotherapy. One patient had 8 BU/mL FVIII inhibitor and there was not any bleeding symptom. In this case AHA was attributed to atypical pneumonia and after initiating glucocorticoids APTT, FVIII and inhibitor levels were came back to normal range. Four patients received red blood cell transfusion with a median value of 3.5 units (3-5). After initiation of first line treatment four of five patients achieved full recovery. Adequate response was not achieved in an 84-year-old male patient and Rituximab was used as a second line therapy. He achieved partial response with values of APTT 56 s, FVIII 6.3% and FVIII inhibitor 1.4 BU/mL. The underlying etiology could not be revealed. The mean time from symptom onset to diagnosis was 23 ± 15 days (median 22, range: 4-46).

Discussion/Conclusion: AHA is an uncommon and important cause of potentially serious bleeding. It should be considered in the differential diagnosis of patients with spontaneous hemorrhage and isolated prolongation of the aPTT. Early suspicion and fast actions are required to gain a quick and definitive diagnose in patients with severe or life threatening bleeding.

Disclosure of Interest: None declared.

P105 | Genotype analysis by next generation sequencing in severe FXI deficiency patients: A single center experience

F. Riccardi; G. Quintavalle; A. Matichecchia; A. Coppola; G. F. Rivolta*; A. Tagliaferri

Regional Reference Centre for Inherited Bleeding Disorders – University Hospital of Parma, Parma, Italy

Introduction: Factor XI (FXI) deficiency (#612416) is an autosomal bleeding disorder characterized by decreased levels/activity of FXI protein in plasma (FXI levels <15-20 IU/dL). Bleedings usually occur after trauma or surgery and seem to be poorly correlated with FXI levels. Severe patients (prevalence ~1:10^6) are usually homozygotes or compound heterozygotes for a causative variant of FXI gene (*F11*, 4q35.2). In the FXI Deficiency Mutation Database are currently reported 192 disease causing variants

Methods: In this study, we reported molecular analysis of seven unrelated patients (P1-P7) (M/F = 5/2, age 21-66) from Hemophilia Centre of Parma (Italy) with inherited severe FXI deficiency (0.2-7.5 IU/dL). Two females had menorrhagia (P1) or post-partum hemorrhage (P2). Four males (P3, P5, P6, P7) were asymptomatic; the remaining (P4) had post-dental surgery bleeding. The molecular screening was performed on genomic DNA by Next-Generation Sequencing (NGS). Libraries were prepared with targeted sequencing method using TruSeq Custom Amplicon protocol. Massively sequencing was performed on MiSeq Illumina Instrument. Pathogenic variants were validated by Sanger sequencing

Results: All patients resulted compound heterozygotes/homozygotes. P1 had two recurrent causative nonsense variants: c.67C>T (Q23*) and c.403G>T (E135*). P2 had the same c.403G>T and a splicing defect c.595 + 3A>G that causes the skipping of the affected exon and intracellularly degradation of the protein. This splice site variant was detected also in P3, together with c.325G>A (A109T). This is located in the last position of exon 4 and abolishes the physiologic donor splice site. P4 had c.67C>T (Q23*) and an acceptor splice site novel variant c.219-1G>C. P5 had a nonsense c.403G>T and a missense c.449C>T (T150M) variant. Two novel changes were identified in heterozygosis in P6: c.943G>A (E315K) and c.1052C>A (S351K). Finally, in P7 was characterized a frameshift in homozygosis, c.1043dup (L348Ffs*11)

Discussion/Conclusion: This study confirm the presence of a compound heterozygote or homozygote *F11* genotype in severe patients showing a relationship between genotype and FXI activity. The poor bleeding tendency of these patients suggests the presence of different phenotype determinants in FXI deficiency. NGS is a useful and fast sequencing method for molecular screening. Finally, 3 novel variants were found

Disclosure of Interest: None declared.

P106 | Bleeding phenotype and baseline factor VIII activity in patients with non-severe hemophilia A—preliminary data of a retrospective cohort study

F. Kloosterman[1,*]; A. Abdi[1]; C. Eckhardt[1]; C. Male[2]; G. Castaman[3]; K. Fischer[4]; E. Beckers[5]; M. Kruip[6]; K. Peerlinck[7]; M. Mancuso[8]; C. Santoro[9]; C. Hay[10]; H. Platokouki[11]; J. van der Bom[12]; S. Gouw[1]; D. Hart[13]; C. Fijnvandraat[1]; on behalf of INSIGHT study group

[1]*Department of Pediatric Hematology, Immunology and Infectious Diseases, Emma Children's Hospital, Amsterdam UMC, location AMC, Amsterdam, Netherlands;* [2]*Department of Pediatrics, Medical University of Vienna, Vienna, Austria;* [3]*Center for Bleeding Disorders and Coagulation, Department of Oncology, Careggi University Hospital, Florence, Italy;* [4]*Van Creveldkliniek, University Medical Centre Utrecht, Utrecht;* [5]*Department of Hematology, Maastricht University Medical Center, Maastricht;* [6]*Department of Hematology, Erasmus University Medical Centre, Rotterdam, Netherlands;* [7]*Division of Cardiovascular Disorders, Haemophilia Center, UZ Leuven, Leuven, Belgium;* [8]*Angelo Bianchi Bonomi Haemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano;* [9]*Cellular Biotechnology and Haematology Department, Umberto I University Hospital of Rome, Rome, Italy;* [10]*Department of Hematology, Manchester University, Manchester Royal Infirmary, Manchester, United Kingdom;* [11]*Haemophilia Centre- Haemostasis Unit, "Aghia Sophia" Children's Hospital, Athens, Greece;* [12]*Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands;* [13]*The Royal London Hospital Haemophilia Centre, Barts and The London School of Medicine and Dentistry, London, United Kingdom*

Introduction: Severe hemophilia A (SHA) patients have an increased risk for inhibitor development during the first exposures to factor VIII (FVIII) concentrate. Novel treatment therapies, such as non-replacement therapy and gene therapy, have the potential to convert a severe phenotype into a mild phenotype. If previously untreated SHA patients would be treated with these therapies, it might postpone FVIII exposure, possibly deferring their risk for inhibitor development. Currently there is insufficient data on the natural course of non-severe hemophilia A (NSHA). Therefore, the aims of this study are to assess the timing of FVIII exposures and to calculate the Annualized Bleeding Rate (ABR) in NSHA.

Methods: We performed an analysis in the data of the INSIGHT case-control study that included NSHA inhibitor and non-inhibitor patients (FVIII baseline level 2-40 IU/dL). For inhibitor patients, data on FVIII exposure days (EDs) were collected until the onset of inhibitor development. In order to interpret these data to resemble the unselected complete cohort of the INSIGHT study, re-weighting with the inverse of the sampling fraction was used. We assessed the age at the first exposures to FVIII until the 20th ED in different categories of baseline FVIII level. Furthermore, we will analyze the ABR for spontaneous major bleeds. Sub-analyses will be performed based on year of birth and secular time periods for treatment strategies.

Results: For the current study we included 315 patients. In patients with a FVIII level between 2-5 IU/dl, the median age at the 1st ED was: 12 years (IQR 5-38), the median age at the 5th ED was: 17 years (IQR 6-41), the median age at the 10th ED was: 19 years (IQR

7-40) and the median age at the 20th ED was: 26 years (IQR 12-47). In patients with a FVIII level between 5-15 IU/dl the median age at the 1st ED was: 24 years (IQR 7-45), the median age at the 5th ED was 27 years (IQR 9-48), the median age at the 10th ED was 28 years (IQR 11-52) and the median age at the 20th ED was 29 years (IQR 14-58). The ABR results will be presented during the conference, as verification of the spontaneous bleeds is currently being performed.

Discussion/Conclusion: Our preliminary findings show that patients with a baseline FVIII level of 5-15 IU/dL had their first FVIII infusions at higher ages than patients with a baseline FVIII level of 2-5 IU/dL.

Disclosure of Interest: None declared.

P107 | Can effective bleeding control improve QOL for haemophilia patients with inhibitors?

F. V. M. Booth[1,*]; H. Levy[1]; J. Mahlangu[2]; F. Del Greco[1]

[1]*Catalyst Biosciences, South San Francisco, United States;* [2]*University of the Witwatersrand, Johannesburg, South Africa*

Introduction: Hemophilia A or B morbidity increases throughout life. Factor replacement treats or prevents bleeding episodes. Patients with Hemophilia A or B may develop neutralizing antibodies (inhibitors) vitiating such therapy. Hemophilia patients with inhibitors (HPWI) receive bypassing agents for treatment or prevention of bleeds. The very short half-life of bypass agents means episodic treatment for bleeds rather than prophylaxis, resulting in subjectively inferior quality of life (QOL), significantly higher mortality and worse musculoskeletal outcomes when compared to patients without inhibitors. QOL in hemophilia is evaluated by EQ-5D and Haem-A-QOL, and impaired activity with Haemophilia Activity List (HAL). There is little data on QOL of HPWI.

Methods: We studied Marzeptacog alfa (activated) (MarzAA) an engineered rFVIIa with 4 amino acid substitutions and enhanced biological properties: 6-7× greater potency than wild-type FVIIa and effective bioavailability given daily subcutaneously (SC) in HPWI with ABR >12. We evaluated the baseline scores of 8 subjects in the MAA-201 trial (MARZAAPOP) using Haem-A-QoL and HAL and compared the results to subjects with severe hemophilia but without inhibitors recruited into a long-term prophylaxis trial (A-LONG trial - ALONGREFPOP) and to published reference population baseline values.

Results: Mean baseline Haem-A-QOL summed score for ALONGREFPOP was 29.3 ± 15.7 contrasting sharply with a much worse mean baseline summed score of 42 ± 15.2 for MARZAAPOP in our trial. Using the more function-oriented HAL, MARZAAPOP mean baseline normalized summed score was an inferior activity of 54.0 compared with a reference population score of 69.2. In two subjects completing dosing, baseline normalized HAL scores compared to the score after 50 days of SC dosing showed improvement in 8 and 9 of the 10 domains respectively. Summed scores improved from 70 to 78 for one subject and from 43.8 to 60.5 in the other

Discussion/Conclusion: HPWI patients exhibit QOL scores worse than either of two non-inhibitor haemophilia reference groups representing a necessary opportunity for QOL improvement with effective prophylaxis. Preliminary indicators of improved QOL are encouraging but should be interpreted with caution.

Disclosure of Interest: F. Booth MA MSc BM BCh Consultant for: Catalyst Biosciences, H. Levy MD PhD Shareholder of: Catalyst Biosciences, Employee of: Catalyst Biosciences, J. Mahlangu MBBCH, MMed, FCPath Consultant for: Catalyst Biosciences, F. Del Greco Shareholder of: Catalyst Biosciences, Employee of: Catalyst Biosciences.

P108 | HOPE-B: study design of a phase III trial of an investigational gene therapy AMT-061 in subjects with severe or moderately severe hemophilia B

F. W. G. Leebeek[1,*]; G. Castaman[2]; N. S. Key[3]; S. Lattimore[4]; W. Miesbach[5]; S. Zelenkofske[6]; M. Recht[4]; S. Pipe[7]

[1]*Erasmus University Medical Center, Rotterdam, Netherlands;* [2]*Azienda Ospedaliera Universitaria Careggi, Florence;* [3]*University of North Carolina, Chapel Hill;* [4]*Oregon Health and Science University, Portland, United States;* [5]*University Hospital Frankfurt, Frankfurt, Germany;* [6]*UniQure Inc, Lexington;* [7]*University of Michigan, Ann Arbor, United States*

Introduction: Gene therapy for hemophilia B offers the potential to ameliorate disease severity with a single treatment through continuous endogenous production of FIX protein. Robust preliminary efficacy and safety results have been obtained in 10 patients (pts) with hemophilia B after treatment with AMT-060, an adeno-associated virus (AAV) serotype 5 vector containing a wild-type factor (F) IX gene, in an ongoing Phase I/II trial. At 1.5 years after a single dose of 2×10^{13} gc/kg (n = 5), stable FIX activity (mean 7.2%) was observed, without immune-mediated loss of FIX activity or inhibitor development. AMT-060 was modified to encode the highly active Padua FIX variant (AMT-061), which is expected to increase the activity/protein ratio by approximately 7-9 fold. The purpose of this Phase III trial is to demonstrate the efficacy of AMT-061 in terms of endogenous FIX activity and annualized bleeding rate, and to describe its safety profile in pts with hemophilia B

Methods: Open-label, single-dose, multi-center trial, with sites planned in the United States, the Netherlands, Germany, Denmark, Italy, Ireland, and other European countries. Participants will be adult males with FIX ≤2%, utilizing routine FIX prophylaxis, without history of FIX inhibitors, active hepatitis B or C, or uncontrolled HIV. Pre-existing AAV5 neutralizing antibodies (nAbs) will be assessed but not used as an exclusion criterion. Eligible pts will enter a prospective lead-in phase, during which FIX use and bleeding episodes will be documented. At the completion of the lead-in phase, eligibility will be re-confirmed and pts re-consented prior to receiving the single dose of AMT-061. Post-treatment, pts will be followed for 5 years

Results: Assessments during the post-treatment follow-up phases will include FIX activity, bleeds, use of FIX replacement, adverse events, FIX inhibitors, transaminases, and AAV5 nAbs. Pt reported outcome questionnaires and joint status will also periodically be determined

Discussion/Conclusion: The modification of AMT-060 to AMT-061 with FIX Padua is anticipated to achieve comparable levels of FIX protein but result in higher FIX activity, while preserving the safety profile and absence of T-cell activation observed with AMT-060. By not excluding patients from participating in the study based on nAb status, safety and efficacy can be evaluated in a broader population of patients.

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P109 | Efficacy and safety of prophylaxis with recombinant von Willebrand factor (VWF) in severe von Willebrand disease (VWD): Design of a prospective, phase 3, open-label, international multicenter study

F. W. Leebeek[1,*]; K. Kavakli[2]; F. Genre-Volot[3]; F. Peyvandi[4]; W. Miesbach[5]; A. Shapiro[6]; M. Timofeeva[7]; L. Martell[8]; S. Abrol[8]; G. Özen[8]; B. Mellgård[8]

[1]*Department of Hematology, Erasmus University Medical Center, Rotterdam, Netherlands;* [2]*Ege Universitesi Tip Fakultesi Hematoloji Bilim Dali, Bornova, Izmir, Turkey;* [3]*Centre Hospitalier Universitaire Dijon Bourgogne, Dijon, France;* [4]*Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy;* [5]*Hematology and Oncology, Johann Wolfgang Goethe University Hospital, Frankfurt/Main, Germany;* [6]*Indiana Hemophilia and Thrombosis Center, Indianapolis, United States;* [7]*Federal State Budgetary Research Institution, Kirov Scientific-Research Institute of Hematology and Blood Transfusion of FMBA, Kirov, Russian Federation;* [8]*Shire, Cambridge, United States*

Introduction: VWF is a large multimeric plasma glycoprotein with key hemostatic functions mediating platelet adhesion and aggregation and stabilizing factor VIII. Recombinant VWF (rVWF, VEYVONDI™; Baxalta, part of Shire, Lexington, MA, USA) contains the full multimer profile, including ultra-large multimers that are usually deficient in plasma-derived VWF (pdVWF) concentrates exposed to the ADAMTS13 cleaving protease. Patients with severe VWD may benefit from prophylactic rVWF treatment to reduce the number of spontaneous bleeding episodes (BEs), including hemarthrosis, epistaxis, and GI bleeding. Here we present the design of a study to investigate the efficacy and safety of long-term prophylactic treatment with rVWF.

Methods: Patients eligible for this phase 3 study (EudraCT No.: 2016-001478-14, NCT02973087) are ≥18 years of age, diagnosed with severe VWD (baseline VWF:RCo <20 IU/dL) that required therapy with VWF either on an on-demand (OD arm) or prophylactic (switch arm) regimen to control bleeding in the last 12 months. Study exclusion criteria include history or presence of VWF or FVIII inhibitors; Type 2N or platelet-VWD or a coagulation disorder other than VWD; prophylactic treatment of >5 infusions or >240 IU/kg per week; renal disease or significant liver disease; platelet count of <100 000/mL at screening. Patients transitioning from OD treatment or switching from prophylactic pdVWF will receive rVWF prophylaxis for 1 year. Primary study objective is to evaluate annualized bleeding rates (ABRs) for spontaneous bleeds in patients on prophylactic rVWF treatment and to compare it to the subject's historical ABR for spontaneous BEs. Secondary objectives include assessing additional efficacy in patients previously treated with OD or prophylactic VWF; spontaneous ABRs by bleed location; weight-adjusted rVWF consumption; number of infusions; safety (assessed by monitoring adverse events, vital signs, clinical laboratory parameters, immunogenicity to VWF and FVIII, thrombogenicity and hypersensitivity); rVWF pharmacokinetics and pharmacodynamics.

Results: The study started in Dec 2017 and is ongoing.

Discussion/Conclusion: Results from this prospective, phase 3 study will provide data on the efficacy and safety of rVWF for prophylaxis against spontaneous bleeds in patients with severe VWD.

Disclosure of Interest: F. Leebeek Grant/Research support from: CSL Behring and Shire for studies on VWD. He is a DSMB member of a study sponsored by Roche, Consultant for: UniQure, NovoNordisk and Shire (fees go to the institution), K. Kavakli Consultant for: Pfizer, Bayer, Shire and Novo Nordisk, F. Genre-Volot Grant/Research support from: Shire, Roche, LFB, Sobi, Bayer, F. Peyvandi Consultant for: Kedrion and LFB, Speaker Bureau of: Ablynx, Alnylam, Bayer, Grifols, Novo Nordisk, Roche, Shire, Sobi, W. Miesbach Grant/Research support from: Shire, Octapharma, CSL Behring and LFB, Speaker Bureau of: Shire, Octapharma, CSL Behring and LFB, A. Shapiro Grant/Research support from: Novo Nordisk, Bayer Healthcare, Bioverativ, Genentech, Prometic Life Sciences, Kedrion, Sangamo Biosciences, Bio Products Laboratory, Octapharma, OPKO, Daiichi Sankyo, Chugai Pharmaceutical, Glover Blood Therapeutics, Shire, M. Timofeeva: None declared., L. Martell Employee of: Shire, S. Abrol Employee of: Shire, G. Özen Shareholder of: Shire, Employee of: Shire, B. Mellgård Employee of: Shire.

P110 | Anticoagulant therapy in patients with factor VII deficiency

G. Quintavalle[1,*]; F. Riccardi[1]; P. M. Ferrini[2]; A. Coppola[1]; G. F. Rivolta[1,*]; A. Matichecchia[1]; A. Tagliaferri[1]

[1]*Regional Reference Centre for Inherited Bleeding Disorders - University Hospital of Parma;* [2]*Internal Medicine, Angiology and Coagulation Unit - University Hospital of Parma, Parma, Italy*

Introduction: Factor VII (FVII) Deficiency is a rare bleeding disorder although, in some cases, it has been described to be associated with thromboembolic events. The choice of starting an antithrombotic treatment is often puzzling(?) due to the bleeding tendency of these patients and data are lacking. This study reports the experience of a single center with anticoagulant therapy in patients with FVII deficiency and evaluates an eventual association between genotype and thrombosis risk

Methods: We collected baseline information, bleeding history, reason, type and duration of antithrombotic treatment in 4 patients with FVII deficiency, followed at Parma Haemophilia Centre who were currently or previously treated with anticoagulant therapy. Molecular analysis by direct sequencing of the *F7* gene and screening for thrombophilia were also performed.

Results: Age at study, mean ± 1 SD, was 62.2 ± 12. Three patients had FVII>0.2 IU/dL (0.21; 0.25 and 0.4 IU/dL respectively) without bleeding history. They presented a heterozygous *F7* genotype (two missense and one intragenic mutation). One patient had FVII 0.12 IU/dL and he presented bleedings after dental procedures, with a genotype compound heterozygous for two missense mutations. Acquired or congenital thrombophilia were not detected in any patients. Three patients started low molecular weight heparin/fondaparinux or a direct oral anticoagulant (Dabigatran and Rivaroxaban) for 4 thrombotic events (3 pulmonary embolism and a thrombophlebitis), all but one related to trigger factors (ankle fracture, hormone therapy and the concurrence of surgery, neoplasm and replacement therapy with rFVIIa). Another patient assumed Rivaroxaban for 6 months for atrial fibrillation. The minimum duration of therapy was 6 months (mean 12.5 ± 6.6 months). No bleedings occurred during the treatment.

Discussion/Conclusion: Mild or moderate FVII deficiency do not guarantee protection against thrombotic events and, after a risk-stratification, it is possible to start antithrombotic treatment, when needed. In our experience, the choice of a limited or long-term therapy with direct anticoagulants revealed itself a safe option, without the risk of FVII inhibition or over-range treatment with warfarin. The detected mutation were not previously associated to thrombosis and, given the presence of a trigger cause in most events, an association of genotype and thrombotic risk could not be found

Disclosure of Interest: None declared.

P111 | The working group setting up the EAHAD psychosocial committee

G. Golan[1]; P. Buckova[2]; A. Torres-Ortuño[3]; K. Vandenabeele[4]; C. Burgess[5]; L. Haverman[6,*]; on behalf of Lotte Haverman, Petra Bučková, Ana Torres-Ortuño, Karen Vandenabeele, Gaby Golan, Christina Burgess

[1]*Medical Psycho, Israel National Nemophila center, Ramat Gran, Israel;* [2]*Department of clinical psychology, University Hospital Brno, Brno, Czech Republic;* [3]*Psychology, EAHAD, Murcia, Spain;* [4]*Psychology, EAHAD, Brussels, Belgium;* [5]*Psychology, EAHAD, London, United Kingdom;* [6]*Psychology, EAHAD, Amsterdam, Netherlands*

Introduction: Within the European Association for Haemophilia and allied disorders are two different committees established to improve multidisciplinary care for patients; the nurses and physiotherapists committees. Because it is important to incorporate psychosocial care as well, we are working on setting up the EAHAD psychosocial committee. The provision of high quality psychosocial care of patients and their families with haemophilia and allied disorders throughout Europe. Through enhancing psychosocial services as a core component of comprehensive care and supporting psychosocial research and to create international standards of psychosocial care.

Methods: The psychosocial committee working group was formed at EAHAD 2017 in Paris. The working group has held some teleconferences and meetings in the last two years. The group completed the terms of reference and is now working on the strategy documents.

Results: So far, the group agreed on the following aspects; Any registered or qualified psychologist, social worker or any other psychosocial profession, with an interest in the management of haemophilia and allied disorders will be eligible to be a member of the EAHAD psychosocial committee. The executive committee will be formed and include at least 4 members from different European Countries. Committee members must be qualified psychologists, able to speak English and have experience in haemophilia and preferably aligned to a Haemophilia Treatment Centre.

Discussion/Conclusion: The first steps towards a psychosocial committee have been taken. Within the next few years we hope to be acknowledged as an official EAHAD committee.

Disclosure of Interest: None declared.

[Correction added on 31 January 2019, after print publication: The presenting author has been changed from G. Golan to L. Haverman.]

P112 | Acquired hemophilia management: Experience of two centres

G. Sottilotta[1]; F. Luise[1]; V. Oriana[1]; A. Piromalli[1]; V. Calafiore[2]; V. Cutuli[3]; D. Nicolosi[2]; G. Giuffrida[2,*]

[1]*UOSD Microcitemie - Centro Emofilia Servizio Emostasi e Trombosi G.O.M. Reggio Calabria, Reggio Calabria;* [2]*Divisione di Ematologia - A.O.U Policlinico Vittorio Emanuele, Centro di riferimento regionale per la prevenzione, diagnosi e cura delle malattie rare;* [3]*A.O.U Policlinico Vittorio Emanuele, Laboratorio Analisi II Presidio Rodolico, Catania, Italy*

Introduction: Acquired Hemophilia A (AHA) is a rare bleeding disorder related to formation of autoantibodies to Factor VIII. AHA is commonly associated with autoimmune disorders, such as

rheumatoid arthritis, as well as postpartum state and malignancies, but in approximately half of the cases the etiology remains unclear. Both sexes can be affected with similar frequency. The incidence of AHA increases with age, being a very uncommon condition in children.

Methods: A retrospective review of the AHA managements over a ten-year period at the Hemophilia Centres of Reggio Calabria and Catania (Italy) was made.

Results: Eight males and 12 females, with an age range of 5 to 87 years (median 57.3) were identified. In 50% of patients the AHA was idiopathic, the other cases were associated with post-partum (25%), chronic obstructive pulmonary disease (5%), autoimmune thyroiditis (5%), non-Hodgkin lymphoma (5%), other malignancies (10%). Seven of these patients did not present bleeding at diagnosis, four evidenced skin bleedings, five showed limb muscle hematomas, one had hematuria, one had hemarthrosis and two post partum hemorrhage. All the hemorrhagic patients were successfully treated with bypassing agents: 8 patients received recombinant activated factor VII, five patients were treated with activated prothrombin complex concentrate. As regards the immunosuppressive treatment, in three cases the inhibitor disappeared spontaneously; the other patients (85%) were treated with cortisone, cyclophosphamide, azathioprine, rituximab and high dose immunoglobulin. All patients achieved the inhibitor eradication except two who died from pneumonia probably related to the immunosuppressive therapy and from cancer-related causes.

Discussion/Conclusion: Our experience seems to confirm the epidemiological data from literature about age, sex distribution, and etiopathogenesis. A variety of immunosuppressive regimens were used according to the patients' age, comorbidities and also to different doctors' decisions in the various wards where patients were admitted.

Disclosure of Interest: None declared.

P113 | Towards evaluation of hemophilia therapies in the Netherlands: A nationwide patient registry and digital infusion log

G. Goedhart-De Wolf[1,*]; F. Van der Meer[1]; M. Driessens[2]; K. Van Beurden[1]; K. Fischer[3]; on behalf of HemoNED Steering Committee

[1]Thrombosis and Hemostasis, LUMC, Leiden; [2]Netherlands Hemophilia Patient Society, Nijkerk; [3]Van Creveldkliniek, University Medical Center Utrecht, Utrecht, Netherlands

Introduction: Patient registries are crucial in the evaluation of hemophilia therapies, even more in the light of promising innovative products. Additionally, increasing attention is paid to digital personal health environments for patients.

Methods: From 2015 on in the Netherlands the hemophilia treaters society together with the hemophilia patient organization developed and implemented a nationwide hemophilia patient registry ('HemoNED') and a digital infusion log ('VastePrik'). VastePrik is available as a mobile and web application. On the webpage both patient and care takers find an overview of the information entered in the app.

Results: The start-up phase took 2 years and included the set-up of a legal entity, developing project governance, gaining (financial) support and legal (e.g., privacy law) and ethical approvals. Starting December 2017 patients were included into the HemoNED registry after informed consent, with priority for severe hemophilia patients. By September 2018 929 patients were included. The mean age of the patients is 39 (range 0-88) years. Most patients (72%) have Hemophilia A (severe 60%; moderate 14%; mild 26%). Other diagnoses entered were Hemophilia B (11%), Von Willebrand Disease (12%), carriers (2%) and other rare bleeding disorders (3%). For 294 patients their viral and inhibitor status were completed: 11% dealt with or currently had an inhibitor; 31% scored positive on having (had) an infection (Hepatitis C 72%; Hepatitis B 25%; HIV 3%). Prospective data including treatment plan and side effects of treatment will be entered in the registry from 2019. Since April 2018 the VastePrik app was available. By September 2018 640 patients had received a personal account; 157 patients used the app regularly (at least once a week) to register their infusions and bleedings.

Discussion/Conclusion: The Dutch hemophilia registry was successfully implemented in all six hemophilia treatment centers. Once prospective data registration starts adverse events will centrally be collected and reported to national and international (e.g., EUHASS) safety registries. The digital infusion log is a first step towards a digital personal health environment for hemophilia patients. Bleedings and treatment are increasingly being entered in the app, although starting problems are recognized. In 2019 scanning the barcode of factor concentrates will be implemented to improve infusion registration.

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P114 | Real-life experience of treating patients with severe haemophilia A with rFVIIIFc

G. Kampelos*; A. Apostolopoulou; V. Tsevrenis; M. Mpelia; E. Nomikou

[1]General Hospital of Athens Hippokration Haemophilia center, General Hospital of Athens Hippokration, Athens, Greece

Introduction: Efmoroctocog alfa is the first available Extended Half Life product for Haemophilia A available in Greece. It is a recombinant human coagulation factor VIII, Fc fusion protein (rFVIIIFc).

We describe the experience of prophylaxis in severe Haemophilia A patients in our Centre (Haemophilia Centre of Ippokrateio General Hospital of Athens) the last 15 months.

Methods: Patients were switched to rFVIIIFc based on their numbers of bleeds, frequency of injections, the condition of their veins, their level of activity and their life style. Blood samples were collected at several time intervals in order to calculate the trough levels of FVIII. The additional data are collected from their medical files.

Results: All patients were treated with 27-40 IU/ Kgr, 2 times per week. Patients' blood samples at 96 hours showed trough levels of 2%-3%. From the 8 patients, only 2 patients with heavy arthropathy had joint bleeds that were resolved without additional administration of FVIII. None of the 8 patients presented a bleed in another system. The number of injections was reduced for each patient by at least 1 per week compared to the previous standard rFVIII. None of the patients treated with rFVIIIFc developed inhibitors or any Adverse Event.

Discussion/Conclusion: Our experience showed that patients in prophylaxis with rFVIIIFc maintained trough levels 2%-3% at 96 hours after drug infusion. Most of the patients didn't have bleeding episodes, which allowed them to improve their level of activity and to reduce the number of infusions. rFVIIIFc was safe and didn't trigger the development of inhibitors in any of the patients.

Disclosure of Interest: None declared.

P115 | Immune tolerance induction with human-cl rhFVIII in patients with severe haemophilia A and inhibitors

G. Hall[1,*]; N. Bhatnagar[1]; K. Khair[2]; A. Wilkinson[1]; L. Belyanskaya[3]; R. Liesner[2]

[1]Children's Hospital Oxford, Oxford Haemophilia and Thrombosis Comprehensive Care Centre, Oxford University Hospitals NHS Foundation Trust, Oxford; [2]Haemophilia Comprehensive Care Centre, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, United Kingdom; [3]Octapharma AG, Lachen, Switzerland

Introduction: The risk of developing inhibitors to coagulation factor VIII (FVIII) remains a serious concern when treating children with haemophilia A. Immune tolerance induction (ITI) with FVIII is currently the most clinically effective approach to eradicate inhibitors. We present a case series of six PUPs with severe haemophilia A, who, having developed inhibitors to human cell line-derived recombinant FVIII (human-cl rhFVIII) (simoctocog alfa, Nuwiq®), received ITI using the same product.

Methods: Six PUPs with severe haemophilia A who developed inhibitors to human-cl rhFVIII were treated with human-cl rhFVIII for ITI. Success of ITI was assessed based on achievement of an undetectable inhibitor titre (<0.6 BU/mL), FVIII recovery ≥66% and half-life ≥6 hours. Bleeding rate, tolerability and safety were also assessed.

Results: Four patients were Caucasian and two were African. All had a *F8* mutation associated with poor ITI outcome and two had an additional risk factor for ITI failure. Four patients had a peak historical inhibitor titre ≥10 BU/mL, one >5 BU/mL but ≤10 BU/mL, and one <5 BU/mL. The number of exposure days prior to inhibitor detection ranged from 9-33. Age at ITI start ranged from 8-186 months. ITI treatment consistent of 100 IU/kg human-cl rhFVIII daily for five patients, with two patients increasing to 150 IU/kg due to persistent bleeding or bruising, and 90 IU/kg every other day for one patient. One patient has achieved complete tolerisation, with an undetectable inhibitor titre after 9 months, and is receiving standard prophylactic treatment. This success was despite an inhibitor titre ≥10 BU/mL at ITI start. Three more patients achieved an undetectable inhibitor titre after 1, 6 and 18 months, respectively, and have normalised FVIII recovery. These patients are receiving weaning doses as FVIII half-life extends. One patient discontinued with ITI after 15 months due to an increasing inhibitor level; this patient was 15 years old at ITI start and had severe arthropathy following 15 years without treatment. One patient started ITI 6 months ago and treatment is ongoing.

Discussion/Conclusion: ITI with human-cl rhFVIII has eradicated inhibitors in four of six patients (67%) to date. All patients had risk factors for poor ITI outcome. These data suggest that human-cl rhFVIII may be an effective option for ITI in patients with haemophilia A and inhibitors.

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P116 | Evaluation of laboratory safety data from patients with severe von Willebrand disease (VWD) in association with infusion of recombinant von Willebrand factor (VWF) in a phase 3, multicenter, open-label study

G. Castaman[1,*]; B. Ploder[2]; B. Ewenstein[3]; G. Özen[3]; B. Mellgård[3]

[1]Center for Bleeding Disorders and Coagulation, Department of Oncology, Careggi University Hospital, Florence, Italy; [2]Shire, Vienna, Austria; [3]Shire, Cambridge, United States

Introduction: Efficacy and safety of recombinant VWF (rVWF, VEYVONDI™; Baxalta, part of Shire, Lexington, MA, USA) for on-demand (OD) treatment of bleeding events (BEs) was studied in adults with severe VWD in a Ph 3 OD trial. rVWF has a full multimeric profile since it is not exposed to ADAMTS13 during production.

Considering the presence of ultra-large multimers (ULMs) in rVWF and a hypothetically associated risk of thrombogenicity, selected laboratory (lab) parameters from this trial were analyzed to identify any potential pattern in changes observed between pre- and post-rVWF infusion (pre-I & post-I).

Methods: 37 adults with severe VWD were enrolled in the study (NCT01410227; EudraCT 2010-024108-84) and received ≥1 rVWF dose. Patients received OD rVWF for BEs, alone or with recombinant FVIII. Changes between pre-I & post-I (within 96 hours post-I) values in selected lab parameters (D-dimer, platelet counts, hemoglobin [Hb], lactate dehydrogenase [LDH]) were evaluated.

Results: Lab values were obtained from 31/37 patients. None of the out-of-reference-range (OORR) values were considered adverse events (AE) by investigators (PIs). Median [range] pre-I and post-I D-Dimer values were 220 [50-1194] and 223 [50-1608] ng/mL (FEU), respectively. OORR D-Dimer values were observed in 7 patients (including 3 pre-I and +4 post-I); all were considered non-clinically significant (NCS) by PIs. Median pre-I and post-I platelet counts were 242.5 [128-503] and 251.5 [128-511] GI/L, respectively; OORR low values were observed in only 1 patient pre-I and post-I, both were considered NCS. Median pre-I and post-I Hb values were 129 [90-159] and 128 [82-164] g/L, respectively; OORR low clinically significant values were observed in 5 patients pre-I and post-I and in 1 additional patient post-I; all 6 patients had a history of anemia, GI bleeds, or menorrhagia. Median pre-I and post-I LDH values were 164 [103-233] U/L and 159 [101-290] U/L, respectively; OORR LDH values were observed in 2 post-I patients at 1 time point for each. Changes in lab values from pre-I to post-I did not indicate any pattern in any patient. No thrombotic AEs were reported.

Discussion/Conclusion: Analysis of selected lab parameters in this study showed no changes indicative of a new safety signal, consistent with the known safety profile of rVWF.

Disclosure of Interest: G. Castaman Grant/Research support from: CSL Behring and Pfizer, Speaker Bureau of: CSL Behring, Kedrion, Novo Nordisk, Pfizer, Roche, Shire, Sobi, UniQure, B. Ploder Employee of: Shire, B. Ewenstein Shareholder of: Shire, Employee of: Shire, G. Özen Shareholder of: Shire, Employee of: Shire, B. Mellgård Employee of: Shire.

P117 | Prompt response and long term remission of refractory MGUS related acquired hemophilia with Bortezomib

G. Di Prinzio[1,*]; G. Goldmann[1]; N. Marquardt[1]; S. Horneff[1]; C. Klein[1]; H. Zeitler[2]; J. Nadal[3]; J. Oldenburg[1]

[1]Hämophilie Zentrum Bonn; [2]Medizinische Klinik I; [3]Institut für Medizinische Biometrie, Informatik und Epidemiologie, Bonn, Germany

Introduction: Acquired Haemophilia A is a rare condition causing coagulation impairment and potentially fatal bleeding complications. Although in most cases no related condition can be found, links with monoclonal gammopathies are known.

Methods: We describe the case of an 81 years old woman who was admitted in the neurology ward of a tertiary university referral hospital for the work-up of relapsing syncopal events. During her stay a spontaneous right elbow bleeding appeared and a coagulation factor determination showed a FVIII concentration <1%.

Results: Acquired Haemophilia A (AHA) was suspected and methylprednisolone therapy was promptly started. As bleeding was continuing the patient received Prothrombin Concentrate and tranexamic acid. A Factor VIII-inhibitor with 65.75 Bethesda Units (BU) was detected. Three months of full treatment with corticoids, cyclophosphamide, immune-adsorption and high-dose FVIII infusion failed to achieve complete bleeding control and inhibitor elimination. After an IgA kappa Monoclonal Gammopathy of Undetermined Significance (MGUS) had been diagnosed, assuming that paraproteinemia can act as inhibitor, the patient was started on Bortezomib, a proteasome 26S inhibitor, employed in the care of Multiple Myeloma (MM). After two cycles the patient achieved complete remission without developing any side effects.

Discussion/Conclusion: The efficacy of bortezomib in MGUS associated AH is as far as we know not observed. In our patient bortezomib was introduced as a 3rd line therapy and achieved a prompt and dramatic response. Finally, the effect of the intensive pre treatment trials on the success of the proteasome inhibitor therapy cannot be estimated definitively.

During long term follow up of 6 months the patient was still in complete remission and required no further maintenance treatment, proposing that a proteasome inhibitor based treatment might be even more effective in MGUS associated AH than in MM associated cases.

Conclusion: Bortezomib based treatment schedule should be considered in MGUS associated AH patients non-responding to conventional immunosuppressive treatment.

Disclosure of Interest: None declared.

P118 | Experience in the treatment of acquired haemophilia A (AHA) in 26 patients in relation to bleeding control and induction of immune tolerance

G. Di Prinzio[1,*]; G. Goldmann[1]; S. Horneff[1]; C. Klein[1]; N. Marquardt[1]; J. Nadal[2]; H. Zeitler[3]; J. Oldenburg[1]

[1]Hämophilie Zentrum Bonn; [2]Institut für Medizinische Biometrie, Informatik und Epidemiologie, Bonn; [3]Medizinische Klinik I - Uniklinikumm Bonn, Bonn, Germany

Introduction: Acquired Haemophilia A (AHA) is a rare and difficult-to-treat disease, with high mortality. For more than 25 years we have treated patients with AHA in our hospital. By most of them high dose FVIII concentrates have been employed to control bleeding.

Methods: We conducted a retrospective review on 26 patients with AHA who had been treated between 2011 and 2017 at our

institution. In most patients the disease presented with bleeding symptoms, that were treated with high dose FVIII infusion. We evaluated the effectivity of FVIII in controlling bleeding, as well as other therapeutic interventions, in lowering bleeding rates and in achieving more rapidly complete/partial remission. Subgroup analysis was performed according to different patients base-characteristics (age, inhibitor titer, FVIII concentrations at diagnosis, comorbidities) and combination of therapeutic interventions.

Results: 19 patients presented a high antibody titer (> 5 Bethesda Units, BU) while in 7 patients the antibody titer was < 5 BU. The average antibody titer was 32.95 BU and complete remission was achieved after a median of 43 days. In our preliminary analysis the patient-group with a low inhibitor titer (<5 BU) and a high residual FVIII activity presented less bleeding events, a shorter FVIII substitution time and hospital stay as well as a reduced number of infections and episodes of leukopenia. The application of Rituximab, Immunoadsorption and continuous infusion of FVIII did not seem to be associated with a better outcome. Employment of activated Factor VII (FVIIa) was transitory required in 6 patients. The median value of the time needed for FVIII increase to > 10% was 4 days.

Discussion/Conclusion: Our experience primarily suggests that replacement with high-dose FVIII in AH allows a rapid FVIII-level increase and a rapid bleeding-control.

Disclosure of Interest: None declared.

P119 | Cancer induced hyperfibrinolysis in a 59-year-old woman with congenital hyperfibrinogenemia

G. Di Prinzio[1,*]; G. Goldmann[1]; S. Horneff[1]; N. Marquardt[1]; J. Nadal[2]; H. Zeitler[3]; J. Oldenburg[1]

[1]Hämophilie Zentrum Bonn; [2]Institut für Medizinische Biometrie, Informatik und Epidemiologie—Uniklinikum Bonn; [3]Medizinische Klinik I—Uniklinikum Bonn, Bonn, Germany

Introduction: Disseminated Intravascular Coagulation with hyperfibrinolytic phenotype is a condition well known in medicine of critical area. The setting in which it takes place in our case is quite rare: a patient with a breast cancer relapse and a congenital hypofibrinogenemia.

Methods: We report the case of a 59-years-old woman who presented a metastatic breast cancer relapse and a known congenital hypofibrinogenemia. On admission the patient presented with subcutaneous hematomas and the biologic work-up put into evidence an undetectable level of fibrinogen, a slightly reduced level of FV, Alpha-2-antiplasmin, Plasminogen Activator Inhibitor (PAI1) and a strongly prolonged Reptilase time. A grade III thrombocytopenia was also present. This constellation of biologic findings suggested the presence of a hyperfibrinolytic environment.

Results: The patient was therefore started on tranexamic acid on continuous infusion. Because of the spurious laboratory frame, could have been also consistent with a Disseminated Intravascular Coagulation with hyperfibrinolytic phenotype, an Unfractionated Heparin Infusion was introduced at the second day of treatment. Over the following weeks an improvement of the lab tests occurred, with normalization of PAI-1 and Alpha-2-antiplasmin activity, and no bleeding appeared. Despite the introduction of a chemotherapeutic regimen for the underlying disease, the platelets count increased and the patient could be discharged on oral tranexamic acid.

Discussion/Conclusion: With this brief case report we want to highlight the importance of recognizing a hyperfibrinolytic phenotype in order to choose the adequate treatment and to minimize the bleeding as well the thrombotic risks. Indeed, although hyperfibrinolysis remains a quite rare manifestation apart from coagulation impairment of traumatic origin, it can be triggered by some conditions such as M3 Acute Myeloid Leukemia or some Adenocarcinomas. It's intriguing to think that in such a setting the presence of a congenital hypofibrinogenemia could have played a role in the setting of the hyperfibrinolysis.

Disclosure of Interest: None declared.

P120 | Use of an integrated medical file in the monitoring and treatment of arthropathy in patients with hemophilia

G. Sottilotta[1,*]; F. Branca[2]; V. Polimeni[3]; A. Panuccio[3]; F. Luise[1]; M. F. Mansueto[4]; V. Oriana[1]; A. Piromalli[1]; on behalf of Associazione Emofilici di Reggio Calabria ONLUS

[1]UOSD Microcitemie - Centro Emofilia Servizio Emostasi e Trombosi, G.O.M. Bianchi-Melacrino-Morelli, Reggio Calabria; [2]Nova Salus, Villa San Giovanni; [3]UOC Recupero e Riabilitazione, G.O.M. Bianchi-Melacrino-Morelli, Reggio Calabria; [4]UO Ematologia, Policlinico, Palermo, Italy

Introduction: Early diagnosis, treatment and prevention of arthropathy in patients with hemophilia (PWH) is fundamental for comprehensive care, with particular attention to the hematologic and physiatric aspects.

Methods: A summary hematologic and physiatric medical file was created for each PWH in order to assess their muscle-skeletal and laboratory variations. The laboratory tests also involved the bone metabolic indicators. The assessment scales Tinetti, MRC, HJHS 2.1, and HEAD-US ultrasound score were also included. The HAL scale was used for psychological evaluation. The study started in July 2017: each patient was assessed every three months on muscle-skeletal scales, every 6 months with laboratory tests, and every 12 months by a psychological questionnaire. Twenty PWH (17 HA, 3 HB: 1 with severe hemophilia, 3 with inhibitor and 6 with moderate or mild hemophilia), aged 7 to 63 years (mean 34.1) were enrolled; 3 had inhibitor; 10 patients with severe hemophilia were in prophylaxis, the others 10 were on demand.

Results: We found hypovitaminosis D in 70% and hyperparathyroidism in 15% of the patients. Tinetti's assessment evidenced lower than normal results in 30% of the PWH: no variations after the first

check. The MRC scale showed an average 4.85 score with 15% of the PWH with lower results than normal. This data improved to 4.91 after three months. The HJHS showed an initial average score of 14.4(1-74) which improved to 13.9(1-58), at the 2nd trimester assessment after a personalized physiotherapy program. The HAL showed an average result of 211.3(84-288). The HEAD-US scores were stable at the first check-up compared to the initial data in all patients except one.

Discussion/Conclusion: These results confirm that PWH who started prophylaxis early do not develop arthropathy. Adults with inhibitors had a worse joint condition than pediatrics. Hypovitaminosis D confirms the literature findings about PWH. The high psychological scores show how comprehensive care supports PWH globally. In only three months we observed how the implementation of an integrated clinical file can improve the management of the PWH. This will probably lead to an improvement in patients' health and quality of life.

Disclosure of Interest: None declared.

P121 | Real-world experience of rIX-FP demonstrates favourable outcomes in two young patients

G. Sottilotta*; F. Luise; V. Oriana; A. Piromalli

UOSD Microcitemie. Centro Emofilia—Servizio Emostasi e Trombosi. Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

Introduction: rIX-FP (IDELVION®) is a recombinant, long-acting, human coagulation factor IX (FIX) that is fused to recombinant human albumin via a cleavable linker and is used to treat haemophilia B. Real-world evidence offers valuable insight into how the lives of patients can be improved with therapy. We present data on clinical parameters and patient-centric outcomes following switching from a regular-acting FIX product (BeneFIX®) to rIX-FP.

Methods: Two brothers with a history of severe haemophilia B were switched from BeneFIX® (40 IU/kg twice weekly) to rIX-FP in August 2017. In both cases, the dosing regimen was selected to extend the dosing interval while maintaining FIX levels >5%. FIX activity was measured at defined time points after a single infusion of rIX-FP following a 7-day washout period. Breakthrough bleeds, joint bleeds and the development of inhibitors were monitored, and physical activity was assessed before and after switching.

Results: Following the 7-day washout, patient 1 (12 years old) had FIX activity at 0.82% and patient 2 (9 years old) had FIX activity at 0.91%. Patient 1 and patient 2 were switched to 43 IU/kg and 50 IU/kg rIX- FP every 10 days, respectively. At 15 minutes post-infusion, FIX activity levels were 110% (patient 1) and 89.4% (patient 2). By day 7, both patients maintained FIX activity above 10%. On day 10, when the next dose was scheduled, patient 1 and patient 2 maintained FIX activity at 6.13% and 5.46%, respectively. Since switching to rIX-FP prophylaxis, no breakthrough bleeds have occurred in either patient and no joint involvement has been observed. While on prophylaxis with regular-acting FIX, the patients only occasionally exercised in the swimming pool. Since switching, both patients became involved in gym activities 2-3 times per week plus motor activity at school twice per week. No inhibitors have been observed in either case, and patient 1 learned to self-infuse for the first time.

Discussion/Conclusion: In two paediatric patients with severe haemophilia B, extended 10-day dosing of rIX-FP was effective at maintaining FIX levels >5%. In these patients, rIX-FP provided effective bleed prevention, was well tolerated, and had a positive impact on the patients and their caregivers, leading to increased treatment satisfaction and improved compliance in both cases.

Disclosure of Interest: G. Sottilotta Speaker Bureau of: Bayer, Shire, Pfizer, CSL Behring, Novo Nordisk, Sobi and Octapharma, F. Luise: None declared., V. Oriana: None declared., A. Piromalli: None declared.

P122 | Telemedicine and its tools to improve rehabilitation in hemophilia

G. Dallari*; V. Begnozzi; E. Boccalandro

IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Introduction: In persons with hemophilia (PWH) the importance of physiotherapy and physical activity in preventing bleeding, joint damage and secondary diseases is established. However, since hemophilia is a chronic disease, physiotherapy often requires interventions carried out for a prolonged period of time, that sometime create problems of adherence for patients. Driven by continuous technological innovation, telemedicine is being more and more proposed as an alternative method to provide patients with services concerning their health at home, saving the time and costs needed to reach the hemophilia and rehabilitation center and thus increasing adherence. The aim of this report is to identify the studies available in the literature regarding the management of PWH through the use of tools based upon telemedicine.

Methods: The survey was carried out using the PubMed and PEDro Scientific Data Banks and websites specialized in hemophilia and telemedicine. English-language publications only were considered in this review, without temporal restrictions on the publication date.

Results: Our survey did show that an array of tools such as video conferencing, mobile applications, handheld sensors and exergames have been used and accepted by PWH with a good degree of satisfaction and adherence. Video conferences are helpful to obtain a more rapid and objective evaluation of bleeding episodes by the personnel of the distant treatment center. Cell phones and associated apps offer tools that improve the performance of prophylaxis and help PWH to foster better lifestyles. They also provide support and advice from peers with hemophilia, as implemented in the frame of a number of platforms. Portable sensors have the goal to trigger the attainment of a given number of daily walking steps and thus monitor the degree of physical activity. Exergames have the advantage of improving the musculoskeletal function by exploiting the recreational features of videogames.

Discussion/Conclusion: Telemedicine can be a useful tool in the management of hemophiliacs, especially for those living far from the specialized center and the physiotherapist. However, being a recent and rapidly evolving branch of medicine, studies in the literature have involved so far only a limited number of patients with hemophilia. Therefore, additional evidence is warranted by means of the accrual of cumulative data from multiple centers specialized in hemophilia.

Disclosure of Interest: None declared.

P123 | Congenital factor deficiencies in children presenting with intracranial hemorrhage

G. Aydogan*; Z. Salcioglu; F. Akici; T. N. Tahtakesen; E. Yilmaz; N. Ozdemir; N. Bayram

Pediatric Hematology, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey

Introduction: Intracranial hemorrhage (ICH) is a life-threatening bleeding among all kinds of congenital factor deficiencies. In our study, we discussed the treatment of ICH in congenital factor deficiencies and evaluated the condition, which required prophylaxis.

Methods: We retrospectively evaluated 37 patients, who had ICH episodes among 432 patients with CFDs. Coagulation parameters and the activity of coagulation factors were studied. Cranial ultrasonography, cranial CT or MRI were performed. The age both at the present and at the time of bleeding and the location and frequency of bleeding were recorded. The patients were administrated with commercial factor concentrates, anticonvulsive drugs and supportive therapy. Surgical intervention was performed whenever necessary according to clinical criteria.

Results: 37 patients had 52 CNS bleeding episodes (8.56%). 17 patients were under three months of life. Among 52 CNS bleedings, intracerebral localizations were the most common localization (n = 28; 53.8%). It is followed by subdural bleeding (n = 11; 21.2%), subarachnoidal bleeding (n = 10; 19.2%), epidural bleeding (n = 2; 3.8%) and intraventricular bleeding (n = 1;1.9%). Three patients, two factor VII and one factor X deficiency had 15 recurrent CNS bleeding episodes. Most frequent symptoms were drowsiness, vomiting, nausea, seizures and headache. All patients were submitted to replacement therapy. Neurosurgical intervention was performed in nine patients (24.3%). Residual psychomotor or neurologic abnormalities were seen in twelve patients (32.4%). One death was recorded due to sepsis ten months later after the CNS bleeding. Prophylaxis was applied in 22 patients (59.4%).

Discussion/Conclusion: Central nervous system hemorrhage is one of the most common causes of mortality in patients with congenital factor deficiencies. During the 28 year period, 52 episodes of CNS bleedings were documented in 37 patients from a total population of 432 children with congenital factor deficiencies, represented an overall incidence of 8.56%. Therefore, we observed a higher incidence of CNS bleedings then those reported in the literature ranging from 2.0% to 7.8%. In conclusion, mortality of haemophilic patients with CNS bleeding is greatly reduced, as there is prompt administration of coagulation factor concentrates and a multidisciplinary team approach. Our results indicate that some CFDs require early prophylactic treatment to prevent CNS bleeding.

Disclosure of Interest: None declared.

P124 | AAV based hemophilia B gene therapy in mice using FIX-CB2679d

G. E. Blouse[1,*]; N. Nair[2]; T. VandenDriessche[2]; M. K. Chuah[2]; J. Landau[1]

[1]*Catalyst Biosciences, South San Francisco, United States;* [2]*Department of Gene Therapy & Regenerative Medicine, Vrije University of Brussels (VUB), Brussels, Belgium*

Introduction: Catalyst Biosciences has developed a next-generation engineered coagulation Factor IX, Dalcinonacog alfa (formerly CB2679d/ISU304) using rational protein design, which includes triplet substitutions (R318Y, T343R and R338E) that increase catalytic activity, increase resistance to antithrombin inhibition and improve affinity for activated FVIII. These enhancements result in a 22-fold enhanced potency enabling administration by subcutaneous (SC) injection for routine prophylaxis. The aim of this study is to provide preclinical proof of concept in hemophilia B mice for an AAV-based gene therapy and demonstrate the superior activity of an AAV vector encoding FIX-CB2679d that compares favorably with an AAV vector encoding FIX-R338L Padua.

Methods: Codon-optimized (co) versions of CB2679d and R338L Padua were prepared on the T148A background of Padua and cloned into an adeno-associated viral vector downstream of a robust hepatocyte-specific promoter. The two resulting vectors FIX-Padua (*scAAV-AAT- FIXcoR338L Padua*) and FIX-CB2679d (*scAAV-AAT-* FIXco (R318Y, R338E, T343R, T148A) were prepared as AAV/DJ8 research grade vectors with titers ranging from 5.2×10^{12} -1.3×10^{13} vg/mL. The *in vivo* performance of the AAV encoding FIX-CB2679d and FIX-Padua vectors were assessed in FIX-deficient hemophilia B mice injected with 1×10^{9} vg/mouse, 5×10^{9} vg/mouse, 1×10^{10} vg/mouse or vector alone and followed for up to nine weeks. The potency of each vector was assessed by measuring the respective FIX antigen and activity levels by ELISA and aPTT.

Results: FIX antigen levels increased with vector dose. Reductions in clotting time were observed within the 1st week and remained reduced throughout the study for both the AAV-encoding FIX-CB2679d and FIX-Padua vectors. Statistically significant improvements in the clotting time of AAV-encoding FIX-2679d over FIX-Padua at equivalent doses suggests that the FIX-2679d variant exhibits a superior hemostatic potency compared with FIX-Padua.

Discussion/Conclusion: This study demonstrates the potential of an AAV-encoding CB2679d for gene therapy and suggests improvement in functionality of the clotting Factor IX CB2679d as measured by a reduction in clotting time over Padua.

Disclosure of Interest: G. Blouse Shareholder of: Catalyst Biosciences, Employee of: Catalyst Biosciences, N. Nair: None declared., T. VandenDriessche Grant/Research support from: Catalyst Biosciences, M. Chuah Grant/Research support from: Catalyst Biosciences, J. Landau Shareholder of: Catalyst Biosciences, Employee of: Catalyst Biosciences.

P125 | Correcting hemophilia A using human FVIII produced in vivo by Afibromer™ shielded engineered allogeneic cells

G. Carmona*; L. Barney; J. Sewell; R. Newman; C. Carroll; O. O'Connor; J. Huang; D. Moller; R. Miller; D. Smith; D. Peritt; R. Vivaldi

Sigilon Therapeutics, Inc, Cambridge, United States

Introduction: Current hemophilia therapies require frequent protein infusions yet are unable to address long-term complications due to poor patient compliance, non-ideal treatment kinetics and generation of inhibitory antibodies. To overcome these drawbacks in hemophilia, alternative modalities such as gene therapy and cell therapy are being investigated. Cell encapsulation using Afibromer™ biomaterials shield the therapeutic cells from the innate immune system while inhibiting the formation of a fibrous capsule around the implant. Prevention of this fibrotic response enables the implanted, engineered cells to deliver proteins at a therapeutic level for extended periods of time. Our aim is to evaluate whether chronic delivery of blood clotting factors by implantation of engineered cells producing human Factor VIII (hFVIII) is more programmable, sustainable and potentially offers a better clinical outcomes in patients when compared to bolus dosing.

Methods: SIG-001 is a non-transformed human cell line, shielded within Afibromer™ capsules, that is engineered to express high levels of human B-domain-deleted hFVIII (hFVIII-BDD). These cells are contact inhibited in the capsule and maintain long term (> 6 mo. in rodents) in vivo viability and sustained protein production.

Results: Intraperitoneal administration of SIG-001 to hemophilia A mice produced in dose-dependent levels of functional hFVIII-BDD in plasma. Moreover, sustained therapeutic hFVIII-BDD levels were achieved along with a corresponding correction of bleeding time and blood loss in a tail bleeding model.

Discussion/Conclusion: Taken together, these data demonstrate that implantation of engineered, shielded human cells that produce hFVIII-BDD is efficacious and well-tolerated in a preclinical model of hemophilia A. The sustained hFVIII-BDD secretion achieved with SIG-001 - our shielded engineered cells - creates a viable alternative to traditional protein delivery or gene therapy with several important advantages. Our aim is to pursue clinical studies of SIG-001 in patients with Hemophilia A and to develop additional therapeutics using Shielded Living Therapeutics™, as a new class of medicines for other serious chronic disorders.

Disclosure of Interest: G. Carmona Employee of: Sigilon Therapeutics, Inc, L. Barney Employee of: Sigilon Therapeutics, Inc, J. Sewell Employee of: Sigilon Therapeutics, Inc, R. Newman Employee of: Sigilon Therapeutics, Inc, C. Carroll Employee of: Sigilon Therapeutics, Inc, O. O'Connor Employee of: Sigilon Therapeutics, Inc, J. Huang Employee of: Sigilon Therapeutics, Inc, D. Moller Employee of: Sigilon Therapeutics, Inc, R. Miller Employee of: Sigilon Therapeutics, Inc, D. Smith Employee of: Sigilon Therapeutics, Inc, D. Peritt Employee of: Sigilon Therapeutics, Inc, R. Vivaldi Employee of: Sigilon Therapeutics, Inc.

P126 | Monitoring of emicizumab (ACE910): comparison between clotting and Chromogenic assay

H. Türkantoz*; D. Varnholt; A. Tiede

Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany

Introduction: Emicizumab is a humanized monoclonal antibody which binds to coagulation factors (F) IX/IXa and X. By connecting FIXa and FX emicizumab mimics the cofactor function of FVIIIa, which is deficient in patients with congenital or acquired hemophilia A. Emicizumab plasma levels have not been associated with clinical outcomes and monitoring is not routinely recommended. However, the ability to monitor the drug may be useful in difficult cases, lack of efficacy, intoxication or unexpected adverse events.

Methods: Standard APPT-based one-stage FVIII clot assay (OS) cannot monitor emicizumab because it does not need to be activated like natural FVIII, resulting in an overestimation of its effect. A modified OS has been proposed using a high sample dilution (1:80) and emicizumab as a calibrator (r2 Diagnostics, Haemochrom Diagnostica GmbH). Chromogenic substrate assays (CS) using bovine FIX and FX cannot detect emicizumab activity because of lack of cross-species reactivity. However, a CS using human FIX and FX is available (Biophen FVIII assay, CoaChrom Diagnostica GmbH). We compared emicizumab detection by these assays using spiked plasma and clinical samples from inhibitor patients.

Results: We show that the modified OS is able to quantify emicizumab plasma concentrations between 10-100 µg/mL. The choice of APTT reagent and dilution buffer resulted in variable precision, in particular for higher emicizumab concentrations. The best combination of APTT reagent and buffer was found with a repeatability coefficient of variation (CV_r) of 8.47% and 3.1% for high and low emicizumab concentrations, respectively. Separate measurements using the same lots of reagents yielded a reproducibility coefficient of variation (CV_R) of 10.64% and 13.26% for high and low emicizumab concentrations, respectively. The Biophen CS was able to quantify emicizumab concentrations between 10-150 µg/mL. The emicizumab calibration curve was more dynamic for higher concentrations compared to the modified OS. We found a CV_r of 3.88%

and 5.59% for high and low concentrations, respectively. Human or porcine FVIII added to emicizumab samples yielded false high results with both assays.

Discussion/Conclusion: Emicizumab can be monitored with sufficient precision using a modified OS or CS. Choice of APTT and buffer reagents may affect the precision of OS. Both assays are not specific for emicizumab because human or porcine FVIII disturb its quantification.

Disclosure of Interest: None declared.

P127 | Prekallikrein deficiency associated with severe mucosal bleeding in a child with Hashimoto thyroiditis: A challenging diagnosis

H. Abouelkhel[1,2,*]

[1]*SQUH, Muscat, Oman;* [2]*Alexandria Faculty of Medicine, Alexandria, Egypt*

Introduction: Severe prekallikrein deficiency is a rare autosomal recessive disorder that is known to be associated with prolonged aPTT without clinically significant bleeding. However, rare cases have been reported to be associated with mucosal bleeding. Hereby, we report on a child with Hashimoto thyroiditis and prekallikrein deficiency, that presented with severe prepubertal vaginal bleeding and recurrent hematemesis.

Methods: SJ is a 13 year-old female, diagnosed with Hashimoto thyroiditis, with poor compliance on L- thyroxin replacement. At the age of 10 years, she was referred to Sultan Qaboos University Hospital for evaluation of persistently prolonged aPTT and recurrent bleeding. Past history was marked for easy bruising, prolonged prepubertal vaginal bleeding for 21 days, and 4 episodes of hematemesis over a period of 6 months. Her family history was negative for bleeding tendency. Clinical examination revealed severe pallor and tachycardia, otherwise, clinical examination was unremarkable.

Results: Laboratory tests revealed severe microcytic hypochromic anemia (Hb 4.4 g/dL, HCT 0.151 L/L, MCV 62 fl, MCH 18 pg, MCHC 29 g/dL, RDW 20.9%), and iron deficiency (serum iron 1 µg/L, and Ferritin 4 µg/L. Coagulation screening revealed normal PT (12 sec), INR (1.1), TT (19 sec), and fibrinogen levels (1.7 g/dL), while aPTT was markedly prolonged (119.8 sec).

Because of her neglected hypothyroidism, next step in her evaluation was to rule out acquired VWD and other coagulation factor deficiencies. VWD workup was normal twice, and coagulation factors assay was normal (F VIII: 1.083 (N 0.495-1.382), F IX: 0.943 (N 0.630-0.890), F XI: 0.851(N 0.520-1.200), F XII: 1.123 (N0.600-1.400). In view of her primary diagnosis of Hashimoto thyroiditis, lupus anticoagulant was requested, and was normal. Upper GIT endoscopy was reported normal twice, and Meckel's diverticulum scintigraphy showed normal uptake. Preoperative management with FFP transfusion before dental extraction resulted in normalization of aPTT, and no post-operative bleeding. HMWK was normal (0.858 u/mL), while prekallikrein was severely deficient (< 0.062) (N 0.530-1.450 u/mL).

Discussion/Conclusion: After ruling out other possibilities, and successful preoperative management with FFP transfusion, we believe that her recurrent severe mucosal bleeding is related to prekallikrein deficiency.

Disclosure of Interest: None declared.

P128 | Effects of weight bearing exercises on lower extremity muscle strength and functional performance in children with hemophilia A

H. Guney Deniz[1,*]; S. Aytac[2]

[1]*Physiotherapy and Rehabilitation Department, Hacettepe University Faculty of Health Sciences Physiotherapy and Rehabilitation Department;* [2]*Division of Pediatric Hematology, Hacettepe University Faculty of Medicine, Ankara, Turkey*

Introduction: Recurrent articular bleeding of the target joints results with a long period of immobilization and mainly affects the muscles around these joints in children with Hemophilia. Exercise therapy is strongly recommended in this population and the functional exercises such as partial weight bearing exercises seem to be more effective than static or short arc exercises for improving muscle strength. The aim of this study is to investigate the effects of lower extremity weight bearing exercises on muscle strength and functional performance in children with Hemophilia A.

Methods: Fifteen children with Hemophilia A (mean age: 10.3 ± 2.2 years, mean BMI: 15.2 ± 1.2 kg/m^2) were included in the study. All the participants were inhibitor negative and were on prophylaxis treatment with a mean usage of 3000 U/week (1000-6000 U/week). A 6-week weight bearing exercise therapy program that included wall squats, single leg stance and jumping activities were applied three times a week. Hemophilia Joint Health Score (HJHS) was used to determine the joint health. The hand held dynamometer was used to determine the strength of the knee flexors and extensors, ankle dorsiflexors and plantarflexors and hip abductors, extensors and external rotators. For the functional performance assessment, 10-step stair climbing test was used. All the tests were applied before and after the exercise therapy. Wilcoxon test was used for statistical analysis.

Results: HJHS scores were similar before (range between 0-6) and after (range between 0-6) the weight bearing exercise therapy ($P > 0.05$). There was no bleeding occurred during the exercise therapy period. Knee, hip and ankle muscle strength increase after treatment when compared to the pre-treatment levels ($P < 0.01$). The stair climbing test results improved after the exercise therapy.

Discussion/Conclusion: Since hemophilia is a rare disease, patient and disease specific exercise therapy is needed. The data of this study showed that the weight bearing exercises improve the lower extremity muscle strength and performance in children with Hemophilia A. The concept of individualized exercise therapy may improve the physical levels in these children and weight-bearing exercises could be a part of this concept

Disclosure of Interest: None declared.

P129 | Evaluation of inter-extremity muscle strength differences in adolescent hemophilia patients

H. Guney Deniz[1,*]; S. Onal[2]; G. I. Kinikli[3]; S. Aytac[4]

[1]Physiotherapy and Rehabilitation Department, Hacettepe University Faculty of Health Sciences; [2]Physiotherapy and Rehabilitation Department, Adnan Menderes University, Faculty of Health Sciences; [3]Physiotherapy and Rehabilitation Department, Hacettepe University, Faculty of Health Sciences; [4]Division of Pediatric Hematology, Hacettepe University, Faculty of Medicine, Ankara, Turkey

Introduction: Bleeding of target joints and muscles typically result with the loss of muscle strength in patients with Hemophilia (PwH). Muscle weakness in one extremity is associated with higher risk of inter-extremity difference. The documentation of the strength differences between the extremities is very important to balance the weight load and protect the affected limb in PwH. The aim of this study is to investigate the strength differences between the muscles of the right and left knee, ankle and elbow joints.

Methods: Ten patients with Hemophilia A (age between 7-17 years and BMI between 11.7-21.2 kg/m^2) were included in the study. All the participants were inhibitor negative and were on prophylaxis treatment range between 1000 U-6000 U/week. Hemophilia Joint Health Score (HJHS) was used to determine the target joints and previous bleeding history was recorded. The hand held dynamometer was used to determine the strength of Quadriceps femoris (QF), Hamstring (Ham), Biceps brachii (BB), Triceps brachii (TB), Dorsiflexors (DF) and Plantarflexors (PF). The differences of muscle strength between the extremities were determined with the use of Wilcoxon test.

Discussion/Conclusion: The knee and elbow muscle strength levels were different between right and left extremities in PwH. The inter-extremity strength differences in PwH are based on the protection of the more affected limb resulting with an overload of the contralateral extremity. It is important to document the strength differences in PwH for balancing the weight load and for designing the appropriate therapy.

Disclosure of Interest: None declared.

P130 | The use of port-a-cath in children with hemophilia in Cukurova region

H. I. Sasmaz[1,2,*]; B. Antmen[1]; B. S. Karagun[1]; G. Leblebisatan[2]

[1]Pediatric Hematology, Acibadem Hospital; [2]Pediatric Hematology, Cukurova University, Adana, Turkey

Introduction: Safe peripheral venous access is essential for the replacement of coagulation factor concentrates to the patients with hemophilia. Frequent infusion of coagulation factors may be challenging especially in young boys for prophylaxis or bleeding therapy. Port-a-cath may need to be placed to facilitate reliable venous access in these patients who require frequent venous access. In this study we presented our experiences in inserting port-a-cath in children with clotting disorders.

Methods: From 2008 to 2018, 16 port-a cath catheters were inserted in 11 patients with clotting disorders at Çukurova University and Acibadem Adana Hospital, Hemophilia center. Patient characteristics data was collected including date of birth, diagnosis, age at port-a-cath placement and associated complications. Port-a-caths were inserted using open operative technique with fluoroscopy in all patients. The treatment strategies were noted.

Results: We evaluated 11 patients with clotting disorders in 16 port-a-cath insertion. There were nine patients with severe hemophilia A; of these 3 had high responder inhibitors, one patient with hemophilia B with high responder inhibitors and one patient with factor X deficiency. Port-a-caths were inserted at a median age of 3.2 years (range; from 5 months to 9 years). While no complications were experienced during port-a-cath insertion, three boys of which two has inhibitors developed postoperative hematoma at the operation site. In five patients due to skin perforation at catheter site catheters were removed between 6 months to 2 years (Average 1.25 years induration). Port-a-cath was reinserted to a different site in all four patients. In one patient, Enterobacter cloaca was found from the port catheter therefore catheter was removed after two years.

Discussion/Conclusion: Our experience showed that the use of port-a-cath in children with hemophilia is safe under appropriate conditions in hemophilia centers with appropriate facility and experienced doctors.

Disclosure of Interest: None declared.

P131 | Association of null mutations with inhibitors development in Tunisian hemophiliacs B

H. Elmahmoudi*; R. Ben Othman; F. Ben Lakhal; W. Borji; S. Fekih; M. Achour; K. Zahra; B. Meddeb; E. Gouider

UR14ES11, Tunis, Tunisia

Introduction: Development of inhibitors is less common in PWHB than PWHA. It is associated among others with the type of the F9 gene mutation especially the null mutations. Our aim was to identify mutational profile related to inhibitors in Tunisian PWHB.

Methods: Clinical data are collected from the registry of hemophilia center in Aziza Othmana Hospital and the patient' file. 20 patients with hemophilia B are included among them 2 are severe and developed inhibitors. Molecular analyses are done using PCR/sequencing procedure.

Results: Molecular analysis demonstrates the presence of 2 nonsense mutations in association with inhibitors development. The 2 mutations are p.Glu202X and p.Trp261X identified in 2 hemophiliacs B aged 11 and 10 years old respectively. They developed inhibitors at the age of 3 years and they don't respond to treatment.

As a result of theses 2 mutations, the synthetized factor 9 will be truncated, so it will be unable to achieve the clotting process which correlates with the severe phenotype observed in the 2 patients and also would be explain the inhibitor development genetically.

Discussion/Conclusion: In Tunisia and according the HC of Aziza Othmana data, the prevalence of inhibitors in PWH is lower than the reported one in literature. For patients with hemophilia B only 4 patients developed inhibitors. Null mutations are present in 2 of them. This finding is in accordance with the reported data since the non-sense mutations are the most associated with inhibitors development in hemophilia B. For the 2 other patients molecular analysis is in progress.

Disclosure of Interest: None declared.

P132 | Application of bleeding score in children referred due to preoperative assessment

H. Pergantou*; A. Dettoraki; A. Michalopoulou; M. Mazarakis; S. Saslis; H. Karelioti; Z. Kapsimali; H. Platokouki

Haemophilia Centre/Haemostasis and Thrombosis Unit, "Aghia Sophia" Children's Hospital, Athens, Greece

Introduction: Preoperative risk assessment in children with the application of a screening bleeding questionnaire may help to identify patients at risk for bleeding. Aim: to evaluate the bleeding phenotype in children referred due to preoperative assessment and to investigate the correlations with laboratory results.

Methods: Children referred during the last two years' period for preoperative assessment were included. Bleeding phenotype was determined using the International Society of Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) with supplementary paediatric-specific bleeding symptoms (Bleeding Score-BS: 0-56). Laboratory assessment included haemostasis screening, fibrinogen and also factor VIII, Ristocetin Cofactor (RCof), von Willebrand Factor Antigen (vWFAg), factor XIII or other coagulation factors and platelet function assays, if required.

Results: In total, 83 children (boys: 51.8%), of mean age 8.5 ± 4.1 years, were investigated. Ninety three percent were referred because of preoperative evaluation (54% due to laboratory findings out of normal values-ONV in external laboratory) and 7% because of postoperative bleeding. In 24% of children the abnormal results were not confirmed. In 13.3, 15.6 and 4.8% of children the BS was found 1, 2-5 and 5-12, respectively, while 66.3% had a zero BS. In children with laboratory results ONV and positive bleeding score (20/83) mild vWF deficiency, mild FVII deficiency and other rare bleeding disorders were found (45%, 25% and 30% respectively). In those who had laboratory results ONV and negative bleeding score mild vWF deficiency was revealed in 39%. Children with positive BS had increased probability to have laboratory results ONV and specifically, if BS ≥1: three times higher risk ($P = 0.05$, OR = 3.06, CI: 1.013-9.28), if BS ≥2: 4.6 times higher risk ($P = 0.046$, OR = 4.6, CI: 0.96-21.7). The BS had satisfying specificity (81.5%) and high positive prognostic value (PPV 82.1%), but decreased sensitivity (41%). BS had better sensitivity and specificity in children older than 9 years old.

Discussion/Conclusion: The paediatric ISTH-BAT could be used as a preoperative screening tool for assessing the probability of haemorrhagic events in children, in combination with the laboratory coagulation testing, notably in children of younger ages.

Disclosure of Interest: None declared.

P133 | Summer camp for teens coping with haemophilia

H. Landa*; G. Golan; D. Bashari; R. Tiktinsky; S. Lalezari; A. Barg; S. Levy Mendelovich; T. Barazani Brutman; L. Tevet; G. Kenet

The Israeli National Hemophilia And Thrombosis Institute, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

Introduction: Over 670 Hemophilia A and B patients are being treated at the Israeli National multidisciplinary comprehensive care Hemophilia Center. *The Jordan River Village is a unique overnight camp for children living with chronic, serious or life-threatening illnesses and disorders as well as children with special needs.*

Methods: Every summer 40-45 children and adolescents aged 9 -18 years are hosted in a special summer camp for 4-5 days, accompanied by our medical and psychosocial team. The camp provides a forum for dialogue and free expression, with supportive surroundings that enable: Self-infusion workshop, conducted by a nurse and doctors, psychological support groups, conducted by the psychologist and social worker, education via lectures related to hemophilia, art workshops, swimming, climbing Wall, sports and other outdoor training. All activities are held in secure facilities and supervision.

Results: The ability to participate in these camps contributes to adolescents knowledge, self-confidence, opportunities to socialize, respect for others, independence and individual responsibility which leads to the empowerment of the disease and a better quality of life.

Although teens come home with a whole new set of physical skills, they also gain personal skills. Children learn how to share, cooperate in a group and differentiate between right and wrong. Attendance in the camp has a way of changing children. As they make a new set of friends, teens gain self-esteem and learn how to lead.

Discussion/Conclusion: The following quote of a young patient with Hemophilia expresses the hallmark of summer camp upon our patients: "When you're having a bad day and you're late for school and everybody is stressed out, you think about summer camp and you remember that there are other people in your situation," "A little piece of camp stays with you, no matter what you're doing. It's a brotherhood."

Disclosure of Interest: None declared.

P134 | Recombinant factor VIII Fc (rFVIIIFc) in real life: Clinical and economic outcomes

N. Delmotte[1]; M. Roche[2,3]; R. Giraud[1]; M. Roche[4]; C. Falaise[4]; H. Chambost[4,5,*]; S. Gensollen[1]

[1]*Pharmacie de la Conception, Assistance Publique - Hôpitaux de Marseille;* [2]*UMR CNRS 7273, Aix Marseille Univ;* [3]*Service Central des Opérations Pharmaceutiques SCOP;* [4]*Centre de Traitement de l'Hémophile (CTH), Assistance Publique - Hôpitaux de Marseille;* [5]*INSERM, INRA, C2VN, Aix Marseille Univ, Marseille, France*

Introduction: Recombinant factor VIII Fc fusion protein (rFVIIIFc) has been marketed in October 2016 in France that makes the analysis of switches in real life conditions study of concern two years later. The aim of this study is to analyse rFVIIIFc switches according to clinical and economic outcomes during a 12 months period

Methods: All patients treated with rFVIIIFc at Marseille Hemophilia centre for the considered period were eligible. None estimation on prescribed regimen have been realized. All data were related to patient's infusions (*i.e.* annual number of infusions, weekly dose/kg, and annual consumption) and bleeding reports. The statistical analysis was conducted using GraphPad Prism 6.0 software (*i.e.* average, medians noted med, percentages and inter quartile ranges noted IQR, Student *t*-test and Wilcoxon signed-rank test). Statistical significance was set at $P < 0.005$. Only clotting factor costs are taken into account. We neglected other costs (e.g. dispositive, nurse intervention…).

Results: 52 patients were concerned, 17 excluded for an insufficient period subsequent to the switch, 2 because of clinical trial inclusion. The median age was 18 years (IQR = 17). 94% of patients were previously on full time prophylaxis. The analysis reported a slight increase of clotting factor consumption consecutive to the switch (2%, P = NS 0.7220) with a total utilization of 6453500 IU (med = 176000, IQR = 155500) for rFVIII and 6553500 IU (med = 200000, IQR = 168000) for rFVIIIFc. It is important to note that 26% of patients were < 12 years of age and 28.5% of patients were related to adjustment of doses for weight evolution, clinical need or ease of use. These data were combined with a significant reduction of annual infusions number (−23%, med = 146, IQR = 67 for rFVIII; med = 105 IQR = 25 for rFVIIIFc, $P < 0.0001$) and bleedings (−51%, med = 4.5, IQR = 7.25 for rFVIII; med = 1, IQR = 4 for rFVIIIFc, $P = 0.0003$). Concerning the cost, we noted a non-significant decrease (−5%, med = 126720 €, IQR = 140760 for rFVIII; med = 138096€, IQR = 122670 for rFVIIIFc; P = NS 0.2690)

Discussion/Conclusion: All results suggest that rFVIIIFc may improve the treatment and this analysis seems to corroborate predictive studies already described if we consider each type of patients (age, regimen). This study is a real life evaluation of rFVIIIFc product switches, but should be completed since the switch impacted factor consumption and cost but also quality of life of these patients

Disclosure of Interest: None declared.

P135 | Outcome measures in patients with hemophilia by orthopedists and physiatrists compared with by pediatricians and internists

H. Takedani[1,*]; Y. Tanaka[2]; K. Yamamoto[3]; N. Haga[4]; K. Takikawa[5]; K. Shimada[6]; K. Amano[7]; R. Ueno[8]; M. Shima[9]; K. Makino[10]; Y. Inagaki[2]; N. Ishiguro[11]

[1]*Department of Joint Surgery, Research Hospital, The Institute Of Medical Science The University Of Tokyo, Tokyo;* [2]*Department of Orthopedic Surgery, Nara Medical University, Nara;* [3]*Department of Orthopedic Surgery, Tokyo Medical University;* [4]*Department of Rehabilitation Medicine, The University of Tokyo, Tokyo,* [5] *Department of Pediatric Orthopedics, Shizuoka Children's Hospital, Shizuoka,* [6] *Department of Emergency/Sports Medicine, JCHO Osaka Hospital, Osaka;* [7]*Department of Laboratory Medicine, Tokyo Medical University;* [8]*Department of Rehabilitation Medicine, Tokyo medical university hospital rehabilitation center, Tokyo;* [9]*Department of Pediatrics, Nara Medical University, Nara;* [10]*Department of Rehabilitation Medicine, Shin Ouji Hospital, Kitakyushu;* [11]*Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan*

Introduction: Outcome measurement is one of the most important factors due to evaluate hemostatic control for persons with hemophilia (PwH). This study was conducted to reveal the Japanese status of comprehensive hemophilia care by means of the investigation of outcome measure implementation by internist group (pediatrician and internist) and orthopedist group (orthopedist and physiatrist).

Methods: Questionnaire sheet was send to sixteen institutes which are major hemophilia treatment institutes. The sheets was consisted three domains; respondent domain (specialty, majority of PWH, number of out- and in- PwH), outcome measure domain (symptom, examination, medical resource and life activity) and measurement tool domain (physical findings, imaging and participation and activity).

Results: 27 answered sheets were returned from sixteen institutes and 17 were from internist group (pediatrician and internist) and 10 from orthopedist group (orthopedist and physiatrist). Number of out- and in- patients of orthopedist group were smaller than those of internist group. The interview ratio routinely (per every visit or a couple visit) about most items by internist group were similar or higher than those by orthopedist group. The ratio about physical and articular imaging examination by orthopedist group were higher than those by internists group and orthopedist group know and understand physical and articular imaging examination tool better than internist group. However the ratio about participation and activity by both groups were almost zero and understood not well.

Discussion/Conclusion: In Japan, there are no authorized hemophilia treatment center (HTC) but we have several so-called HTCs. We thought that orthopedists and physiatrists in most of these HTC lack the knowledge and experience about hemophilia and have poor relationship with internist and pediatrician. However our study results showed the improvement in awareness of orthopedist group physicians and better relationship among them. This study results showed evaluation of participation and activity are minor concern

for Japanese physicians compared with outcome measures, as well. In Japan, we are on the way to establish the hemophilia comprehensive care system and we believe it is a timing to do it as hemophilic treatment center.

Disclosure of Interest: None declared.

P136 | Platelet rich plasma for synovitis treatment: 1 year follow up

M. Landro[1]; C. Daffunchio[1]; G. Cambiaggi[1]; G. Galatro[1]; E. Honorat[2]; H. Caviglia[1,*]

[1]*Hospital General de Agudos Dr. Juan A. Fernandez;* [2]*Fundacion de la hemofilia, CABA, Argentina*

Introduction: Haemophilic synovitis is caused by chronic accumulation of blood in the joint. Conservative treatment does not prevent bleeding. We began using PRP for haemophilic synovitis treatment due to its anti-inflammatory properties, and because it contains chondrogenic factors.

The aim of this study was to describe the evolution of chronic haemophilic synovitis treatment by means of PRP injection into the joint after one year follow up.

Methods: 39 patients with 66 chronic synovitis joints were treated and one year followed up. 38 patients were haemophilia type A and 1 type B (32 severe, 6 moderate, 1 mild). Four patients had inhibitors. Mean age was 25 years old (8-48). 38 were located in the knee (57.6%), 15 in the elbow (22.7%) 13 in the ankle (19.7%) joints. Patients were evaluated for Joint perimeter measure, visual analogue scale (VAS), number of bleeding episodes (BE), Haemophilia Joint Health Score (HJHS), range of movement (ROM) before treatment and 3 months, 6 months and 12 months after treatment. PRP was obtained by intravenous blood centrifugation for 8 minutes at 1600 rpm and were injected into the joint cavity of each patient.

Results: The average volume of blood extracted was 15 ml (10-35). The average volume of PRP injected was 4 ml (2-9). The average platelet count was 420 10^3/mL (200-850). All patients reported pain relief, the average VAS before treatment was 5, patients reported pain relief 3, 6 and 12 months after treatment ($P < 0.001$), decrease in joint bleeding episodes was statistically significant ($P < 0.001$) 3 months, 6 months, 12 months after treatment. The HJHS before treatment vs. 3 months, 6 and 12 months after treatment was also statistical significant ($P < 0.001$). Joint perimeter measures also improved 3 months, 6 and 12 months after treatment and was statistically significant for ankle and elbow joints ($P = 0.011$, $P = 0.008$). The range of movement (flexion and extension) improved in all patients but wasn't statistically significant.

Discussion/Conclusion: All patients reported benefit of the PRP therapy. The improvement was very important in the first 3 months, and continues until one year up follow up.

Disclosure of Interest: None declared.

P137 | New synovitis classification

M. Landro; A. Douglas Price; C. Daffunchio; G. Cambiaggi; D. Pereyra; H. Caviglia*

Hospital General de Agudos Dr. Juan A. Fernandez, CABA, Argentina

Introduction: The aim of this work is to present a new synovitis classification adding new information obtained from clinical examination (CE), ultrasound (US) and X-ray (XR) images.

Methods: The new classification establishes a correlation between synovitis type, numbers bleeding episodes (BE), CE, presence of effusion, US and XR.

Results: Grade I: BE: 2 in 6 months; CE windows inflammation (WI) negative; Effusion US (EUS) negative; Synovium US (SUS) absent or starting inflammation; Cartilage US (CUS) normal; PDUS Doppler (PDUSD) absence no vessels, signal in the region; XR normal

Grade II: BE: 3 in 6 months; CE WI positive; EUS slight; SUS mild; CUS: US texture abnormalities focal partial full thickness loss of the articular cartilage, without longitudinal damage of the cartilage; PDUSD absence no vessels, signal in the region or 1 flag, XR normal

Grade III Active Synovitis (AS): BE: recurrent; CE WI: large joint distension; EUS large; SUS moderate or severe; CUS: US texture abnormalities focal partial full thickness loss of the articular cartilage, with longitudinal damage of the cartilage; PDUSD signal in the region 3 flags, XR regional osteoporosis

Grade IV AS: BE: recurrent; CE WI: moderate joint distension; EUS moderate; SUS moderate or severe; CUS: US texture abnormalities focal partial full thickness loss of the articular cartilage, subchondral cyst initial, osteophytes around the joints; PDUSD signal in the region 3 or less flags, XR slight epiphyseal deformity, slight joint narrowing, subchondral cyst, osteophytes.

Grade V Sequel of Synovitis: BE: scarce; CE WI: slight joint distension; EUS slight; SUS moderate; CUS: complete cartilage destruction or absent visualization of the articular cartilage on the target bony surface, presence of prominent osteophytes around the joint; PDUSD absence of vessels signal, XR mild epiphyseal deformity, mild Joint narrowing.

Grade VI Sequel of Synovitis: BE: infrequent; CE WI: slight or absent; EUS slight or absent; SUS moderate or absent; CUS: complete cartilage destruction, presence of prominent osteophytes around the joint; PDUSD no vessels signal, XR moderate or severe epiphyseal deformity, severe joint narrowing.

Discussion/Conclusion: New Technologies allows us to understand the evolution of joint damage after bleeding episodes occurred.

Disclosure of Interest: None declared.

P138 | PRP treatment for chronic synovitis in patients with haemophilia (PWH) and inhibitors

M. Landro; C. Daffunchio; G. Cambiaggi; H. Caviglia*

Hospital General de Agudos Dr. Juan A. Fernandez, CABA, Argentina

Introduction: The development of neutralizing antibodies (inhibitors) directed against factor VIII or FIX is the most serious and costly

complication of replacement therapy in haemophiliacs. Develop inhibitory antibodies which render replacement therapy ineffective, potentially leading to life-threatening bleeding events.

The aim of this work is to show the effectiveness of PRP application for chronic synovitis joints in patients with haemophilia and inhibitors.

Methods: Between 2015 and 2017 nine PWH with 16 chronic synovitis joints (5 knees, 5 ankle, 5 elbow, 1 shoulder) were treated with intra-articular injection of PRP. All were inhibitors patients 8 were haemophilia type A severe, and one type B severe. The average age was 16 years-old (8-27). Patients were evaluated before treatment for Visual Analogue Scale (VAS), number of Bleeding Episodes (BE), Haemophilia Joint Health Score (HJHS), and 6 months followed-up after treatment. PRP was obtained by intravenous blood centrifugation for 8 minutes at 1600 rpm and were injected into the joint cavity of each patient.

Results: All patients reported pain relief and decrease in joint bleeding episodes. The average values before treatment were: VAS 3.7 (0-8), BE 2.3 (1-6), HJHS 14 (8-22) and after treatment were VAS 1.2 (0-10), BE 0.2 (0-1), HJHS 11.1(6-18) and this differences were statistically significant. The mean age of inhibitors patients (16) is lower than the mean age of non-inhibitors patients (25) with synovitis A second PRP application were performed in three patients and a third application were performed in one patient with good results

Discussion/Conclusion: We believe that PRP injection is a simple, safe and mini invasive treatment for joint chronic synovitis, also in patients with inhibitors with good evolution, improving the quality of life of PWH.

Disclosure of Interest: None declared.

P139 | Platelet Rich-Plasma vs chemical synovectomy in patients with chronic synovitis. Cost analysis

G. Galatro[1]; G. Cambiaggi[1]; F. Isobe[1]; M. Landro[1,2]; C. Daffunchio[1]; E. Honorat[2]; H. Caviglia[1,*]

[1]*Hospital General de Agudos Dr. Juan A. Fernandez;* [2]*Fundacion de la hemofilia, CABA, Argentina*

Introduction: Chronic synovitis represents a very frequently pathology in patients with hemophilia, which represents an important cause in the deterioration of the quality of patients life. Platelet Rich-Plasma (PRP) is defined as a biological treatment based on the intra-articular delivery of autologous platelet growth factors. Rifampicin treatment is an intra-articular injection of a commercial antibiotic. Chemical synovectomy is effective in small joints and ineffective in big joints as in the knee. The aim of this work is to compare the cost of intra-articular injection of PRP vs Rifocin for chronic synovitis joints in PWH

Methods: The Chemical Synovectomy and the application of PRP are outpatient procedures performed in the operating room with aseptic technique and intra-articular injection of the Rifampicin or PRP respectively. The chemical synovectomy can be done in two ways. One is in the office and the other in the operating room. We carry out a cost evaluation describing the basic materials (gauzes, surgical fields, etc.) and the specifics materials required for each procedure (Tubes BD Vacutainer with ACD, butterfly needles, pipettes, Rifampicin, etc).

Results: The total cost of disposable supplies that involves the Chemical Synovectomy using Rifampicin is US$ 38 each application but an average of 3 applications are necessary for each small joint. The cost for the application of PRP is US$ 50 including professional fees and the laboratory equipment. Other associated expenses should be considered in both treatments such as the cost of the clotting factor (7000 Units/US$ 5900-8400 for patients without or with inhibitors respectively), the operating room is US$ 150 for each application. According to our calculations, no significant differences were found in terms of individual cost. It is very important to consider the cost-benefit, as we have seen that the application of Rifampicin causes pain in 16% of cases and is not effective in large joints and several applications are necessary in small joints, increasing the cost.

Discussion/Conclusion: The intra-articular injection of Rifampicin is similar to PRP, but is not effective in large joints, presents pain in 16% of applications, more than one application is needed and in some countries it is not authorized intra-articular application.

Disclosure of Interest: None declared.

P140 | Cost comparison between PRP injection vs radioactive synovectomy in patients with chronic synovitis

M. Landro[1,2]; T. Etcheverry[1]; C. Daffunchio[1]; G. Cambiaggi[1]; D. Neme[2]; H. Caviglia[1,*]

[1]*Hospital General de Agudos Dr. Juan A. Fernandez;* [2]*Fundacion de la hemofilia, CABA, Argentina*

Introduction: Chronic synovitis represents a common pathology in patients with haemophilia (PWH). Many treatments have been described for this pathology, with different results and costs. Radioactive Synovectomy is a minimally invasive method for treating persistent joint inflammation. It consists in an only dose intra-articular injection of radioactive colloids which induces hypertrophic synovial membrane necrosis and fibrosis. Platelet Rich-Plasma is defined as a biological treatment based on intra-articular injection of autologous platelet growth factors. The aim of this work is to perform a cost comparative study of PRP injection versus radioactive synovectomy with Yttrium or Phosphorus isotopes treatment in patients with chronic synovitis.

Methods: Both techniques are outpatient procedures performed at the surgery room with aseptic technique, which have shown favorable results in swelling, pain and joint bleeding episodes decrease. The use of radioactive substances requires, a professional and a

place authorized for its application and storage, which is not allowed in low complexity centers, and to perform it, patients must come together to make the best use of the isotope. We made a cost evaluation in association with the accounting department, detailing the basic supplies (gauzes, surgical fields) and technic-associated special supplies (tubes, butterfly needles, pipettes, radioisotopes, etc) of each procedure, and the cost of clotting factors substitutes.

Results: The cost of intra-articular PRP injection is US$ 50 including the professional fares. The cost of the procedure is US$ 186 plus US$ 30 of disposable materials. The total cost of Radioactive Synovectomy depends on the isotope, for Yttrium is US$ 4716 (Yttrium US$4500); for phosphorus is US$ 966 Phosphorous US$750). Ninety-five and nineteen times more expensive than PRP. The clotting factor cost is the same for the radioactive synovectomy and for PRP according to the patient needs, and the surgical room and clothes cost is US$150 for each procedure.

Discussion/Conclusion: The radioactive synovectomy in our country it is an expensive technique and should be used in early stages of the disease and requires a professional and a place authorized for its application.

Disclosure of Interest: None declared.

P141 | Comparison between the cost of PRP versus synovioangiolysis in patients with chronic hemophilic joint synovitis

M. Landro[1]; C. Daffunchio[1]; G. Cambiaggi[1]; G. Galatro[1]; E. Honorat[2]; M. Margullies[1]; R. Lunardon[1]; H. Caviglia[1,*]

[1]*Hospital General de Agudos Dr. Juan A. Fernandez;* [2]*Fundacion de la hemofilia, CABA, Argentina*

Introduction: Synovioangiolysis is a selective procedure of depreciation of the synovium affected by synovitis. To perform this procedure requires facilities to perform angiography and trained radiologist for the realization of synovial ablation.PRP is an effective and simple method to treat synovitis. We are comparing the costs between both techniques: PRP injection and Synovioangiolysis. The aim of this work is to compare the cost of PRP application for chronic synovitis in patients with hemophilia (PWH) vs synovioangiolysis.

Methods: The techniques to be evaluated are the synovioangiolysis and the intra-articular application of platelet-rich plasma. Synovioangiolysis is performed in the angiography suite by puncturing the femoral artery to reach the affected region with the catheter. Requires hospitalization for 5 days. PRP is outpatient and simple procedure. We carried out a complete cost evaluation (gauzes, surgical fields, etc.) and inputs per se (ACD tubes BD Vacutainer, butterfly needles, pipettes, etc) of each procedures.

Results: The cost of the PRP injection is US$ 50 and must be prepared by a trained professional using specific laboratory equipment to obtain a safe product. The intra-articular injection must be performed in an operating room. The cost of using the operating room US$ 150, sterile surgical drops, clothes and gloves US$ 25 should be taken into account. Making it a grand total of US$ 225.

The cost of the synovioangiolysis procedure is US$ 1800 and must add the cost of the materials for embolization of each artery (coils US$ 400 /doses).

Other associated expenses should be considered, such as the use of the clotting factor cost for PRP application between US$ 5900-8400 and for synovioangiolysis is US$25 725-36 000 (is not or is an inhibitor patient) also the fees of the medical professional who performs the injection must be considered.

Discussion/Conclusion: Although both techniques have been proven useful in the treatment of haemophilic synovitis, the PRP injections have lower overall requirements and costs, making it the preferable option in most centers.

Disclosure of Interest: None declared.

P142 | Comparison between the costs of PRP vs arthroscopic synovectomy in patients with chronic synovitis

M. Landro[1]; G. Cambiaggi[1]; G. Galatro[1]; E. Honorat[2]; M. Margullies[1]; H. Caviglia[1,*]

[1]*Hospital General de Agudos Dr. Juan A. Fernandez;* [2]*Fundacion de la hemofilia, CABA, Argentina*

Introduction: Chronic synovitis represents a very frequently pathology associated with patients with hemophilia, which in turn represents an important cause in the deterioration of patient's quality of life. The arthroscopic synovectomy is a demanding procedure and requires considerable resources including skilled personnel, surgical equipment. The PRP injection has lower requirements and is a simpler technique. The aim of this work is to compare the cost of PRP application vs arthroscopic synovectomy for chronic synovitis joints in patients with hemophilia.

Methods: The techniques to be evaluated are the arthroscopic synovectomy and the intra-articular application of platelet-rich plasma. The PRP injection is an ambulatory procedure, meanwhile, the arthroscopic synovectomy requires 7 days of hospitalization. Both performed in the operating room with aseptic technique, and both have shown favorable results by decreasing swelling, pain and recurrence of joint bleeding, and preserving joint function.

We carried out a complete cost evaluation of each of the procedures (tubes BD Vacutainer with ACD, butterfly needles, pipettes, shaver cannula, etc), also taking into account the cost of substitute coagulation factors needed for each procedure.

Results: The cost of the PRP injection is US$ 50 and must be prepared by a trained professional using specific laboratory equipment to obtain a safe product. The intra-articular injection must be performed in an operating room with a cost of US$ 150, sterile surgical drops, clothes and gloves US$ 25 should be taken into account.

Making it a grand total of US$ 225. PRP requires 7000 Units of clotting factor (US$ 5950-8200).

The cost of the arthroscopic synovectomy procedure is US$ 1160 (surgical time, disposables, 2 shaver cannulae and 1 arthroscopic radiofrequency wand, sterile clothes). Being patients with hemophilia, seven days hospitalization are required with a cost of US$ 120 per day (total US$ 960) and an average of 49000 Units of clotting factor (US$ 41820) are needed with a total cost of US$ 43946.

Discussion/Conclusion: Although both techniques have been proven useful in the treatment of hemophilic synovitis, the PRP injections have lower overall requirements and costs, with very good results making it the preferable option in most centers.

Disclosure of Interest: None declared.

P143 | Platelet Rich-Plasma for chronic synovitis treatment: open vs closed obtaining technique

M. Landro; C. Daffunchio; G. Cambiaggi; G. Galatro; H. Caviglia*

Hospital General de Agudos Dr. Juan A. Fernandez, CABA, Argentina

Introduction: Platelet Rich-Plasma (PRP) is used to stimulate healing of the joint and provide symptomatic relief. The biological rationale behind this kind of treatment is the topical administration of several molecules involved in joint homeostasis, healing mechanisms and tissue regeneration.

The aim of this work is to evaluate the costs of chronic synovitis treatment using Platelet Rich-Plasma (PRP) open vs closed technique.

Methods: PRP is defined as a biological treatment based on the intra-articular delivery of autologous platelet growth factors. It was obtained by centrifugation of autologous blood. It can be obtained by open or close technique. In the open technique an average of three ACD tubes a butterfly, and a holder (BD Vacutainer ® blood collection set) were used. The blood was centrifuged for 8 minutes at 1600 rpm (Presvac® centrifuge). PRP was separated in a biological safety cabinet (Esco® II) under sterile conditions and placed in a syringe with a needle for the intra-articular injection. The cost of disposable materials was US$ 15. Use of laboratory equipment and a professional who prepares the PRP US$ 35 must be added.

Results: The total cost of the open technique is US$ 50 and must be prepared by a trained professional using specific laboratory equipment to obtain a safe product.

The commercial closed device (Regen Lab SA, Switzerland) all materials and equipment are included in the kit. Since it is a closed device, has the advantage that can be applied in any institution since it does not need specialized personnel or complex equipment for its elaboration and avoids the contamination of the professionals by manipulation of the plasma. The cost of the kit is US$ 300.

In both cases the intra-articular injection must be performed in an operating room. The cost of using the operating room US$ 150, sterile surgical drops, clothes and gloves US$ 25 should be taken into account. Other associated expenses should be considered, such as the use of the coagulation factor cost between US$ 5900-8400/7000 units (is not or is an inhibitor patient) and the fees of the medical professional who performs the injection.

Discussion/Conclusion: We believe that PRP injection is a simple, safe, inexpensive and mini-invasive treatment for joint chronic synovitis, no matter which of the two obtaining techniques is used, that will depend on the possibilities of each institution and the regulations of each country.

Disclosure of Interest: None declared.

P144 | Thromboelastometry may be useful to guide treatment for breakthrough and perioperative bleeds of patients on prophylaxis with emicizumab

I. Fernandez-Bello[1,*]; M. Alvarez-Roman[1]; M. Martin-Salces[1]; I. Rivas-Pollmar[1]; S. Garcia-Barcenilla[1]; M. D. C. Garcia-Martinez[2]; T. Cebanu[1]; P. Acuña-Butta[1]; R. Justo-Sanz[1]; E. Monzon-Manzano[1]; N. Butta-Coll[1]; V. Jimenez-Yuste[1]

[1]*Haematology, La Paz University Hospital-IdiPAZ;* [2]*Haematology, La Paz University Hospital, Madrid, Spain*

Introduction: There is concern on what dose of factor concentrates should be used to treat breakthrough or perioperative bleeds in patients on prophylaxis with emicizumab. We anticipated that thromboelastometry (ROTEM®) might be useful to guide treatment in this setting.

Methods: 11 adult patients (5 with inhibitors) on prophylaxis with emicizumab and 10 healthy controls were included. Whole blood was drawn using sodium citrate (3.2%) tube prefilled with corn trypsin inhibitor (50 µg/mL final concentration, HT, USA). In case of treatment with factor concentrates, one sample before and 10 minutes after treatments were obtained. ROTEM® was activated by 10 µL of tissue factor (final dilution 1:200 000 Recombiplastin, Werfen, Spain) and 20 µL of $CaCl_2$ (star-tem, Werfen, Spain). rFVIIa [Novoseven], aPCC [FEIBA] or FVIII were added *in vitro* to reach final concentrations equivalents to those obtained after *in vivo* administration of 90-45-23 µg/kg rFVIIa, 50-10-5-2.5 UF/kg aPCC and 25-12.5 IU/kg FVIII respectively. ROTEM® was initiated after adding 300 µL of blood. Clotting-time (CT) and maximum clot firmness (MCF) were recorded. Statistical analysis was performed with GraphPad Prism 5.

Results: 4 patients (36%) normalized their procoagulant function after 4 doses of charge (3 mg/kg/week) of emicizumab. In vitro spiking showed normalization of all ROTEM® profiles with concentrations equivalent to 2.5 IU/kg aPCC, 23 µg/kg rFVIIa and 25 IU/kg FVIII (patients without inhibitors). Interesting, ROTEM® profiles were normalized in 66% of patients without inhibitors after *in vitro* addition of 25 IU/dL of FVIII. One cholecystectomy in 1 patient with inhibitors was followed by ROTEM® and successfully covered by 1 dose of 90 µg/kg of rFVIIa. ROTEM® showed good correspondence

between *in vitro* and *ex-vivo* effect of rFVIIa so prophylactic doses of 23 μg/kg/day were used during 4 days and no bleeding events were observed.

Discussion/Conclusion: ROTEM® might be helpful for tailoring treatments with factor concentrates in patients on prophylaxis with emicizumab. Low doses of 23 μg/kg rFVIIa, 2.5 IU/kg aPCC or 25 IU/kg of FVIII (patients without inhibitors) might be enough to normalize procoagulant function in patients on prophylaxis with emicizumab. Low doses of rFVIIa might be useful as prophylactic treatment in the post-surgical setting in these patients.

Disclosure of Interest: I. Fernandez-Bello Grant/Research support from: Pfizer, Consultant for: Novo Nordisk, Paid Instructor at: Pfizer, Roche, Novartis, M. Alvarez-Roman Grant/Research support from: Shire, Consultant for: Pfizer, Sobi, Paid Instructor at: Pfizer, Roche, Novartis, M. Martin-Salces Paid Instructor at: Pfizer, Roche, Novartis, I. Rivas-Pollmar Paid Instructor at: Pfizer, Roche, Novartis, S. Garcia-Barcenilla Consultant for: Novo Nordisk, Paid Instructor at: Pfizer, Roche, M. D. C. Garcia-Martinez: None declared., T. Cebanu: None declared., P. Acuña-Butta: None declared., R. Justo-Sanz: None declared., E. Monzon-Manzano: None declared., N. Butta-Coll Paid Instructor at: Pfizer, Roche, Novartis, V. Jimenez-Yuste Grant/Research support from: Pfizer, Consultant for: Shire, Bayer, CSL-Behring, Grifols, Novo Nordisk, Sobi, Roche, Octapharma and Pfizer, Paid Instructor at: Pfizer, Roche, Novartis, Speaker Bureau of: Shire, Bayer, CSL-Behring, Grifols, Novo Nordisk, Sobi, Roche, Octapharma and Pfizer.

P145 | Ultrasonography detects joint alterations in pediatric patients with severe haemophilia A on long term prophylaxis

I. Fernandez-Bello[1,*]; H. De la Corte-Rodriguez[2]; N. Butta-Coll[1]; M. Alvarez-Roman[1]; M. Martin-Salces[1]; I. Rivas-Pollmar[1]; V. Jimenez-Yuste[1]

[1]Haematology, La Paz University Hospital-IdiPAZ; [2]Physical Medicine and Rehabilitation, La Paz University Hospital, Madrid, Spain

Introduction: Joint bleeds (haemarthrosis) are the most frequent cause of morbidity in patients with severe haemophilia (SH). Recurrent haemarthrosis leads to the development of chronic arthropathy that causes pain and increases the cost of the treatments. Prophylactic infusion of factor concentrates decreases the number of joint bleeds and therefore may protect patients from the development of joint damage. We aimed to determine the join condition of pediatric patients on long term prophylaxis by the Hemophilia Joint Health Score (HJHS) and the Hemophilia Early Arthropathy Detection with Ultra Sound (HEAD-US) scoring system.

Methods: Children with SHA on long term prophylaxis treatment were invited to participate in the study. Joint condition was evaluated using HJHS and HEAD-US scores by the same expert. Statistical analysis was done with SPSS 17.0 (USA).

Results: 24 children with SHA without inhibitors were included. Age (mean±SD) was 8.7 ± 3.6 years old. Only 4 patients (16.7%) had HJHS>0 (median [25p-75p]= 17 [11-41]). HEAD-US score showed higher number of patients with joint alterations (29%) which suggested better sensibility of HEAD-US score compared with the HJHS for evaluation of the joint condition in this type of patient.

Discussion/Conclusion: Pediatric patients with SHA under long term prophylaxis treatment may have joint alterations. This joints alteration may be better detected using ultrasound examination (HEAD-US). Further studies are needed to determine causes involved in the development of joint damage in this type of patients. This study was funded by SOBI.

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P146 | Thromboelastography may be useful for tailoring treatment of breakthrough bleeds in patients on prophylaxis with Concizumab

I. Fernandez-Bello[1,*]; M. Alvarez-Roman[1]; M. Martin-Salces[1]; I. Rivas-Pollmar[1]; S. Garcia-Barcenilla[1]; M. D. C. Garcia-Martinez[2]; T. Cebanu[1]; P. Acuña-Butta[1]; R. Justo-Sanz[1]; E. Monzon-Manzano[1]; N. Butta-Coll[1]; V. Jimenez-Yuste[1]

[1]Haematology, La Paz University Hospital-IdiPAZ; [2]Haematology, La Paz University Hospital, Madrid, Spain

Introduction: There is concern on what dose of factor concentrates should be administered to treat breakthrough bleeds in patients with severe haemophilia (SH) on prophylaxis with concizumab. We anticipated that thromboelastography (TEG) might be useful in this setting.

Methods: 3 adult patients (2 SHB with inhibitors and 1 SHA) on concizumab prophylaxis and 6 healthy controls were included. Sodium citrate tube (SARSTEDT) prefilled with corn trypsin inhibitor (50 μg/mL final concentration, HT, USA) was used for sampling. In case of bleeds, one sample before and 10 minutes after treatments with factor concentrates were obtained. For TEG, 10 μL of tissue factor (final dilution 1:200 000 Recombiplastin, Werfen, Spain), 20 μL of $CaCl_2$ (0.2 M, TEG Hemostasis System, USA) and 10 μL of rFVIIa

[Novoseven], aPCC [FEIBA] or FVIII were added to reach final concentration equivalents to the in vivo administration of 90-45-10 μg/kg rFVIIa, 50-25-10 UF/kg aPCC or 25 IU/kg FVIII. TEG was initiated after adding 340 μL of blood. Reaction-time (R), kinetic-time (K), alpha angle (α) and maximum amplitude (MA) were recorded. Statistical analysis was done with GraphPad Prism 5.

Results: K and α were not obtained in most of the tests evaluated at trough level of concizumab. R but not MA correlated with increasing concentrations of factor concentrates, therefore R was the chosen parameter for describing the procoagulant function of subjects. At trough levels of concizumab, mean R value was much longer than the normal range. However, minimal concentrations of rFVIIa, aPCC or FVIII, equivalents to the administration of 10 μg/kg rFVIIa, 10 IU/kg aPCC or 25 IU/kg FVIII normalized the TEG profiles of patients (13 ± 2 minutes for rFVIIa, 5 ± 1 minutes for aPCC and 42 minutes for FVIII; healthy controls: 39 ± 9 min). In correspondence with these data, 1-3 doses of 20 μg/kg/day of rFVIIa and 1 dose of 25 IU/kg/day of FVIII were sufficient to control several breakthrough bleeds in patients with inhibitors (3 mild haemarthrosis and 1 mild hematoma) and in the patient without inhibitor (2 shoulder mild haemarthrosis) respectively.

Discussion/Conclusion: TEG might be helpful for tailoring treatments with factor concentrates in patients on prophylaxis with concizumab. Low doses of rFVIIa or FVIII were useful to control mild bleeds in these patients. Low doses of aPCC might be also helpful for control bleeding in this type of patients.

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P147 | Bone lesions in patients with inherited bleeding disorders: Analysis of 4 cases

A. Koca Yozgat[1]; I. Ok Bozkaya[1,*]; T. Demirkan[2]; V. Çulha[1]; N. Y. Özbek[1]

[1]*Pediatric Hematology and Oncology;* [2]*Pediatric Radiology, Pediatrics Hematology Oncology Training and Research Hospital of Ankara Health Sciences University, Ankara, ANKARA, Turkey*

Introduction: Haemophilia is a common cause of genetically inherited bleeding disorders and bone lesions are rarely seen in hemophilic patients. Hemophilic pseudotumor is an encapsulated hematoma resulting of repeated episodes of bleeding in the bone, subperiosteum or soft tissue. It is reported in 1%-2% of haemophilic patients. The lesion most frequently occurs in the femur. A hemophilic pseudotumor may cause no symptoms and remain unchanged for decades and then suddenly becomes the source of bleeding and perforation.

Methods: Here, we present bone lesions of three patients with hemophilia A and one patient with afibrinogenemia. Only one patient had symptoms, such as pain. The other lesions were incidentally detected during target joint magnetic resonance imaging (MRI).

Results: Patient 1 was 16 years old boy with afibrinogenemia. We determined cystic lesions in both fibulas, that were suggestive of hemophilic intraosseous pseudotumors, when imaging his target joint of left ankle 10 months ago (Figure 1). He was on prophylaxis with fibrinogen concentrate for 9 months after detection of hemophilic pseudotumor.

Patient 2 was 21 years old boy with hemophilia type A. He was on prophylaxis with factor VIII for 7 years. We determined 15 mm subchondral cystic lesion in right tibia, that was called hemophilic pseudotumor, during target joint MRI without symptoms 4 years ago (Figure 2). We did not change the treatment and he is on follow up without symptoms since detection of hemophilic pseudotumor.

Patient 3 was 13 years old boy with hemophilia A. He was on prophylaxis with factor VIII for 8 years. His target joint was left knee and during MRI nonossifying fibroma was determined on proximal tibia 5 years ago. Up to date, he has no symptoms and on follow up with prophylaxis.

Patient 4 was 16 years old boy with hemophilia A. His factor level is 4 IU and he has no bleeding symptom. He was admitted complaint of pain in the right knee 2 years ago. On MRI there was an exocytosis in right proximal tibia, 9 months ago. Follow up was recommended by orthopedist.

During follow up, there was neither enlargement of the bone lesions nor new lesions formation.

Discussion/Conclusion: The pseudotumor is a well known complication of hemophilia. Management of hemophilic pseudotumors is not well established. In hemophilic patients, we recommend careful imaging for other bone lesions. In our patients no therapy is needed. Since their lesions were stable without symptoms.

Disclosure of Interest: None declared.

P148 | Congenital combined deficiency of coagulation factors VII and XIII: About two cases

I. Frikha[1,*]; M. Fatma[2]; B. A. Imen[3]; R. Taycir[4]; M. Héla[4]; K. Choumous[2]; M. Moez[1]; E. Moez[1]

[1]*Hematology, Hedi Chaker Hospital, Sfax, Tunisia;* [2]*Laboratory Hematology, Habib Bourguiba Hospital;* [3]*Clinical Hematology;* [4]*CRTS, Hedi Chaker Hospital, Sfax, Tunisia, Sfax, Tunisia*

Introduction: Combined deficiency of coagulation factors is considered as an extremely rare inherited bleeding disorder. We describe

two cases family with a combined deficiency of coagulation factor VII and XIII.

Methods: We report our experience about a combined congenital deficiency of factor VII and XIII.

Results: *Case 1:* A 2-year-old male patient was admitted to hematology department following the occurrence of an expanded scalp hematoma secondary to benign cranial trauma. He was the offspring of a consanguineous marriage. His parents and sister had no history of hemorrhage. The laboratory tests showed a prolonged prothrombin time PT = 36%, corrected using a mixing study. Prolonged activated partial thromboplastin time(aPTT) and fibrinogen levels were normal. The factor VII activity (FVIIC) has dropped to reach 2%. Our patient was then diagnosed with a congenital FVII deficiency. The family survey revealed heterozygous F7 genotypes for both parents and the sister. Their FVIIC levels were respectively of 40%, 44% and 50%. Over the following thirty years, our patient showed several clinical bleedings manifestations: scalp hematoma, and hemarthrosis treated with FFP infusions with a good response. Case 2: A 34-year-old woman, the sister of case 1. Since seven years old, she was diagnosed with a heterozygous FVII deficiency. At January 2018, she suffered from an acute abdomen pain. The tomography scan revealed an abundant haemoperitoneum. Laboratory data revealed severe anemia (hemoglobin = 5 g/dL). Haemostasis showed normal levels of PT, aPTT and fibrinogen. The analysis of factor XIII showed an activity of 0% and a FVIIC level of 50%. Immediately, she received repeated injections of FFP and red blood cells transfusions with a good response. We retrospectively analyzed her brother's factor XIII activity which was 0% concluding to combined FVII and XIII deficiency. The search of mutations for our two patients is underway.

Discussion/Conclusion: Combined deficiencies of coagulation factors are considered as uncommon inherited bleeding disorders. In fact, only few cases of FVII deficiency have been reported in combination with others factors deficiencies and one single case was reported with a combined FVII and FXIII deficiency. Added to that, the spontaneous haemoperitoneum couldn't be explained by a simple heterozygosity in F7 genotype. It would be, then, interesting to search for combined factor defects to explain bleeding disorders.

Disclosure of Interest: None declared.

P149 | Congenital factor XIII deficiency and pregnancy case report

I. Frikha[1,*]; M. Medhaffer[1]; H. Gassara[1]; C. Kallel[1]; C. Kais[2]; M. Elloumi[1]

[1]*Hematology;* [2]*Gynecology department, Hedi Chaker Hospital, Sfax, Tunisia*

Introduction: Congenital Factor XIII (FXIII) deficiencies a rare genetic bleeding disorder, which can result in life-threatening hemorrhage. This disease is associated with some clinical complications including umbilical bleeding, intracranial bleeding, subcutaneous or soft tissue bleeding and also pregnancy loss in affected women. In this study, we report a case of congenital FXIII deficiency with 2 successful pregnancies.

Methods: we report a case of congenital FXIII deficiency with 2 successful pregnancies.

Results: *Case report:* A 13-year-old girl patient was admitted to our clinical hematology department following the occurrence of an expanded mandibular spontaneous hematoma. She was the offspring of a consanguineous marriage. She has five siblings with one sister had a history of recurrent hemorrhages. Suspecting bleeding disorder, prothrombin time, activated partial thromboplastin time, bleeding time and platelet count were investigated. All these laboratory tests were within normal limits. As the patient had the history of bleeding from healthy umbilical cord and an expanded spontaneous hematoma, we complete the analysis with factor XIII activity which was 0% and the level of factor XIII subunit A was 0 UI/dL, concluding to the congenital FXIII A deficiency. Our patient showed several clinical bleedings manifestations as well as umbilical stump, soft tissue bleeding and hematoma in the right to intramuscular injection. The management of bleeding disorders was based on fresh frozen plasma (FFP) infusions with good response associated with a mensual long-term prophylactic regimen. Our patient became pregnant twice, in 2014 and 2017; during pregnancy, the FFP monthly administration schedule was not modified, and gave birth to 2 healthy babies after a cesarean sections without any pre-partum or post-partum hemorrhage.

Discussion/Conclusion: Congenital factor XIII deficiency is a rare genetic bleeding disorder that is inherited in an autosomal recessive manner. Umbilical cord hemorrhage remains the earliest and most characteristic hemorrhage. In addition to menorrhagia, pregnant women, without a prophylactic treatment by FXIII concentrates, have a risk of miscarriage in 68%, a premature delivery in 28% and postpartum hemorrhage in 25% of cases. So that the replacement therapy must be recommended during pregnancy to maintain the level of plasma XIII activity during pregnancy and labor.

Disclosure of Interest: None declared.

P150 | Finding the smallest detectable change (SDC) of the haemophilia activities list (HAL): preliminary results

I. A. Kuijlaars[1,*]; J. van der Net[2]; R. E. Schutgens[1]; K. Fischer[1]

[1]*Van Creveldkliniek, University Medical Center Utrecht, Utrecht University;* [2]*Child Development and Exercise Center, University Medical Center Utrecht, Utrecht University, University Children's Hospital, Utrecht, Netherlands*

Introduction: The Haemophilia Activities List (HAL) measures self-reported limitations in activities and participation in adult patients with haemophilia. The Smallest Detectable Change (SDC) is a measure for reliability; it is the smallest change in score that you can detect above the measurement error. This study aimed to determine the SDC of the HAL.

Methods: Adult patients (≥18 years) with mild to severe haemophilia completed the HAL repeatedly between September 2017—September 2018. The first HAL (T0) was completed during a visit at the Van Creveldkliniek, Utrecht, The Netherlands. The second HAL (T1) was sent by mail after three weeks and patients were asked to complete the questionnaire within one week. Patients were excluded if they had a recent bleed at T0 or T1. The HAL score ranges from 0-100, with 100 as optimum score. The SDC, agreement was calculated for sum and component scores. The SDC, agreement include the systematic difference. A total of 50 patients will be included in this study, according the COSMIN guidelines.

Results: Thirty-seven patients with haemophilia A/B (24% mild/3% moderate/72% severe, median 52 years [range 20-79]) were included. The median (interquartile range [IQR: P25-P75]) HAL sum score at T0 was 73.5 (59.1-95.7). The median (IQR) HAL sum score at T1 was 77.8 (60.8-98.0). Median (IQR) time between measurement at T0 and T1 was 3.7 weeks (3.0-5.4). The SDC, agreement for the sum score was 9.3, for the basic lower extremity component 15.8, for the complex lower extremity component 13.6 and for the upper extremity component 9.6.

Discussion/Conclusion: The SDC of the HAL sum score in Dutch patients with mild to severe haemophilia was 9.3, determined in this preliminary analysis with 37 patients. A change of the HAL >9.3 in one patient signifies a true change. To improve interpretation of HAL scores, the SDC should be combined with clinical patient evaluation (Minimally Important Change). This will establish the smallest change in score which patients perceive as important.

Disclosure of Interest: None declared.

P151 | Using individual pharmacokinetic parameters on octocog alfa to predict individual pharmacokinetic parameters on efmoroctocog alfa in persons with hemophilia A

J. Yu[1,*]; P. Chelle[1]; A. Iorio[2,3]; A. Edginton[1]

[1]*School of Pharmacy, University of Waterloo, Waterloo;* [2]*Health Research Methods, Evidence, and Impact;* [3]*Medicine, McMaster University, Hamilton, Canada*

Introduction: Not accounting for between-subject PK variability (BSV) when switching between products may increase bleeding risk or waste resources. There is no established way of predicting an individual subject's PK before using a new product. This study proposes a method to forecast the subject's dose on a new product by combining the individual PK profile before the switch with the PopPK model of the new product.

Methods: Individual dense PK data of subjects switching from octocog alfa (OCT) to efmoroctocog alfa (EFM) were obtained from a phase 3 study. [1] The PopPK models for OCT and EFM were those currently used in WAPPS-Hemo. Three methods to estimate individual PK parameters of EFM were compared. All used the EFM PopPK model: Method A used EFM's average population value; method B used EFM's population values for an individual with the same covariates as the study; and method C used individual scaled eta-values (η). The η is the individual deviation from the typical population value. The η of OCT (~N(0,1)) was normalized to the η of EFM (~N(0,1)). The individual η for EFM was calculated by multiplying the ratio between the standard deviations of the BSV on OCT and EFM and the individual η of OCT. Mean relative errors of predicted versus observed were reported. Regression slopes and 95% confidence intervals were calculated between the predicted and observed PK parameters. A regression line with a confidence interval including the line of identity (slope of 1) indicated a valid prediction.

Results: Twenty-nine subjects switched from OCT to EFM. The median [range] age of the subjects was 31 [15-62] years, body weight of 74 [56-129] kg, and height of 173 [163-188] cm. The mean relative errors [range] for CL, V1, and half-life for method C were 15% [0-45%], 8% [0-22%], and 12% [0-28%] respectively, and were lowest compared to methods A and B across all PK parameters. The regression slopes (95% CI) of all methods were significantly different from the line of identity, except for V1 of method C showing a slope of 0.84 (0.68, 1.01).

Discussion/Conclusion: Our study confirms that our proposed method (method C) produced the most accurate prediction of the expected individual PK profile on EFM and can thus guide clinicians in tailoring the initial regimen on a new product before giving the first dose.

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P152 | Factor-life: Patient lifestyle factors associated with optimal haemophilia A management in children

J. O'hara[1,*]; C. Hirst[2]; S. Kessabi[2]; R. Farej[3]; T. Burke[1]

[1]*HCD Economics, University of Chester, Chester, United Kingdom;* [2]*Bayer, Basel, Switzerland;* [3]*Bayer, Whippany, United States*

Introduction: Despite recent treatment advances, many children with moderate and severe haemophilia A (CWHA) still experience pain, mobility issues, and compromise in daily activities. The objectives of this study were firstly to describe non-clinical aspects of life with haemophilia (levels of physical and social activity, perceived compromise, health-related quality of life [HRQoL]) in CWHA, and secondly to report influences upon these (such as disease severity, comorbidities and treatment regimen).

Methods: A descriptive analysis was conducted of data from a cross-sectional survey and chart review study conducted in 2018 (CHESS Pediatrics; comprising 1050 CWHA). From this large dataset, responses from 256 patients with documented moderate or severe haemophilia A, residing in France, Germany, Italy, Spain,

or the UK, and who completed a patient survey, were included in this analysis.

Results: Across the CWHA, substantial levels of compromise and lifestyle impact were reported. Impact of haemophilia on usual activities was reported as 'some' or 'a lot' in 52% of school-aged children. Those reporting negative impact also reported higher anxiety and bleed rates and more joint damage and target joints; more of these patients had history of FVIII inhibitors. The mean IU/kg dose, frequency of injections and both physician- and patient-reported adherence were similar in those with and without impact. Rates of comorbidities were also higher in CWHA with lifestyle impact than those without. A high proportion of all patients/caregivers reported a significant impact of haemophilia on family life, notably 94% of caregivers for patients aged 0-4 years. Caregiver involvement in treatment decisions was highest in this age group and declined into adolescence.

Discussion/Conclusion: The CHESS Paediatric study provides one of the richest sources of linked clinical and patient-reported data for CWHA. In these preliminary analyses, an association was noted between compromise in lifestyle and severe clinical phenotype (bleeding rates, target joints and inhibitor history). However, this subgroup was not associated with more intensive treatment compared to those without lifestyle compromise. This analysis suggests that personalisation of treatment regimen to an individual's lifestyle may not be widely practised.

Disclosure of Interest: J. O'hara Shareholder of: HCD economics Ltd, Consultant for: Alnylam, Pfizer, Roche, Bayer, Shire, SOBI, Novo Nordisk, Paid Instructor at: EHC, UKHS, C. Hirst Employee of: Bayer, S. Kessabi Employee of: Bayer, R. Farej Employee of: Bayer, T. Burke: None declared.

P153 | BAY 81-8973 in the real world: clinical effectiveness and safety in patients with haemophilia A across the us and europe

J. O'Hara[1,2,*]; C. Hirst[2]; S. Rauchensteiner[3]; T. Burke[2]

[1]*University of Chester;* [2]*HCD Economics, Chester, United Kingdom;* [3]*Bayer, Basel, Switzerland*

Introduction: BAY 81-8973 (Kovaltry®, Bayer) is an unmodified, full-length, recombinant FVIII for the treatment of haemophilia A. BAY 81-8973 was extensively studied in the LEOPOLD clinical trials, which reported consistent efficacy and safety in children and adults. Since its initial 2016 launch, 8031 patient-years of exposure (to 31 Aug 2018) have accumulated. Here, we describe aggregated data from international cohorts of patients treated with BAY 81-8973 in the real-world setting.

Methods: The CHESS 2018 programme investigated the clinical, social and economic and burden of moderate and severe haemophilia in Europe (France, Germany, Italy, Spain, UK [EU5]; CHESS Pediatric; 1050 children ≤17 years) and the USA (CHESS US; 568 adults >17 years). Data were obtained between Dec 2017 and Apr 2018 via medical chart abstraction, including 12 months of retrospective clinical data, and cross-sectional surveys sent to physicians and patients/caregivers. BAY 81-8973 was newly available or launched during the study period in France, Germany, Italy and Spain, and is not available in the UK.

Results: From the CHESS cohorts, 49 patients (29 children, 20 adults) reported current treatment with BAY 81-8973. Most children (76%) and adults (55%) received BAY 81-8973 for regular prophylaxis. Regardless of regimen, median (Q1; Q3) ABR was 3 (1; 4) for children and 1.5 (0; 2) for adults, and overall 26.5% of patients were free of bleeds. In patients receiving prophylactic treatment, the mean weekly number of infusions was 2.45 in children and 2.00 in adults. Most patients were free from target joints (85.7%) and/or arthropathy (81.6%). Perception of full adherence differed between patients (42%) and their physicians (71%). For patient-reported outcomes, most patients (83%) reported no compromise in self-care/mobility due to haemophilia. Children/their caregivers, but not adults, reported an impact of haemophilia on lifestyle/usual activities. All patients were satisfied with their treatment (100% scored 5-10/10), while 60% were very satisfied (8-10/10). There were no reports of inhibitor development, nor of adverse events for BAY 81-8973.

Discussion/Conclusion: Aggregated post-launch data from the EU5 and the US suggest that the established pharmacokinetic and clinical profile of BAY 81-8973 is associated with reported real-world benefits for both children and adults with moderate and severe haemophilia A.

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P154 | "Problem Joint" a more patient relevant definition for joint morbidity in haemophilia

J. O'Hara[1,2,*]; K. Khair[3]; P. McLaughlin[4]; B. O'Mahony[5]; M. Laffan[6]; J. Pasi[7]; P. Chowdary[8]; R. Curtis[9]; M. Skinner[10,11]; D. Noone[2]; J. Willan[12]; T. Burke[2]

[1]*Health and Social Care, University of Chester, Chester;* [2]*HCD Economics, Daresbury;* [3]*Great Ormond Street Hospital;* [4]*Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London, United Kingdom;* [5]*European Haemophilia Consortium, Brussels, Belgium;* [6]*Haematology, Imperial College London;* [7]*Haematology, Barts Health NHS Trust;* [8]*The Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free Hampstead NHS Trust, London, United Kingdom;* [9]*University of Southern California, Los Angeles;* [10]*Institute for Policy Advancement Ltd., Washington, United States;* [11]*Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada;* [12]*Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom*

Introduction: Chronic joint morbidity is a common and disabling complication of severe haemophilia. However, how it is quantified can be fragmented and inconsistent. The haemophilia joint score and target joint measure (ISTH definition) whilst clinically relevant, may underreport joint damage. Joint morbidity can occur in any joint without

persistent bleeding, which may not be captured by conventional metrics, likely impacting patient lifestyle, activities and quality of life.

Methods: In a recent workshop including six clinical experts (n = 4 haematologists; n = 1 specialist physiotherapist; and n = 1 nurse specialist) and subsequent consultation with wider subject matter experts (including authors), it was agreed that a more holistic and patient relevant definition was required.

Results: Following the workshop and subsequent consultation the following definition was agreed upon; Problem Joint: Any joint that has been permanently damaged as a result of patients bleeding disorder, with or without persistent bleeding. A "Problem Joint" can be defined as having chronic joint pain &/or limited range of movement due to compromised joint integrity (i.e. chronic synovitis &/or haemophilic arthropathy).

Discussion/Conclusion: The definition provides a patient relevant perspective, it is equipped to capture long term joint morbidity, which may be overlooked by conventional clinical definitions. The limitation of the measure, is that it does not capture the extent of damage to individual joints, but does more comprehensively identify joint sites that are impacted.

Disclosure of Interest: None declared.

P155 | Factor XIII deficiency-Case report

J. Zolkova[1,*]; I. Plamenova[2]; I. Plamenova[2]; Z. Snahnicanova[1]; Z. Snahnicanova[1]; T. Simurda[1]; T. Simurda[1]; Z. Lasabova[1]; P. Kubisz[1]; P. Kubisz[1]; J. Stasko[3]; J. Stasko[3]; J. Ivankova[2]

[1]Jessenius Faculty of Medicine, Comenius University in Bratislava, Slovakia; [2]University Hospital Martin, Martin; [3]Jessenius Faculty of Medicine, Comenius University in Bratislava, Slovakia, Gemerska Poloma, Slovakia

Introduction: Inherited coagulation factor XIII deficiency is rare autosomal recessive bleeding disorder. Based on genotype, the most common is FXIII-A subunit deficiency, caused by mutations in the F13A1 gene. FXIII-B subunit deficiency is caused by mutations in the F13B gene. Homozygous or compound heterozygous patients experience severe lifelong bleeding, characteristically from the umbilical cord and intracranial bleeding. Also delayed wound healing have been reported.

Methods: We investigated 2 siblings (3-years old girl, 1 year old boy) and their parents. Both children manifested with bleeding from the umbilical cord at birth, delayed wound healing; parents are without bleeding episodes. In laboratory diagnostics, we performed basic coagulation examinations (PT, APTT, TT) (Sysmex CA-1500® Japan) which were within the range of reference values. We used the Berichrom® FXIII assay for the chromogenic determination of FXIII activity (Siemens, the Netherlands). Reference range is 70-140%. Qualitative determination of FXIII was evaluated by solubility test of the fibrin coagulum in 5M urea. In the case of FXIII deficiency coagulum dissolves in less than 48 hours. Sequence analysis F13A1 and F13B genes in these patients was performed using direct Sanger sequencing. All exons of both genes were amplified and subsequently sequenced using BigDye v1.1 Cycle Sequencing kit (Thermo Fisher Scientific, USA) on ABI 3500 Genetic Analyzer (Applied Biosystems, USA). Base changes were identified by comparison with the reference sequence (NCBI Reference Sequence: NP_000120.2 and NP_001985.2)

Results: We identified 2 mutations, each parent was identified to be heterozygous for one of these variants in F13A1 gene. Due to autosomal recessive type of inheritance, they are without bleeding symptoms. Affected children are heterozygous for both identified variants. We suppose accumulative effect these variants.

Discussion/Conclusion: Usually, homozygous patients experience severe lifelong bleeding. We would like to point out, also compound heterozygous patients suffer for such bleeding manifestations.

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P156 | Analysis of joint bleeding events from a phase 3, multicenter, open-label study of on-demand recombinant von Willebrand factor (VWF) treatment in patients with severe von Willebrand disease (VWD)

J. Windyga[1,*]; K. Chojnowski[2]; J. Pasi[3]; B. Ploder[4]; A. Mital[5]; F. Truong Berthoz[6]; B. Ewenstein[7]; B. Mellgård[7]

[1]Department of Hemostasis Disorders and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw; [2]Department of Haemostasis Disorders, Medical University of Lodz, Lodz, Poland; [3]Haemophilia Centre, Barts and the London School of Medicine and Dentistry, London, UK; [4]Shire, Vienna, Austria; [5]Department of Hematology and Transplantology, Medical University of Gdańsk, Gdańsk, Poland; [6]Shire, Zug, Switzerland; [7]Shire, Cambridge, MA, USA

Introduction: VWD is often associated with mucocutaneous bleeding and menorrhagia; however, joint bleeding events (BEs) also

commonly occur, particularly in patients with severe disease and very low FVIII clotting activity. The efficacy and safety of recombinant VWF (rVWF, VEYVONDI™; part of Shire, Lexington, MA, USA) has been demonstrated for on-demand treatment of bleeds in patients with severe VWD. Here we present post hoc analyses from a subset of patients with joint BEs.

Methods: Patients eligible for the phase 3 study (NCT01410227; EudraCT 2010-024108-84) were 18-65 years old, diagnosed with severe VWD. Enrolled patients received on-demand treatment for BEs (recommended initial dose of 40-80 IU/kg rVWF). Subsequent doses of rVWF (20-60 IU/kg up to 24 hours apart) were administered to maintain VWF:RCo and FVIII levels ≥30 IU/dL as required. If a patient's baseline FVIII activity was <40%, recombinant FVIII (rFVIII; 30-45 IU/kg) was administered with the first rVWF infusion.

Results: Overall, the annualized joint bleeding rate (AJBR) was higher than predicted from comparable baseline FVIII levels in hemophilia A. Nine of 31 enrolled patients had 59 joint BEs treated with rVWF and all of these were type 3 VWD; 6/9 had spontaneous and traumatic BEs, 2/9 had spontaneous bleeds only, and 1/9 had traumatic BEs only. Eight patients received rVWF to treat 46 spontaneous joint BEs (2 major, 11 moderate and 33 minor). Hemostatic efficacy was rated as excellent or good in all spontaneous joint BEs (44/46 [95.7%] excellent; 2/46 [4.4%] good), after a median dose of 48.2 IU/kg of rVWF and 1 (range 1-2) infusion. There were 13 traumatic joint BEs (1 major, 3 moderate, and 9 minor) in 7 patients and hemostatic efficacy was rated as excellent in all cases after a median dose of 52.5 IU/kg and 1 (range 1-3) infusion. Of the 59 joint BEs, 58 received co-administration with rFVIII (median 34.9 IU/kg [16.6-129.3] for 50 BEs), 15 BEs required a second infusion of rVWF (9 BEs with rFVIII) and only two BEs required a third infusion of rVWF (1 BE with rFVIII).

Discussion/Conclusion: These study results demonstrate that hemarthrosis is a common manifestation of severe VWD and the efficacy of rVWF in the treatment of spontaneous and traumatic joint BEs in these patients.

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P157 | Demographic and baseline data from patients with hemophilia and inhibitors enrolled in the feiba global outcomes ("FEIBA GO") study

J. Windyga[1,*]; P. A. Holme[2]; C. Hermans[3]; A. R. Cid[4]; C. Négrier[5]; L. Renault[6]; P. Wang[7]; V. Cano[6]; C. Escuriola-Ettingshausen[8]

[1]*Department of Hemostasis Disorders and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland;* [2]*Department of Haematology, Oslo University Hospital and Institute for Clinical Medicine, University of Oslo, Oslo, Norway;* [3]*Saint-Luc University Hospital, Brussels, Belgium;* [4]*Unidad de Hemostasia y Trombosis, Hospital Universitario y Politécnico La Fe, València, Spain;* [5]*Louis Pradel Cardiology Hospital, University Claude Bernard, Lyon, France;* [6]*Shire, Zug, Switzerland;* [7]*Shire, Lexington, USA;* [8]*HZRM, Haemophilia Centre Rhine-Main, Frankfurt-Mörfelden, Germany*

Introduction: Over 4 decades of clinical data have established activated prothrombin complex concentrate (aPCC; FEIBA NF®, Baxalta, part of Shire, Lexington, MA, USA) as an effective, well-tolerated therapy for preventing and managing bleeding in patients with hemophilia A (HA) or B (HB) and inhibitors (PwHI). The primary objective of FEIBA GO is to describe the long-term, real-world effectiveness of aPCC in different clinical settings. Secondary outcomes include safety assessments, joint functionality, pain assessments and health-related quality of life (HRQoL) data. This analysis focuses on demographic and baseline data from the study.

Methods: FEIBA GO (EUPAS6691) is an ongoing post-authorization, prospective, observational, multicenter cohort study. PwHI (males with high-responding inhibitors of any titer diagnosed before study entry and prescribed treatment with aPCC) will be followed over 4 years; treatment regimens (prophylaxis, on demand, or immune tolerance induction [ITI]) are prescribed at the physician's discretion.

Results: Enrollment was completed on Dec 31, 2017, with 53 PwHI from 27 sites in 11 countries (52 HA, 1 HB; median age 18 years [range: 2-71]). Ethnicity was recorded for 46 patients, with 85% classified as white and 9% black. aPCC treatment at baseline included prophylaxis (n = 36), on demand (n = 11), ITI (n = 1) and unknown (n = 5). Most patients on prophylaxis were ≤18 years (23/36, 64%), while the majority receiving on-demand treatment were >18 years (8/11, 73%). For patients with HA, the median of first FVIII inhibitor titer was 12.0 BU (n = 46, range: 0.7-2410), while the first FIX inhibitor titer was 13.8 BU in the patient with HB. At screening, PwHI had a mean of 1.1 target joints (n = 50, range: 0-10). At baseline (n = 53), joint function scores (Gilbert scale) were available for 23% of patients, pain assessments (NRS/Wong-Baker Faces Scale) for 49% and daily activity levels (HAL/PEDHAL) for 74%. HRQoL data (SF-12 [adult]/SF-10 [pediatric], EQ-5D) were available for 68% and 72%, respectively. Baseline thrombin generation assay data were only available for one patient.

Discussion/Conclusion: These baseline real-world data from FEIBA GO show that the standard of care in younger PwHI is based predominantly on prophylaxis. Long-term follow-up data from this study will help to describe the impact of this approach on clinical outcomes.

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P158 | Improvements in joint health during long-term use of recombinant factor VIII Fc fusion protein prophylaxis in subjects with haemophilia A

J. Oldenburg[1,*]; J. Pasi[2]; I. Pabinger[3]; B. Nolan[4]; R. Kulkarni[5]; V. Blanchette[6]; N. Tripkovic[7]; J. Feng[8]; N. Jain[8]

[1]Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany; [2]Barts and the London Comprehensive Care Center, London, UK; [3]Medizinische Universität Wien, Vienna, Austria; [4]Our Lady's Children's Hospital, Dublin, Ireland; [5]Michigan State University, East Lansing, MI, USA; [6]The Hospital for Sick Children, Toronto, ON, Canada; [7]Sobi, Stockholm, Sweden; [8]Bioverativ, a Sanofi Company, Waltham, MA, USA

Introduction: Recombinant factor VIII Fc fusion protein (rFVIIIFc) is an extended half-life therapy that demonstrated safety and efficacy in subjects with severe haemophilia A in the Phase 3 A-LONG (NCT01181128) and Kids A-LONG (NCT01458106) trials, and the ASPIRE extension trial (NCT01454739). Here we report the results of a post hoc analysis of rFVIIIFc treatment on joint health.

Methods: In this longitudinal post hoc analysis, subjects aged ≥12 years who enrolled in A-LONG and continued in ASPIRE received individualised prophylaxis (IP; 25–65 IU/kg every 3-5 days, or twice weekly), weekly prophylaxis (WP; 65 IU/kg every 7 days), modified prophylaxis (MP), or episodic dosing. Subjects aged <12 years from Kids A-LONG received IP or MP. Change in modified haemophilia joint health scores (mHJHS) from A-LONG (mHJHS)/Kids A-LONG (HJHS) baseline to end of ASPIRE was analysed. Annualised bleeding rate (ABR) in the target joint and their resolution were analysed. Target joints were defined as a major joint with ≥3 bleeding episodes in a 6-month period; target joint resolution was defined as ≤2 spontaneous bleeds in the joint in a 12-month period. Median and interquartile range (25th and 75th percentile) are presented, unless otherwise stated.

Results: Mean (standard deviation [SD]) change in mHJHS from baseline (21.6 [17.7]) to end of A-LONG/ASPIRE was −3.5 (7.5; n = 78). For subjects in Kids A-LONG/ASPIRE, the mean (SD) change in HJHS was −1.0 (2.5) from a baseline of 1.5 (2.7; n = 42). Follow-up duration was 3.72 (2.87-5.08) and 3.69 (2.56-4.38) years for A-LONG/ASPIRE and Kids A-LONG/ASPIRE, respectively. For the 82 IP subjects in A-LONG/ASPIRE and 13 IP subjects in Kids A-LONG/ASPIRE who reported a target joint at baseline, the spontaneous ABR in previously reported target joints was 0 (0-0.64) and 0 (0-2.02), respectively. Overall, 99.6% and 100% of target joints were resolved in A-LONG/ASPIRE (235 evaluable) and Kids A-LONG (9 evaluable), respectively; of those target joints with ≥6 months of follow-up post-resolution, 95% and 100% showed no target joint reoccurrence, respectively.

Discussion/Conclusion: Prophylaxis with rFVIIIFc provided long-term, sustained improvement in functional outcomes with low target joint ABRs and resolution of target joints in adults and kids with severe haemophilia A.

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P159 | Annualised bleeding rates ≤2 with every-5-day and every-7-day dosing of BAY 94-9027 in the protect VIII study

J. Oldenburg[1,*]; P. Holme[2]; J. Ducore[3]; M. Maas Enriquez[4]; M. Wang[5]

[1]Institute for Experimental Haematology and Transfusion Medicine, Bonn, Germany; [2]Oslo University Hospital and Institute of Clinical Medicine, Oslo University Hospital, Oslo, Norway; [3]Hemophilia Treatment Center, University of California Davis Health, California, USA; [4]Bayer AG, Wuppertal, Germany; [5]Bayer US, Whippany, USA

Introduction: BAY 94-9027 is a B-domain-deleted recombinant factor VIII (FVIII) site-specifically PEGylated with a 60-kDa (2 × 30-kDa) polyethylene glycol (PEG) to extend half-life. Efficacy and

safety of BAY 94-9027 as prophylactic and on-demand therapy for severe haemophilia A were demonstrated in the phase II/III PROTECT VIII trial (NCT01580293) and its extension. Here, we present a subanalysis of bleeding outcomes using data pooled from patients in the every-5- and every-7-day prophylaxis groups in PROTECT VIII.

Methods: PROTECT VIII was a partially randomised, open-label trial of 134 males aged 12-65 years with severe haemophilia A (FVIII <1%) and ≥150 FVIII exposure days. Prophylaxis patients received BAY 94-9027 25 IU/kg twice weekly for a 10-week run-in period. Patients with ≤1 spontaneous, joint or muscle bleed during this period were randomised to 45-60 IU/kg every 5 days (E5D) or 60 IU/kg every 7 days (E7D) for the main 26-week study period; patients enrolling after the randomisation arms were full, or with ≥2 bleeds in the run-in period, received 30-40 IU/kg 2×/week. In this subanalysis, annualised bleeding rate (ABR), joint ABR (JABR) and number of target joint bleeds were assessed in patients randomised to receive either BAY 94-9027 E5D or E7D for the 26-week main period of PROTECT VIII.

Results: Of the 86 intent-to-treat patients included in this subanalysis, 75 received BAY 94-9027 E5D or E7D and remained at the same dosing interval throughout (E5D, n = 43; E7D, n = 32); 11 patients were switched to more frequent dosing (all from the E7D regimen). E7D patients who did not switch (E7DR) had the lowest median ABR (0.96 [Q1; Q3, 0.00; 4.26]), while median ABR for patients in both the E5D only and E5D + E7D combined (non-rescued) groups was 1.93 (0.00; 4.23). Overall, median JABR was low (total cohort = 1.92 [0.00; 4.17]) and was 0.00 (0.00; 3.99) and 0.00 (0.00; 2.12) for E5D + E7DR and E7DR patients, respectively. While 45/86 patients (52%) had joint bleeds and 29 (34%) had bleeds into pre-existing target joints, the majority did not bleed into pre-existing target joints with E5D or E7D dosing.

Discussion/Conclusion: Patients receiving extended dosing intervals of BAY 94-9027 experienced low median ABR (≤2), low median JABR (<2) and few bleeds into target joints.

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P160 | Comparison of rFIX utilization and bleed rates in German haemophilia B patients who switched from nonacog alfa to rIX-FP

A. Tiede[1]; S. Yan[2]; G. Maro[3]; G. Krishnarajah[2]; J. Oldenburg[4,*]

[1]*Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany;* [2]*CSL Behring, King of Prussia;* [3]*Adivo Associates, San Francisco, USA;* [4]*Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany*

Introduction: In recent years, long-acting recombinant factor IX (rFIX) therapies have become available for use in Germany providing additional therapeutic options to the previous armamentarium of standard-acting rFIX, nonacog alfa, and plasma-derived FIX therapies. One such long-acting rFIX is rIX-FP, a recombinant fusion protein linking human FIX with human albumin. Real-world utilization and outcomes need to be considered when evaluating different FIX products in clinical practice. This analysis aimed to determine real-world FIX consumption and annualised bleeding rate (ABR) in patients switching from nonacog alfa to rIX-FP.

Methods: De-identified clinical patient chart information was obtained from 24 German healthcare providers (haematologists and haemophilia treatment centres) for 81 patients treated with rIX-FP for at least 8 weeks. ABR was calculated by annualising the number of bleeds reported over a minimum period of 8 weeks up to 1 year for prophylaxis or on-demand treatment. Prescribed dosing and infusion frequency were used to calculate FIX prophylaxis consumption for rIX-FP and the prior FIX drug used.

Results: Of the 81 patients, 59 received prophylaxis both with rIX-FP and their prior FIX drug. The mean duration of rIX-FP treatment was 36.9 weeks (range 8-89). In a subset of patients who switched from nonacog alfa prophylaxis where bleeding data was available (n = 28), mean ABR (±SD) decreased from 3.2 ± 3.1 with nonacog alfa to 0.4 ± 0.7 with rIX-FP prophylaxis. The number of patients with zero bleeds increased from 14% with nonacog alfa prophylaxis to 75% with rIX-FP prophylaxis. Mean weekly FIX consumption with rIX-FP prophylaxis (43.5 IU/kg/week) was 50% lower than prior prophylaxis with nonacog alfa (85.5 IU/kg) [n = 42].

Discussion/Conclusion: This study suggests switching from prophylaxis with nonacog alfa to rIX-FP may lead to improved bleed control and lower consumption.

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P161 | Safety and efficacy of rVIII-SingleChain in surgical prophylaxis: Results from 43 surgeries

J. Mahlangu[1]; F. Abdul Karim[2]; C. Djambas Khayat[3]; J. Ong[4]; S. P'Ng[5]; J. Oldenburg[6,*]; A. Brainsky[7]; S. Lucas[7]; I. Pabinger[8]; on behalf of the AFFINITY Study Group

[1]*University of the Witwatersrand, NHLS and Charlotte Maxeke Hospital, Johannesburg, South Africa;* [2]*National Blood Centre, Kuala Lumpur, Malaysia;* [3]*Hotel-Dieu de France Hospital, Ashrafieh, Lebanon;* [4]*Brokenshire Integrated, Davao City, Philippines;* [5]*Royal Perth Hospital, Perth, Australia;* [6]*Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany;* [7]*CSL Behring, King of Prussia, Pennsylvania, USA;* [8]*Clinical Division of Haematology and Haemostaseology, Medical University Vienna, Vienna, Austria*

Introduction: rVIII-SingleChain is a novel B-domain truncated recombinant factor VIII (rFVIII) construct with a covalent bond between the heavy and light chain. rVIII-SingleChain was designed to have a higher affinity to von Willebrand factor than rFVIII. The AFFINITY clinical trial programme demonstrated the safety and efficacy of rVIII-SingleChain as prophylaxis in patients with haemophilia A. Surgical sub-studies are investigating the safety and efficacy of rVIII-SingleChain in surgical haemostasis.

Methods: The study included previously treated patients with severe haemophilia A requiring surgery (defined as a procedure requiring general, spinal or regional anaesthesia). rVIII-SingleChain was administered as either a bolus or as a continuous infusion; dosing of rVIII-SingleChain was determined by the investigator, guided by WFH recommendations, the type of surgery and local practice guidelines. The investigator rated haemostatic efficacy using a 4-point rating scale (poor/none; moderate; good; excellent); treatment success was defined as a rating of excellent or good.

Results: A total of 43 surgeries were performed on 32 patients with a median (range) age of 32 (5-64) years. Over 50% (n = 22) of the surgeries were orthopaedic; 17 surgeries were related to haemophilia or its complications. One surgery, an appendectomy, was considered an emergency surgery. Overall, rVIII-SingleChain was used as a bolus dose in 35 surgeries, and as a continuous infusion in 8 surgeries. rVIII-SingleChain was well tolerated; no related adverse events or serious adverse events were observed during the perioperative period. Haemostatic efficacy was rated as excellent and good in 38 (88%) and 5 (12%) surgeries, respectively. Of the orthopaedic surgeries, 18 (82%) were rated as excellent, and 4 (18%) were rated as good. Median consumption was 532 IU/kg, including pre- and post-surgery doses (up until 336 hours or until the patient restarted prophylaxis).

Discussion/Conclusion: rVIII-SingleChain was well tolerated and effective in achieving surgical and perioperative haemostasis, whether dosed by bolus or continuous infusion, with an overall treatment success of 100%.

Disclosure of Interest: J. Mahlangu Grant/Research support from: Baxalta, Bayer, Biogen, CSL Behring, Novo Nordisk and Roche, Consultant for: Amgen, Baxalta, Bayer, Novo Nordisk and Roche, F. Abdul Karim: None declared, C. Djambas Khayat: None declared, J. Ong: None declared, S. P'Ng: None declared, J. Oldenburg Grant/Research support from: Baxter, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma and Pfizer, Consultant for: Baxter, Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum, Speaker Bureau of: Baxter, Bayer, Biogen Idec, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer and Swedish Orphan Biovitrum, A. Brainsky Employee of: CSL Behring, S. Lucas Employee of: CSL Behring, I. Pabinger Grant/Research support from: CSL Behring, Consultant for: CSL Behring.

P162 | Effect of societal position and disease-related impairment of certain aspects of the patient's life on clinical and psychosocial outcomes in patients with inherited bleeding disorders (PWBD) in Kenya

J. K. Ngugi

International Journal of Social Science and Entrepreneurship, Nairobi, Kenya

Introduction: Hemophilia A affects 1 in 10, 000 live male births 2, hemophilia B 1 in 30.0003 and around: 1600 patients are known with hemophilia in the Kenya.

Objective of the Study: To determine effect of societal position and disease-related impairment of certain aspects of the patient's life on clinical and psychosocial outcomes in patients with inherited bleeding disorders (PWBD) In Kenya.

Methods: Both Primary data and secondary data were employed used to collect the data. Consecutive patients of a single centre were assessed by questionnaires on social status and quality of life (SF-36). Social status was defined by school and professional education, employment and financial income of patients as well as school education of their parents.

Results: Fifty-seven PWBD (mean age, 38 ± 16 years) were enrolled, 60% were treated on-demand; PWBD had a median number of 2.5 (0-34) annual bleeds and a median orthopaedic joint score of 6 (0-38). No significant differences were found for clinical and psychosocial outcomes across social status groups. More than half of the patients reported that haemophilia had an impact on their school education, childhood and leisure activities. Patients with a high impact of haemophilia on their lives were less satisfied with their lives ($P < 0.002$), reported worse quality of life in all domains of the SF-36, had a worse joint score ($P < 0.024$) and reported more pain ($P < 0.013$).

Discussion/Conclusion: The perceived effect of haemophilia on patients' lives seems to have a stronger impact on clinical and psychosocial outcomes than patients' actual social status in Kenya.

Disclosure of Interest: None declared.

P163 | Reconstituted BAY 81-8973 factor VIII stability supports its suitability for continuous infusion for up to 24 hours

J. M. Teare[1,*]; J. Trefethen[1]; S. Garger[1]; P. Mathew[2]

[1]Bayer, Berkeley, USA; [2]Bayer, Whippany, USA

Introduction: Continuous infusion (CI) is used in many treatment centers as an option at the time when patients with hemophilia A undergo major surgical procedures, but stability and long-term potency of FVIII products under CI conditions have been shown to exhibit variability. Thus, it is important to demonstrate stability for each product used in CI applications. BAY 81-8973 (Kovaltry®, Bayer, Berkeley, CA, USA) is an unmodified, full-length recombinant human FVIII product with a primary amino acid sequence identical to that of sucrose-formulated recombinant FVIII (rFVIII-FS; Kogenate® FS, Bayer). rFVIII-FS was shown previously to be stable in solution for up to 7 days, to be safe and effective for CI during surgery, and suitable for pediatric and adult patients. The present study investigated whether BAY 81-8973 has adequate potency and purity up to 24 hours after reconstitution, which may indicate suitability for CI applications.

Methods: BAY 81-8973 drug product in 250-IU or 500-IU formula strengths was tested 0, 4, 8, 12, and 24 hours after reconstitution with sterile water for injection and storage at room temperature in 30-mL polypropylene syringes (BD Plastipak™, BD, Franklin Lakes, NJ, USA). The drug product was tested for potency (chromogenic assay), purity (high-performance liquid chromatography – size exclusion chromatography [HPLC-SEC]), total protein, pH, clarity, and particulate matter (high accuracy liquid particle counting – subvisible particles [HIAC-SVP]).

Results: No notable changes were observed in potency, purity, total protein, pH, clarity, or particulate matter with either 250-IU or 500-IU BAY 81-8973 for up to 24 hours. Between the 0-hour and 24-hour time points, potency differed only by 2 IU/mL, and the relative percentage of peak area covered by the high molecular weight fraction remained at <1% (indicating lack of aggregation). Results were consistent with the demonstrated safety and efficacy of rFVIII-FS for CI during surgery.

Discussion/Conclusion: These data indicate that BAY 81-8973 may be suitable for CI during surgery.

Disclosure of Interest: J. Teare Employee of: Bayer, J. Trefethen Employee of: Bayer, S. Garger Employee of: Bayer, P. Mathew Employee of: Bayer.

P164 | Complete phenotyping and genotyping studies for a Spanish patient with thrombocytopenia-absent radius syndrome

J. M. Bastida[1,2,*]; A. Rodriguez-Alen[3]; N. Mota[4]; N. Rollon[3]; J. Cuesta[3]; J. Padilla[4]; A. Marin-Quilez[2]; V. Palma-Barqueros[4]; E. Lumbreras[2]; M. Martin-Izquierdo[2]; V. Vicente[4]; J. R. Gonzalez-Porras[1,2]; M. L. Lozano[4,5]; J. Rivera[4,5]

[1]Department of Hematology, Hospital Universitario de Salamanca; [2]Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca; [3]Department of Hematology, Complejo Hospitalario de Toledo, Toledo; [4]Department of Hematology and Oncology, Hospital Universitario Morales Meseguer, Centro Regional de Hemodonación, Universidad de Murcia, IMIB-Arrixaca, Murcia; [5]CB15/00055-CIBERER, Madrid, Spain

Introduction: Thrombocytopenia-absent radius syndrome (TAR) is a rare autosomal recessive disease characterized by congenital and syndromic thrombocytopenia associated to skeletal abnormalities. TAR syndrome results from complex genetic alterations related to *RBM8A*. The goal of our study was: to assess the clinical, platelet phenotype and the genetic defect of patient with TAR syndrome.

Methods: Platelet phenotyping included peripheral blood smear, platelet aggregation (LTA) and flow cytometry (FC). Patient DNA was analyzed by a target gene sequencing (TGS) panel and array CGH.

Results: A 45-year-old nulliparous female from a healthy non-consanguineous family presenting with congenital thrombocytopenia with normal platelet size, was diagnosed with TAR syndrome at birth. The patient has a mild bleeding tendency. She has received platelet transfusions only in orthopedic interventions, and takes ferrous salts and tranexamic acid pills periodically because of a myomatous uterus. She has a bicuspid aortic valve and cow's milk intolerance. Physical examination showed bilateral radio-ulnar agenesis with intact thumbs, hip dysplasia, facial dysmorphism and other skeletal malformations. Moderate thrombocytopenia ($80x10^9$/L) with normal leukocyte and red blood cell count was present. LTA showed a marked aggregation defect (50%) with CRP and U46619 and normal response to other agonists. The platelet glycoprotein Ib-IX and GPIIb-IIIa levels measured by FC were also normal. The fibrinogen binding induced by ADP, PAR1, PAR4 and PMA was normal, but reduced in response to CRP and U46619. Molecular analysis revealed not only a hemizygous substitution (c.-21 G>A (rs139428292) in *RBM8A* detected by TGS but also the array CGH revealed a spontaneous 1q21.1 microdeletion of 709 Kb.

Discussion/Conclusion: We have performed a detailed study, including clinical, phenotypic and molecular genetic testing, in a patient with clinical suspicion of TAR syndrome. This patient represents the first case of TAR having been molecularly characterized in Spain, confirming the benefit of including TGS in the clinical practice for the diagnosis of inherited platelet disorders.

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Disclosure of Interest: None declared.

P165 | Evaluation of adherence to standard and PK tailored prophylaxis in an hemophilia A population

J. M. Sanchez-Raga[1,*]; M. M. Santandreu-Estelrich[2]; A. Palomero[2]; B. Galmés[1]; L. Elias[3]; N. Koulaimah[3]; A. Sampol[1]; M. Canaro[1]

[1]Hematology, Hospital Universitari Son Espases, Palma, Spain; [2]Pharmacy, Hospital Universitari Son Espases, Palma, Spain; [3]Physical Therapy, Hospital Universitari Son Espases, Palma, Spain

Introduction: Prophylaxis treatment in hemophilia A (HA) patients should be tailored based on bleeding phenotype, physical activity, musculoskeletal status and FVIII pharmacokinetics (PK). Adherence is one of the main limitations to reach zero bleeds. Our main aim is to describe the effects of PK guided prophylaxis on an HA population in terms of clinical outcomes, FVIII consumption and adherence to treatment.

Methods: The analysis was performed on a population of 11 patients with severe and moderate HA. Clinical data included age, weight, *F8* mutation and FVIII basal level. Patients were all receiving rFVIII prophylactic treatment. PK parameters were determined using the online medical device myPKFiT. Prophylaxis regimens were adjusted to maintain a FVIII trough level above 2 or 3%, depending on their physical activity (Broderick bleeding risk scale) and joint status (Hemophilia Joint Health Score). Standard (based on weight, bleeding phenotype and lifestyle) and PK-guided prophylaxis regimens were recorded. Clinical outcomes (annual joint bleeding rates) and FVIII annual consumptions (provided by hospital pharmacy) were documented during the standard and PK tailored prophylaxis periods.

Results: PK parameters showed high variability between patients, with a FVIII half-life ranging from 7.7 to 14.8 hours. Prophylaxis regimen was modified (FVIII dose and/or frequency of infusion) in 6 patients after PK analysis with myPKFiT. PK tailored prophylaxis led to the reduction of AJBR in 4 patients. The other 7 patients had zero AJBR during both prophylaxis regimens. However a clear discrepancy between the theoretical (calculated based on prescribed prophylactic regimen) and real FVIII annual consumption (based on pharmacy records) was found in 4 patients. These differences were reduced during the PK guided prophylaxis period. More detailed information will be included in tables.

Discussion/Conclusion: Prophylaxis protocols should be tailored considering the patient clinical and lifestyle features. Adherence to treatment must be evaluated and promoted in those patients in order to reach zero bleeds and avoid joint disease. In our experience, the use of myPKFiT graphs as an educational tool have contributed to increase adherence. It is also relevant the multidisciplinary collaboration between professionals involved in HA patients treatment to determine and improve compliance levels.

Disclosure of Interest: None declared.

P166 | Telemedicine impact on hemophilia treatment management

M. M. Santandreu-Estelrich[1]; J. M. Sánchez-Raga[2,2,*]; A. Palomero[1]; B. Galmés[2]; M. Gómez-Zamora[1]; L. Elias[3]; N. Koulaimah[3]; O. Delgado[1]; A. Sampol[2]; M. Canaro[2]

[1]Pharmacy, Hospital Universitari Son Espases, Palma, Spain; [2]Hematology, Hospital Universitari Son Espases, Palma, Spain; [3]Physical Therapy, Hospital Universitari Son Espases, Palma, Spain

Introduction: Telemedicine (TM) is an interesting tool for the control and monitoring of chronic patients and rare diseases. Since 2016, our hospital uses a mobile application and a real-time therapy management system for patients with hemophilia (*Haemoassist*™, Stat Consult). We analyze the impact of its implementation.

Methods: Retrospective observational study carried out in a hemophilia reference center. Patients with hemophilia A (HA) and B (HB) in prophylactic treatment with factor VIII and IX who use the mobile application with a minimum of 6 months of follow-up are included. The socio-demographic, clinical and treatment variables are collected 6 months before and after the application. The sources of information consulted are the electronic medical history (Millennium-Cerner™), the outpatient pharmacy dispensing program (Hospiwin™) and the web version of the application.

Results: A total of 27 patients with severe and moderate HA and HB in prophylactic treatment were included. The average age was 22 years (3-57). The median factor consumption per patient was 84 000 IU in the six months prior using the app (range: 29 000-240 000) and 141 000 IU (range: 36 500-381 000) in the six months after. The median adherence increased from 71.15% (range 30.77-100%) to 100% (range 51.28-100%) and the median of the differences between the study periods was 17.22%. In the satisfaction survey, 95.3% of users declared to be satisfied or very satisfied with the use of the application.

Discussion/Conclusion: The use of TM in the field of hemophilia is still in development in most hospitals in the world, being telemonitoring the most widely used. Our experience supports its implementation in daily practice, highlighting the improvement in adherence to treatment, the traceability of the drug and patients satisfaction.

Disclosure of Interest: None declared.

P167 | Improvement in target joint bleeding during long-term use of recombinant factor IX Fc fusion protein prophylaxis in subjects with haemophilia B

J. Pasi[1,*]; R. Kulkarni[2]; H. Chambost[3]; A. Willemze[4]; J. Feng[5]; N. Jain[5]

[1]*Barts and the London Comprehensive Care Center, London, UK;* [2]*Michigan State University, East Lansing, MI, USA;* [3]*Centre Hospitalier Universitaire, Marseille, France;* [4]*Sobi, Stockholm, Sweden;* [5]*Bioverativ, a Sanofi Company, Waltham, MA, USA*

Introduction: Recombinant factor IX Fc fusion protein (rFIXFc) is an extended half-life therapy that demonstrated consistent and sustained safety and efficacy in previously treated adults and adolescents with severe or moderate haemophilia B in the Phase 3 B-LONG parent (NCT01027364) and B-YOND extension (NCT01425723) trials. Here we report the final analysis of this combined dataset to evaluate long-term target joint bleeding control, resolution, and reoccurrence during rFIXFc treatment.

Methods: In this longitudinal post hoc analysis, subjects ≥12 years of age who enrolled in B-LONG and continued in B-YOND received one of the four following rFIXFc regimens: weekly dose-adjusted prophylaxis (20-100 IU/kg every 7 days), individualized interval-adjusted prophylaxis (100 IU/kg every 8-16 days), modified prophylaxis, or episodic treatment. Subjects could switch treatment groups at any time during B-YOND. Annualised bleeding rate (ABR) in the target joint and their resolution were analysed. Target joints were defined as a major joint with ≥3 bleeding episodes in a 3-month period. Target joint resolution was defined as ≤2 spontaneous bleeds in the joint in a 12-month period, and reoccurrence as ≥3 spontaneous bleeds in a single joint within a consecutive 6-month period after resolution. Median and interquartile range are presented.

Results: Overall, 60 subjects with target joints were included in the analysis. Cumulative duration on rFIXFc was 3.6 (1.4-6.0) years, weekly dose was 49.7 (39.7-64.6) IU/kg, and dosing interval was 7.0 (6.9-7.1) days. For the 41 subjects in B-LONG/B-YOND on weekly dose-adjusted prophylaxis who reported a target joint at baseline, the spontaneous ABR in previously reported target joints was 0.33 (0-1.20). Of 93 evaluable target joints in 37 subjects on prophylactic regimens, 100% were resolved and, of those target joints with ≥6 months of follow-up post-resolution, 90.2% showed no target joint reoccurrence. The spontaneous ABR per target joint after resolution was 0 (0-0.4) during a follow-up of 47.4 (19.7-60.6) months.

Discussion/Conclusion: For individuals with haemophilia B previously on prophylactic or episodic regimens, long-term prophylaxis with rFIXFc was associated with 100% target joint resolution with low ABRs and 90.2% of resolved target joints having no reoccurrence for a median of 4 years after target joint resolution.

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P168 | Comparison of patient experience (PE) and health-related quality of life (HRQoL) in people with severe factor IX deficiency before and after an en-masse switch to an extended half-life (EHL) factor IX (FIX) concentrate

K. Johnston[1,*]; E. Singleton[2]; K. Ryan[2]; N. O'Connell[2]; on behalf of National Coagulation Centre, St. James' Hospital, Dublin, Ireland

[1]*School of Medicine, Trinity College Dublin;* [2]*National Coagulation Centre (NCC), St. James' Hospital, Dublin, Ireland*

Introduction: EHL FIX prophylactic treatment in people with severe FIX deficiency may improve HRQoL. In 2017 an en-masse switch to rFIX Fc fusion protein (rFIXFc; Alprolix®, SOBI) was undertaken in Ireland; a unique opportunity to assess EHL FIX effect on PE.

Methods: Adult patients with severe FIX deficiency at the NCC completed switchover from standard half-life rFIX to rFIXFc in 2017. EuroQoL EQ5D5L questionnaires were completed pre and 3 months post-switchover. Data analysis involved descriptive statistics and EQ5D5L Crosswalk Index Calculator. On-demand factor usage for bleeding episodes was analysed 12 months pre and post-switchover via mproHomescan app and treatment sheets.

Results: 24 of 29 patients completed the EQ5D5L questionnaire pre and 3 months post-switchover. Pre-switchover, dimensions "mobility" and "pain/discomfort" had the most problems. "Self-care" had the fewest problems. EQVAS mean was 71; a difference was seen in the mean value for patients with "no problems" vs those with "at least one problem" (88 vs 69). The overall mean EQ5D5L Index value score was 0.7.

3 months post-switchover, "self-care" remained the dimension with the least problems. "Mobility" had the most problems. The overall EQVAS mean, mean for patients with "no problems" and mean for patients with "at least one problem" were unchanged as was the overall mean EQ5D5L Index value score.

No minimally clinical important difference was observed in EQ5D5L HRQoL data pre and 3 months post-switchover. However PE reports high levels of satisfaction with reduced infusion burden and confidence in prophylaxis efficacy.

The number of on-demand infusions used to resolve bleeding episodes decreased. Prior to switchover, 90.2% of bleeding episodes were resolved by 1 or 2 injections vs 97.6% post-switchover.

Discussion/Conclusion: Despite the EQ5D5L data, PE suggests that improvements in HRQoL have occurred post rFIXFc switchover.

HRQoL improvements, as assessed via Haemophilia-specific Quality of Life Questionnaires, were observed at 26 weeks post-switchover in previous studies. To better understand changes in PE and HRQoL post rFIXFc enrollment, we aim to repeat EQ5D5L questionnaires 12 months post-switchover and complete qualitative, semi-structured interviews, focusing on HRQoL, chronic pain and pain-coping strategies.

Disclosure of Interest: None declared.

P169 | Thromboprophylaxis and surgical outcomes in people with haemophilia undergoing orthopaedic surgery: Establishing a local standard of care

Y. Seldon[1]; K. Johnston[1,*]; N. O'Connell[2]; E. Singleton[2]; N. Boland[2]; S. Roche[2]; M. Byrne[2]; N. Hogan[3]; T. McCarthy[3]; J. O'Donnell[2]; K. Ryan[2]

[1]*Trinity College Dublin, Dublin, Ireland;* [2]*National Coagulation Centre, St. James's Hospital, Dublin, Ireland;* [3]*Orthopaedics, St. James's Hospital, St. James's Hospital, Dublin, Ireland*

Introduction: There are currently no international standards of care regarding thromboprophylaxis for people with haemophilia (PWH) undergoing orthopaedic surgery. This study aims to analyse surgical outcomes (bleeding and thrombosis) of a cohort of 29 PWH undergoing 38 surgeries in a 4 year period in order to develop optimal guidelines regarding use of thromboprophylaxis in this setting

Methods: A retrospective study from 2014-2017 of PWH undergoing orthopaedic surgery in a single national Haemophilia Comprehensive Care Centre was conducted. Outcomes analysed were immediate bleeding, delayed bleeding, and symptomatic above-knee deep vein thrombosis and pulmonary embolism ≤4 weeks post-surgery. Patient demographics were obtained using The National Haemophilia Electronic Health record (Clintech™) and local hospital Electronic Patient Records.

Results: A total of 38 surgeries were performed in 29 patients. Surgeries included 22 major procedures and 16 minor procedures. The majority of surgeries involved the lower limb with three procedures involving the upper limb. The cohort consisted of 20 patients with FVIII deficiency; 6 with mild, 1 with moderate, 9 with severe and 4 with severe deficiency and a history of inhibitors but none had a current inhibitor. Of 9 patients with FIX deficiency, 1 had mild, 1 had moderate and 7 had severe deficiency. At surgery, the mean age was 48 years (range, 21-74), the mean body mass index (BMI) was 28 kg/m2 (range, 19-44). All procedures were covered with standard half-life FVIII and FIX concentrates. There were 12 incidences of bleeding (31.6%). Of these 12 incidences, 10 were delayed bleeds and 2 were immediate bleeds. No thrombosis was recorded as per the inclusion criteria although one patient with mild FIX deficiency developed a below-knee DVT.

Discussion/Conclusion: We recommend against the use of routine pharmacological thromboprophylaxis in PWH undergoing orthopaedic surgery due to the higher risk of immediate and delayed post-operative bleeding vs the risk of thrombosis. We recommend the use of graduated compression stockings to reduce the risk of thrombosis in all patients. We also propose the identification of individual risk factors for surgical complications (bleeding and thrombosis) pre-operatively. This may allow individualisation of surgical management but pre-operative assessment tools would require validation.

Disclosure of Interest: None declared.

P170 | Bone mineral density and bone microstructure in patients with haemophilia in northern Germany: Preliminary findings of a single centre study

K. Holstein[1,*]; L. Witt[2]; T. Rolvien[3]; T. Schmidt[3]; M. Amling[3]; F. Barvencik[3]; A. Matysiak[2]; F. Langer[1]

[1]*II. Medical Department, Haemophilia Centre, Hamburg, Germany;* [2]*University Medical Centre Hamburg-Eppendorf, Hamburg, Germany;* [3]*Institute for Osteology and Biomechanics (IOBM), University Medical Centre Hamburg-Eppendorf, Hamburg, Germany*

Introduction: Reduced bone mineral density (BMD) is a common comorbidity in patients with haemophilia (PWH). Our aim was to describe the prevalence of reduced BMD in PWH in Northern Germany and to further determine the bone microstructure and contributing factors to possible bone alterations.

Methods: BMD, bone microstructure, laboratory parameters of bone metabolism, pain and orthopaedic joint status (OJS) were assessed routinely during check-ups. BMD was assessed by dual energy X-Ray absorptiometry (DXA) and bone microstructure by high-resolution peripheral quantitative computed tomography (HR-pQCT). Patients completed questionnaires on their activity and lifestyle.

Results: So far, data of 75 PWH (median age 33 years, range 18-77) could be retrospectively analysed, of whom 62 had haemophilia A and 13 haemophilia B. 54 PWH (72%) had severe, 7 (9%) moderate, 14 (19%) mild haemophilia, 7 patients (9%) had a previous inhibitor. Mean BMI was 25.7 ± 3.9 kg/m^2, and mean vitamin D level was 16.9 ± 7.5 µg/l; 69 PWH (92%) had vitamin D deficiency (<30 µg/l), 15 (20%) severe deficiency (<10 µg/l). 12 PWH (16%) had osteoporosis, and 35 (46%) osteopenia, as defined by a T-score of ≤ -2.5 and <-1.0 (hip or spine), respectively. Among the 3 groups (normal BMD, osteopenia, osteoporosis), an association was found to BMI, OJS, Haemophilia Activities List (HAL) (PWH with osteoporosis had lower BMI, $P = 0.041$, higher OJS, $P < 0.01$, lower HAL, $P = 0.012$). All patients with a previous inhibitor (n = 7) had osteopenia or osteoporosis. Of PWH, 39% had an impaired bone microstructure at the distal radius, and 45% at the tibia. In the radius 32% had isolated reduced cortical thickness (<70% of the age and gender matched mean), 3% a trabecular deficit and 7% a combined. In the tibia, 27% had an isolated trabecular, 7% a cortical and 12% a combined bone structural deficit. Regarding markers for bone metabolism, in

PWH with osteoporosis a higher level of osteocalcin was observed ($P = 0.036$).

Discussion/Conclusion: Reduced BMD is common in our population of PWH in Northern Germany. An association to having a previous inhibitor, worse joint status and physical function was observed. Interestingly, bone structure deficits in radius are dominated by reduced cortical thickness whereas in the tibia a trabecular or combined structural deficit predominates, suggesting different pathophysiological mechanisms.

Disclosure of Interest: None declared.

P171 | LPS-induced expression of monocyte tissue factor (TF) antigen correlates with markers of systemic inflammation in patients with hemophilia A and B

K. Holstein[1,*]; A. Matysiak[2]; L. Witt[2]; B. Sievers[1]; C. Lehr[1]; F. Langer[1]

[1]II. Medical department, Haemophilia Centre; [2]University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

Introduction: In congenital hemophilia, deficiency in plasma factor VIII or IX activity results in a severely impaired intrinsic amplification loop of blood coagulation. At sites of vascular injury, thrombin generation and fibrin deposition are thus critically dependent on the extrinsic, TF-driven coagulation pathway. Although cytokine-mediated activation of monocytes/macrophages is a hallmark of blood-induced synovitis, no previous study has systematically investigated the link between inflammatory markers and monocyte TF expression in patients with hemophilia A and B.

Methods: We used an ex-vivo endotoxinemia model to study the expression of monocyte TF under inflammatory conditions. Citrate-anticoagulated whole blood was labeled with FITC-conjugated anti-CD14 and PE-conjugated anti-TF directly after blood draw (baseline) and after incubation with buffer (PBS) or lipopolysaccharide (LPS) for 4 hours at 37°C. TF antigen on CD14+ monocytes was subsequently analyzed by two-color flow cytometry, and results were expressed as percent TF+ cells and TF-specific mean fluorescence intensity (MFI). High-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) in baseline serum samples were measured by standard laboratory techniques.

Results: We studied 40 patients (34 ± 12 years) with moderate or severe hemophilia A (n = 31) or B (n = 9) in comparison to 20 age-matched healthy male controls. While essentially no TF antigen (i.e. TF+ cells < 1 % and TF-specific MFI < 1) was detectable on CD14+ monocytes in baseline and PBS-treated samples from both groups, stimulation with LPS increased TF+ monocytes (patients vs controls) to 14.4 ± 9.0 % vs 11.0 ± 6.0 % ($P = 0.14$) and TF-specific MFI to 6.0 ± 3.2 vs 4.6 ± 2.5 ($P = 0.08$). Importantly, TF-specific MFI of CD14+ monocytes in LPS-treated patient samples significantly correlated with baseline hs-CRP ($r = 0.46$, $P < 0.01$) and IL-6 ($r = 0.40$, $P < 0.05$) serum levels.

Discussion/Conclusion: Our findings indicate a novel link between systemic inflammation and inducible monocyte TF expression in patients with congenital hemophilia A and B, which could be of pathophysiological relevance in the development and progression of hemophilic arthropathy.

Disclosure of Interest: None declared.

P172 | Case report: Severe FVII deficiency in a boy homozygous for the known mutation in F7 p.Ser90.Term – when is prophylactic treatment indicated?

K. M. Harder[1,*]; E. Bartels[2]; M. F. Birkedal[1]; B. Strarup[1]; M. Hoffmann[1]

[1]Dept. of Pediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen, Copenhagen, Denmark; [2]Dept. of Clinical Biochemistry, Rigshospitalet, Copenhagen, Copenhagen, Denmark

Introduction: Severe bleeding tendency in children can be caused by severe F7 deficiency, a rare autosomal recessive disorder with heterogeneous clinical presentation.

Methods: A three days old boy was admitted due to extensive bruising on truncus and extremities, delivery had been uneventful. Routine lab evaluation revealed increased prothrombin time (PT) international normalized ratio (INR) >8.0 (normal range 0.9-1.2). The parents originated from the same village in Turkey. The mothers' great grandmother and the fathers' grandfather were cousins. The mothers' grandmother had given birth to 6 boys who all died within the first month of life.

Results: Further evaluation revealed undetectable levels of F7 caused by the rare mutation in F7 p.Ser90.Term, also known as p.Ser52 Stop and F7 p.Ser112X, resulting in a non functional truncated protein. As the patient demonstrated a severe bleeding phenotype, a permanent central venous port was inserted, and prophylactic treatment with rFVIIa 30 ug/kg three times weekly was initiated at the age of 5 weeks. The boy presents neurologically intact at 12 months, but MRI has revealed sequelae after a hemorrhage with substance loss in the left cerebral hemisphere as well as multiple minor hemorrhages in both hemispheres.

Discussion/Conclusion: Inherited F7 deficiency is rare and awareness of the condition as well as availability of laboratory analyses is crucial for immediate diagnosis and treatment. Prophylactic treatment with rFVIIa or pdFVII should be considered in patients with a severe bleeding phenotype.

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P173 | Boys with haemophilia posture, joint health, physical activity and quality of life research

K. Kočan; on behalf of Agnė Juodytė, Sonata Saulyte-Trakymienė, Juozas Raistenskis, Veslava Radzevic

Children's Hospital, Affiliate of Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania

Introduction: There are only a few researches in Lithuania about the effect of the disease on children with haemophilia general health condition, their daily activities or quality of life. Furthermore, the lack of specific guidelines for safe physical activity participation poses a barrier to increasing activity.

Methods: The study involved 14 boys suffering from haemophilia. Study participants were from 4 to 18 years old. Diers Formetric 4D system was used to evaluate the posture. For physical activity evaluation was used the basic activity questionnaire for children with haemophilia. The joint health was assessed according to the international haemophilia joint health scale. The life quality indicators were evaluated using a disease-specific measure of quality of life in children with haemophilia.

Results: A higher pelvic tilt was observed in assessing the posture of the subjects in the frontal plane; 10 subjects' back was asleep forward in assessing the posture in a sagittal plane, 10 of all subjects have a decreased kyphosis angle, and 7 subjects have a lordosis angle decrease. The assessment of the joint health in boys with haemophilia revealed that the most damaged was the ankle articular joint (N-11), knee had a lower damage (N-10), a slight damage was observed in elbow joints (N-7). After physical activity evaluating, it was found that 6 subjects have difficulty in leisure activities and sporting, 12 subjects singled out self-esteem as the least stressful physical activity. More than one third of the problems related to quality of life were experienced by only one boy. A strong correlation between the size of the lordotic angle assessment of quality of life ($r = 0.71$) was found, and between the evaluation of pelvic tilt and pelvic rotation ($r = 0.68$). A strong correlation ($r = 0.64$) was found between lateral rotation and surface rotation. Between physical activity and life quality also established a strong correlation ($r = 0.62$).

Discussion/Conclusion: The study showed that the joint health assessment has no statistically significant relationship with posture, what means that joint damage was not as noticeable to have affected the posture. It has been determined that the increase of lordotic angle has a positive effect on the quality of life. According to the study, higher physical activity positively affects the quality of life for children with haemophilia.

Disclosure of Interest: None declared.

P174 | An improved in vitro assay for the detection of anti-AAV neutralizing antibodies

K. Kuranda*; Y. Chen; Y. Feng; R. Patel; S. Kutza; M. Willet; J. Silverberg; W. Li; M. Crosariol; X. M. Anguela; F. Mingozzi

Spark Therapeutics, Inc., Philadelphia, PA, USA

Introduction: Neutralizing antibodies (NAbs) against adeno-associated virus (AAV) vector capsids may decrease transduction efficiency when vectors are systemically delivered and represent an exclusion criterion in liver-directed gene therapy trials. Here we describe an improved cell-based assay to detect anti-AAV NAbs that provides a readout even in samples with nonspecific inhibitory or enhancing factors.

Methods: The assay relies on the transduction of an AAV-permissive cell line with a reporter vector and the use of empty AAV capsids to adsorb AAV-specific enhancing or inhibitory factors. Key steps were further optimized to reduce the time of assay completion and variability. We assayed samples donated by hemophilia A subjects and healthy individuals and validated the method with samples from healthy donors.

Results: We developed and validated an improved, streamlined assay to measure anti-AAV NAbs in individuals with hemophilia, to support the selection of subjects for inclusion in gene therapy trials. Compared to a conventional NAb assay (Meliani 2015), the intra-assay variation, assessed by Coefficient of Variation (%CV) of triplicate measures was reduced from 30.5% to 8.7%. The inter-assay precision assessment on the novel assay revealed a %CV of 12.5% for the quality control sample. Of hemophilia A samples tested 62.5% had a NAb titer of <1:1 (or negative) to an AAV-Spark200 vector; 18% had a titer ≥1:1 but ≤1:10. Current efforts are focused on expanding the analysis of seroprevalence to the general population.

Discussion/Conclusion: AAV gene transfer has demonstrated efficacy in clinical trials for hemophilia A and B. Due to exposure to wild-type AAV, some individuals are positive for antibodies against the AAV capsid. These are usually neutralizing and can prevent liver transduction and reduce efficacy; consequently, NAb-positive subjects are excluded from liver-targeted AAV-based trials. Binding assays to detect anti-capsid antibodies cannot discriminate between neutralizing and non-neutralizing (or binding) antibodies. Notably, it has recently been shown that binding antibodies can increase liver transduction (Fitzpatrick 2018). The cell-based NAb assay described here directly measures the extent of vector transduction inhibition mediated by anti-AAV Nabs even in the presence of serum factors that do not directly interact with the vector but may influence AAV transduction.

Disclosure of Interest: K. Kuranda Employee of: Spark Therapeutics, Inc., Y. Chen Employee of: Spark Therapeutics, Inc., Y. Feng Employee of: Spark Therapeutics, Inc., R. Patel Employee of: Spark Therapeutics, Inc., S. Kutza Employee of: Spark Therapeutics, Inc., M. Willet Employee of: Spark Therapeutics, Inc., J. Silverberg Employee of: Spark Therapeutics, Inc., W. Li Employee of: Spark Therapeutics,

Inc., M. Crosariol Employee of: Spark Therapeutics, Inc., X. Anguela Employee of: Spark Therapeutics, Inc., F. Mingozzi Employee of: Spark Therapeutics, Inc.

P175 | Quality of life of children with haemophilia living in Greece

K. Panagiotopoulou[1,*]; V. Koliopoulou[1]; H. Pergantou[1]; A. Dettoraki[1]; A. Michalopoulou[1]; I. Stamati[1]; E. Charmandari[2]; H. Platokouki[1]

[1]*Haemophilia Centre/Haemostasis and Thrombosis Unit, "Aghia Sophia" Children's Hospital;* [2]*First Department of Paediatrics, National and Kapodistrian University of Athens, "Aghia Sophia" Children's Hospital, Athens, Greece*

Introduction: Quality of life has been studied in children with haemophilia in order to comprehend children's perception of well-being and functioning in different domains. *Aim*: To evaluate health-related quality of life (HRQoL) and correlate with clinical variables in children with haemophilia.

Methods: The three different age-group (Group I:4-7, II: 8-12, III: 13-16 years) disease-specific questionnaire Haemo-QoL was implemented to 56 haemophilic children (mean age: 12.1 ± 4.0 years), during the first trimester of 2018. Questionnaire's overall scores range from 0 to 100, with 0 representing best QOL. Clinical data were collected from the medical records. Statistical analysis of validity, internal consistency reliability and descriptive statistical measures for distributions were applied. The level of significance was set at $P < .05$.

Results: Of 47 patients responded, 97.7% had Haemophilia A, 76.6% severe A/B (FVIII/IX<1%), 87.2% were on prophylaxis. Regarding the total questions mean scores, HRQoL showed low impairment. The highest impairment (mean: 32.3) was found in the youngest children who were impaired mainly in the domains "family" (53.6) and "treatment" (46.4). Patients from Group II and III showed relatively low impairments (mean: 23 and 20.2, respectively). Additionally, high scores were observed in the subscale "sport and school" (43.3 and 35.7, respectively). Furthermore, in Group III, children with severe haemophilia had significantly better QoL in comparison to those with mild/moderate ($P < .001$). Correlation analysis of the Haemo-QOL with the number of bleeds, significantly differed ($P = .029$) between children with and without joint bleeds or major bleeding events (in 26% of severe vs 66.7% of mild/moderate cases) in the previous twelve months, indicating higher impairment in HRQoL for children with bleeds.

Discussion/Conclusion: Haemophilic children's concerns change during their development. It seems that young children are distressed of family and treatment-related issues. Adolescents' concerns are related to sports and school matters. In this age group, the number of joint bleeds had an impact on HRQoL, indicating that children with joint bleeds in the previous twelve months, as presented in moderate/mild cases, had higher impairment in HRQoL. Prophylaxis seems to induce a burden for younger children, but proved to be the most preventive measure over time for minimizing HRQoL impairment.

Disclosure of Interest: None declared.

P176 | Facilitated peer learning encourages self-infusion

L. Oyesiku[1,*]; S. Dodgson[2]

[1]*Haemophilia, Basingstoke and North Hampshire Hospitals, Basingstoke, UK;* [2]*Haemnet, London, UK*

Introduction: Transfer from child to adult services is significantly enhanced when boys with haemophilia are able to self-infuse and manage their condition. Bringing peers together to share knowledge and experience has long been recognised as a route to facilitating learning. As part of the Haemnet Transforming Transition programme, it was proposed that a peer-led masterclass could facilitate peer learning as well as creating resources that clinicians in other centres can share with patients.

Methods: A Saturday workshop was arranged by a specialist nurse and attracted 9 young people with bleeding disorders. Moderated discussion focused on mapping the stages in the process of self-infusion, drawing on the knowledge of everyone in the room, supplemented by the opportunity to watch a demonstration from a boy who was confident with self-infusing and practice under supervision from a nurse. Participants were encouraged to share hints and tips that they found helpful. The meeting was digitally recorded (with the permission of participants) and a graphic artist also attended.

Results: Participating in the event was described as fun and most participants volunteered to be recorded describing the hints and tips they had identified for use in the subsequent animated video. The demonstration by a boy who was able to self-infuse had a positive impact on the willingness of others in the room to practice: those who previously had difficulty with infusing said they were more willing to learn to self-treat as a result. Arrival of the parents later in the day offered an opportunity for further discussion. They also described being able to share their knowledge and experiences of having a son with haemophilia as something they hadn't thought they needed or rarely had an opportunity to do but which they found positive.

Discussion/Conclusion: Recordings of the event have been used to produce animated videos incorporating the voices of participants, and some memes that are available for clinicians to share with their patients. These are freely accessible to nurses on the Haemnet website (www.haemnet.com). Bringing these young people together with an experienced specialist nurse provided a positive opportunity to share experiences, to learn from each other and to build confidence. Contributing to development of an animated video provided a shared learning experience that was of benefit to everyone in the room.

Disclosure of Interest: L. Oyesiku Grant/Research support from: CSL Behring, Speaker Bureau of: Shire, Roche/Chugai, S. Dodgson: None declared.

P177 | Clinical features and therapeutic approach to AHA: A single-centre experience

L. Valdre*; L. Piscitelli; C. Manzi; G. Rodorigo

Sant'orsola University Hospital, Bologna, Italy

Introduction: Acquired haemophilia A (AHA) is a rare bleeding disorder characterized by autoantibodies directed against circulating coagulation Factor VIII. When it is not early diagnosed and treated, it may be dangerous for life due to haemorrhage. The aim of this study is to report our single-centre experience about clinical features, laboratory diagnosis, prognostic factors and therapeutic management of patients with AHA.

Methods: From the 1st of January 2001 to the 30th June 2018, 35 patients were referred to our Haemophilia Centre based on prolonged aPTT and bleeding diathesis.

Results: 18/35 of the patients at diagnosis were female, median age 78 years (range 47-98), and the age distribution was as follows: 8 patients were younger than 65, 21 between 65-80 and 6 patients were older than 85. All patients presented bleeding symptoms at diagnosis. In particular, 21 patients showed a major bleeding as clinical presentation but no fatal events occurred in acute phase. 19 patients required blood transfusion; in 5 patients plasma was infused too. By-passing agents were used for achieving the haemostatic control in 14 cases: 8 with rFactor VIIa, 3 with aPCC, 2 case with both; 1 patient was treated with porcine rFVIII after no response to rFVIIa and aPCC. Fourteen patients presented mild haemorrhage, which required no therapy. It was noted that there is a correlation between severe bleeding and the age of the patients.

Residual Factor VIII (Chromogenic Assay) and inhibitor titre varied and was not useful to identify patients with more severe phenotype. An underlying disease was found in 9 patients out of 35.

Immunosuppressive therapy with steroid (1 mg/Kg) was started in all patients immediately after the confirmation of AHA. 11 patients did not achieve a complete remission. Five of 11 were treated with a variety second line treatment; two patients achieved complete response after anti-CD20 treatment. Ten patients received low-dose steroid therapy long time.

Discussion/Conclusion: Our experience confirms AHA is a rare but challenging disease and that collecting data is very useful to better define therapeutic approach.

In our cases the therapy response was not affected by gender, age, underlying aetiology, by presenting inhibitor titre and FVIII level.

Disclosure of Interest: None declared.

P178 | The development of a game to facilitate pediatric patient participation in hospital care, research and intervention development

L. Teela[1]; L. Verhagen[1]; M. Gruppen[2]; M. Grootenhuis[3]; L. Haverman[1,*]

[1]*Psychosocial Department, Emma Children's Hospital, Amsterdam UMC, Amsterdam;* [2]*Pediatrics, Emma Children's Hospital, Amsterdam UMC, Amsterdam;* [3]*Psychosoc, Research & Zorginnovatie, Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands*

Introduction: Participation of patients in hospital care is essential, because patients can be seen as experts. Although this is increasingly acknowledged, professionals still find it hard to realize this, especially within pediatric patients. Therefore, the goal of this project is to develop a game for adolescents, called 'All Voices Count' ('Alle Stemmen Tellen'), which can be used by professionals to incorporate patient participation in hospital care, research and intervention development.

Methods: The game was developed in 3 steps; 1) focus groups with fifteen adolescents (age range 12-18y) with a chronic disease resulted in 10 major themes for adolescents regarding hospital care (e.g. my hospital and like me) and preferences for a group game that contains a winning element. 2) A first version of the game was developed based on the topics. Fourteen adolescents (age range 12-18y) gave their opinion about the draft version; the game helps adolescents to give their opinion more easily and the images on the cards should be more recognizable for adolescents. 3) Adjustments were made to the game. A pilot workshop with four adolescents (age range 13-16y) was held: the game is easy to play and a word accompanying the image would be supportive.

Results: A final version of the game was developed and can now be provided to researchers and health care professionals.

Discussion/Conclusion: With this game we provide professionals a tool to include the input from pediatric patients in the decision-making process of hospital care.

Disclosure of Interest: None declared.

P179 | Update on the verITI-8 study: A global, multicentre, open-label, interventional study evaluating recombinant factor VIII Fc fusion protein for first-time immune tolerance induction (ITI) therapy

L. Malec[1,*]; E. Tsao[2]; S. Lethagen[3]; N. Jain[2]

[1]*BloodCenter of Wisconsin, Milwaukee, WI, USA;* [2]*Bioverativ, a Sanofi Company, Waltham, MA, USA;* [3]*Sobi, Stockholm, Sweden*

Introduction: Inhibitor development is the most serious complication of haemophilia A therapy. ITI is the gold standard for inhibitor eradication and eventual restoration of factor VIII (FVIII) responsiveness. To date, only retrospective data exist for ITI therapy using recombinant FVIII Fc fusion protein (rFVIIIFc; Carcao, et al. Haemophilia.

2018). The verITI-8 study (NCT03093480) evaluates time to tolerization using rFVIIIFc for first-time ITI.

Methods: This prospective, open-label, single-arm, interventional, multicentre study aims to enrol 30 subjects of any age with severe haemophilia A and high-titre inhibitors (≥5 BU/mL) undergoing first-time ITI therapy with rFVIIIFc. The study consists of screening (≤4 weeks), ITI (≤48 weeks), tapering (≥16 weeks, to achieve prophylactic dosing), and follow-up (32 weeks) periods. During the ITI period, rFVIIIFc is administered at 200 IU/kg/day (once-daily or divided-daily doses). The primary endpoint is time to tolerization with rFVIIIFc. Secondary endpoints include the number of bleeding episodes, hospitalization days, ITI success or relapse rates, missed days from work/school, rFVIIIFc consumption, treatment adherence, and adverse events. Inhibitor eradication (ITI success) is defined by: 1) negative inhibitor titre (<0.6 BU/mL by Nijmegen-modified Bethesda assay) measured twice within 2 weeks, 2) incremental recovery ≥1.32 IU/dL per IU/kg (≥66% of the expected IR) at 2 consecutive visits, and 3) a rFVIIIFc half-life of ≥7 hours.

Results: As of Oct 2018, 11 patients have been enrolled. The first patient enrolled in Nov 2017 and the rest from Mar 2018. Patients were evenly distributed between North America (n = 6) and the EU (n = 5). Seven patients are in the ITI period receiving rFVIIIFc 200 IU/kg daily and 4 moved into the tapering period receiving 100 IU/kg daily or every other day. An interim analysis is planned when ≥10 patients have completed ≥6 months of ITI treatment.

Discussion/Conclusion: This ongoing study of first-time ITI with rFVIIIFc will examine the time to tolerization in subjects with severe haemophilia A and high-titre inhibitors. A potentially decreased time on ITI therapy and to restoration of FVIII efficacy could lead to improved clinical outcomes and quality of life, decreased ITI factor consumption, and earlier return to regular FVIII replacement prophylaxis.

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P180 | Factor XII deficiency: Single centre experience

M. C. Ar*; U. Kimyon; A. Ercaliskan; Z. Baslar

[1]*Dept. Internal Medicine Div. of Haematology, Istanbul University-Cerrahpasa Cerrahpasa Medical Faculty Dep. Of Internal Medicine, Istanbul, Turkey*

Introduction: Factor XII deficiency is an autosomal recessive congenital disorder that is not associated with a bleeding disorder. Typically, patients present in late adulthood with isolated prolonged aPTT. Homozygous patients have undetectable FXII levels, whereas heterozygous individuals have FXII levels ranging between 20% and 60%. Almost all patients are asymptomatic. Rarely patients manifest with mucosal or skin bleeding. FXII deficiency have been associated with an increased risk of arterial and venous thrombosis, myocardial infarction and pulmonary embolism.

Methods: All outpatient patient files between 2005 and 2017 at the Haematology Department of Cerrahpasa Medical Faculty were retrospectively reviewed. Nine cases with FXII deficiency were identified in our cohort of 328 patients with coagulation defects.

Results: Patient characteristics are given in Table 1. None of our patients had a bleeding history except 2 who experienced occasional epistaxis and ecchymotic skin lesions. One patient was homozygous having a FXII level of 0.2%. Others were heterozygous with a median FXII of 22.2%. Only one female patient gave a history of multiple pregnancy losses. Half of the female patients have reported to experience menometrorrhagia. Median age of diagnosis was 35 (17-80) years. Only one patient had a family history of factor XII deficiency.

TABLE 1. Patient characteristics

Age at diagnosis (y)	35 (17-80)
Male/Female (n)	3/6
Median Factor XII level (%)	19 (0.2-27.8)
Menometrorrhagia (n)	3/6
Thrombosis (n)	—
Miscarriage (n)	1
History of prior surgery (n)	9/9

Discussion/Conclusion: FXII deficiency, leading to prolonged aPTT, creates a challenge for routine clinical practice. Laboratory results indicating impaired coagulation do not correspond to clinical bleeding. Furthermore, controversial results have been reported on the relationship between FXII deficiency and increased tendency for thrombosis. Our limited number of patients do not deviate from the literature with regard to clinical phenotype. In accordance with literature diagnosis was in late adulthood. None of our patients had a history of thrombosis. They all had a history of prior uneventful surgical intervention. Menometrorrhagia was a frequent finding. In one patient there was a history of delayed wound healing. Physiologic significance of FXII with regard to haemostasis and other related functions such as induction of immune response and wound healing requires further investigation.

Disclosure of Interest: None declared.

P181 | E-exercise haemophilic arthropathy: Development of a blended physiotherapy intervention

M. Timmer[1,*]; C. Kloek[2]; P. de Kleijn[1]; R. Schutgens[1]; C. Veenhof[3]; M. Pisters[3]

[1]van Creveldkliniek, University Medical Center Utrecht; [2]Research Group Innovation of Human Movement Care, University of applied sciences Utrecht; [3]Department of Rehabilitation, Physical Therapy Science and Sport, University Medical Center Utrecht, Utrecht, Netherlands

Introduction: Several exercise programs are used to improve physical functioning in persons with haemophilia (PWH). However these programs don't intervene on a person's daily physical activity behaviour. Furthermore, regular physiotherapy sessions with an experienced physiotherapist (PT) in the field of haemophilia are for many PWH not feasible. Blended care integrates the advantages of E-health with regular face-to-face physiotherapy. It is an innovative opportunity to support the participant at home with performing the advised movement behaviour, with performing the prescribed home exercises and with providing information 24/7. Therefore, blended physiotherapy has the opportunity to support behavioural change and encourage self-control, requiring less face-to-face contact. The aim of this study was to develop a blended physiotherapy intervention for persons with haemophilic arthropathy (HA).

Methods: E-Exercise HA was developed in co-creation with PTs, patients, developers, a commercial E-Health entrepreneur and researchers. The content of e-Exercise HA was compiled using the first two steps of the CeHRes-roadmap model (contextual inquiry and value specification) including 1) experience with the development of previous blended physiotherapy interventions, 2) a literature search, and 3) focus groups with PWH and PTs. Draft versions were provided from feedback by PWH and PTs.

Results: Focus groups revealed that 1) physiotherapy for persons with HA shows great similarities to osteoarthritis, 2) specific information is required for PWH and PTs, 2) PWH prefer to do meaningful daily life activities and work towards a goal, 3) PWH prefer choices and variability in exercises and 4) a personalized program is required. A 12 weeks blended physiotherapy intervention was developed consisting of video-supported information modules for PWH and PTs (themes are based on focus groups), a graded activity program and video-supported exercises. The intervention can be personalized by 1) selecting exercises from a database of 1500 exercises, 2) adjusting intensity and repetitions of the exercises, 3) selecting a tailored activity and 4) adjusting the baseline level of this activity. PWH can give feedback on the performance of the activity.

Discussion/Conclusion: A blended physiotherapy intervention for persons with HA was developed in co-creation with PWH and PTs. Future research will focus on feasibility and effectiveness of the intervention.

Disclosure of Interest: None declared.

P182 | The use of WFH humanitarian aid long lasting clotting factor concentrates (CFCs) in surgical prophylaxis; two Egyptian centers experience

M. El Ekiaby[1,*]; M. El Alfy[2]; N. Gamal[2]

[1]Blood Transfusion and Hemophilia Treatment Center, Shabrawishi Hospital, Giza; [2]Pediatric Hematology, Ain Shams Medical School, Cairo, Egypt

Introduction: Access to CFCs for treatment of patients with hemophilia in Egypt is limited.

In 2014 WFH Humanitarian Aid Program committed to provide Egypt annually with 2-5 million IU of long lasting CFCs. In response to the donation program Egypt MoH committed to cover cost of surgeries for patients with hemophilia who use the donated CFCs for surgical prophylaxis.

Methods: We here report that surgical experience of two centers, namely Ain Shams Hemophilia and Shabrawishi Hemophilia Treatment Centers.

Both centers performed 34 surgeries. Surgical prophylaxis protocol was set as follows:

1-Minor surgery: target FVIII/FIX level is 40% for one or two days

2-Moderate Surgery: target FVIII/IX level is 50% pre-surgery and maintenance dose to achieve 30% level for 2-4 days

3-Major surgery: 80% pre surgery and maintenance to achieve 50% for 2 days then 30% for three days

4-Arthroplasty surgery: 100% pre surgery and for 3 days, 70% for 4 days, 50% for 10 days then twice weekly prophylaxis for 3 months

Doses for FVIII were given on daily basis and for FIX were given on daily basis for first 3 days in major surgery then every other day for subsequent maintenance days.

Results: Surgeries included 4 knee arthroplasty, corrective orthopedic surgeries, hernia repair, anal fissure repair, correction of fractures, evacuation of intracranial hematoma, arthroscopic knee synovial cautery for treatment of joint synovitis, evacuation of muscle hematoma, repair of hemorrhagic bone cyst, renal calculi urolithiasis, circumcisions. All patients did not report post operative bleeding until they were discharged except for one patient who had prolonged recurrent post operative bleeding after knee arthroplasty. No patient reported adverse event due to the use of long lasting CFCs.

Discussion/Conclusion: WFH Humanitarian Aid donation program had a great impact in improving the care for patients with hemophilia in Egypt. The use of long lasting CFCs was both effective and safe even at the low dose surgical prophylaxis adopted by the two centers to increase the number of patients to treat more patients.

Disclosure of Interest: None declared.

P184 | Incorporation of evidence based guidelines on bleeding risk assessment prior to ENT surgery into practice: Real time experience

M. Al Mazrooei[1,*]; N. Al-Marhoobi[2]; M. Elshinawy[3]; H. Nazir[3]; K. Al Hashmi[4]; R. Al-Abri[5]; K. Macki[6]; A. Al-Rawas[3]; Y. Wali[3]

[1]Pediatrics, Muscat, Oman; [2]Oman Medical Specialty Board, Muscat, Oman; [3]Child Health Department, Sultan Qaboos University Hospital, Muscat, Oman; [4]Hematology Department, Armed Force Hospital, Muscat, Oman; [5]ENT Surgery, Sultan Qaboos University Hospital, Muscat, Oman; [6]ENT Surgery, Armed Force Hospital, Muscat, Oman

Introduction: Despite guidelines recommending the no need for coagulation profile prior to ENT surgeries when challenging history of bleeding is negative, yet surgeons still practice it. Cost and delaying surgeries are major issues faced when abnormalities are found in the coagulation profile results. In 2008, British Committee for Standards of Hematology has published guidelines on assessing the bleeding risk prior to surgeries or invasive procedures; the indication for sending a coagulation profile is based on the bleeding history of the patient. We aim to identify the reasons of ENT surgeons for requesting pre-operative coagulation screening; PT and APTT despite the available evidence and guidelines of their poor correlation with bleeding risk.

Methods: The current work was based on a survey conducted at 3 tertiary care facilities in the Oman for surgeons who performed ENT surgical procedures between 1st Jan 2017 to 1st September 2017 to identify their practice prior to surgeries, either getting a challenging bleeding history or requesting a coagulation profile. Surgeons who decide to do coagulation profile were requested to identify their reason. Patients with proven or suspected bleeding disorder were excluded.

Results: The study included data from 730 patients who underwent ENT surgical procedures. They were 432 males and 298 females. Their mean age was 19.6 ± 16.92 year. Out the 730 patients, 372 were interviewed for a challenging bleeding history alone (group 1) and 358 were interviewed plus a pre-operative coagulation profile check (Group 2). Two patients had an intraoperative minor bleed that requires stitching (one in each group). Three patients in group 2 had post-operative secondary bleeding after 1 week that responded to local hemostatic measures. Twenty eight surgeons who preferred to do the coagulation profile for their patients answered the survey. Twenty two (78.5%) gave the reason of habitual practice and overprotection, 4 were not confident with the current evidence and 2 had previous bleeding experience with their patients.

Discussion/Conclusion: Despite the current evidence of meta-analysis and the hospital guidelines, still many surgeons prefer to do coagulation check before ENT surgeries for different reasons. Surgeons need to be educated more on the current evidence of the superiority of the challenging bleeding history over the routine coagulation tests.

Disclosure of Interest: None declared.

P185 | Swedish national registry for bleeding disorders – a second report

M. Holmström[1,*]; J. Astermark[2]; F. Baghaei[3]; E. Brodin[4]; N. Gretenkort-Andersson[5]; M. Axelsson[6]; A. Olsson[7]; G. Jacobsson-Ekman[8]; L. Myrin-Westesson[7]; E. Olsson[9]; P. Petrini[10]

[1]Coagulation Unit, Patient Area Hematology, Karolinska University Hospital, Dept of Medicine Karolinska Institutet Solna, Stockholm; [2]Thrombosis and Haemostasis, Skåne University Hospital, Malmö; [3]Coagulation Centre Sahlgrenska University Hospital, Department of Medicine/Hematology and Coagulation Disorders; [4]3Department of Physiotherapy, Sahlgrenska University Hospital/ Sahlgrenska Institutet of Neuroscience and Physiology- Section for Clinical Neuroscience and Rehabilitation, The Sahlgrenska Academy, University of Gothenburg, Gothenburg; [5]2Department for Thrombosis and Haemostasis, Skåne University Hospital; [6]2Department for Thrombosis and Haemostasis, Skåne University Hospital, Malmö; [7]Coagulation Centre, Department of Medicine/Hematology and Coagulation Disorders, Gothenburg; [8]QRC Stockholm, Karolinska Institutet and Stockholm County Council; [9]Coagulation Unit, Patient Area Hematology, Karolinska University Hospital, Dept of Medicine Karolinska Institutet Solna; [10]Coagulation Unit, Astrid Lindgrens Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

Introduction: Hemophilia Care in Sweden is centralized to three different and certified European Hemophilia Care Centers (EHCCs) (Stockholm, Gothenburg and Malmö[f1]). A recent web-based National registry has been set up for patients with bleeding disorders in Sweden. The registry is mainly funded by Swedish authorities.

Methods: A multi-professional steering committee is running the registry with representatives from all three centers including physicians, nurses, physiotherapist and also a patient representative. A web-based platform, Real-Q, is used for the registry.

Results: By the 31st Dec 2017, a total number of 1030 patients with bleeding disorders were included in the registry, mainly patients with hemophilia A, B and Von Willebrand disease. Data regarding bleedings, treatment modality and type of product, inhibitor status, viral infections are collected. Likewise patient reported outcome measurements (PROM)- such as pain and quality of life[.

The number of patients with hemophilia A, B and Von Willebrand disease in 2016 resp 2017 were as follows:

Hemophilia A; n = 243 in 2016 and n= 691 in 2017.

Hemophilia B: n = 49 in 2016 and n = 191 in 2017.

Von Willebrand disease: n = 11 in 2016 and n = 152 in 2017.

[LMW1] are registered.

[LMW2] are registered on a regular basis?

Discussion/Conclusion: The number of patients in the Swedish National Registry for bleeding disorders has increased significantly during the last year; from a total of 308 Dec 31st 2016 to 1030 in Dec 31st 2017. Increasing amount of data will enable further evaluation of treatment data and also joint status, quality of life and bleeding reports.

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P186 | AHEAD international and German studies: Effectiveness, safety, and quality of life outcomes in hemophilia A patients treated with antihemophilic factor (recombinant) in a real world setting over 5 years

M. C. Ozelo[1,*]; J. Oldenburg[2]; A. Huth-Kühne[3]; R. Klamroth[4]; R. Parra[5]; K. Kurnik[6]; E. Santagostino[7]; D. A. Tsakiris[8]; C. Hermans[9]; H. Jiang[10]; G. R. Chiu[10]; L. Renault[11]; A. Fernandez[11]; K. Khair[12]

[1]Hemocentro UNICAMP, University of Campinas, Campinas, SP, Brazil; [2]Institute for Experimental Hematology and Transfusion Medicine, Bonn University Clinic, Bonn; [3]SRH Kurpfalzkrankenhaus and Haemophilia Centre Heidelberg GmbH, Heidelberg; [4]Department for Internal Medicine, Vascular Medicine and Haemostaseology, Vivantes Klinikum Friedrichshain, Berlin, Germany; [5]Unidad de Hemofilia, Hospital Universitari General Vall d'Hebron, Barcelona, Spain; [6]Dr. von Haunersches Kinderspital Klinikum der Universität München, München, Germany; [7]Foundation IRCCS Ca' Granda, Maggiore Hospital Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy; [8]University Hospital Basel, Basel, Switzerland; [9]Haemophilia Centre, Saint-Luc University Hospital, Brussels, Belgium; [10]Shire, Cambridge, MA, USA; [11]Shire, Zug, Switzerland; [12]Centre for Outcomes and Experience Research in Children's Health, Illness and Disability (ORCHID), Great Ormond Street Hospital for Children, London, UK

Introduction: The German (GER) and international (INT) antihemophilic factor (recombinant) (ADVATE®) Hemophilia A (HA) outcome Database (AHEAD) studies were designed to assess long-term, real-world outcomes in patients with severe or moderate HA receiving antihemophilic factor (recombinant) (rFVIII; ADVATE®, Baxalta [part of Shire, Lexington, MA, USA]).

Methods: These 2 non-interventional, prospective, long-term, multicenter studies began in June 2010 (GER; DRKS 00000556) and June 2011 (INT; NCT02078427) and include previously treated/untreated/minimally treated patients (PTP/PUP/MTP) currently receiving treatment with rFVIII. Key outcomes include annualized bleeding rates (ABRs), adverse event (AE) rates, inhibitory antibody development, and quality of life (QoL) parameters. 5-year observation results are reported herein (data cut-off 13 April 2018).

Results: The GER safety analysis set included 376 patients (307 severe, 69 moderate HA), median (range) age 25 (1-80) years; treatment at baseline: 301 prophylaxis (PRO), 70 on-demand (OD), 5 immune tolerance induction (ITI). The INT safety analysis set included 705 patients (495 severe, 208 moderate HA), median (range) age 14 (0-78) years; treatment at baseline: 577 PRO, 111 OD, 17 ITI. Median (range) ABRs GER: year 1, PRO 2.1 (0.0-57.7), OD 8.4 (0.0-75.9); year 5, PRO 1.8 (0-29.9); OD 3.2 (0.0-41.0). Median (range) ABRs INT: year 1, PRO 1.2 (0.0-30.5), OD 4.1 (0.0-61.0); year 5, PRO 1.1 (0.0-21.3), OD 1.8 (0.0-49.7). Overall AEs were reported in 289/376 (77%) GER and 340/705 (48%) INT patients, including serious AEs considered treatment-related (mainly inhibitor development) in 15/376 (4.0%) GER and 5/705 (0.7%) INT. Confirmed *de novo* inhibitors observed: GER, 9 patients, 2 with persistent high titers (1 PUP, 1 unknown previous treatment; both currently receiving ITI); INT, 10 patients, 3 had high titers (2 PTP, 1 MTP; all transient). QoL scores were consistent overall throughout the observation period.

Discussion/Conclusion: Although differences in data collection between the INT and GER databases from the AHEAD studies preclude direct comparisons, these 5-year follow-up data show long-term effectiveness and tolerability of rFVIII therapy in a large patient population with HA in a real-world setting.

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P187 | Accidental arterial venipuncture management in a patient with severe hemophilia A and inhibitor

M. D. C. García Martínez[1,*]; S. García Barcenilla[2]; M. D. C. García Rivera[1]; A. Hernández Verde[1]; A. Castro Blanco[1]; M. I. Pérez Vaquero[1]; A. Sánchez Martín[1]

[1]Haematology, nurse staff, La Paz University Hospital, Madrid, Spain; [2]Haematology, nurse staff, La Paz University Hospital-IdiPAZ, Madrid, Spain

Introduction: Background: currently induction to immune tolerance (ITI) involves several intravenous punctures. Nurses are used to deal with potential complications of venous puncture, but arterial puncture are very unusual and there is a lack of experience managing this situation. We report our first case of accidental arterial puncture in our Unit.

Methods: A 15 months of age patient with severe hemophilia A with inhibitors on ITI daily regimen with inhibitor titre <10 BU suffered an accidental arterial puncture (day 0). This caused active arterial bleeding in brachial artery and edema with suspected compartment syndrome. Day +1 (first assessment in our Unit): severe hematoma observed secondary to arterial brachial bleeding, edema and increased diameter of arm. Treatment with bypass agent (BA) (rFVIIa) started <1 h of assessment. Patient continued on rFVIIa under a standard protocol. Day +2: interventional angiography via femoral to thrombose the bleeding point. Edema progression, initial coldness and paleness in distal area of hand but with conserved pulses. Treatment with high doses of FVIII was decided to achieve levels around 100% saturating circulating inhibitor and stopping acute bleeding. BA could be restored and decreased gradually according to haematoma resolution. Day +7: pseudoaneurysm detected in femoral artery secondary to angiography. Therapeutical actions were local compression and spaced BA. Inhibitor: 755 BU, peripheral venous access was very limited. Patient presented ulcerated lesion in antecubital area due to ischemia, tension and edema generated by hematoma. Topic treatment with nitrofurazone and sulfadiazine argentum initiated. Compassionate use of emicizumab was requested, approved and prescribed.

Results: Day +45: discharge. Complete resolution of acute arterial bleeding without motor and sensory sequelae. Complete healing of necrotic area in upper limb. Complete thrombosis of pseudoaneurysm managed avoiding surgery.

Discussion/Conclusion: Good communication and collaboration between all the members of the team is crucial to manage and avoid worsening complications, and nurses have an active role coordinating units and procedures. Due to the complexity of the serious complications of patients with hemophilia, more studies are needed to confirm the importance of nurses specialized in hemophilia.

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P188 | High estimated success rate for every-5-day prophylaxis with BAY 94-9027 based on data from the protect VIII study

M. Elisa Mancuso[1,*]; S. Rangarajan[2]; T. Liu[3]; S. Lalezari[4]; J. Ducore[5]

[1]*Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy;* [2]*University Hospital Southampton NHS Foundation Trust, Southampton, UK;* [3]*Bayer AG, Berlin, Germany;* [4]*National Haemophilia Centre, Chaim Sheba Medical Centre, Tel-Hashomer, Israel;* [5]*Hemophilia Treatment Center, University of California Davis School of Medicine, California, USA*

Introduction: Efficacy and safety of BAY 94-9027 as prophylactic and on-demand therapy for patients with severe haemophilia A were shown in the phase II/III PROTECT VIII trial (NCT01580293) and its extension. In PROTECT VIII, patients with 0 or 1 breakthrough bleeds on BAY 94-9027 2×/week at 25 IU/kg for 10 weeks were eligible for treatment with extended-interval dosing. To investigate the clinical benefits of extended intervals, we made a post hoc analysis of bleeding outcomes and the success rate of every-5-day (E5D) BAY 94-9027 prophylaxis.

Methods: PROTECT VIII was a part-randomised, open-label trial of 134 males aged 12-65 years with severe haemophilia A (FVIII <1%) and ≥150 FVIII exposure days. In prophylaxis groups, patients with >1 breakthrough bleed in a 10-week run-in period received 30-40 IU/kg 2×/week; patients with ≤1 breakthrough bleed were eligible for randomisation and received 30-40 IU/kg 2×/week, 45-60 IU/kg E5D or 60 IU/kg every 7 days (E7D) for the main 26-week study period. Patients completing the main study could enter an extension. We used a negative binomial model to compare annualised bleeding rates (ABRs) pairwise between groups in the full study period; success rate of E5D treatment across all prophylaxis groups was estimated for the period from randomisation to the end of year 1 of the extension.

Results: Using data from the full study period and a negative binomial model, mean ABRs (95% CI) were comparable between patients on 2×/week (eligible for randomisation, n = 8) and E5D dosing (n = 30): 2.90 (1.16, 7.28) vs 3.73 (2.32, 6.01), respectively (P = 0.6335). The success rate of E5D prophylaxis was estimated for the 104 on-study patients at the end of extension year 1 (n = 21, 2×/week; n = 41, E5D; n = 42, E7D). A patient moved to 2×/week dosing during this period. Assuming this group was representative of the whole cohort (and excluding 11 patients who had >1 bleed in the run-in), a success-rate estimate suggests that 87.2% of patients receiving BAY 94-9027 as prophylaxis in both main and extension periods would remain on E5D dosing.

Discussion/Conclusion: Negative binomial analysis suggests the ABRs between 2×/week and E5D dosing are comparable. The majority (87.5%) of prophylaxis patients are predicted to succeed on E5D dosing using a success-rate estimation. These analyses support the use of extended-interval (E5D) dosing in most patients on BAY 94-9027 prophylaxis.

Disclosure of Interest: M. Elisa Mancuso Consultant for: Bayer Healthcare, CSL Behring, Novo Nordisk, Roche, Pfizer, Baxalta/Shire, Kedrion, Catalyst, Speaker Bureau of: Bayer Healthcare, CSL Behring, Novo Nordisk, Roche, Baxalta/Shire, Biotest, Octapharma, Roche, S. Rangarajan Grant/Research support from: Sangamo Institutional grant, Speaker Bureau of: Shire, T. Liu Employee of: Bayer, S. Lalezari Consultant for: Bayer, Teva Pharmaceuticals, Pfizer., Speaker Bureau of: Pfizer, J. Ducore Grant/Research support from: Octapharma, Consultant for: Bayer, Octapharma, Baxalta (Shire), Hema Biologics (LFB)

P189 | Clinical impact and pharmacoeconomic analysis of efmoroctocog alfa treatment in patients with severe hemophilia A

M. F. García[1,*]; M. Fernández Caballero[1]; J. C. Juárez Giménez[2]; Á. Serna Pareja[1]; M. Sitges Arriaga[3]; E. Johansson[1]; M. Cerdá Sabater[1]; N. Soto Bonet[1]; R. Cardona López[1]; M. J. Pravos González[1]; F. Bosch Albareda[4]; A. Santamaría Ortiz[5]

[1]Hematology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [2]Department of Hospital Pharmacy, Vall d'Hebron University Hospital, Barcelona, Spain; [3]Hematology Department, Germans Trias i Pujol University Hospital, Barcelona, Spain; [4]Head of the Hematology Department, Head of the Hemophilia Unit, Vall d'Hebron University Hospital, Barcelona, Spain; [5]Hematology Department, Head of the Hemophilia Unit, Vall d'Hebron University Hospital, Barcelona, Spain

Introduction: The recombinant factor VIIIFc (efmoroctocog alfa) is the first extended half life (EHL) factor VIII (FVIII) available in Spain. The use of this factor could offer the possibility of reducing the number of weekly infusions in some patients or increase the hemostatic protection. The aim of this study was to test the clinical impact due to the hemostatic protection and infusions reduction in the patients from our unit; and show our experience with this EHL, as well as if there is an economical benefit.

Methods: We performed an observational and retrospective study with 36 patients diagnosed with severe hemophilia A treated at the Hemophilia Unit of Vall d'Hebron Hospital in Barcelona, who changed their treatment from conventional FVIII (CFVIII) to rVIIIFc with at least a 3 months follow-up. We collected data about FVIII consumption and number of total and spontaneous hemorrhages. We compared the variables collected during the time with treatment with CFVIII against the ones collected during the treatment with to rVIIIFc.

Results: The mean of follow up was 6.2 months (3-12 months) for each period of treatment. Two patients (5.5%) had pediatric age and the rest were adults with a mean age of 39 years old (20-64 years old). Twenty two patients (61%) were on prophylactic treatment before the switch of treatment while the rest were on demand. After changing to rVIIIFc treatment all patients except one changed to prophylactic treatment (97.2%).

Of the 22 patients with previous prophylaxis, 73% (16) decreased the number of monthly infusions. This way the FVIII units consumption decreased 15% monthly in these patients, even so there were reported 51% less hemorrhages during the rVIIIFc treatment, being the majority post traumatic hemorrhages.

We reviewed the economic impact of the prophylactic treatment and the economic spending was reduced in approximately 32% monthly.

Discussion/Conclusion: We showed a significant reduction in the consumption of FVIII destined to the prophylactic treatment as well as a diminution of hemorrhages in our patients under prophylactic treatment with rVIIIFc. The switch of treatment caused a lower injection burden and a better treatment adherence in most our patients. In terms of costs, the prophylactic treatment with rVIIIFc allowed us to save the 32% of the monthly cost of prophylaxis in patients that previously received prophylaxis with CFVIII.

Disclosure of Interest: None declared.

P190 | Epidemiology of rare congenital bleeding disorders at a reference center of congenital coagulopathies in Spain

M. F. Martínez García[1,*]; M. Fernández Caballero[1]; M. Santos Gómez[2]; E. Johansson[1]; M. Cerdá Sabater[1]; Á. Serna Pareja[1]; N. Soto Bonet[1]; M. J. Pravos González[3]; F. Bosch Albareda[3]; A. Santamaría Ortiz[4]

[1]Hematology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [2]Hematology Department, Germans Trias i Pujol University Hospital, Barcelona, Spain; [3]Head of the Hematology Department, Head of the Hemophilia Unit, Vall d'Hebron University Hospital, Barcelona, Spain; [4]Hematology department, Head of the Hemophilia Unit, Vall d'Hebron University Hospital, Barcelona, Spain

Introduction: Rare bleeding disorders (RBD) constitute 5% of the total congenital bleeding disorders, although the number could be higher, due to the presence of undiagnosed asymptomatic patients. The objective of this study was to analyze the prevalence and characteristics of patients with RBD with levels <20% diagnosed in our center.

Methods: We analyzed the patients with RBD with factor levels <20% visited in our center, Vall d'Hebron University Hospital, between January 2014 and December 2016.

Results: A total of 58 patients were analyzed, of which 50% were male, with a median age at diagnosis of 23.5 years (range 0.3 - 75). The most frequent RBD in our population was the FVII deficiency (33%), followed by the FXI deficiency and fibrinogen deficit with 30% and 14% respectively. Regarding the diagnostic reason, the most frequent cause was a preoperative analysis (35%) and only 24% had spontaneous bleeding symptoms. Fifty-seven percent had received replacement treatment mostly as prophylaxis prior to invasive procedures. Although 67% had carried out the genetic study, we could not establish a correlation between genotype and phenotype.

Discussion/Conclusion: The distribution of RBD in our center is similar to the one reported in the literature. The majority of RBD have been diagnosed from a preoperative analysis and this has allowed a preparation prior to surgical interventions thus avoiding bleeding complications. Only the 25% had bleeding symptoms at diagnosis so studies are needed to stablish the correlation of factor levels with the bleeding phenotype.

Disclosure of Interest: None declared.

P191 | Emicizumab treatment in hemophilia A with inhibitors. A case report and cost-minimization analysis of a non-responder to conventional treatment patient

M. F. Martínez García[1,*]; M. Fernández Caballero[1]; J. C. Juárez Giménez[2]; Á. Serna Pareja[1]; M. Cerdá Sabater[1]; E. Johansson[1]; E. Álvarez Martínez[1]; C. Fernández Sarmiento[1]; F. Bosch Albareda[3]; A. Santamaría Ortiz[4]

[1]*Hematology Department, Head of the Hemophilia Unit, Vall d'Hebron University Hospital, Barcelona, Spain;* [2]*Department of Hospital Pharmacy, Head of the Hemophilia Unit, Vall d'Hebron University Hospital, Barcelona, Spain;* [3]*Head of the Hematology Department, Head of the Hemophilia Unit, Vall d'Hebron University Hospital, Barcelona, Spain;* [4]*Hematology department, Head of the Hemophilia Unit, Vall d'Hebron University Hospital, Barcelona, Spain*

Introduction: The treatment of patients with hemophilia A (HA) with inhibitors has been based on conventional immune tolerance induction (ITI) treatment and bypass agents. Emicizumab, a humanized immunoglobulin IgG4 antibody that mimics the effect of activated factor VIII has been approved recently as treatment of this condition. It showed a decrease of annual bleeding rate compared to bypass agents in pivotal analysis; however, in our country is only reimbursed in non-responder to the conventional therapy (CT) patients. We report one of the first cases in our country of a patient with severe HA with inhibitors that received emicizumab as compassionate use outside a clinical trial.

Methods: A 16 years-old male with severe HA with inhibitors that previously received ITI and immunosuppression with rituximab at the age of 5 years old achieving to eradicate the inhibitor. He was on prophylaxis with plasma-derived FVIII until he was 16 years old when he developed inhibitors again while presenting frequent hemorrhages especially hemarthrosis and a severe case of psoas hemorrhage. In order to control the bleeding we changed the treatment to an intense therapy with aPCC and rFVIIa. After solving the hemorrhage he continued with prophylaxis with aPCC but kept presenting bleeding events as hematuria and musculoskeletal hemorrhages. Considering the clinical situation we recommended the use of emicizumab and rFVIIa as bypass agent if needed.

We performed a 2-year cost-minimization analysis of emicizumab treatment in order to compare it with the cost of the CT, taking into account the cost of emicizumab was estimated considering the standard weekly doses as well as the cost of the CT with high doses of rFVIIa and aPCC as prophylaxis and hemorrhage treatment.

Results: The total cost of his previous treatment was 1 170 742 € (891 562 € for rFVIIa; 147 420 € for high doses of plasma derived FVIII and 131 760 € for aPCC). The total cost of emicizumab was 1 291 596 €. The two years incremental cost was 120 854 €, which represents an increase of 10%.

Compassionate use was approved and started and during the three-months follow-up there was a good response to the treatment with no adverse events and no bleedings reported.

Discussion/Conclusion: The use of emicizumab in this patient was successful on preventing hemorrhagic episodes without involve a significant cost increment.

Disclosure of Interest: None declared.

P192 | Non-additive effect on thrombin generation of FVIII/VWF combined with emicizumab in haemophilia A plasma: An in vitro study

M. I. Bravo[1,*]; A. Raventos[1]; A. M. Ortiz[1]; M. Costa[1]; T. Willis[2]; S. Grancha[1]; J. I. Jorquera[1]

[1]*Grifols Bioscience Research Group, Grifols, Barcelona, Spain;* [2]*Grifols Bioscience Research Group, Grifols, North Carolina, USA*

Introduction: Emicizumab (Hemlibra, Chugai-Roche) is a haemophilia A chronic treatment but may be associated with breakthrough bleeds (eg. surgery) that require concomitant acute haemostatic treatment (eg. FVIII, rFVIIa, aPCC). The use of aPCC in the presence of emicizumab has been related to fatal thromboembolic events. This risk has not been observed with rFVIIa and FVIII, although further studies are still needed. In this study, we assessed thrombin generation (TG) in vitro when a plasma-derived VWF/FVIII (Alphanate/Fanhdi, Grifols) was added to haemophilia A plasma (HAp) with emicizumab.

Methods: A pool of HAp alone or containing therapeutic doses of emicizumab (50 and 100 µg/mL) was combined with aPCC at 0.5 to 2.5 U/ml (≈25 to 125 U/kg), rFVIIa at 0.5 to 15 µg/ml (≈27 to 810 µg/kg), or FVIII/VWF at 0.1 to 4.5 IU/ml (≈0.1 to 200 IU/kg). Samples were analyzed with TG assays (tissue factor: PPP-Reagent Low, Stago) and reaction parameters (thrombin peak and ETP [Endogenous Thrombin Potential]), calculated using Calibrated Automated Thrombogram software. TG of HAp with emicizumab alone or combined with the different products were compared.

Results: For thrombin peak, TG results of HAp with emicizumab combined with aPCC 0.5 U/ml increased the peak by ≈9-11 fold; rFVIIa moderately increased peak from 2 fold at 0.5 µg/ml to 5 fold at 15 µg/ml; FVIII/VWF up to prophylaxis dose (0.1 to 1 IU/ml) slightly increased peak from 1.2 to 3 fold while FVIII/VWF up to ITI dose (2 to 4.5 IU/ml) increased peak from 3 to 7 fold. For ETP, addition of aPCC to HAp with emicizumab increased results by ≈3-4 fold; rFVIIa increased from 1.3 fold (rFVIIa 0.5 µg/ml) to 2 fold (rFVIIa 15 µg/ml); FVIII/VWF increased by 1.1 fold to 1.7 (until prophylaxis dose) and 1.5 to 2.1 (ITI dose).

Discussion/Conclusion: Addition of aPCC to HAp with emicizumab had a synergistic effect on TG even at low doses. Addition of rFVIIa resulted in a moderate dose-related increase in TG but within normal ranges. By contrast, addition of FVIII/VWF (Alphanate/Fanhdi) at doses ranging from 1 IU/ml to as high as 4.5 IU/ml showed a non-additive effect, since TG was unchanged to that observed in HAp without emicizumab. These results may suggest that emicizumab has limited ability to promote FX activation in presence of natural FVIII/VWF reducing the risk of overdosing, and are in agreement with those observed in HAVEN 3 clinical trial.

Disclosure of Interest: M. I. Bravo Employee of: Grifols, a manufacturer of plasma-derived FVIII/VWF, A. Raventos Employee of: Grifols, a manufacturer of plasma-derived FVIII/VWF, A. M. Ortiz Employee of: Grifols, a manufacturer of plasma-derived FVIII/VWF, M. Costa Employee of: Grifols, a manufacturer of plasma-derived

FVIII/VWF, T. Willis Employee of: Grifols, a manufacturer of plasma-derived FVIII/VWF, S. Grancha Employee of: Grifols, a manufacturer of plasma-derived FVIII/VWF, J. I. Jorquera Employee of: Grifols, a manufacturer of plasma-derived FVIII/VWF.

P193 | Subclinical bleeds in patients with hemophilia (PWH)

M. Landro; M. Margulies; T. Etcheverry; G. Perez Ballester; C. Daffunchio; H. Caviglia*

Hospital General de Agudos Dr. Juan A. Fernandez, CABA, Argentina

Introduction: Detecting subclinical intra-articular bleeds is a big challenge to provide an adequate coagulation clotting factor management and to prevent joint damage. Repeated bleeding episodes may lead to degenerative arthropathy that is the most frequent complication in PWH. Ultrasound (US) has been proven capable of detecting and quantifying the most relevant biomarkers of disease activity (joint effusion and synovial hypertrophy) and degenerative damages (osteo-chondral changes). We think this could be a useful method for subclinical bleeds diagnosis. There is no knowledge about what is the minimum intra-articular volume of blood detected by ultrasound in the different joints. The aim of this work is to know the minimum volume of blood detected by ultrasound in ankle, elbow and knee joints.
Methods: At the Hospital morgue 5 man corsets (10 ankle, 10 elbow and 10 knee joints) with an averaged high 177 cm (168 -183) were used to carry out this work. Intra-articular blood (from the blood bank) injections were performed in each joint. We started injecting 1 ml of blood and we increased the volume by one millilitre at the time until achieving the visualization of the hemarthrosis in the ultrasound image. The images of the ultrasound were analyzed by a specialized professional
Results: Analyzing the ultrasound images we shown that the minimum intra-articular volume of blood detected by ultrasound image in elbow joints was 4 ml, in ankle joints was 2 ml and in knee joints was 7 ml, in average.
Discussion/Conclusion: This work demonstrates the minimal amount of blood that was detectable by ecosound. We believe that ecosound is a good diagnostic tool, but if hemarthrosis is lower than the detected values, another method must be found to validate its presence
Disclosure of Interest: None declared.

P194 | Analysis of the education and work situations in adult patients with hemophilia

M. S. Cruz*; J. Santillán; A. Guzmán

Fundación de La Hemofilia de Salta, Salta, Argentina

Introduction: The nature of hemophilia and its effects have an influence on the social environment, and tend to give shape to patients with a low self-esteem personality, which does not allow them to interact accurately and maintain stable interpersonal relationships. This results in school and work absenteeism.
We have to take into account that the adult patients did not have access to the prophylactic treatment throughout their childhood. Thus, they suffered disabling effects due to severe bleeding episodes. In Argentina, the National Law N° 18.910 enables patients with more than 76% of physical inability to access a disability to work pension. This law impedes them from having a formal job, as it would not be consistent with the pension system.
Work opportunities depend on the educational level obtained. In Argentina, the primary level education is compulsory and free, and the secondary level education is also free, but only compulsory for those who want to get a formal job.
The low educational level, plus the inability pension granted, put the patient in a risk situation, as their income is stable but low even to meet basic needs. In some cases, they may be below the poverty line.
Methods: A survey to 18-65-year-old patients with hemophilia was conducted. It assessed complete educational level (primary, secondary and higher education), work condition (formal job, informal job, no job), and whether they had access to an inability pension.
Results: The data collected from 22 patients (100%) were: mean age 33.6 years, educational level: primary level: 100% (22); secondary level: 68.2% (15); higher education: 36.4% (8), work situation: formal job: 31.8% (7); informal job: 54.5% (12); no job: 13.6% (3), and inability pension beneficiaries: 27.3% (6).
Discussion/Conclusion: The patients have a low level of education, more than half of them do not have a formal job, and more than a quarter of them was granted an inability pension, hence they could not have access to better paid jobs, affecting their quality of life.
The foundation will enforce strategies in order to raise the educational level in patients, by providing them with information tools, so they can access and finish their studies. Regarding the work situation, the foundation will contact state employment offices, so they can provide trainings that would help them get formal jobs.
Disclosure of Interest: None declared.

P195 | Update to the manual on dental management in hemophilia and von Willebrand patients

M. S. Cruz*; L. Forzani

Fundación de la Hemofilia de Salta, Salta, Argentina

Introduction: The first manual was prepared by professionals from the Foundation of Hemophilia of Salta and the Dental Care Program launched by the Ministry of Health Care of Salta in 2014, approved by the Ministerial Resolution 271/14 and the National Directorate of Dental Care of the Ministry of Health of the Nation, which aimed to regulate the dental assistance practice on patients with hemophilia and EvW. As a result of our effort, dentists are now aware of the main facts they need to take into account to treat patients with hemostasis alterations, hence carry out the appropriate treatments and provide hemophilia and EvW patients with a longer and better quality of life.

For four years, we have been working on the dentists' role at the evaluation, diagnosis, preventive treatment, and remedial stages. Also, in educating the patient, as well as their parents, in relation to dental care through the multidisciplinary health care team. It is for this reason that in 2018, we decided to update the manual.

Methods: For the elaboration of this manual, we consulted the treatment guidelines provided by the World Federation of Hemophilia, protocols in different countries, literature search, papers, research studies, consultations to skilled professionals, clinics experience, and all of these were considered in accordance to the reality and necessity of the patient, as well as of the dentist at the province of Salta.

The edition and approval of both manuals was in charge of the Dentists Association of the Province, the Ministry of Public Health of the Province and the Ministry of Health of the Nation.

Results: The first edition of this manual was rapidly put into practice by dentists, and patients received the proper and timely treatment, hence preventing oral diseases.

Since 2014, the dentists are the ones who, most of the times, suspect of those patients suffering from clotting alterations and make a referral to the Foundation of Hemophilia of Salta for further studies. With this update we will be able to keep the professionals up-to-date.

Discussion/Conclusion: We think that maintaining this manual updated is of utmost importance because there have been great improvements in the treatments and approach to patients with these conditions during the last few years.

Disclosure of Interest: None declared.

P196 | Off-pump technique and replacement therapy for coronary artery bypass surgery in a patient with haemophilia B

M. Fernández Caballero[1,*]; M. Santos-Gomez[2]; F. Martínez[1]; N. E. Palmer[3]; G. Oristrell[4]; M. Cerdá Sabater[1]; E. Johansson[1]; S. Franco[1]; C. Fernández[1]; R. Cardona[1]; J. M. Castaño[1]; M. J. Pravos[5]; J. C. Juarez[6]; F. Bosch[7]; A. Santamaría[8]

[1]Hemophilia and Thrombosis Unit. Department of Hematology, Vall d'Hebron Universitary Hospital, Barcelona, Spain; [2]Department of Hematology, Germans Trias i Pujol Hospital, Barcelona, Spain; [3]Department of Cardiac Surgery and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]Department of Cardiology and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [5]Hemophilia Unit and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [6]Department of Pharmacy and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [7]Department of Hematology and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [8]Hemophilia and Thrombosis Unit, Department of Hematology, Vall d'Hebron Universitary Hospital, Barcelona, Spain

Introduction: The life expectancy in patients with haemophilia (PWH) over the last years, has increased cardiovascular complications and the need of antithrombotic therapy or invasive procedures. Herein the case of a 68 year-old patient with mild hemophilia B and multivessel coronary disease who underwent coronary artery bypass grafting surgery (CABG) is described.

Methods: Perioperative management was performed between haemophilia unit, anesthesia and cardiac surgery unit from our center. FIX levels were measured using a standard one-stage APTT-based assay. Inhibitor assays were performed by the Bethesda method.

Results: The FIX basal level of the patient was 5% and anti-FIX inhibitor was negative. According to his weight, 84 kg, 6000 IU of FIX (Benefix®) was administrated prior to the surgery, in order to raise FIX levels above 100%. Subsequently, continuous FIX (Benefix®) infusion was set up. Off-pump technique was selected and complete heparinization was started with 2 mgr/kg of unfractionated heparin (UFH) in order to achieve APTT >200 s. Primary median sternotomy was performed with dissection of the internal saphenous vein and left internal thoracic artery plus pericardiectomy and coronary arteries were dissected and coronary macular bypass to distal anterior descending and first diagonal. Aortic lateral clamping was performed and aortocoronary bypass with saphenous to posterior descending. Finally, the vein grafts were unclamped, atrial and ventricular cables were placed and protamine infusion was administrated. After 7 hours of surgery without complications, FIX level was 108%, so FIX concentrate infusion was continued at the same rate during days 1-3. Antiaggregant treatment was initiated after 24 h post-surgery. On day 4 continuous infusion was stopped and switched to bolus infusion every 8 hours firstly and gradually decreased to every 24 hours. His daily FIX level were stable between 60-80%. On 14th day post-surgery no complications have been presented, so the patient was discharged continuing antiaggregant treatment.

Discussion/Conclusion: Coronary artery disease treatment is challenging in PWH and multidisciplinary approach is needed. Off-pump surgery with continuous infusion FIX treatment is easy to administrate, avoids fluctuations in FIX levels and reduces thrombotic or bleeding risk during the procedure.

Disclosure of Interest: None declared.

P197 | Severe hemophilia A in a girl with family history caused by skewed X chromosome inactivation

M. Fernández-Caballero[1,*]; F. Martínez[2]; E. Tizzano[3]; A. Serna[4]; E. Johansson[5]; M. Cerdá[5]; S. Franco[5]; E. Álvarez[6]; M. Melado Delgado[6]; N. Soto[6]; A. Agout[6]; F. Bosch[7]; A. Santamaria[8]

[1]Hemophilia and Thrombosis Unit. Department of Hematology, Vall d'Hebron Universitary Hospital, Barcelona, Spain; [2]Hemophilia and Thrombosis Unit. Department of Hematology, Vall d'Hebron University Hospital, Barcelona, Spain; [3]Unit of Clinical Genetics and Molecular Medicine, Vall d'Hebron Universitary Hospital, Barcelona, Spain; [4]Department of Hematology, Vall d'Hebron Universitary Hospital, Barcelona, Spain; [5]Hemophilia and Thrombosis Unit. Department of Hematology, Vall d'Hebron Universitary Hospital, Barcelona, Spain; [6]Hemophilia Unit, Vall d'Hebron Universitary Hospital, Barcelona, Spain; [7]Department of Hematology and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [8]Hemophilia and Thrombosis Unit. Department of Hematology, Vall d'Hebron Universitary Hospital, Barcelona, Spain

Introduction: Hemophilia A (HA) is a bleeding disorder caused by mutations in the FVIII clotting factor gene, F8. HA as a X-linked recessive disorder typically affects males, whereas females transmit

the disease, and only in very rare cases manifest the disease. There are a variety of genetic mechanisms that can lead to phenotypical expression of HA in females. We present the case of a 4 years-old girl with a family history of severe HA that suffered from the disease by a skewed X chromosome inactivation.

Methods: FVIII was measured by one-stage method and chromogenic assay. Regarding molecular diagnosis, F8 gene was examined by direct sequencing. Inactivation of X chromosome was studied by PCR analysis of a polymorphic CAG repeat in the first exon of the human androgen receptor (HUMARA) gene. With this technique the DNA is cleavaged by HpaII, an enzyme that is not active when DNA is methylated.

Results: The patient is the second child of a known carrier mother, who was diagnosed as a carrier after having a severe HA son. During pregnancy, fetal sex was determined. The girl was born at term by elective cesarean section due to obstetric indication, she did not present neonatal complications. At the age of 10 months, due to spontaneous bruising, a blood test was performed and coagulation assays showed a prolonged APTT and factor VIII was < 0.01 IU/mL. The familial mutation, a single nucleotide substitution in exon 16 position 5389 C>T (nonsense mutation), was identified. In order to discard numerical or structural X chromosome anomalies, we analysed her karyotype which revealed a normal 46,XX female. Then X chromosome inactivation was studied by PCR. The X chromosome showed a skewed inactivation pattern. After the digestion, the active X chromosome (maternal), in peak 230, disappeared and only the inactive one (paternal) in peak 233 was shown due to only the inactive methylated X-chromosome resists cleavage by HpaII enzyme. With the diagnosis of HA she started prophylaxis with rFVIII at dose of 25 IU/kg body weight per week.

Discussion/Conclusion: We report the case of a hemophilia A girl caused by the concomitant presence of a F8 nonsense mutation in one allele and a skewed X chromosome inactivation. This condition, although is very infrequent, should be taken into consideration in case of a girl presenting bleeding symptoms and with familial history of hemophilia.

Disclosure of Interest: None declared.

P198 | Personalised prophylaxis with simoctocog -alfa (human-cl rhFVIII): A real-life experience on children and moderate haemophilia A patients

M. Napolitano[1,*]; S. Raso[2]; M. F. Mansueto[2]; A. Passannanti[2]; L. LoCoco[3]; M. Sardo[4]; S. Siragusa[1]

[1]*Biomedical Department of Internal Medicine and Specialties (DIBiMIS), Palermo, Italy*; [2]*Università di Palermo, Palermo, Italy*; [3]*Central Laboratory, Hemostasis section, University Hospital "P.Giaccone", Palermo, Italy*; [4]*Hematology Unit, Università di Palermo, Palermo, Italy*

Introduction: Human-cl rhFVIII launched in Italy in June 2015, is currently adopted in all segments and different ages: prophylaxis, on demand, surgery and ITI treatments. Results from NuPrewiq study showed the efficacy of personalized prophylaxis in adults with severe haemophilia A. We here report results of personalized prophylactic treatment with Nuwiq® (simoctocog-alfa) adopted also for children and patients with moderate haemophilia A

Methods: We have analyzed available data related to adolescent and moderate haemophilia A patients receiving a prophylactic regimen with human-cl rhFVIII, defined after pharmacokinetic (PK) studies (either individual or population PK). All the subjects treated by our Reference Regional Center for Haemophilia with available 12 months follow-up after starting a personalized prophylaxis regimen. Secondary aim of the study was to evaluate any change in health-related quality of life as determined by EQ-5D (adults), EQ-5DY-3L (for children) and EQ-VAS (routinely administered in our Center at each regular follow-up visit, since 2016).

Results: Five patients met the above defined criteria for the current analysis: 2 children (7 and 13 yo) with severe haemophilia A and 3 adults with moderate haemophilia A and target joints. Prophylaxis was personalized after individual PK in 2 cases and population PK (WAPPS-haemo) in 2 children and one adult. At 12-month follow-up, the median dosing interval during personalized prophylaxis was 2.5 days, with all adults on 2 weekly dosing. Mean annual bleeding rates during personalized prophylaxis were 2.5, of note bleeding occurred only in adults with arthropathy under secondary prophylaxis while children under primary prophylaxis did not experience any breakthrough bleeding. Health related quality of life scores showed an overall improvement at 12-months, with particular reference to the following parameters: mobility and depression dimension for adults and usual activities dimension in children.

Discussion/Conclusion: The current 12-months follow-up analysis confirms the efficacy of a personalized treatment approach with human-cl rhFVIII also in children and subjects with moderate haemophilia A.

Disclosure of Interest: M. Napolitano Consultant for: NovoNordisk, Bayer, Speaker Bureau of: Octapharma, Shire, BioFVIIx, S. Raso: None declared, M. F. Mansueto: None declared, A. Passannanti: None declared, L. LoCoco: None declared, M. Sardo: None declared, S. Siragusa: None declared.

P199 | Fostering drug storage, preparation and treatment modalities improves adherence to treatment with turoctocog-alfa in patients with haemophilia A: Results from a short-term follow-up

M. Napolitano[1,*]; R. Marino[2]; E. Bldacci[3]; A. Coluccia[4]; D. Cultrera[5]; M. Luciani[6]; S. Pasca[7]; L. Pieri[8]; I. Ricca[9]; G. Barillari[10]; C. Ettorre[11]; S. Linari[12]; F. Valeri[13]; S. Siragusa[14]; A. Rocino[15]

[1]Internal Medicine and Specialties Department (DiBIMIS), Università di Palermo, Palermo; [2]Haemophilia Center, Policliinco di Bari, Bari; [3]Haematology Department, "Gemelli" University Hospital, Roma; [4]Internal medicine, General Hospital, Lecce, Roma; [5]Hematology Department, University Hospital, Catania, Roma; [6]Hematology Department, IRCCS Ospedale Pediatrico Bambino Gesù, Roma; [7]Haemophilia Center, University Hospital of Padova, Padova; [8]Haematology Department, University Hospital "Careggi", Firenze; [9]Transfusion Center, CITTA' DELLA SALUTE E DELLA SCIENZA DI TORINO, Torino; [10]Haemophilia and Thrombosis Center, barillarigiovanni@yahoo.it Udine; [11]Haemophilia and thrombosis Center, University Hospital of Bari, Bari; [12]Haematology Unit, University Hospital "Careggi", Firenze; [13]Haematology Unit, Azienda Ospedaliera San Giovanni Battista, Torino; [14]DiBIMIS, Università di Palermo, Palermo; [15]Haematology Unit and Reference Regional Center, Hospital "Loreto Mare", Napoli, Italy

Introduction: Adherence to treatment in haemophilia A is crucial to allow good clinical outcomes. Several drug-related aspects including storage flexibility (temperature), reconstitution device, and administration frequency have been recently reported to affect patient satisfaction (Patient Prefer Adherence. 2018 Mar 26;12:431-441). Aim of the current prospective analysis was to evaluate any change in treatment adherence measures after switching to turoctocog-alfa (Novoeight®) for treatment of patients with haemophilia A.

Methods: Patients enrolled in the current prospective analysis were asked to fill the Veritas–Pro questionnaire (Haemophilia. 2010 Mar;16(2):247-55) before switching and up to three months after starting treatment with turoctocog-alfa. Indication to start treatment with turoctocog-alfa were based on clinical needs and patients style of life. At each clinical encounter, aspects related to drug storage, preparation and reconstitution were accurately described.

Results: Uptodate, 11 patients have been followed-up for three months Turoctocog-alfa resulted effective and safe in all cases. The median global score at first administration was 36 (SD: 17), while it decreased to 33 (SD: 1428) at 3 months follow-up. The majority of subjects (N = 8) received prophylaxis for severe haemophilia A and started to store their drug outside the refrigerator only after the first clinical encounter.

Discussion/Conclusion: Current results confirm that better communication from health care providers to explain product storage and administration modalities of a room temperature (up to 40°C)stable drug is able to further improve adherence to treatment, at least in the short term.

Disclosure of Interest: None declared.

P200 | A single centre patient/parent experience of immunisation practice in children with bleeding disorders

M. Eales*; A. Wilkinson; S. Pool; G. W. Hall; N. Bhatnagar

Paediatric Haemophilia Centre, Oxford Haemophilia Comprehensive Care Centre, Oxford, UK

Introduction: The delivery of immunisations in children with bleeding disorders is variable within the community. The Green Book gives guidance on how immunisations should be given to patients with bleeding disorders via a 'deep subcutaneous' (SC) route rather than intramuscularly (IM). However, patients have reported that immunisations are still administered IM causing bruising and bleeding. We therefore identified a need to assess patient/parent experience of immunisation practice at the Paediatric Oxford Haemophilia Comprehensive Care centre as there is paucity of data regarding this in literature.

Methods: A survey was used in the format of questionnaire and was distributed via an online survey and also given out during patient clinic appointments. A total of 45 parents/patients were targeted at random over a 2-month period.

Results: 32 (71%) responses were received. The results showed a variable response consisting of both positive and negative experiences. This was regards to care delivered from GP practices and at both primary and secondary school. The survey confirmed that patients/parents often advise GP's and nurses that immunisations should be given SC and still the injection is administered IM causing bleeding/bruising and distrust in primary care services.

Discussion/Conclusion: This survey highlighted that there is considerable variability in the delivery of immunisations to children with bleeding disorders in primary care. Areas of good practice were identified and will be shared with other health professionals within the bleeding disorder community. Areas of improvements were also identified and we plan to discuss this with the Oxford Vaccine Group to raise awareness that patients with a bleeding disorder who require immunisations are often facing difficulties in obtaining immunisations via a SC route rather than IM. Further training may be required for practitioners who deliver immunisations in the primary care setting. We plan to develop a patient/parent information leaflet about immunisations as this would be beneficial to our patient group to help improve their understanding on how immunisations should be delivered. A repeat survey will be conducted once these changes are in place.

Disclosure of Interest: None declared.

P201 | Peripartum management and outcome in hemophilia carriers: A systematic review

M. Punt[1,*]; M. Waning[1]; E. Mauser-Bunschoten[1]; M. Kruip[2]; J. Eikenboom[3]; L. Nieuwenhuizen[4]; A. Makelburg[5]; M. Driessens[6]; H. Duvekot[7]; M. Peters[8]; A. Middeldorp[9]; K. Bloemenkamp[10]; R. Schutgens[1]; T. Lely[10]; K. van Galen[1]

[1]Van Creveldkliniek, University Medical Center Utrecht, Utrecht, Netherlands; [2]Department of Hematology, Erasmus University Medical Center, Rotterdam, Netherlands; [3]Department of Internal Medicine, Leiden University Medical Center, Leiden, Netherlands; [4]Department of Internal Medicine, Maxima Medical Center, Veldhoven, Netherlands; [5]Department of Hematology, University Medical Center Groningen, Groningen, Netherlands; [6]Netherlands Hemophilia Patient Society, Nijkerk, Netherlands; [7]Department of Gynaecology and Obstetrics, Erasmus University Medical Center, Rotterdam, Netherlands; [8]Amsterdam Haemophilia Treatment Center, Amsterdam University Medical Center, Amsterdam, Netherlands; [9]Department of Obstetrics, Leiden University Medical Center, Leiden, Netherlands; [10]Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht, Netherlands

Introduction: Hemophilia carriers are at an increased risk of developing postpartum hemorrhage (PPH) as compared to other women. Peripartum management in these women is mainly based on expert opinion. The aim of this systematic review is to evaluate all published peripartum management strategies and outcomes of pregnancy for hemophilia carriers.

Methods: PubMed/MEDLINE, The Cochrane Library, EMBASE and CINAHL were searched on April 10th 2018 for publications on peripartum management for known carriers of hemophilia and the relation to maternal or neonatal outcomes after pregnancy. Only papers containing original patient data were eligible for inclusion. Study selection, data extraction and risk of bias assessment were completed by two independent authors. Peripartum management included hematologic, obstetric and anesthetic interventions. Data extraction included maternal and neonatal outcome. Primary PPH was defined as PPH of 500 ml or more within 24 hours after childbirth. Prophylactic treatment includes correction of clotting factor levels and/or prophylactic tranexamic acid prescription. Risk of bias was assessed by the Chamber method.

Results: Twenty-four studies were included in this review: 17 case-reports and -series and 7 cohort studies. From 94 deliveries, individual patient data could be extracted and 256 deliveries were described in cohort data (of which 22 deliveries are mentioned in both categories). Only the largest included cohort study reported the primary PPH incidence, which was 24% (23/95) for hemophilia A and 26% (5/19) for hemophilia B carriers. The overall PPH incidence in the individual patient data was 57% (43/76) of the deliveries. PPH incidence was 44% (17/39) for those women who received prophylactic treatment to prevent PPH and 69% (25/36) for those who did not (*P*-value = 0.024). Neonatal bleeding events were reported in 10% (2/21) of the deliveries with data on neonatal outcome. Overall risk of bias of included studies was graded as 'poor'.

Discussion/Conclusion: Low quality evidence, mainly case series, is available on peripartum management of carriers of hemophilia. The ongoing high risk for these women to develop PPH is evident, data are not conclusive on the effect of prophylactic treatment. This review highlights the need for larger prospective cohort studies to improve management strategies and lower the peripartum bleeding risk for both mother and child with inherited hemophilia.

Disclosure of Interest: None declared.

P202 | Peripartum management and outcome in women with von Willebrand disease: A systematic review

M. Punt[1,*]; M. Waning[1]; E. Mauser-Bunschoten[1]; M. Kruip[2]; J. Eikenboom[3]; L. Nieuwenhuizen[4]; A. Makelburg[5]; M. Driessens[6]; H. Duvekot[7]; M. Peters[8]; A. Middeldorp[9]; K. Bloemenkamp[10]; R. Schutgens[1]; T. Lely[10]; K. van Galen[1]

[1]Van Creveldkliniek, University Medical Center Utrecht, Utrecht, Netherlands; [2]Department of Hematology, Erasmus University Medical Center, Rotterdam, Netherlands; [3]Department of Internal Medicine, Leiden University Medical Center, Leiden, Netherlands; [4]Department of Internal Medicine, Maxima Medical Center, Veldhoven, Netherlands; [5]Department of Hematology, University Medical Center Groningen, Groningen, Netherlands; [6]Netherlands Hemophilia Patient Society, Nijkerk, Netherlands; [7]Department of Gynaecology and Obstetrics, Erasmus University Medical Center, Rotterdam, Netherlands; [8]Amsterdam Haemophilia Treatment Center, Amsterdam University Medical Center, Amsterdam, Netherlands; [9]Department of Obstetrics, Leiden University Medical Center, Leiden, Netherlands; [10]Department of Gynaecology and Obstetrics, University Medical Center Utrecht, Utrecht, Netherlands

Introduction: Women with von Willebrand disease (VWD) are at an increased risk of developing postpartum hemorrhage (PPH) as compared to other women. Peripartum management in VWD is mainly based on expert opinion. The aim of this systematic review is to evaluate all published evidence on peripartum management strategies and outcome in women with VWD.

Methods: PubMed/MEDLINE, The Cochrane Library, EMBASE and CINAHL were searched on April 10th 2018 for publications on peripartum management for women with VWD and the relation to maternal and neonatal outcomes. Only papers containing original patient data were eligible for inclusion. Study selection, data extraction and risk of bias assessment were completed by two independent authors. Peripartum management included hematologic, obstetric and anesthetic interventions. Data extraction included maternal and neonatal outcome. Primary PPH was defined as PPH of 500 ml or more within 24 hours after childbirth, secondary PPH as excessive blood loss between 24 hours and 12 weeks after childbirth. Prophylactic treatment includes correction of clotting factor levels and/or tranexamic acid prescription. Risk of bias was assessed by the Chamber method.

Results: Eighty-five studies were included: 70 case-reports and -series and 15 cohort studies. Individual patient data could be extracted from 363 deliveries and 619 deliveries were described in cohort data (of which 64 deliveries are mentioned in both categories). The cohort studies report primary PPH in 32% (58/180), secondary PPH in 13% (14/109) and bleeding complications in 13% (15/110) of deliveries. The overall PPH incidence in the individual patient data

was in 34% (109/325) of the deliveries. PPH incidence was 31% (63/204) for women who received prophylactic treatment to prevent PPH and 31% (33/108) for those without prophylaxis. Neonatal bleeding events were reported in 4.6% (3/65) of the deliveries with data on neonatal outcome. Overall risk of bias of the included studies was graded as 'poor'.

Discussion/Conclusion: Low quality evidence, mainly from case series, is available on peripartum management in women with VWD. The high risk for PPH is evident, despite prophylactic treatment: no difference in PHH incidence was observed. This review highlights the need for higher quality evidence from larger prospective cohort studies to improve management strategies and lower the peripartum bleeding risk for both mother and child with VWD.

Disclosure of Interest: None declared.

P203 | Neuro-linguistic programming (NLP) in haemophilia practice

M. Ortelee*; F. Balkestein; G. Mulders

Erasmus University Medical Center, Rotterdam, Netherlands

Introduction: Self-treatment with intravenous infusion of clotting factor-concentrates is a practice unique to patients with haemophilia. Adequate education and guidance of the patient and their caregivers is required. Treatment regimens to reduce bleeding episodes, maintain joint health and quality of live are beneficial when patients are adherent. Especially in the phase of transition of care: improving education and guidance among adolescents, who are at high risk of discontinuing prophylaxis and poor adherence. Neuro-linguistic programming (NLP) refers to the science and art of reaching success and perfection. It is a collection of the skills based on human beings' psychological characteristics through which the individuals obtain the ability to use their personal capabilities as much as possible.

Methods: NLP emphasizes that human behavior originates from neurological processes. A wide spectrum of human behaviors are mediated and regulated by human language. The importance of NLP lies in the fact that this programming is a collection of skills based on psychological characteristics of the human beings through which the individuals obtain the ability to use their personal capabilities as much as possible.

Results: We see that NLP can reach success and have a positive effect on various dimensions. Motivational techniques and behavioral strategies to improve self-care is needed. Patients who take part in their own health care and decision-making develop their own autonomy and responsibility for their own health and risk behaviors. In some patients; we see a better compliance and more confidence.

Discussion/Conclusion: With all new treatment regimens and developments of new products, patients still have to do some kind of administration. Dosing reminders to promote adherence may be helpful, but to help them using LNP to turn on their intrinsic factor seems to be worthwhile in some cases. It is especially important to create strategies targeting adolescents, as they become increasingly independent and take on responsibility for self-care, including factor infusions.

NLP is been used in our haemophilia practice. It helps patients to get in control of their mind, their emotional state in order to get their treatment done, especially in the adolescent stage.

Disclosure of Interest: None declared.

P204 | Part-time employment and early retirement in people with severe haemophilia: Insights from the PROBE study

M. W. Skinner[1,2,*]; C. Chai-Adisaksopha[3]; D. Noone[4,5]; R. Curtis[6]; N. Frick[7]; M. Nichol[8]; B. O'Mahony[9,10]; D. Page[11]; A. Pastarnak[7]; J. Stonebraker[12]; A. Iorio[2]; on behalf of the Patient Reported Outcomes Burdens and Experiences (PROBE) Study Investigator Group

[1]Institute for Policy Advancement Ltd., Washington, USA; [2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada; [3]Department of Medicine, McMaster University, Hamilton, Canada; [4]European Haemophilia Consortium, Brussels, Belgium; [5]Health Decision Consultants, Dublin, Ireland; [6]Factor VIII Computing, Berkeley; [7]National Hemophilia Foundation, New York City, NY, USA; [8]Sol Price School of Public Policy, University of Southern California, Los Angeles, USA; [9]Irish Haemophilia Society, Dublin, Ireland; [10]Trinity College Dublin, Dublin, Ireland; [11]Canadian Hemophilia Society, Montreal, Canada; [12]Poole College of Management, North Carolina State University, Raleigh, USA

Introduction: Despite treatment advances economic, social and educational barriers still remain for people with severe haemophilia. Contextual factors such as the lifetime impact of haemophilia on employment and overall work life are not well understood.

Methods: People with severe haemophilia A/B (PwSH) and controls with no bleeding disorder (NoBD) reporting working part-time or having retired early due to their health were compared with those reporting working full-time. Patient Reported Outcome Burdens and Experiences (PROBE) Study data of 1008 participants age 18 and over from 21 countries were analyzed (550 PwSH, 458 NoBD). Descriptive statistics were used to present results as n (%), and odds ratio (95% CI) were calculated for the associations for participants with any health problems—use of mobility aids, use of pain medication, having acute or chronic pain, difficulties with activities of daily living and history of joint surgery—and assessed for their statistical significance.

Results: 250 PwSH (45.5%) and 263 NoBD (57.4%) reported working full time. 86 PwSH (15.6%) and 80 NoBD (17.5%) reported working part-time. 27 of the 86 PwSH (31.4%) and 3 of the 80 NoBD (3.8%) reported working part-time due to health. 52 PwSH (9.5%) and 28 NoBD (6.1%) reported taking early retirement. 25 of the 52 PwSH (48.1%) and 1 of the 28 NoBD (3.6%) reported taking early retirement due to health. Association between reporting a health-related problem and working part-time or taking early retirement due to health were [n (%), Odds Ratio (95% CI), *P*-value]: use of mobility aids 77.7 (3.8-1645) 0.0005, having acute pain 41.2 (2-831.8) 0.01, use of pain medication 23 (2.05-258.1) 0.01, participants experiencing any

health problems 22.5 (2-252.6) 0.01, having chronic pain 16.5 (1.5-179.2) 0.02, difficulty with activities of daily living (ADL) 16.5 (1.5-179.2) 0.02, and history of joint surgery 7.3 (0.4-148) 0.197. Mean participant age: PwSH 39 (14.4 SD) and NoBD 45.3 (13.7 SD).

Discussion/Conclusion: Haemophilia has a significant negative impact on work life. PwSH report a higher rate of retiring early or working part-time due to health than age-matched controls. Use of mobility aids, acute/chronic pain, difficulty with ADL and history of joint surgery are associated with retiring early or working part-time. The lifetime impact of haemophilia on employment should be more fully considered within health technology assessments.

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P205 | Nonclinical safety evaluation of a next generation factor IX (FIX) gene therapy construct (SHP648) in mice

M. Weiller[1,*]; S. Coulibaly[1]; H. Gritsch[1]; H. Wang[2]; H. Rottensteiner[1]; M. K. Chuah[3,4]; T. VandenDriessche[3,4]; M. Schmidt[5]; F. Scheiflinger[1]; W. Höllriegl[1]

[1]Shire, Vienna, Austria; [2]Shire, Cambridge, USA; [3]Belgium and Center for Molecular and Vascular Biology, Department of Cardiovascular Sciences, University of Leuven, Leuven; [4]Department of Gene Therapy and Regenerative Medicine, Free University of Brussels (VUB), Brussels, Belgium; [5]Genewerk, Heidelberg, Germany

Introduction: AAV-based gene therapy has potential to provide clinical benefit in patients with hemophilia B. SHP648 (Baxalta part of Shire, Lexington, MA) is being developed as a next generation vector for FIX gene therapy. The improved vector design includes insertion of 3 hepatocyte-specific cis-regulatory elements (CRM8) to increase the strength of the liver-specific transthyretin (TTR) promoter driving FIX-Padua (R338L) transgene expression. This safety evaluation investigated potential toxicity, as well as vector integration events into the genome, after systemic administration of SHP648 in mice.

Methods: To evaluate toxicity, C57BL/6J mice were treated with rSHP648 at $3x10^{11}$, $1x10^{12}$, or $2x10^{12}$ vector genomes (vg)/kg and sacrificed at day 3, week 3, or week 18 post treatment. To determine vector integration events, male FIX knockout (KO) mice received an intravenous (i.v.) injection of SHP648 ($1x10^{12}$ or $1x10^{13}$ vg/kg); liver tissue was harvested at day 28 and vector copy number determined by vector specific qPCR. Non-restrictive (nr) and standard linear amplification-mediated (LAM) PCR was used to identify genomic sequences flanking the integrated AAV vector DNA. (nr)LAM-PCR amplicons were sequenced after sample preparation.

Results: Single i.v. SHP648 injections were well tolerated in mice at all dose levels, with no toxicologically relevant effects or changes in clinical or anatomical pathology. SHP648 treatment resulted in higher levels of FIX activity and huFIX antigen vs pre-treatment baseline, thus confirming FIX transgene expression. SHP648 treatment of FIX KO mice resulted in dose-dependent supraphysiological FIX activity levels, indicating successful transduction. At the $1x10^{13}$ vg/kg vector dose, the number of integration sites was 3.6-fold higher than mice treated with the lower dose; integration frequency was ≤0.01%. Integration site analysis showed measurable, yet minimal integration with no indication of side effects (no clonal outgrowth or preferred integrations in or next to genes previously implicated in hepatocellular carcinoma formation).

Discussion/Conclusion: SHP648 administered to mice at doses up to $2x10^{12}$ vg/kg was well tolerated with no toxicologically relevant effects observed. The No-Observed-Adverse-Effect-Level (NOAEL) was $2x10^{12}$ vg/kg, the highest dose tested. Integration site analyses after administration of SHP648 in FIX KO mice did not indicate potential side effects.

Disclosure of Interest: M. Weiller Employee of: Shire, S. Coulibaly Employee of: Shire, H. Gritsch Employee of: Shire, H. Wang Shareholder of: Shire, Employee of: Shire, H. Rottensteiner Shareholder of: Shire, Employee of: Shire, M. Chuah Employee of: Vrije Universiteit Brussel (VUB), Brussels, Belgium, T. VandenDriessche Employee of: Vrije Universiteit Brussel (VUB), Brussels, Belgium, M. Schmidt Employee of: Co-Founder and CEO of Genewerk GmbH, Heidelberg, Germany and Section Head, Molecular and Gene Therapy, Department of Translational Oncology, National Center for Tumor Diseases and German Cancer Research Center, Heidelberg, Germany, F. Scheiflinger Shareholder of: Shire, and co-author of related patents, Employee of: Shire, W. Höllriegl Shareholder of: Shire, Employee of: Shire.

P206 | Melatonin antiplatelets effect through breastfeeding: A sobering case

M. Luciani[1,*]; M. Massoud[1]; S. Foligno[1]; G. Di Felice[2]; F. Pulcinelli[3]; N. Rapini[4]

[1]Department of Hematology Oncology and Transfusion Medicine, Bambino Gesu' Children's Hospital, Rome, Italy; [2]Department of Laboratories, Bambino Gesù Children's Hospital, Rome, Italy; [3]Department of Experimental Medicine, "Sapienza" University of Rome, Rome, Italy; [4]Unit of Endocrinology and Diabetes, Bambino Gesù Children's Hospital, Rome, Italy

Introduction: We present a case of anti-aggregating effect of melatonin taken through breast milk in an 18- month-old child. The child was referred to our haematology outpatient clinic because of bleeding episodes occurring since birth. Blood tests excluded the presence of blood coagulation diseases. Family history was negative for bleeding events or coagulation disorders. The child did not assume any drugs, food supplements, herbal teas or infusions. We performed a platelet aggregation test, which showed a reduced platelet aggregation after the child was breastfed. We speculated that breast milk could interfere with the result of the test and we decided to repeat

the test in a fasting state. The repeated test showed a normal time of aggregation. We learned that the child's mother was occasionally assuming melatonin during and after pregnancy. Thus, we decided to suspend maternal intake of melatonin and perform a new platelet aggregation test after three months. The test result was negative. After the suspension of melatonin, the patient did not present further bleeding events.

Methods: Platelet aggregation test was performed after 30 min of breastfeeding. Repeated test after one week in a fasting taste. The third platelet aggregation test after three months of Melatonin suspension.

Results: The first aggregation test showed a reduced platelet aggregation. The second in a fasting state and the third after Melatonin suspension were normal.

Discussion/Conclusion: Melatonin inhibits several physiological processes in platelets, including aggregation, release of adenosine triphosphate peroxidase and serotonin (indexes of the platelet secretor mechanism), and production of thromboxane B2. With this case, we would like to suggest the role of melatonin to induce bleeding in infants through breastfeeding. With this report we would like to highlight the side effects of melatonin and the importance to include in clinical history collection

Disclosure of Interest: None declared.

P207 | In the presence of emicizumab, factor VIIa activation of factor IX contributes to factor Xa generation

D. M. Monroe[1]; M. Ezban[2]; M. Hoffman[3,*]

[1]Hematology/Oncology, University Of North Carolina, Chapel Hill, USA; [2]Global Drug Discovery, Novo Nordisk, Måløv, Denmark; [3]Pathology, Duke University, Durham, NC, USA

Introduction: Emicizumab (Hemlibra®) is a bivalent antibody with one arm that binds to factor IXa and another arm that binds to factor X; this binding enhances factor IXa activation of factor X. Emicizumab can be administered subcutaneously resulting in circulating levels of about 55 μg/mL (about 400 nM). In patients from the Haven clinical programme using emicizumab for prophylaxis, breakthrough bleeding has been treated with recombinant factor VIIa (eptacog alfa activated, NovoSeven®). Our goal was to study the biochemical mechanism of action of factor VIIa in the presence of emicizumab.

Methods: Factor VIIa/tissue factor activation of factor IX was measured with 0.5 nM VIIa/tissue factor complex with and without 50 μM emicizumab. Factor VIIa activation of factor IX in the absence of tissue factor was measured with varied factor VIIa (25-100 nM), fixed factor IX (80 nM), fixed lipid (100 μM), and either no emicizumab, 400 nM, or 50 μM. Factor Xa generation was measured in the presence of lipids (100 μM) and factor X (135 nM) with or without factor IX (80 nM) and emicizumab (400 nM).

Results: We have previously reported that emicizumab reduces the rate at which the factor VIIa/tissue factor complex activates factor X. By contrast, emicizumab does not reduce the rate at which the factor VIIa/tissue factor complex activates factor IX. On a lipid surface, factor VIIa alone can activate factors X and IX; emicizumab does not reduce the rate of activation of either factor X or factor IX. In a reaction with factor VIIa, factor X, and emicizumab on lipid vesicles, addition of factor IX enhances the rate of factor X activation.

Discussion/Conclusion: When used as a bypassing agent, factor VIIa binds to the surface of activated platelets and activates factor X. While factor VIIa can also activate factor IX on the platelet surface, in hemophilia A patients with inhibitors this is not thought to contributing to hemostatic efficacy since factor IXa activation of factor X is inefficient in the absence of a cofactor. However, in a purified system using emicizumab and lipid vesicles, factor IXa generated by factor VIIa can bind to emicizumab and activate factor X. This suggests that factor IX activation by factor VIIa might contribute to overall factor Xa generation in the presence of emicizumab. Further studies will be needed to better understand the effect of factor VIIa in presence of emicizumab and platelets.

Disclosure of Interest: D. Monroe Grant/Research support from: Novo Nordisk, M. Ezban Employee of: Novo Nordisk, M. Hoffman Grant/Research support from: Novo Nordisk, Speaker Bureau of: Novo Nordisk.

P208 | Physical activity and haemophilic joint arthropathy amongst adults with severe haemophilia in Ireland: The Irish personalised approach to the treatment of haemophilia (IPATH) study

M. Kennedy[1,*]; S. Roche[2]; M. McGowan[2]; E. Singleton[2]; A. Patel[2,3]; R. C. Jones[2]; B. O' Mahony[4]; K. Ryan[2]; N. M. O' Connell[2]; M. Lavin[2,3]; P. L. Turecek[5]; J. S. O' Donnell[2,3]; J. Gormley[1]

[1]Discipline of Physiotherapy, Trinity College Dublin, Dublin, Ireland; [2]National Coagulation Centre, St. James's Hospital, Dublin, Ireland; [3]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland; [4]Irish Haemophilia Society, Dublin, Ireland; [5]Baxalta (now part of the Shire group of companies), Vienna, Austria

Introduction: In order to achieve optimal health benefits, it is recommended adults attain at least 150 minutes of moderate and/or 75 minutes of vigorous intensity physical activity (PA) (in bouts of ≥10 minutes) per week. In people with severe haemophilia (PWSH), the presence of haemophilic joint arthropathy (HJA) may limit PA. The relationship between objectively measured PA and HJA was explored in a cohort of Irish PWSH as part of the Irish Personalised Approach to the Treatment of Haemophilia (iPATH) study.

Methods: PA was assessed in males aged ≥18 years (y) with severe factor VIII (FVIII) or factor IX (FIX) deficiency. Following written, informed consent, basic demographics, including body mass index (BMI) and Haemophilia Joint Health Score (HJHS), were collected. Using 7-day recording on an accelerometer (ActiGraph GT3X-BT), habitual PA was classified as light, moderate or vigorous, recorded

in minutes/week (mins/wk). Statistics were performed using mean ± standard deviation and Spearman's rank order correlation for the relationship between PA and HJHS as well as PA and BMI.

Results: Twenty-five PWSH (FVIII n = 17; FIX n = 8) were enrolled. The cohort was predominantly older (43.0 ± 12.9 y) with established arthropathy (mean HJHS 25.9 ± 11.8) and increased BMI (26.7 ± 4.1 kg/m^2). Overall 60% met moderate activity guidelines of 150 mins/wk (216.8 ± 170.2 mins/wk) but only 8% reached the target of 75 mins/wk for vigorous PA (12.8 ± 36.1 mins/wk). The majority of time was spent in light activity (1863 ± 727.8 mins/wk). Examining bouts (≥10 minutes) of moderate PA, only 12% achieved a target of 15 bouts/wk. Indeed, the average number of bouts was much lower than target PA levels (6.0 ± 6.4). HJHS impacted on PA, with a significant negative correlation between knee scores and vigorous PA (r_s = −0.410; P = 0.042). Ankle arthropathy and BMI did not significantly impact on PA.

Discussion/Conclusion: These data highlight the PA levels in a cohort of older PWSH. Long term arthropathy, particularly knee arthropathy, has a negative impact on PA. Vigorous PA was limited in this cohort; only a minority of PWSH undertook even short bouts of increased activity. The negative health impact of reduced PA and increased BMI in an aging population is well described and new strategies are required to engage with PWSH to boost PA.

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P209 | Barriers to physical activity amongst adults with moderate and severe haemophilia in Ireland: The Irish personalised approach to the treatment of haemophilia (iPATH) study

M. Kennedy[1,*]; A. Monaghan[1]; S. Roche[2]; M. McGowan[2]; A. Patel[2,3]; R. C. Jones[2]; B. O' Mahony[4]; K. Ryan[2]; N. M. O' Connell[2]; P. L. Turecek[5]; M. Lavin[2,3]; J. S. O' Donnell[2,3]; J. Gormley[1]

[1]Discipline of Physiotherapy, Trinity College Dublin, Dublin, Ireland; [2]National Coagulation Centre, St. James's Hospital, Dublin, Ireland; [3]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland; [4]Irish Haemophilia Society, Dublin, Ireland; [5]Baxalta (now part of the Shire group of Companies), Vienna, Austria

Introduction: Ensuring and promoting adequate levels of physical activity (PA) is one of the main challenges facing modern healthcare. For people with haemophilia (PWH), the development of arthropathy imposes further difficulties in reaching PA targets. However, many barriers to PA exist, identification of which is vital for promotion of increased PA. Using an established tool for examination of barriers to PA, this important issue was examined in a cohort of Irish PWH as part of the Irish Personalised Approach to the Treatment of Haemophilia (iPATH) study.

Methods: Barriers to PA were assessed in males aged ≥18 years (y) with moderate and severe factor VIII (FVIII) or factor IX (FIX) deficiency as a part of the iPATH project. Following written, informed consent, basic demographics, including body mass index (BMI), were collected. The participants completed the "Barriers to Being Active Quiz" (US Department of Health and Human Services, 1999). Descriptive statistics (mean ± standard deviation) and frequency percentages were calculated using Statistical Package for the Social Sciences (IBM SPSS). Age group comparisons over and under 45 y were made using independent sample t-tests for descriptive statistics. A P-value of <0.05 was deemed statistically significant.

Results: Thirty-six PWH enrolled (severe FVIII n = 20; moderate FVIII n = 5; severe FIX n = 10; moderate FIX n = 1). Mean age was 44.1 ± 13.7 y and BMI was 26.9 ± 4.1 kg/m^2. No significant difference was observed for BMI between groups (t = −1.054, P = 0.299). Comparing those <45 y (n = 17) and ≥45 y (n = 19), key barriers to PA in the younger group were "lack of time" (35.3% vs 10.5%) and "lack of willpower" (47.1% vs 36.8%). For the older group, "fear of injury" (0% vs 15.8%) and "lack of skill" (5.9% vs 42.1%) were more frequently identified as barriers to PA. For all age groups "lack of energy" contributed to PA levels (29.4% vs 21.1%).

Discussion/Conclusion: Promotion of adequate PA is essential for adult PWH. This study identifies the varying barriers experienced by PWH. For younger PWH, lack of time and willpower were the main challenge, whilst fear of injury and lack of skill were more significant barriers in older adults. For all ages, lack of energy was a barrier. Personalised approaches to exercise programmes may help tackle these barriers, improving PA and health outcomes in PWH.

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P210 | What is the prevalence of Autism Spectrum Disorder in children with haemophilia?

M. Bladen[1,*]; N. Thorpe[1]; E. Main[2]; A. Barrie[1]; A. Griffioen[1]; N. Hubert[1]; L. Watson[3]; A. Mance[4]; E. McGibbon[4]; D. Ridout[2]; K. Khair[5]; R. Liesner[1]

[1]Haemophilia Centre, Great Ormond St Hospital For Children NHS Foundation Trust, London, UK; [2]Institute of Child Health, University College London, London, UK; [3]Clinical Psychology, University of Surrey, London, UK; [4]Wolfson Neurodisability Service, London, UK; [5]ORCHID, Great Ormond St Hospital For Children NHS Foundation Trust, London, UK

Introduction: Autism Spectrum Disorders (ASD) are diagnosed by the presence of social communication difficulties, strong, narrow interests and/or repetitive and stereotyped behaviour. Literature suggests that around 10/1000 of the general population have ASD, with a 3:1 prevalence in boys. There is no known relationship between haemophilia and ASD, but clinical observation of apparently high ASD prevalence at Great Ormond Street Hospital warranted further investigation. The aim of this study was to identify if there was a higher prevalence of ASD in boys with haemophilia than the general population.

Methods: Between May 2014 - July 2017, boys aged 5-16 years with mild, moderate and severe haemophilia A and B were recruited for this study. Parents and teachers completed questionnaires to screen for difficulties in social interaction, executive functioning, communication and behaviour. If the threshold on all 3 questionnaires was reached, boys were referred for formal ASD assessment. Boys with a prior diagnosis of ASD (n = 13) did not complete questionnaires, but were included in analysis.

Results: Of 214 boys with haemophilia born between July 1997-May 2012, who were eligible for the study, 81 families completed questionnaires and 133 boys were excluded (13 had a prior diagnosis of ASD, 23 declined, 15 due to research burden, 27 did not consent, 12 overseas patients, 43 other reasons). The prevalence of ASD in unaffected boys aged 8 years has been identified as 3.9/1000 (Taylor 2013). The 13/214 boys with a prior diagnosis of ASD in this study (mean age at diagnosis 6.4 years) equated to a prevalence of 60.7/1000 (95% CI: 32.7, 101.6), with an increased risk ratio of 15.5, 95% CI (8.2, 26.9). Of these, 9 (69%) had haemophilia A (7 severe), 3 (23%) had haemophilia B (2 severe) and 1 had mild haemophilia B Leyden. A history of intracranial haemorrhage was evident in 3/13 (23%) boys.

A further 3 boys (5, 9 and 12 years old: 2 severe A, 1 severe B) of the 81 who underwent questionnaire screening were diagnosed with ASD, equating to a total prevalence of 16/214; 74.8 per 1000, (95% CI: 43.3, 118.6) (mean age at diagnosis 6.46 years).

Discussion/Conclusion: This study has identified a higher prevalence of ASD in boys with haemophilia compared to both the general population and unaffected boys aged 8. Further research is required to explain findings and to explore risk factors for ASD in boys with haemophilia.

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P211 | Single center experience: Intracranial hemorrhage in children with hemophilia

M. S. Evim*; B. Baytan; A. Meral Güneş; M. Ertekin

Pediatric hematology, Uludag Unv. Pediatric Hematology, Bursa, Turkey

Introduction: Intracranial hemorrhage (ICH) is life threatening bleeding in hemophilia. The incidence of ICH in haemophilic children varies between 3-7.5%. These patients should be closely monitored for neurological sequelae. We evaluated ICH in our hemophilic patients.

Methods: We investigated the medical records of our hemophilia patients for ICH. The age of bleeding, hemophilia type and missing factor level, trauma or other facilitating factors, neurological symptoms, site of bleeding, time interval between initial symptoms and operation, neurological outcome and inhibitory status were recorded.

Results: Between January 2005-October 2018 ICH was occured in five hemophilic patients. The incidence of ICH in our series was 5.25%. Two of them were hemophilia B and their factor levels were 2.49% and 2.7%. The other were severe hemophilia A. Two of them was in neonatal period and none had birth trauma. One of the three patients after the neonatal period had a history of falling from the bed and the other two had a history of antibiotic or symptomatic drug use due to upper respiratory tract infection. All of the patients at the time of the event were under 1 year old. Four of the five patients had not a diagnosis of hemophilia before ICH, and their first diagnosis was with ICH. One of the patients' brother was hemophilic and for this reason his diagnosis was known before the ICH and he had never had a bleeding attack before. The most common neurologic complain was convulsion (n:3). Others complain were somnolence, vomiting, irritability. Intracerebral bleeding was occured five of them. Two of them developed inhibitors after ICH. One of them had epilepsy and severe motor and mental retardation. Two only used epileptic drugs for three years after the operation.

Discussion/Conclusion: ICH is a life-threatening bleeding site in hemophilic patients. It may have severe neurological outcome if not treated effectively and timely. Although the prevalence of ICH decreases in patients with hemophilia after widespread use of prophylactic factor replacement and giving information about trauma and drugs, the first diagnosis of the disease can be made with ICH as in our series. In terms of bleeding diathesis, pediatricians and neurosurgeons must be alert and proper orientation of the patient is important for effective and timely treatment.

Disclosure of Interest: None declared.

P212 | Von Willebrand disease and other bleeding disorders in women, experience of center in Algiers

M. Bensadok; N. Ferroudj; K. Chennoukh; M. Belhani; S. Nekkal

Hematologie hospital benimessous algiers algeria, Algiers, Algeria

Introduction: The prevalence of menorrhagia in women with VWD increases according to severity of VWD type, with a higher percentage in VWD type 3 and sever bleeding disorders

Methods: We follow up at our center 44 patients with VWD, 51 factor VII deficiency(D), 6 F X(D), 7 F V(D), patients with F XIII(D), 5 afibrinogenemia, 3 (D), 1 with HB, 2 F V - VIII (D). Their ages are between(12-54)years. Variables collected included: age, VWD type, factor deficiency type, frequency of bleeding episodes, menorrhagia, pregnancy and delivery, the different treatments used the initiation of prophylaxis, Effectiveness of treatment or prophylaxis was based on resolution or reduction of bleeding.

Results: we should manage menorrhagia in women with bleeding disorders gynecologic evaluation is required to evaluate other causes of bleeding tranexamic acid (1-1.5 g, 3-4 times/day; "may be given in severe VWD, and other RBD, coagulation factor replacement is required. Combined hormonal contraception will play multiple roles, Hormonal therapy may also be used in conjunction with nonhormonal treatments such as tranexamic acid or aminocaproic acid, and coagulation factor replacement Cryoprecipitate administration should be administered in RBD. Women in the third trimester should be treated in gynecologic consultation with a hematologist to ensure an adequate hemostatic condition for delivery. Women should deliver at a specialized center

Discussion/Conclusion: An awareness of bleeding disorders (such as VWD, RBDs) is an important asset for obstetricians and gynecologists and hematologist. These disorders remain underdiagnosed in women with menorrhagia. Responding to these clues facilitates collaboration among obstetrician-gynecologists and hematologists. This, in turn, should lead to improved QoL and school and work performance indicators in these women. consensus and recommendations will aid obstetricians – gynecologists and hematologist to better anticipate, prepare for, and manage cases of abnormal reproductive tract bleeding in women with bleeding disorders

Disclosure of Interest: None declared.

P213 | Insights into the evolution of haemophiliac arthropathy: The Irish personalised approach to the treatment of haemophilia (iPATH) study

M. Lavin[1,2,*]; R. C. Jones[2]; E. Singleton[2]; S. Roche[2]; A. Patel[1,2]; M. Kennedy[3]; K. Ryan[2]; B. O'Mahony[4]; J. Gormley[3]; N. M. O'Connell[2]; P. L. Turecek[5]; J. S. O'Donnell[1,2]

[1]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin 2, Ireland; [2]National Coagulation Centre, St. James's Hospital Dublin, Ireland; [3]Department of Physiotherapy, Trinity Centre for Health Sciences, Trinity College Dublin, Dublin, Ireland; [4]Irish Haemophilia Society, Dublin 8, Ireland; [5]Baxalta (now part of the Shire group of Companies), Vienna, Austria

Introduction: For people with severe haemophilia (PWSH), recurrent haemarthroses result in significant arthropathy. Regular prophylaxis with recombinant FVIII (rFVIII) reduces bleeding episodes however long term joint outcome data is limited. In addition, both prophylaxis regimens and bleeding phenotype vary considerably. We investigated the impact of these factors in the Irish Personalised Approach to the Treatment of Haemophilia (iPATH) study.

Methods: Following written informed consent, adult PWSH (>18 years) enrolled. Age, BMI, Haemophilia Joint Health Score, (HJHS) and rFVIII usage (antihemophilic factor [recombinant]; ADVATE®, Baxalta [part of Shire], Westlake Village, CA, USA) over 5 years (2013-18) were collated. rFVIII use was adjusted for weight (IU/kg/week). Data was analysed by quartiles by age (Q1: 19-27yo, Q2: 27.5-38yo, Q3: 38-49yo and Q4: 49-75yo).

Results: 50 PWSH enrolled (median age 38yo, range 18.7-74.9), 94% on regular rFVIII prophylaxis (median 69 IU/kg/week). Significant arthropathy was evident (mean HJHS 25.5), but with considerable variation (range 0-51). Arthropathy significantly increased with age (mean HJHS Q1 = 10 vs Q4 = 37; $P < 0.0001$) but paradoxically rFVIII usage decreased significantly in older PWSH (mean Q1 98 IU/kg/wk vs Q4 47 IU/kg/wk; $P < 0.0001$). Longer FVIII half-lives may contribute, however the shorter history of prophylaxis usage in older PWSH is likely a factor. No significant difference in BMI was seen by age, with BMI > 25 in 53% overall. Although arthropathy may limit physical activity, no correlation was seen between HJHS and BMI ($r^2 = 0.02$, $P = 0.4$).

Ankle arthropathy was most prominent, with abnormal scores even in Q1, increasing with age (median Q1 = 1, range 0-11; Q4 = 6, range 1-10). Sparing of knee arthropathy was observed in PWSH with earlier access to prophylaxis (median Q1 = 0, Q2 = 1, Q3 = 1) in comparison to older PWSH (Q4 = 4). Surprisingly, elbow arthropathy was quite marked and not significantly different to ankle scores (median 4.1 vs 4.8, $P = 0.2$) although later onset was noted (elbow median Q1 = 0, Q2 = 0.5, Q3 = 6.5, Q4 = 7).

Discussion/Conclusion: This study highlights the evolution of arthropathy in PWSH. Although early ankle changes are evident, ultimately elbow and ankle arthropathy are not significantly different. Challenges for prophylaxis remain, including rising BMI and equitable uptake of prophylaxis in older PWSH.

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P214 | An overview of turoctocog alfa pegol assay performance: Implications for post-infusion monitoring

M. Hansen; E. Persson; M. Ezban*

Novo Nordisk A/S, Måløv, Denmark

Introduction: Turoctocog alfa pegol (N8-GP; Novo Nordisk A/S) is a glycoPEGylated extended half-life recombinant factor VIII (rFVIII) molecule shown to be efficacious and safe for the prevention and treatment of bleeding episodes in children, adolescents and adults with haemophilia A. To ensure optimal patient care, accurate FVIII activity (FVIII:C) potency labelling and post-infusion monitoring is required. The performance of some modified FVIII products using one-stage activated partial thromboplastin time (aPTT)-based clotting (OSC) or chromogenic substrate (CS) assays may vary. Novo Nordisk A/S have performed an extensive programme to assess the precision and accuracy of laboratory assays to measure turoctocog alfa pegol FVIII:C.

Methods: The impact of PEGylation on the functionality of the resulting turoctocog alfa pegol molecule was carefully evaluated by *in vitro* and *in vivo* studies. Commercially available OSC and CS assays were tested in different settings, including an international, multi-centre, comparative field study. FVIII:C measurements were performed in haemophilia A plasma samples spiked with turoctocog alfa pegol or comparators using routine assay procedures, reagents, calibrators and instruments.

Results: The functional activity of turoctocog alfa pegol was not affected by glycoPEGylation. Valid estimates for potency labelling were obtained using a FVIII CS assay and the WHO 8th FVIII international concentrate standard. Accurate measurement of turoctocog alfa pegol activity in a post-administration setting was possible with most commonly used OSC aPTT reagents (C.K. Prest®, SynthASil®, SynthAFax®, Actin® FS, Actin® FSL, Pathromtin® SL, APTT-SLA, DG Synth) and available CS FVIII activity assays (Coamatic®, Coatest® SP, BIOPHEN® FVIII:C, Technochrome® FVIII:C, DG Chrom FVIII, FVIII Chromogenic, Electrachrome®), without the need for a product-specific standard. Three silica-based aPTT reagents (APTT-SP, TriniCLOT™, STA® PTT-Automate) gave an underestimated turoctocog alfa pegol recovery in OSC assays, presumably attributable to decelerated activation of turoctocog alfa pegol by thrombin in their presence.

Discussion/Conclusion: Turoctocog alfa pegol FVIII:C can be accurately measured using available CS assays, or in OSC assays with the majority of available aPTT reagents using a normal human plasma calibrator.

Disclosure of Interest: M. Hansen Shareholder of: Novo Nordisk, Employee of: Novo Nordisk, E. Persson Shareholder of: Novo Nordisk, Employee of: Novo Nordisk (former), M. Ezban Shareholder of: Novo Nordisk, Employee of: Novo Nordisk.

P215 | Successful use of recombinant activated factor VII (rFVIIa) perioperative management and outcome of urgent appendectomy in a patient with congenital factor VII deficiency

M. Söker[1,*]; H. Uzel[1]; K. Öncel[1]; E. Basuguy[2]; S. Söker[3]

[1]Pediatric Hematology and Oncology, Dicle University Medical Faculty, Diyarbakır, Turkey; [2]Pediatric Surgery, Dicle University Medical Faculty, Diyarbakır, Turkey; [3]Histology and Embryology, Dicle University Medical Faculty, Diyarbakır, Turkey

Introduction: Congenital factor VII (FVII) deficiency is the most common among the rare autosomal recessive hemorrhagic disorder worldwide. In FVII deficient patients, the severity and clinical manifestations cannot be reliably determined by FVII levels. Perioperative administration of recombinant activated factor VII (rFVIIa) reduces postoperative hemorrhagic complications in patients with congenital FVII deficiency, who were undergoing elective surgical procedures.

Methods: We report the presentation of acute appendicitis in an 16-year-old girl with congenital FVII deficiency. We managed the case according to recommendations regarding rFVIIa replacement in perioperative period to ensure adequate hemostasis.

Results: An 16-year-old girl with congenital FVII deficiency admitted to pediatric emergency unit with half a day of right-sided abdominal pain, nausea and vomiting. Physical examination findings revealed tenderness to palpation in the right lower quadrant with rebound tenderness. Laboratory studies revealed, white blood cell count $8.21x10^3$/mL, hemoglobin 14.1 g/dl, platelet count of $256x10^3$/mL, 30.4 sec of aPTT, 19.4 sec of PT, 1.3 of INR, FVII level 16.3%. Radiologic imaging studies abdomen and pelvic ultrasonography was performed to determine an enlarged appendix(8 mm), thickened wall with adjacent mesenteric edema. The patient was administered rFVIIa 30 microg kg(-1)) immediately before surgery. The patient underwent open appendectomy without complication. Her appendix was acutely inflamed but not perforated. Intraoperative bleeding was minimal. After appendectomy, the second intravenous dose of rFVIIa (30 microg kg(-1)) was administered. Patient did not experience any re-bleeding during this phase. No complications related to rFVIIa were observed.

Discussion/Conclusion: The main complication of patients with FVII deficiency is recurrent bleeding events. Appropriate treatment is essential for full recovery following general surgical procedures of patients with congenital FVII deficiency. The perioperative care of a

patient with hemophilia requires a coordinated effort that includes the surgeon and hematologist.

Disclosure of Interest: None declared.

P216 | Low dose ITI in severe haemophilia A and high responders inhibitors: Experience for haematology department of university hospital of constantine in Algeria

N. Salhi*; N. Sidi Mansour

Hematology, University Hospital of Constantine, Constantine, Algeria

Introduction: In congenital haemophilia A, the development of inhibitors against factor VIII continues to be the most serious complication of haemophilia A management. As Cost issues in developing countries limit to use of high dose ITI protocols. Low dose protocols remain an efficient result. Our experience concerns 4 severe haemophiliacs A with high titer inhibitors treated with low dose protocol.

Methods: 4 patients haemophiliacs A severe, their range of age is 12 years (4 years-18 years). All with unknown gene mutation. 02 patients received prophylaxis treatment with rFVIII (Kogenate FS), one of them was a PUP. He developed inhibitors after 55 exposures days (EDs). The others were on demand therapy with plFVIII. The treatment of ITI has begun with the same FVIII which is prescribed before ITI for all the patients. The youngest patients received 50UI/KG 3 times a week, the oldest received 100UI/kg 3 times a week. Prophylaxis with by passing agent (aPCC) is indicated for one patient.

Results: The duration averages of follow-up of the patients is 10 months (9-12 months) ITI is always in progress. The last control is in class. No patient has negatived his inhibitors yet, however the titer of inhibitors reduced significantly (20%) after 6 months for 2 patients. Only one patient had a high pick titre (747UB) in the first month of treatment, and we switched to 100UI/kg of plasma derived FVIII every other day. The pick titres of inhibitors are: 123 UB in the second month of treatment for the second patient and we switched to 50UI/kg of Kogenate FS every each day, 31UB in the second month of treatment of the third patient (PUP's), so we maintained the same dose: 50UI/kg of Kogenate FS 3 times a week, 71UB 2 months after treatment, so we maintained 100UI/kg of plFVIII 3 times a week.

Discussion/Conclusion: The final results of ITI is not achieved yet. 2 patients had a good risk features: age<8 years, pic historic titers <200UB, pre ITI titer <10UB, however a long time between developing inhibitors and the beginning of treatment: 18 months and 20 months respectively. The 2 others had a poor risk features age >8 years, pre ITI inhibitor titer >10 UB and a long time between starting ITI and developing inhibitors 2 and 3 years. Negative outcome may be related with longer waiting time and inhibitor's higher pick levels.

Disclosure of Interest: None declared.

P217 | The new method purification of factors VIII/von Willebrand complex

N. Shurko*; T. Danysh; V. Novak

State Institution «Institute of Blood Pathology and Transfusion Medicine NAMS of Ukraine», Lviv, Ukraine

Introduction: Factor VIII (FVIII) circulates in plasma complexed with von Willebrand's factor (vWF). The functions of the latter are stabilizing and protecting it from proteolytic degradation of FVIII, of bridge formation between vessel wall and the platelets and of platelet agglutination. Willebrand's disease together with hemophilia is the most common diseases of the hemostasis system. The concentrate of factor VIII coagulation is used for the treatment of these diseases.

Purpose of the work: Investigate the proportion of FVIII/vWF complex at various stages of the technology of obtaining an antihemophilic concentrate.

Methods: Precipitation of proteins, ion exchange on DEAE-Sepharose and dye-ligand affinity chromatography.

Results: We researched that FVIII and vWF aren't absorbed with dye-silica sorbents. The initial relationship of FVIII/vWF complex (0.78) is retained. This property we used in the technology of obtaining of FVIII/vWF complex. The created method for isolation and purification of FVIII/vWF complex is provided combination precipitation of proteins with ion-exchange and dye-ligand affinity chromatography.

Our investigation have shown that at the stage of protein precipitation of PEG-4000 and $Al(OH)_3$ the ratio of FVIII/vWF practically does not change (0.82).

The main changes were at the stage of ion-exchange chromatography. We used a buffer with an ionic strength of 0.3 M NaCl for correlation of FVIII and vWF. However, the elution of vWF is already starting at 0.15 M NaCl. This is the main reason for the change in the ratio. The ratio of complex in the resulting eluate was 1.72.

At the stage of dye-ligand affinity chromatography, changes in the ratio almost were not. The purification of the complex at this stage was due to the phenomenon of negative affinity sorption. The ratio of FVIII/vWF complex in the eluate Diasorb-Procion Blue HB was 1.75. Received the concentrate of FVIII with specific activity 65.38 ± 3.63 IU/mg protein.

Discussion/Conclusion: Installed, that the method of dye-ligand affinity chromatography on silica sorbents provides preservation of the initial level of the ratio of FVIII/vWF complex.

Disclosure of Interest: None declared.

P218 | Real-world experience with BAY 81-8973 for haemophilia A at the bonn center: Good effectiveness for prophylaxis, on-demand and perioperative use

N. Marquardt; G. Goldmann; J. Oldenburg

Institute of Experimental Haematology and Transfusion Medicine, Bonn, Germany

Introduction: BAY 81-8973 (Kovaltry®, Bayer) is an unmodified full-length recombinant (r)FVIII, with an enhanced pharmacokinetic profile

vs rFVIII-FS and rAHF-PFM. It is indicated for prophylaxis, perioperative management and on-demand treatment of bleeding in patients with haemophilia A. Following launch in 2016, BAY 81-8973 had accumulated 8031 patient-years of exposure to 31 Aug 2018. The Hemophilia Treatment Center (HTC) Bonn, in Germany, accumulated 954 patient-years of experience with BAY 81-8973 to 20 Mar 2018.

Methods: We report the experiences of the HTC Bonn since March 2016 in treating patients with BAY 81-8973 after switching them from other rFVIII.

Results: At the data cut-off, 131 patients had switched to BAY 81-8973, of whom 61 had severe disease (<1% FVIII), 30 moderate disease (1-5% FVIII), 25 mild disease (6-49% FVIII) and 15 were carriers. Thirty-three patients had arthropathic joints, predominantly ankle or knee joints. The patients were mostly adults (18-59 years old, n = 81), with the remainder being <12 (n = 14), 12-18 (n = 12) or ≥60 (n = 24) years old. The most common prior treatment was rFVIII-FS (Kogenate®; n = 66). Sixty-five patients were treated prophylactically (of whom 61 had severe disease): the rest were treated on demand and/or perioperatively. Prophylaxis dose ranged from 8-80 IU/kg and patients were mostly treated every-other day (n = 27), with the remainder treated 7x/week (n = 7), 4x/week (n = 2), 3x/week (n = 15), 2x/week (n = 13), or 1x/week (n = 1). During a mean prophylaxis period of 17.6 months, there were 13 joint bleeds, 6 of which were spontaneous and all of which were in patients with severe disease. Spontaneous joint and major bleeds could be resolved with BAY 81-8973 on-demand treatment. As is standard at HTC Bonn, there was intensive bleed follow-up, with daily injections of BAY 81-8973 after joint and major bleeds to prevent joint damage. Outcomes for 51 major and minor surgeries with perioperative use of BAY 81-8973 will be presented. Measured trough levels at 48 hours postdose were in general higher or at least at the same level as with rFVIII-FS (>2% FVIII:C). There was no development of inhibitors.

Discussion/Conclusion: This extensive single-centre experience suggests that BAY 81-8973 is effective for prophylaxis, perioperative management, and on-demand treatment of bleeds across a range of patient ages and disease severities.

Disclosure of Interest: N. Marquardt Consultant for: CSL Behring, Novo Nordisk, Bayer, Pfizer, SOBI, G. Goldmann Consultant for: Bayer, Shire, Novo Nordisk, SOBI, Octapharma, Pfizer, CSL Behring, J. Oldenburg Grant/Research support from: Bayer, Biotest, CSL-Behring, Novo Nordisk, Octapharma and Shire, Consultant for: Bayer, Biogen Idec, Biotest, Chugai, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire, and SOBI, Speaker Bureau of: Bayer, Biogen Idec, Biotest, Chugai, CSL-Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire, and SOBI.

P219 | Evaluation of postural balance during monopedal stance in haemophilic children: Have target joint in knee

N. M. Tat*; A. M. Tat; A. F. Öner; A. B. Antmen; S. Kaplan; F. Can

[1]*Physiotherapy and Rehabilitation, Necmettin Erbakan University Faculty of Health Sciences, Konya;* [2]*Paediatric Haematology and Oncology, Yuzuncu Yil University Faculty of Medicine, Van, Turkey;* [3]*Paediatric Haematology and Oncology, Acibadem University Faculty of Medicine, Adana, Turkey;* [4]*Sports Medicine, Yuzuncu Yil University Faculty of Medicine, Van, Turkey;* [5]*Physiotherapy and Rehabilitation, Hacettepe University Faculty of Health Sciences, Ankara, Turkey*

Introduction: Children with haemophilia (CwH) recurrent bleedings occur in knee joints that may affect strength, balance and contributed to increase likelihood of falling. Disruption of mechanoreceptors may lead to balance deficit. The aim of this study was to evaluate joint health and postural balance during monopedal stance in CwH with target joint(TJ) have knee and to compare healthy children.

Methods: 12 CwH and 12 healthy boys aged between 7-18 constituted; haemophilic group(HG) and control group(CG). Inclusion criteria in HG had at least TJ in one knee. Children were excluded if they had any disorders that may affect balance. Postural balance was evaluated using a device that have a force platform and sends signal to detect centre of foot pressure (CoP). Test duration was 60s. Ellipse area and perimeter were used to describe static balance. Physical examination of lower limb joints evaluated according to Haemophilia Joint Health Score (HJHS).Range of motion (ROM) measured with goniometer. Muscle strength evaluated with manual muscle tester (MMT).

Results: Of the all CwH six had represent TJ in only right knee, while five had in only left knee. In two CwH TJ represent multiple joint. In six CwH TJ in only right knee, the median score of knee flexion, loss of knee extension and joint HJHS were 123, 3 and 4. In five CwH TJ in only left knee, the median score of knee flexion, loss of knee extension and joint HJHS were 125, 0 and 5. Knee extensors, flexors and ankle dorsiflexors muscle strength significantly decreased in TJ developed on right knee joint. Although muscle strength decreased in TJ developed on left knee joint this was not significantly. Ellipse area and perimeter were significantly increased in HG on right foot stance position. On left foot stance position ellipse area and perimeter were increased in HG but differences were not significant. Medio-lateral velocity (MLV) and medio-lateral standard deviation (MLSD) increased in HG on right foot stance position.

Discussion/Conclusion: CwH have target joint in the knee displayed significant disturbance in postural balance compared with healthy children. Postural compensatory movements increase to maintain postural balance with base of support in the normal limits. The determination of postural balance disturbance in CwH give us more information about the joint health. Postural balance exercises should not be omitted while giving the physiotherapy program for CwH.

Disclosure of Interest: None declared.

P220 | Use of von Willebrand factor concentrate in inherited von Willebrand disease. How often is it useful to add factor VIII?

N. Drillaud[1,*]; C. Ternisien[2]; L. Ardillon[1]; M. Sigaud[2]; J. B. Valentin[1]; M. Fouassier[2]; B. Gillet[2]; V. Horvais[2]; Y. Gruel[1]; M. Trossaert[2]

[1]*Haemophilia Center, University Hospital, Tours France;* [2]*Haemophilia Center, University Hospital, Nantes, France*

Introduction: The hemostatic treatment of von Willebrand disease (VWD) is usually based on von Willebrand factor (VWF) concentrates, when the use of desmopressin is not possible and/or antifibrinolytic therapy is not sufficient. To date, most of the concentrates used worldwide consist of a combination of plasma-derived coagulation factors containing various levels of factor VIII (FVIII). At a time when the marketing of pure recombinant VWF concentrate without any associated FVIII is considered, it seemed interesting to evaluate the proportion of patients with inherited VWD for whom the addition of FVIII concentrates will be required for the first injection during the replacement therapy.

Methods: We evaluated, from cohorts of patients followed in 2 French Clinical Hemostasis Centers, the percentage of VWD patients with FVIII levels <40 IU/dL and for whom the hemostatic response to desmopressin was insufficient, thereby requiring substitutive treatment. These percentages were calculated for each type of VWD.

Results: The basal FVIII:C levels were collected in 1410 patients with different types of VWD and globally 27.9% of them had FVIII:C < 40 IU/dL. According to the VWD type, these percentages were: 28/781 (16%) VWD type 1 with VWF:RCo <30 IU/dL; 12/39 (31%) for VWD type 2A(IIA); 20/72 (28%) for VWD 2A(IIE); 37/107 (35%) for VWD 2B; 17/59 (29%) for VWD 2M; 40/73 (55%) for 2M (2A-like); 81/105 (87%) for VWD 2N; 12/37 (32%) for VWD 2 "unclassified" and 26/26 (100%) for VWD type 3.

Among patients with FVIII < 40 IU/dL, a good response to desmopressin was observed in: 100% of VWD type 1; 20% of VWD 2A(IIA); 91% of VWD 2A(IIE); 0% of VWD 2M; 6% of VWD 2M (2A-like); 96% of VWD 2N; 37% of VWD "unclassified" and 0% of VWD 3.

Discussion/Conclusion: Taking into account the FVIII:C levels and the response to desmopressin, only 218/1410 (15.5%) of patients with inherited VWD would require the addition of FVIII concentrates at the first administration of pure VWF. These results obviously do not take into account any comorbidity that would contraindicate the use of desmopressin.

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P221 | Autoimmune markers in children with chronic immune thrombocytopenia

T. N. Tahtakesen Gucer; A. Aycicek; G. Aydogan; Z. Salcioglu; E. Yilmaz; C. Bayram; E. P. Uysalol; N. Ozdemir

Pediatric Hematology Oncology, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey

Introduction: Chronic immune thrombocytopenia (ITP) is defined as isolated thrombocytopenia lasting longer than 12 months. Rheumatologic diseases, immunodeficiencies and thyroid diseases may coexist with chronic ITP due to possible immune dysregulation. Aim of this study is to evaluate the accompanying autoimmune diseases in children with chronic ITP.

Methods: A total of 154 children with chronic ITP diagnosed between 1995 and 2018 were included. Patients were evaluated with immunoglobulin levels, ANA, anti-dsDNA, C3, C4, anti TPO, anti TG, T4, TSH, tissue transglutaminase IgA and IgG.

Results: Of the 154, 79 were female (51.3%) and 75 were male (48.7%). Mean age of the patients was 13.6 ± 5.8 years, mean age of diagnosis was 7 ± 4 years. None of the patients had severe infections requiring hospitalisation. None of the patients had symptoms or findings of an autoimmune disorder. Of 154, two had low IgA levels (<7 mg/dL) and were diagnosed as IgA deficiency. IgM and IgG levels were normal in all. C3 level was low in four (3%) and C4 level was low in one patient (0.7%). ANA was positive in 16 (12%) of the patients and anti-dsDNA was positive in four (0.3%). In three patients, Anti-dsDNA positivity was accompanied with ANA positivity and in one, C3 was low. These patients were followed up by pediatric rheumatology clinic. Twenty two patients had elevated anti TPO (15.5%) and 18 had elevated anti TG (12.7%). Majority of patients with high thyroid autoantibodies were female (67.5%). Out of 129 patients evaluated by thyroid tests including fT4, TSH, AntiTPO and AntiTG, 29 (22.4%) were diagnosed as Hashimoto thyroiditis. Thyroid hormone replacement was started in one patient. Of 93 patients evaluated with anti-tissue transglutaminases, seven were found to have at least one positive TTG IgA or IgG. Two of these patients underwent endoscopy, but no evidence of celiac disease was found. In total, the number of patients with at least one positive autoimmune marker was 54 (35%).

Discussion/Conclusion: Chronic ITP is known to accompany autoimmune diseases. Autoimmune diseases in patients with ITP may occur at any time in 10 years of diagnosis. Further studies for the detection of subclinical autoimmune conditions should be performed with a profit- loss account. Antibodies may be positive even when there is no clinical findings of the diseases. Further follow-up is needed to understand the clinical significance of autoimmune markers in chronic ITP.

Disclosure of Interest: None declared.

P222 | Successful management of infective endocarditis in a child with severe hemophilia A

N. Ozdemir[1,*]; Z. Salcioglu[1]; G. Ersoy[1]; T. N. Tahtakesen[1]; G. Aydogan[1]; H. Gemici[2,3]; H. Bornaun[3]; K. Oztarhan[3]

[1]*Pediatric Hematology Oncology, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey;* [2]*Intensive Care Unit, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey;* [3]*Pediatric Cardiology, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey*

Introduction: Infective endocarditis (IE) is an infection of the endocardium and/or heart valves that involves thrombus formation and results in damage to the endocardial tissue and/or valves. IE is extremely rare in immune-competent children and has been reported in a few patients with hemophilia related to central venous access devices (CVAD).

Methods: Here we present a severe hemophilia A patient without CVAD history who developed IE complicated with mitral valve rupture. Open cardiac surgery and valve replacement were performed under FVIII concentrate and anticoagulant therapy.

Results: A 6 year refugee boy with severe hemophilia A was treated with on demand therapy in native country and had no inhibitors. He presented to our center with target joints and was put on prophylaxis. On follow-up, he was admitted due to diarrhea, fever and fatigue. The family described intermittent fever episodes previously. On examination, a pansystolic murmur at mitral area was detected. *Staphylococcus aureus* was cultured in blood. Echocardiography showed severe mitral failure, pulmonary hypertension and rupture on anterior mitral leaflet. Antibiotherapy was started and he was transferred to ICU due to heart failure. He underwent open cardiac surgery and ring valvuloplasty under FVIII replacement therapy. Prophylaxis frequency was increased. Three months later, he again presented with high fever. Blood culture showed *Candida parapsilosis*. Antifungal treatment was started. He developed headache and vomiting under prophylaxis. Cranial CT showed intracranial bleeding. Repeated inhibitors were negative. He was treated with high dose FVIII however developed a new defect and vegetations on mitral valve. He had a second cardiac surgery and a prosthetic valve was replaced by naive valve this time. He is still under prophylaxis with no neurological defect.

Discussion/Conclusion: Bacterial endocarditis in hemophilia patient with CVAD is not uncommon, however it is rare in patients without catheters. We suspect that our patient had an underlying rheumatic heart disease which may be a predisposing condition. Both early antibiotic treatment and surgery is vital to reach a favourable outcome to avoid septic complications in IE management. The case presented here shows the importance of early detection of other health problems in children with hemophilia especially whom are followed up in other centers.

Disclosure of Interest: None declared.

P223 | What is the feasibility and acceptability of a new exercise test in boys with haemophilia?

N. Thorpe[1,*]; M. Bladen[1]; P. Harniess[1,2]; S. Lee[2]; S. Rand[2]; N. Hubert[1]; R. Liesner[1]

[1]*Haemophilia Centre, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK;* [2]*Great Ormond Street Institute of Child Health, University College London, London, UK*

Introduction: There is a lack of robust functional fitness measures for boys with Haemophilia, with associated control data from typically developing peers. The iSTEP is a newly developed, validated sub-maximal exercise test, originally devised for children aged 6-16y with Cystic Fibrosis, with control data collected during validation. Exercise testing is not performed routinely for boys with Haemophilia, due to practical and medical concerns. The aim of this study was to evaluate the feasibility and acceptability of iSTEP testing in boys with Haemophilia.

Methods: 70 families of boys aged 6-15y with mild, moderate or severe Haemophilia A or B (including inhibitors) attending routine clinics at Great Ormond Street Hospital were identified and approached to take part in the study. The iSTEP protocol was applied using a commercially available, standard 3-height adjustable step; boys stepped up and down to an audio track of externally-paced beats (becoming incrementally faster over 5 levels, 2 mins each), and outcomes measured included: iSTEP level achieved (0-5); total duration of stepping (0-10 mins); plus heart rate and reports of pain before, during and after testing. Feasibility and acceptability criteria included: performance of the iSTEP test without serious adverse events or reactions (SAE/SAR); and efficacy of the study protocol - aims were to recruit 40 boys in 1 year, and complete the testing procedure within a routine clinic appointment timeframe.

Results: A convenience sample of 43 boys proceeded to consent and take part in the study (Jan-Oct 2018); screening excluded 3 boys due to recent bleeds. Feasibility and acceptability criteria were met: 40 boys (median age 10y) completed iSTEP testing within 9 months; no boys stopped due to pain; no SAE/SAR were reported throughout testing; the entire iSTEP protocol was quick to administer in 15-20 mins during routine clinic review. Statistical analysis of iSTEP outcomes measured for this study cohort vs typically developing peers is underway.

Discussion/Conclusion: Feasibility and safety of the iSTEP has been established in this study population, and iSTEP testing was an acceptable addition to the boys' routine clinic appointments. Data analysis will investigate any differences between this study population and typically developing peers. Further psychometric evaluation of the iSTEP in boys with Haemophilia is planned using this proven study protocol.

Disclosure of Interest: None declared.

P224 | Sports participation and sports injuries in relation to age and severity in young persons with haemophilia

O. Versloot[1]; J. van derNet[2]; K. Fischer[1,*]

[1]van Creveldkliniek, UMC Utrecht, Utrecht, Netherlands; [2]Children Development and Exercise Center, UMC Utrecht, Utrecht, Netherlands

Introduction: Knowledge about sports participation and sports injuries in relation to age and haemophilia severity in young PWH remains limited. The aim of this study was to evaluate sports participation characteristics of young, Dutch PWH in relation to age and severity and its association with sports injuries.

Methods: Retrospective data from the three most recent annual clinic visits was collected for all patients with haemophilia aged 6-18 at the Van Creveldkliniek. Data on sports type and frequency, as well as injuries and bleeding was recorded. Sports associated injury risk was classified according to the National Hemophilia Foundation classification (two highest of 5 categories are considered high-risk sports). Sports participation was compared to the Dutch general population. Logistic and linear regression models and chi square tests were performed.

Results: Files of 100 PWH (median age: 13 (IQR: 11-15); 52% severe) were included. Most (89%) were engaged in weekly physical sports), including 71/89 (80%) in high-risk sports. Sports participation was higher than in the age-matched Dutch general population (89% vs 70%). Sports participation was similar in severe and non-severe PWH (median 3.0 (2.0-3.8) vs 3.0 (3.0-3.0); $P = 0.30$). Sports participation increased with age with 1 time per week over 10 years (OR: 2.2 (95% CI: 1.5-3.0)/wk, $P = 0.001$, while participation in high-risk sports remained stable. During 259 person years of follow up, overall bleeding rate was low: median 1 per year (IQR: 0-3). Sports injuries were rare (overall median 0/Yr (IQR: 0-1, 65% reported no injuries in 3 years). 40.8% of severe PWH reported any injury in 3 years, compared to 32.5% of non-severe PWH ($P = 0.419$). The number of injuries was similar for PWH in high-risk sports and non-high-risk sports (median 0 (0-1) vs 0 (0-1), $P = 0.31$). No association between sports participation characteristics and injuries was observed.

Discussion/Conclusion: Most (89%) of Young Dutch PWH were highly active in sports (median 3 x/week), including 71% in high-risk sports. This study suggested that sports participation was not associated with haemophilia severity. The number of bleeds or sports injuries showed no association with sports participation characteristics or severity. A prospective study and objective assessment of sports participation and its association with sports injuries in PWH is warranted to draw further conclusions.

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P225 | Long-term safety and efficacy of rVIII-SingleChain in patients with severe haemophilia A: Interim results from a phase 3B extension study

J. Mahlangu[1]; F. Abdul Karim[2]; O. Stasyshyn[3,*]; B. Korczowski[4]; A. Brainsky[5]; S. Lucas[5]; Y. Li[5]; I. Pabinger[6]; on behalf of the AFFINITY Investigators

[1]University of the Witwatersrand, NHLS and Charlotte Maxeke Hospital, Johannesburg, South Africa; [2]National Blood Centre, Kuala Lumpur, Malaysia; [3]Institute of Blood Pathology and Transfusion Medicine, National Academy of Medical Sciences of Ukraine, Lviv, Ukraine; [4]Department of Pediatrics, Regional Hospital, University of Rzeszów, Rzeszów, Poland; [5]CSL Behring, King of Prussia, USA; [6]Clinical Division of Haematology and Haemostaseology, Medical Clinic I, Medical University Vienna, Vienna, Austria

Introduction: rVIII-SingleChain is a novel B-domain truncated recombinant factor VIII (FVIII) comprising covalently bonded heavy and light chains. rVIII-SingleChain was specifically designed to have a high binding affinity for von Willebrand Factor. The excellent efficacy and favourable safety profile of rVIII-SingleChain has been demonstrated in the AFFINITY clinical trial programme. This Phase 3 multinational extension study is investigating the long-term safety and efficacy of rVIII-SingleChain in previously treated patients (PTPs) with severe haemophilia A.

Methods: PTPs with severe haemophilia A (endogenous FVIII <1%) and >50 previous exposure days (EDs) to FVIII products were treated either on demand or prophylactically with rVIII-SingleChain 2- or 3-times weekly, or on another regimen per the Investigator's discretion. The primary outcome is the incidence of inhibitor formation in PTPs; secondary outcomes include annualised spontaneous bleeding rate (AsBR) and treatment success in treating bleeds.

Results: A total of 222 patients (0 to <12 years, n = 77; ≥12 to ≤65 years, n = 145) were enrolled by the interim cut-off date (September 2017). The median (range) age was 20 (1-64) years. Ninety-five percent of patients (n = 211) achieved ≥100 EDs, with total cumulative EDs of 65 522 in 494 treatment years. rVIII-SingleChain had a favourable safety profile with no serious adverse events related to treatment and no PTP developed an inhibitor in the study. Of the 211 (95%) patients assigned to prophylaxis, 98 (44.1%) were treated 3-times weekly, and 84 (37.8%) were treated 2-times weekly. The median (Q1; Q3) AsBR for all prophylaxis regimens, for patients treated 3-times weekly, and 2-times weekly was 0.35 (0.00; 1.09), 0.35 (0.0; 0.96), and 0.0 (0.0; 1.46) respectively. There were 2162 bleeding events treated with rVIII-SingleChain, of which 2120 were rated for haemostatic efficacy by the investigator. In 85.8% of evaluated bleeds, haemostasis was achieved with 1 or 2 injections.

Discussion/Conclusion: rVIII-SingleChain is effective and well tolerated for the on-demand and prophylactic treatment of patients with severe haemophilia A. rVIII-SingleChain had a favourable safety profile; no PTP patients developed inhibitors.

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Roche, F. Abdul Karim: None declared, O. Stasyshyn: None declared, B. Korczowski Grant/Research support from: CSL Behring, A. Brainsky Employee of: CSL Behring, S. Lucas Employee of: CSL Behring, Y. Li Employee of: CSL Behring, I. Pabinger Grant/Research support from: CSL Behring, Consultant for: CSL Behring.

P226 | Frequency and characteristics of factor VIII inhibitors: Experience of a single center

O. Kassar[1,*]; M. Charfi[1]; F. Megdich[2]; on behalf of R. Kammoun[1], N. Ajmi[1], F. Kallel[1], M. Ghorbel[1], I. Frikha[1], I. Ben Amor[1], M. Mdhaffer[1], H. Bellaaj[1], S. Hdijji[1], C. H. Kallel[2], M. Elloumi[1]

[1]*Hematology, Faculty of Medicine, Treatment Hemophilia Center of Sfax, Hedi Chaker Hospital, University of Sfax, Tunisia;* [2]*Laboratory of Hematology, University of Sfax, Habib Bourguiba Hospital, Sfax, Tunisia*

Introduction: Development of an inhibitory antibody to factor VIII is a rare but serious complication of hemophilia treatment of patients with hemophilia A. The aim of this study is to determine the prevalence of inhibitors in hemophiliac patients and to analyze their characteristics in Treatment Hemophilia Center (HTC) of Sfax, in southern of Tunisia.

Methods: From 1982 to 2018, 128 patients with hemophilia admitted in the department of hematology in Sfax from Tunisia were evaluated. Those who had abnormal mixing study, antibody against FVIII or FIX were measured. High titer inhibitor was defined as having a titer of >5 BU/ mL at any time. Data were collected and analyzed. Our patients received treatment on-demand with plasma-derived or recombinant FVIII or labile blood products (cryoprecipitate/ FFP).

Results: Of the 128 patients with hemophilia enrolled in our study, 20 patients (16%) developed inhibitors. From this group, 19 were with Hemophilia A and only one was with Hemophilia B. The distribution of patients with inhibitors in severe, moderate and mild form were respectively 80%, 20% and 0%. The mean age of patients at inhibitor development was 16 years (2-43 years). Nine patients (45%) were high responders while 11 patients (55%)were low responders. All low inhibitors have disappeared spontaneously despite continued treatment with FVIII. 7 high responder patients have received bypassing agents and only one patient benefited from immune tolerance induction. One patient died by intracranial bleeding and one patient developed compressive spinal hematoma and keeps a flaccid paraplegia.

Discussion/Conclusion: Inhibitors are more frequently encountered in persons with severe hemophilia compared to those with moderate or mild hemophilia. The median age of inhibitor development in our series is higher than in developed countries (three years or less). The eradication of inhibitors by immune tolerance induction protocols may be the most effective long-term but difficult solution in our center. Development of an inhibitory remains a major problem in the management of hemophilia threatening the vital and functional prognosis in our patient population. We need early screening according to an international recommendation.

Disclosure of Interest: None declared.

P227 | Descriptive epidemiology of hemophilia B population in Southern Tunisia

O. Kassar[1,*]; M. Charfi[1]; on behalf of F. Megdich[2], R. Kammoun[1], F. Ben Said[1], N. Ajmi[1], F. Kallel[1], M. Ghorbel[1], I. Frikha[1], I. Ben Amor[1], M. Mdhaffer[1], H. Bellaaj[1], S. Hdijji[1], C. H. Kallel[2], M. Elloumi[1]

[1]*Hematology, Faculty of Medicine, Treatment Hemophilia Center of Sfax, Hedi Chaker Hospital, University of Sfax, Tunisia;* [2]*Laboratory of Hematology, University of Sfax, Habib Bourguiba Hospital, Sfax, Tunisia*

Introduction: Hemophilia B, also called factor IX (FIX) deficiency or Christmas disease, is a rare genetic disorder caused by missing or defective factor IX. The aim of our study is to describe the epidemiology of hemophilia B in the hemophilia treatment center (HTC) of Sfax in Tunisia.

Methods: Our retrospective study included a cohort of patients with hemophilia (PWH) diagnosed and following in HTC in Sfax From Tunisia during a period of 36 years (January 1982-October 2018). Data were collected from a regional hemophilia registry of south Tunisia center.

Results: We included 20 patients with hemophilia B during the period study. They represented 15% of all PWH followed in our HTC. The severe form represents 50% of cases followed by a mild presentation in 40% and moderate in 10%. The mean age at diagnosis was 6 years old with a range from 2 days to 35 years old. The mean presenting symptoms was bleeding event in 80% of cases. Hemorrhagic circumcision was inaugural in four cases. A hematoma cerebral at two days after birth was a circumstance of discovery in one patient. One patient had developed inhibitors after receiving a plasmatic substitution therapy and he died from a severe hemorrhagic accident. Joint arthropathy represented the main complication and was found in 30%. Prophylaxis with plasmatic factor IX is prescribed for the majority of our patient with severe form since 2015.

Discussion/Conclusion: Hemophilia B is a rare and orphan disease. The frequency of hemophilia B in our center is comparable to the literature. The diagnosis of hemophilia is late in our center so we need to carry out family surveys more frequently. Hemorrhagic circumcision is still a circumstance of discovery in our country. A multidisciplinary team and the introduction of prophylactic treatment are necessary to improve the quality of care of our PWH B.

Disclosure of Interest: None declared.

P228 | Arthropathy in patients with hemophilia: A single center experience

O. Kassar[1,*]; M. Charfi[1]; On behalf of F. Megdich[3], R. Kammoun[1,2], M. Triki, Faouzi.Kallel[4], F. Ben Said[1,2], N. Ajmi[2], M. Ghorbel[2], F. Kallel[2], I. Frikha[2], I. Ben Amor[2], M. Mdhaffer[2], H. Bellaaj[2], S. Hdijji[2], C. H. Kallel[3], M. Elloumi[1,2]

[1]*Treatment Hemophilia Center of Sfax, University of Sfax, Tun;* [2]*Hematology, Faculty of Medicine Sfax Tunisia, Sfax, Tunisia*

Introduction: Joint bleeding is the most frequent manifestation in severe hemophilia. Spontaneous joint bleeding and repeated

hemarthrosis lead to hemophilic arthropathy. The aim of our study is to describe the characteristics of hemophilic arthropathy in the hemophilia treatment center (HTC) of Sfax.

Methods: Our study is retrospective, it concerned patients with hemophilia (PWH) followed in the HTC of Sfax during the period from 1982 to 2018 (36 years), who developed hemophilic arthropathy during the evolution of the disease. All patients were clinically examined, plain radiography was used to evaluate the degree of joint damage based on Pettersson score. The joint function was evaluated by Hemophilia Joint Health Score(HJHS).

Results: During the study period, we collected 128 hemophiliacs, 76 patients had a severe form. Joint complications occurred in 54 PAH (42%). Nine patients developed chronic synovitis and 45 patients had chronic hemophilic arthropathy. Patients with severe hemophilia had more chronic arthropathies in 74% followed by moderate and mild hemophilia in 20% and 7% respectively. The knee joint was most frequently involved (55%) followed by elbow and ankle. Arthropathy was mono-articular in 12 patients and polyarticular in 33 patients. The joint damage was of medium severity according to the Pettersson score in the majority of cases (58%). Patients with synovitis were treated by radiosynoviorthesis followed by physiotherapy in all cases. Four patients had a decrease in joint bleeding and improved their HJHS. Failure was noted in 5 cases with recurrent hemarthrosis. Surgical treatment of chronic arthropathy (knee prosthesis) was performed in one case. Long-term physiotherapy was indicated in all patients who developed signs of chronic arthropathy, however, it was only performed for a few patients because of living in a remote area the great distance for patients to the health center and the lack of means.

Discussion/Conclusion: Hemophilic arthropathy is the leading cause of morbidity in severe hemophilia patients in our study, as in other underdeveloped countries. The incidence of hemophilic arthropathy has been decreasing in our center in recent years due to the better availability of replacement therapy. Prophylactic treatment, physiotherapy and multidisciplinary approach are necessary to improve the patients' quality of life.

Disclosure of Interest: None declared.

P229 | Management of hemophilia in hemophilia treatment center of Sfax

O. Kassar[1,*]; on behalf of M. Charfi[1] ,R. Kammoun[1], Y. Fakhfakh[1], F. Megdich[2], M. Ghorbel[1], F. Ben Said[1], N. Ajmi[1], I. Frikha[1], I. Ben Amor[1], M. Mdhaffer[1], S. Hdijji[1], C. H. Kallel[2], M. Elloumi[1]

[1]*Hemophilia treatment center, Hedi Chaker Hospital, University of Sfax, Tunisia;* [2]*Laboratory, Hematology, Faculty of Medicine Sfax Tunisia, Sfax, Tunisia*

Introduction: Hemophilia is the most commonly inherited bleeding disorder. In Tunisia, hemophilia remains a health problem. We report in this work the epidemiological, clinical, therapeutic and evolutionary characteristics of a cohort of patients with hemophilia in southern Tunisia.

Methods: Our study concerned all hemophilia cases followed in hemophilia treatment center of Sfax, during a period of 36 years (from January 1982 to October 2018). Data were collected from a regional hemophilia registry of south Tunisia center.

Results: During the study period, we collected 128 cases of hemophilia, 85% of them had hemophilia A and 15% had hemophilia B. The severe form represented the majority in 59% followed by a moderate form in 29% and minor form in 12%. Familial history of hemophilia was noted in 90 cases (70%) and 38 cases (30%) were sporadic. The mean age of patients at diagnosis was 50 months. The presenting symptoms were bleeding events in 89% of cases and a family investigation in 11% of cases. The hemorrhagic symptoms were represented mainly by hemarthrosis (73% of cases), hematomas (62% of cases) and visceral hemorrhages (28% of cases). Intracranial hemorrhage was noted in 5% of cases. Replacement therapy for bleeding events was administered on demand, it was based on the use of labile blood products (FFP or cryoprecipitate) before 2000 and then, plasmatic clotting factors concentrates were the treatment of choice if available. Since 2009, recombinant clotting factor VII is being available in our center and currently, it's prescribed for 25% of patients with hemophilia A. The majority of our patients are treated on demand in case of bleeding and recently, prophylaxis therapy was initiated in 16 patients. Hemophilic arthropathy was the major orthopedic complication in our patients (38%). The knee and elbow were the most affected joints. 16% of patients in our study developed inhibitors. Transfusion-transmitted infection with HIV and hepatitis C was 2% and 22%, respectively. The mortality rate was 6%.

Discussion/Conclusion: Hemophilia is still a disabling disease in our country. To improve the quality of care in our center of south Tunisia, a multidisciplinary team has been set up and a local dedicated to hemophilia has been created. Relay centers (Gabes and Gafsa) were also created. Furthermore, training sessions for physicians who care for hemophiliacs were conducted as well as patient education sessions.

Disclosure of Interest: None declared.

P230 | Evaluation of cardiac function, blood pressure profiles, and vascular endothelial function in children with hemophilia

Z. C. Özdemir[1]; P. Köşker[2]; Y. Düzenli Kar[1]; Ö. Bör[1,*]

[1]*Pediatric Hematology Oncology, Eskisehir Osmangazi University, Eskişehir, Turkey;* [2]*Pediatric Cardiology, Eskisehir Osmangazi University, Eskişehir, Turkey*

Introduction: The second most common cause of death in patients with hemophilia is cardiovascular disease and the prevalence of hypertension is higher than in the general population. In this study, we investigated the presence of early atherosclerotic changes by evaluating left ventricular function, blood pressure profiles, and vascular endothelial function in children with hemophilia,

considering that the foundations of cardiovascular diseases were laid from childhood.

Methods: In this prospective study, 17 patients with severe hemophilia and 23 healthy children were included. Left ventricular function was evaluated using two-dimensional and pulsed tissue Doppler echocardiography. Myocardial performance index (MPI) values were calculated using tissue Doppler. Intima media thickness of bilateral carotid arteries were measured. Pulse wave analysis was performed based on the average of three separate measurements using oscillometry. The body mass index (BMI) of the patients was calculated by measuring height and weight. Serum glucose, triglyceride (TG), total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol and insulin levels were measured. HOMA-IR index was calculated to evaluate insulin resistance.

Results: The mean FVIII activity was 0.5 ± 0.43%. The mean age of the patient group was 12.05 ± 1.14 years, the mean age of the control group was 12.95 ± 0.50 years. There was no statistically significant difference in terms of age, height, body weight, BMI, serum glucose, TG, total cholesterol, LDL cholesterol, fasting insulin, HOMA-IR index, carotid intima media thickness, systolic, diastolic and mean blood pressure, augmentation index, augmentation pressure, peripheral resistance, and pulse wave velocity between the groups ($P > 0.05$). The mean HDL cholesterol level of the patients was lower than those of healthy children ($P = 0.018$). The MPI value of the patient group was statistically higher ($P = 0.004$) and ejection time was statistically shorter ($P = 0.014$) than the control group.

Discussion/Conclusion: Our study is the first to reflect childhood data. We showed that impairment in vascular endothelial functions and atherosclerotic changes have not yet begun in childhood; however, the systolic and diastolic function of the left ventricle was affected and serum HDL cholesterol levels were lower in children with hemophilia than in the controls.

Disclosure of Interest: None declared.

P231 | Overall annualised bleeding rates <2 in patients with haemophilia A treated with every-5-day or every-7-day BAY 94-9027 prophylaxis for ≥100 exposure days

P. A. Holme[1,*]; L. Poulsen[2]; M. Simpson[3]; T. Liu[4]; M. Maas Enriquez[5]; I. Pabinger-Fasching[6]

[1]*Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway;* [2]*Centre for Haemophilia and Thrombosis, Aarhus University Hospital, Aarhus, Denmark;* [3]*Rush Hemophilia and Thrombophilia Center, Chicago, USA;* [4]*Bayer AG, Berlin, Germany;* [5]*Bayer AG, Wuppertal, Germany;* [6]*Division of Haematology and Haemostaseology, Department of Medicine, Medical University of Vienna, Vienna, Austria*

Introduction: BAY 94-9027 is a B-domain-deleted recombinant factor VIII (FVIII) site-specifically PEGylated with a 60-kDa (2 × 30-kDa) polyethylene glycol (PEG) to extend half-life. Efficacy and safety of BAY 94-9027 prophylaxis and on-demand therapy for severe haemophilia A were demonstrated in the phase II/III PROTECT VIII trial (NCT01580293) and extension. We present bleeding outcomes in patients who received BAY 94-9027 prophylaxis every 5 days (E5D) or every 7 days (E7D) for ≥100 exposure days (EDs) in PROTECT VIII and its extension.

Methods: PROTECT VIII was a randomised, open-label trial of 134 males aged 12-65 years with severe haemophilia A (FVIII <1%) and ≥150 FVIII EDs. In the prophylaxis groups, patients with <2 break through bleeds in the 10-week run-in period were eligible for randomisation to 45-60 IU/kg E5D or 60 IU/kg E7D for the main 26-week study period; 43 patients were randomised to each group. Patients completing the main study could enter an extension; in both the main study and extension, patients could switch dosing regimen. Total annualised bleeding rate (ABR), joint ABR (JABR) and spontaneous ABR were assessed in patients treated continuously with E5D or E7D dosing for ≥100 EDs.

Results: In total, 24 and 9 patients completed E5D and E7D dosing for ≥100 EDs, respectively. Median (quartile [Q]1; Q3) drug exposure (main study + extension) for the E5D and E7D groups was 263.0 (154.5; 357.0) and 249.0 (231.0; 266.0) EDs, respectively. For patients on E5D dosing: median ABR in the main and extension studies, respectively, was 1.93 (0.00; 4.13) and 0.99 (0.11; 2.97); JABR was 0.97 (0.00; 3.98) and 0.76 (0.00; 2.32); and spontaneous ABR was 0.00 (0.00; 4.03) and 0.54 (0.00; 1.93). For patients on E7D dosing: median ABR in the main and extension studies, respectively, was 0.00 (0.00; 0.00) and 0.74 (0.23; 0.87); JABR was 0.00 (0.00; 0.00) and 0.47 (0.23; 0.74); and spontaneous ABR was 0.00 (0.00; 0.00) and 0.47 (0.23; 0.66). There were no discontinuations due to serious adverse events (SAEs) and no study drug-related SAEs in the main or extension study in either group. No patient had confirmed FVIII inhibitors.

Discussion/Conclusion: In patients receiving extended-interval (E5D/E7D) prophylaxis for ≥100 EDs, median ABR, spontaneous ABR and JABR were low (<2), demonstrating sustained efficacy of these dose regimens in appropriate patients.

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P232 | Switching to BAY 81-8973 for haemophilia A: The Norwegian experience

P. Holme[1,*]; H. Glosli[2]; S. Grønhaug[3]

[1]Department of Haematology, Oslo University Hospital, Oslo, Norway; [2]Institute for Paediatric Research, Division for Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway; [3]Centre for Rare Disorders, Division for Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

Introduction: BAY 81-8973 (Kovaltry®, Bayer) is an unmodified full-length recombinant (r)FVIII indicated for prophylaxis and treatment of bleeds in patients with haemophilia A. Launched in 2016, BAY 81-8973 has accumulated 8031 patient-years of exposure (to 31 Aug 2018). Norway has 186 paediatric and adult patients with severe haemophilia A managed by the Oslo Haemophilia Comprehensive Care Centre (HCCC). Of these, ≥80% are on regular prophylaxis; all children start treatment with primary rFVIII prophylaxis. Historically, there has been reluctance to switch rFVIII treatment due to patient/prescriber concerns over inhibitor development, concerns unsupported by clinical evidence. Here, we describe the process of switching patients to BAY 81-8973 as it became available in Norway in Sept 2017, after a tender process.

Methods: Switching treatment is done in conjunction with good background information, provided to patients by the treating physicians and nurses. BAY 81-8973 is initiated at the same dose and frequency as the previous rFVIII, assuming there were no spontaneous bleeds with the previous treatment. As a preference, the first dose is given at the HCCC. A minimal pharmacokinetics (PK) profile is performed at the first follow-up visit. Bleeding is assessed from patient diaries at 4-6 weeks, with dose and dose frequency adjusted, if necessary, based on bleeding pattern and trough levels. Inhibitors are measured before and 3-6 months after switching, or as clinically relevant. Data are available for patients switched up to 30 September 2018.

Results: No patients have refused to switch treatment. The 86 patients switched were aged <12 years (n = 14), 12-18 years (n = 6), or >18 years (n = 66). Most (73) patients had severe disease (<1% FVIII:C); 12 had moderate (1-5% FVIII:C) and 1 had mild (>5%-50% FVIII:C) disease. All patients report satisfaction and none has reverted to previous treatment. No substantial dose/frequency adjustments have been made based on bleeding pattern or trough levels. No adverse events have been reported, and no inhibitors have been detected.

Discussion/Conclusion: Experience in Norway suggests that transition to BAY 81-8973 from another rFVIII can be effectively managed with appropriate education, and high levels of patient satisfaction can be expected when patients are assigned the same dose/frequency as their previous product. Further systematic follow-up is being conducted on these patients.

Disclosure of Interest: P. Holme Grant/Research support from: Bayer, Pfizer, Shire, Octapharma, Consultant for: Bayer, Novo Nordisk, Pfizer Shire, SOBI, H. Glosli Grant/Research support from: Working at a paediatric clinical trial unit at Oslo university hospital and involved in several clinical studies of children with haemophilia. The studies are co-ordinated by the hospital, with specific support from Octapharma, Bayer, Shire, SOBI, respectively., S. Grønhaug: None declared.

P233 | Acquired hemophilia A: Rare but not anecdotal syndrome. The eleven years follow up of hemophilia center of Pavia

P. S. Preti[1,*]; S. Bisegna[2]; A. Lampugnani[3]; M. Ciola[4]; C. Ambaglio[5]

[1]Department of Internal Medicine and Therapeutics, University of Pavia, Hemophilia Center and Congenital Coagulopathies, IRCCS San Matteo Foundation, Pavia, Pavia, Italy; [2]Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy; [3]University of Pavia, IRCCS S. Matteo Foundation, Pavia, Italy; [4]University of Pavia, IRCCS S. Matteo Foundation, Pavia, Italy; [5]Hemophilia Center and Congenital Coagulopathies, IRCCS San Matteo Foundation, Pavia, Italy

Introduction: Acquired Hemophilia A (AHA) is an autoimmune disease caused by autoantibodies against functional epitopes of coagulation factor VIII, characterized by spontaneous or surgery bleedings in patients with no family or personal history of bleeding.

Methods: Between 2007 and June 2018, 28 cases were diagnosed in our Center.

Results: Among the 28 patients, 19 were male and 9 female. Median age 69.1 years. 26 patients experienced at least one bleeding episode at diagnosis: 17 in musculoskeletal compartment, 5 in gastroenteric one, 21 mucosal e 4 genitourinary, 1 case of hemothorax, and 2 retroperitoneal hematoma. The underlying medical condition was reported as malignancy in 12 cases, an autoimmune disorder in 6, dermatologic diseases in 5 and pregnancy in 2. No associated medical condition was identified in 9 patients. The most frequent comorbidities were essential hypertension and ischemic heart disease. Three patients were on antiplatelet therapy. Median hemoglobin level was 9.07 g/dl, PTT 64.12 sec, FVIII level 2.1% and inhibitor titer 18.5 BU/ml. Transfusion support was needed in about half of the cases. A total of 19 patients were treated with hemostatic agents: 2 (10.5%) received rFVIIa, 17 (89.5%) aPCC; 3 FVIII. Among the 17 patients treated with bypassing agents, 2 presented thrombotic events. 11 patients were treated with steroids alone, 17 with a combination of steroids and cyclophosphamide - steroids combined with cyclophosphamide resulted in more stable remission (88%) than steroids alone (69%). The complete response (inhibitor titer negativity, FVIII level >70%, and withdrawal of immunosuppressive therapy) was achieved in 32.1% of patients. The median time to remission and to complete remission was respectively 80.04 and 221.14 days. The median follow up was 39 months. Relapse were reported in 7 patients who presented musculoskeletal bleeding. In four patients the relapse took place within four months from response. During the follow-up, 12 deaths occured. In one case death was

secondary to severe bleeding, in remaining patients was due to infection and underlying conditions.

Discussion/Conclusion: AHA is a rare and potential life-threatening disorder. In this report bleeding control was similar between rFVIIa and aPCC. Steroids combined with cyclophosphamide resulted in more stable complete remission. Thrombotic events were not suspected to be related to treatment with hemostatic agent.

Disclosure of Interest: None declared.

P234 | Pharmacokinetic evaluation before surgery of two patients affected by von Willebrand disease and treated with von Willebrand factor/factor VIII concentrate Wilate®

P. S. Preti; G. Bertolino; C. Spataro; M. Ciola; C. Ambaglio

Department of Internal Medicine and Therapeutics, Centro Emofilia e Coagulopatie Congenite, University of Pavia, IRCCS Policlinico San Matteo

Introduction: Von Willebrand factor (vWF)/factor VIII (FVIII) concentrate Wilate® has a ratio vWF/FVIII close to 1:1 and is effective in perioperative management of patients affected by von Willebrand disease (vWD). No accumulation of FVIII is described.

Methods: We describe pharmacokinetic data obtained after the infusion of Wilate® in two patients with high thrombotic risk due to concomitant diseases (renal carcinoma, coronary disease).

Results: Patient 1, 58 years old, is affected by vWD type 1 with a Bleeding Assessment Tool score of 9 (BAT-ISTH)for bleeding after surgery, frequent epistaxis. Before nephrectomy for renal carcinoma, he underwent pharmacokinetic study, with infusion of 37 U/Kg vWF/FVIII concentrate. Samples were collected at basal time and after 15 and 30 minutes, 1-3-6 and 24 hours from the infusion. APTT(<32″) was: 32.5 -> 27 -> 26.4 -> 27.2 -> 26.4 -> 27.4 -> 28.7″. FVIII:C (70%-120%) was: 30.67 -> 74.58 -> 83.99 -> 89.92 -> 95.1 -> 82 -> 61.35%; vWF RCo (50%-200%) was: 17.04 -> 57.72 -> 62.28 -> 57.48 -> 47.19 -> 34.75 > 22.5%. Patient 2, 87 years old, is affected by vWD type 1 with a BAT-ISTH score of 6 (easy bruising, bleeding from minor wounds, haemorrhage after tooth extraction) For a CT-guided pulmonary biopsy, he was treated with 2000 UI (33 U/Kg) of Wilate®. Samples were collected at basal time, and after 1-3-6-9-24-48 and 72 hours from the infusion. APTT(<32″) was: 34.8 -> 30.5 -> 30.8 -> 30 -> 30.1 -> 30.8 -> 33.4 -> 35.8. FVIII:C (70%-120%) was: 39.8 -> 104.4 -> 108 -> 109.9 -> 113.7 -> 77.3 -> 68.2 -> 50.1%; vWF RCo (50%-200%): 24.7 -> 62.8 -> 52.4 -> 51.4 -> 51.9 -> 38.8 -> 32.9 -> 32.3%. The highest level of FVIII was obtained around the third hour in the first patient and between 3 and 9 hours after infusion in the second patient, with a sort of plateau. vWF antigen and activity rose in the first hour after infusion and decreased slowly; in patient 2, after 72 hours we maintained FVIII levels hemostatically effective and vWF levels over the basal value.

Discussion/Conclusion: Our data show good pharmacokinetic profile without excessive increase of FVIII, which is maintained at a good haemostatic level at more than 24 hours after infusion. Efficacy and tolerability of Wilate were excellent in both cases. Our patients experienced neither perioperative bleeding nor thrombotic events.

Disclosure of Interest: None declared.

P235 | Evaluation of hemorrhage risk in "haemophiliac A" patients with and without inhibitor by means of Calibrated Automatic Thrombogram (CAT)

L. Tomas; P. Marco*; A. Marco

Haematology Department, Hospital General Universitario de Alicante, Alicante, Spain

Introduction: In congenital deficiencies of coagulation factors, there are a tendency clinically relevant to bleeding is observed. The use of the area under the curve (AUC) value of the thrombin generation test (TGT) in patients with bleeding risk may help to optimize the factor substitution therapy.

Methods: The AUC was evaluated using the Calibrated Automatic Thrombogram (CAT, Diagnostica Stago, Paris, France), following the manufacturer's specifications for haemophilic A severe patients in 34 samples between pre and post (30 minutes after) factor dosage, 15 of them with inhibitor. An AUC of 20% or lower was marked as the bleeding trend limit according to Al Dieri R et al. 2002.

Results: In general, we can see the differences between patients with and without inhibitor, and also, if the patient has had the factor dose or not. All patients with inhibitor reach a percentage of bleeding risk in the PRE-infusion of the factor with an average of 8% that is recovered up to 40% after the treatment. On the other hand, patients without inhibitor, in the PRE-dose reach the same average level of AUC that patients with inhibitor and POST-dose (40%). After infusion of the factor, the AUC increase up to 64%. Moreover, between 11 and 20% of patients without inhibitor, we can see that they have an annual bleeding rate of 2-5. Usually, this episodes are caused due to an inadequate dose adjustment or frequency of scheduled prophylaxis and it should be reviewed. This is related with an AUC of 13-20%.

Discussion/Conclusion: It has been possible verify how is the AUC response in haemophiliac patients and how can it serve as a guide for monitoring them. Is remarkable that taking as a reference the minimum level of 20%, it would prevent bleeding episodes.

Disclosure of Interest: None declared.

P236 | Exposure degree to recombinant factors and bleeding episodes in patients with severe haemophilia "A" in a single haemophilia centre

L. Tomas; P. Marco*; A. Marco

Haematology Department, Hospital General Universitario de Alicante, Alicante, Spain

Introduction: Pharmacokinetics (PK) can be a valid tool not only to rationalize pharmaceutical spending but also to improve the

efficiency in the dosage. From a small number of samples, a PK profile is estimated based on a statistical theory that takes into account covariables of the population and FVIII activity.

Methods: FVIII activity was processed using the coagulant method in 6 patients with severe haemophilia A in the Haemostasis and Thrombosis Department at the General University Hospital in Alicante (Spain) with a mean age of 19 years. All patients were treated with recombinant factors. The samples were extracted prior to factor infusion, 4 and 24 h after factor replacement. We obtained an individualized Pk that was correlated with the annual bleeding rate (ABR), in order to establish the parameters levels that can be a good indication of preventing bleeding episodes.

Results: Patients without ABR had an exposure degree above 56 h and FVIII concentration prior infusion around 2-3%. In addition, patients treated with an extended half-life product achieved a greater exposure degree than the other patients obtaining a bioavailability of 92 h. We found special cases with an ABR between 2 and 5. Specifically, although the doses prescribed were high, the pre-dose percentage was below 1% with a bioavailability below 40 h.

Discussion/Conclusion: There is a possible correlation between the parameters of Pk and the FVIII levels of the patients and the bleeding episodes. The exposure degree that is indicated by the area under the curve (AUC), might be a good indication of bleeding episodes prevention. For a protective level, the FVIII prior infusion must be in a range around 2% to achieve an adequate degree of exposure with an AUC higher than 56 h.

Disclosure of Interest: None declared.

P237 | Musculoskeletal ultrasound evaluation of extraarticular effusions in haemophilic pediatric patients

P. Nally[1,*]; F. J. Nally[2]; G. Sliba[3]

[1]*Radiology, Hospital materno infantil "Dr Tetamanti", Mar del plata, Argentina;* [2]*Traumatologos Asociados, Mar del plata, Argentina;* [3]*Hospital Materno Infantil "Dr Tetamanti", Mar del plata, Argentina*

Introduction: The primary objective of the evaluation with ultrasound is to diagnose the involvement of target joints during acute events and to control them to establish treatment and prevent the progression of the disease.

The simultaneity of findings in joint and periarticular processes at admission is not unusual. We highlight the contribution of ultrasound in the differential diagnosis of hemorrhagic affections of soft tissues and periarticular regions, understanding that extra-articular involvement will have a favorable evolution, with resolution of the process in a shorter period, with less sequelae.

Methods: From October 2016 to September 2018 we evaluated 12 severe Hemophilia A patients with acute hemorrhagic events. We performed 3 ultrasound studies in average to each patient in both limbs making a total of 200 evaluations. All the studies were performed by the same operator (NP). We analysed if the effusions were intraarticular, extraarticular or both in the acute event to assess the incidence of extraarticular effusions.

The study of the affected region is evaluated in a comparative way with the normal contralateral limb, systematically evaluating from superficial to deep planes. Hematological collections of the subcutaneous cellular tissue, intramuscular, intermuscular, tendinous, peritendinous plane, as in the case of hemorrhagic tenosynovitis and subperiosteal plane, beyond acute joint involvement, can be detected.

Results: In our study group we had 39 acute extraarticular events, 41 acute intraarticular events and 8 simultaneous acute events. Among the extraarticular diagnosis 9 were tenosynovitis, 17 were intramuscular effusions, 5 were intermuscular and 8 were subcutaneous. Around 50% of the acute events correspond to extraarticular conditions and only near 20% were simultaneous.

Discussion/Conclusion: Ultrasound is fast, effective and safe. Size and location are determined to track their evolution over time, as well as eventual complications as ossifying myositis, fibrosis, encapsulation, neovascularization and the worrisome pseudotumor of the hemophiliac.

The extraarticular effusions may be confused as intraarticular. The clinical impact of extraarticular collections is better handled, with favorable prognosis and resolution. Multidisciplinary work is a priority to improve the quality of life of the hemophiliac patient through the prevention of hemorrhages and the adequate treatment of them.

Disclosure of Interest: None declared.

P238 | Project GYM: Promoting fitness in haemophilia

P. McLaughlin[1,*]; M. Holland[2]; S. Dodgson[2]; K. Khair[3]

[1]*Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust, London, UK;* [2]*Haemnet, London, UK;* [3]*Great Ormond Street Hospital, London, UK*

Introduction: Historically, physical activity was contraindicated in those with haemophilia; today it is recommended where risks can be managed. The focus of haemophilia care is now on "normalising" individual's lives and for many young men this means building muscle through working out. But for some with haemophilia the perception persists that physical activity is harmful and fear of adverse consequences may result in failure to engage in physical activity. Project GYM will investigate the feasibility of engaging young men with haemophilia in a haemophilia-specific gym-based intervention developed by physiotherapy and fitness professionals.

Methods: Project GYM aims to demonstrate that young men with haemophilia can increase their participation in exercise and physical activity through a tailored physical activity educational package along with 6-month gym membership, and that working with a personal trainer can enhance motivation and maintenance.

We recruited young men aged 18-25 years with haemophilia A or B (any severity) who attend the three main adult haemophilia centres in London and live within 90 minutes travelling time of central London. The study received NHS Health Research Authority and ethical approval.

Data are being collected on patient self-efficacy, quality of life, physical activity stage of change, self-reported physical function, self-esteem, and daily activity levels (pre, during and post intervention using a wearable activity tracker).

Results: Invitation letters were sent to 143 young men who met inclusion criteria and attend the study sites. 32 young men (22.5%) responded and 20 consented to participate. The study is underway and baseline demographics and data will be reported.

Discussion/Conclusion: Personal trainers offer a safe route into gym culture, building their clients' confidence in safe use of gym equipment. Evidence suggests that one-to-one personal training is an effective method for changing attitudes and increasing physical activity. We expect this project to demonstrate that bringing together haemophilia professionals and personal trainers will help young men with haemophilia to define, meet and maintain their individual fitness goals and become more physically active, free from the constraints and barriers posed by their bleeding disorder.

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P239 | A 14-year old boy with vascular Ehlers-Danlos syndrome and left fibular artery rupture

K. Koch[1]; P. Laguna[1,*]; R. Rogulski[2]; A. Piotrowska[2]; M. Matysiak[1]

[1]*Dept. Ped. Hem/ONC, Medical University of Warsaw, Warszawa, Poland;* [2]*Surgery, Medical University of Warsaw, Warszawa, Poland*

Introduction: Ehlers-Danlos syndrome(EDS) is an uncommon disorder of connective tissue characterized by skin hyperextensibility, delayed wound healing, joint hypermobility, bleeding tendency and connective tissue fragility. Patients may present with easy bruising, bleeding from the gums after dental extractions and prolonged menstruation. Vascular type of EDS (previous EDS type IV) carries the worst prognosis due to the vascular complications.

Methods: We present the case of 14-year-old boy with vascular Ehlers-Danlos syndrome, a history of deep vein thrombosis and supracondylar amputation of the right leg due to popliteal artery aneurysm rupture a year earlier. The patient constantly required anticoagulation therapy with warfarin due to recurrent thrombosis. In June 2018 the patient underwent urgent surgery due to fibular artery rupture in the left leg. Before surgery the patient received Prothrombin Complex Concentrate(PCC) to reverse the effect of warfarin. During surgery the surgeons attempted to repair the ruptured artery. Unfortunately this was ineffective but the artery was secured. The patient underwent the perioperative period without complications. Low molecular weight heparin (LMWH) was used until the wound healed and long-therm anticoagulation therapy with warfarin was set up again. Patient underwent physiotherapy and in July 2018 he was discharged from hospital with an artificial limb. He had an angioMRI in late September 2018. No adverse vascular events were noted.

Results: xxxxxxxxxxxx.

Discussion/Conclusion: Patients with deep vein thrombosis may have recurrent thrombotic events, despite long term anticoagulation therapy It is essential to take into consideration other vascular adverse events, such as artery rupture or aneurysm formation. Doppler ultrasonography is a basic standard in the diagnosis of vascular complications

Disclosure of Interest: None declared.

P240 | Recombinant activated factor VII (rFVIIa) administered using an automated bolus infusion pump: Implications for the management of congenital haemophilia with inhibitors in the hospital setting

P. Rexen*; J. T. Jensen; N. B. Schwerin; E. Kozina

Novo Nordisk A/S, Bagsvaerd, Denmark

Introduction: rFVIIa is used for the treatment and prevention of bleeding in patients with congenital haemophilia with inhibitors. In hospitals, the schedule of reconstitution and administration of rFVIIa can be a burden on limited time and resources. Dosing rFVIIa by an automated bolus infusion pump could reduce utilisation of personnel and time and also ensure adherence. The objective of this *in vitro* study was to evaluate the physical and chemical stability of room-temperature-stable reconstituted rFVIIa at 25°C over 24 hours in a polypropylene syringe.

Methods: rFVIIa was reconstituted in histidine (diluent) at 1.0 mg/ml, pooled and transferred to a polypropylene syringe. An infusion line was attached to the syringe and mounted in an automated bolus infusion pump to ensure regular injection of the prescribed dose. Bolus injections of 90 µg rFVIIa/kg body weight were sampled at 6, 12 and 24 hours. The acceptance criterion for critical quality parameters (specific activity, rFVIIa content, aggregates and degradation products) was a two-sided 90% confidence interval (CI) for the mean difference between results from bolus injections (test samples) and reference samples, falling within an allowed acceptance interval and within specifications. Sterility was assessed after ≥24 hours of storage.

Results: All critical quality parameter results were within specified shelf-life limits and complied with acceptance criteria; 90% CIs were within the acceptance interval for all rFVIIa batches at all time points. rFVIIa content remained stable for 24 hours and

degradation was the same for the reference and test samples for dosing intervals of 2 and 6 hours. Microbiological growth was not detected during or at the end of incubation when samples were stored at 25°C.

Discussion/Conclusion: Following reconstitution of rFVIIa under controlled and validated aseptic conditions and transfer to the bolus pump apparatus, rFVIIa is physically and chemically stable for up to 24 hours at 25°C in a polypropylene syringe. No microbiological growth was detected during or at the end of incubation of the batches tested. Any pump capable of delivering regular, automated injections can be used, including hardware already available in hospitals.

Disclosure of Interest: P. Rexen Employee of: Novo Nordisk A/S, Denmark, J. Jensen Employee of: Novo Nordisk A/S, Denmark, N. Schwerin Employee of: Novo Nordisk A/S, Denmark, E. Kozina Employee of: Novo Nordisk A/S, Denmark.

P241 | Dilutional linearity demonstrated over the whole measuring range for two extended half life recombinant factor IX (EHL-rFIX) products with a chromogenic factor IX kit

P. Bryngelhed; P. Rosén*

Rossix AB, Molndal, Sweden

Introduction: Analysis of EHL-rFIX products has shown large method discrepancies within one-stage (OS) methods and vs chromogenic substrate (CS) methods. For some methods, the discrepancy is more pronounced at low FIX activities. Adherence to dilutional linearity is an important parameter in assessing method performance. The purpose of this work was to investigate dilutional linearity on analysis of two EHL-rFIX products, one glycoPEGylated (Nonacog beta pegol; N9-GP (Refixia/Rebinyn), Novo Nordisk) and one fused with albumin (albutrepenonacog alfa (Idelvion), CSL Behring), using a chromogenic Factor IX kit.

Methods: FIX doses were prepared in FIX deficient plasma in the range 0.01-2.0 IU/mL. Two independent assay series were run with Rox Factor IX (Rossix AB) on ACL TOP 500 (IL) and on STA-R Evolution (Stago). The 5th IS FIX Concentrate 14/148 and the SSC Secondary Standard SSC/ISTH plasma lot#4 (both from NIBSC, UK) were used as calibrators.

Results: For both EHL-rFIX sources, and irrespective of choice of calibrator, dilutional linearity was demonstrated over the whole measuring range 0.01-2.0 IU/mL. The r^2 values were >0.99 on both ACL TOP 500 and STA-R Evolution and with no trend towards deviations from linearity, especially at low FIX activities. Correlation slopes for the 5th IS vs SSC#4 ranged from 0.95 to 0.98, $r^2 > 0.999$ for both EHL-rFIX products on both instruments.

Discussion/Conclusion: This study shows dilutional linearity in the range 0.01-2.0 IU/mL when applying Rox Factor IX on ACL TOP 500 and STA-R Evolution, for both glycoPEGylated and albumin fused EHL-rFIX using the 5th IS and SSC#4 as calibrators.

Disclosure of Interest: P. Bryngelhed Shareholder of: Rossix AB, P. Rosén Shareholder of: Rossix AB.

P242 | Platelet function analyser in diagnosis of von Willebrand disease

P. Smejkal[1,2,*]; J. Zavrelova[1,2]; O. Zapletal[3]; I. Vangenechten[4]; A. Gadisseur[4]; G. Romanova[1,2]; P. Polak[1]; J. Blatny[3]; J. J. Michiels[5]; M. Penka[1,2]

[1]Department of Clinical Hematology, University Hospital Brno; [2]Department of Laboratory Methods, Faculty of Medicine, Masaryk University; [3]Department of Pediatric Hematology, University Hospital Brno, Brno, Czech Republic; [4]Hemostase Research Unit and Hematology Clinic, University Hospital Antwerp, Antwerp, Belgium; [5]Blood Coagulation and Vascular Medicine Centre, Goodheart Institute and Foundation in Nature Medicine, Rotterdam, Netherlands

Introduction: PFA (platelet function analyser) is a tool for the investigation of primary haemostasis with high sensitivity for the diagnosis of von Willebrand disease (VWD). We assessed relationship between PFA results and von Willebrand factor activity (VWF:Ac).

Methods: PFA was used as a screening of new patients as well as in patients with known diagnosis of VWD. We evaluated the results separately for each type of VWD. In type 1 we specifically analyzed patients with VWF:Ac < 30%, 30% - 39%, 40% - 49%. We also evaluated patients with causal mutation for type 1 VWD and VWF:Ac level ≥ 50% and compared with a group of patients without a causal mutation in which the VWF:Ac was borderline due to blood group 0 at a range of 38% - 65%. We used the normal values recommended by the manufacturer for collagen/epinephrine closure time (CT) 84 s - 160 s and collagen/ADP CT 68 s - 121 s. When CT collagen/epinephrine was normal, CT collagen/ADP testing was not performed.

Results: For CT collagen/epinephrine prolongation, 100% sensitivity was found in all patients with type 3 VWD (7/7), 2A (23/23), 2A/2E (18/18), 2B (12/12), heterozygotes 1/2N (6/6) and type 1 with VWF:Ac level < 30% (35/35). The sensitivity was 95% (19/20) for type 2M. The sensitivity for type 1 VWD was 91% (20/22) for VWF:Ac level 30% - 39%; 67% (10/15) for VWF:Ac level 40% - 49%. In those with confirmed causal mutation for type 1 VWD and VWF:Ac level ≥ 50% (median 63%) PFA sensitivity was the same - 58% (11/19) as for the patients with blood group 0 without a causal mutation in the VWF gene - 58% (11/19) and borderline VWF:Ac level (median 52%). In type 2N CT was normal in both patients (2/2).

Discussion/Conclusion: PFA sensitivity for VWD diagnosis was virtually 100% in all patients with qualitative VWF defect and quantitative defect with VWF:Ac < 30%. Those with type 1 and VWF:Ac level 30% - 39%, the sensitivity slightly decreased to 91%. Sensitivity was significantly lower in patients with higher level VWF:Ac, both for patients with a proven causal mutation for type 1 VWD and for patient without proven VWD. Thus the use of PFA with only collagen/epinephrine cartridge seems to be sufficient for effective screening of VWD.

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P243 | Tertiary prophylaxis in patients with haemophilia A and FVIII inhibitor

P. Smejkal[1,2,*]; G. Romanova[1,2]; P. Polak[1]; M. Penka[1,2]

[1]*Department of Clinical Hematology, University Hospital Brno, Brno, Czech Republic;* [2]*Department of Laboratory Methods, Faculty of Medicine, Masaryk University, Brno, Czech Republic*

Introduction: Prophylaxis with bypassing agents is a promising treatment option in patients with haemophilia and high-responder inhibitor.

Methods: Tertiary prophylaxis was introduced in three patients with haemophilia A and persistent high-responder inhibitor due to frequent or serious bleeds. In patient No. 1 (*1975), it was for advanced joint disease and 19 (18 joint) bleeding episodes within eight months. Due to the low inhibitor titre and planned immune tolerance, recombinant activated factor seven (rFVIIa) was used: approx. 90 μg/kg daily for a month, then four months every other day and then 20 months every third day or twice a week. In the other two patients we used activated prothrombin complex concentrate (aPCC). In Patient No. 2 (*1956) it was due to two serious bleeds in the scar area after implantation of the hip joint prosthesis (one month and four months after surgery). In patient No. 3 (*1941) it was due to two severe thigh muscle bleeds and five bleeds into both knees with persistent synovitis despite the radiosynoviorthesis performed on each of the knees. The dose was 11 weeks, respectively three weeks approx. 50 U/kg a day and then 35 U/kg every other day, respectively thrice a week, which now takes 20 months, respectively 13 months.

Results: Patient No. 1 during the first year of prophylaxis suffered from nine bleeding episodes (8 joint), during the second year from eight (7 joint). rFVIIa consumption was 1829 mg for the first year and 1500 mg for the second year of prophylaxis. Patients No. 2 and 3 had no experience of joint bleeding during prophylaxis; only the subcutaneous hematoma of the thigh in patient No. 2 and subcutaneous haematoma after the introduction of the midline venous catheter in patient No. 3, both without need for treatment with bypassing agents. However, patient No. 3 experienced one bleeding into the muscles of the forearm after work in the garden, which required aPCC treatment. Patient No. 2 consumed 604 000 U of aPCC during the first year of prophylaxis and 547 500 U of aPCC during last year. Patient No. 3 used 62 500 U of aPCC during the first month of prophylaxis and 468 000 U in the following year.

Discussion/Conclusion: Bypassing agents prophylaxis significantly reduced the annual bleeding rate, which was virtually zero in one patient, one in another one and decreased to about 1/3 in the patient with a marked bleeding phenotype.

Disclosure of Interest: None declared.

P244 | Analysis of carriers of type 3 von Willebrand disease caused by heterozygous deletion c.2435delC in South Moravian region

P. Smejkal[1,2,*]; J. Zavrelova[1,2]; O. Zapletal[3]; I. Vangenechten[4]; A. Gadisseur[4]; G. Romanova[1,2]; P. Polak[2]; J. Blatny[3]; J. J. Michiels[5]; M. Penka[1,2]

[1]*Department of Laboratory Methods, Faculty of Medicine, Masaryk University, Brno, Czech Republic;* [2]*Department of Clinical Hematology, University Hospital Brno, Brno, Czech Republic;* [3]*Department of Pediatric Hematology, University Hospital Brno, Brno, Czech Republic;* [4]*Hemostasis Unit and Department of Hematology, University Hospital Antwerp, Antwerp, Belgium;* [5]*Blood Coagulation and Vascular Medicine Centre, Goodheart Institute and Foundation in Nature Medicine, Rotterdam, Netherlands*

Introduction: The frameshift mutation c.2435delC is frequent in von Willebrand disease (VWD) type 3 patients from area surrounding the Baltic Sea with frequencies in Sweden 50%, in Germany 20%, in Poland 75%, in Hungary only 12.5% and zero in Canada.

Methods: We explored phenotype and genotype characteristics of 218 patients with VWD from our South Moravian region including population approx. 1 900 000 inhabitants. A number of laboratory tests was done to distinguish each types of VWD including assay of factor VIII activity (FVIII:C), von Willebrand factor activity (VWF:Ac), VWF antigen (VWF:Ag), VWF collagen binding (VWF:CB), VWF propeptide (VWFpp), multimer analysis and VWF gene analysis.

Results: Among seven patients with type 3 VWD the mutation c.2435delC/p.Pro812Arg fs(X31) was found in homozygous state in two probands and in the other two in heterozygous state together with another mutation (c.115G>A/p.Gly39Arg and c.587G>A/p.Glu197Lys). Heterozygous state of c.2435delC was found in three parents of patients with type 3 VWD and in the other 13 patients from eight families. In four families was explored only one proband and in the other four families this mutation was found in one parent and descend (in one family in two descends). The phenotype of 16 heterozygous of c.2435delC was as type 1 in 12 cases and as normal in four cases. However, in all cases FVIII:C/VWF:Ag ratio was increased in range 1.52-5 (median 2.04). In patients with normal value of FVIII:C, VWF:Ac, VWF:Ag, VWF:CB, VWFpp this ratio was 1.6-1.85 and only in one if these cases VWFpp was in borderline value 39%. The mutation c.2435delC was found in the other three families; in four probands from two families as heterozygous with mutation c.2561G>A/ p.Arg854Gln with phenotype 2N VWD and in two probands from another family as heterozygous with mutation c.4751A>G/ p.Tyr1584Cys with phenotype 1 VWD in daughter and with normal values of FVIII and VWF in her father.

Discussion/Conclusion: Mutation c.2435delC/p.Pro812Argfs(X31) was the most frequent mutation (43%) in patients with type 3 VWD and as heterozygous in type 1 VWD (12% in all cohort of VWD patients). However, in a heterozygous state there was a various penetrance that could be distinguished at a normal value of FVIII:C and VWF:Ag by an increased ratio of FVIII/VWF:Ag ≥ 1.6.

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P245 | Preventing psychosomatic consequences in bleeding disorder

P. Buckova*; H. Neudertová

Department of Clinical Psychology, University Hospital Brno, Brno, Czech Republic

Introduction: Several studies report, that psychological stress and anxiety have been shown to produce an activation of coagulation and fibrinolysis (1,2). According to a clinical experience we can observe, that patients with bleeding disorders face many stressful situations – physical and emotional. The quality of their ability to deal with negative emotions can have an impact on their health status, perception of chronic illness, pain management and on the ability to develop constructive strategies to deal with health problems.

Methods: The speech informs about psychosomatic consequences in haemophilia, based on bio-psycho-social model. Case studies with analyses of emotionally difficult situations are reported.

Results: Possible strategies of reactions in stressful situations are suggested. The strategies are focused on support of patients to integrate emotional and cognitive functioning to get the feeling of control. It is based on principles of gestalt psychotherapy and neuropsychology.

Discussion/Conclusion: Specific situations of anxiety, fear, aggressivity, disappointment, sadness in contact with children and adults will be discussed. Problematic situations in the office of doctor, nurse, physiotherapist, in the home environment will be discussed.

1 Geiser, F. and col. (2008). Association between Anxiety and Factors of Coagulation and fibrinolysis. Psychotherapy and Psychosomatics, 77, 377-383.

2 von Känel, R. (2015). Acute mental stress and hemostases: When physiology becomes vascular harm. Thrombosis Research, 135, S52-S55.

Disclosure of Interest: None declared.

P246 | Stability of citrated plasma for FVIII and fix measurement

P. Toulon*; M. Blois; F. Fischer; A. Appert-Flory; D. Jambou

Hematology, CHU Pasteur, Nice, France

Introduction: Until now, it is recommended evaluating most coagulation parameters within 4 hours after blood collection. As such a delay could be an issue, particularly for add-on tests, this study was carried out to determine at what time point an add-on coagulation test, particularly FVIII:C and FIX, can be safely honored on specimens that have been received and processed in the laboratory earlier. For that purpose, we evaluated blood samples collected into evacuated tubes containing 0.109 M tri-sodium citrate. All tubes underwent the same pre-analytical procedure. They were immediately processed within 2 h after collection (T0) and after a 3 hour-, a 6 hour-, a 12 hour-, and a 24 hour-storage, left capped in vertical position in the instrument racks at room temperature.

Methods: Blood samples were obtained from 148 patients in whom coagulation tests were prescribed: 60 had a normal coagulation profile, 15 had prolonged PT and/or aPTT including hemophilia A patients, and 73 were on vitamin K-antagonist. FVIII:C, FIX as well as routine coagulation tests such as PT/INR, aPTT, fibrinogen, FV, and D-dimer were performed on an ACL TOP 700 CTS analyzer (Werfen, Bedford, USA) using reagents from the same manufacturer.

Results: Due to limitation in plasma volume, all tests were not performed in all of the samples. No significant time-dependent changes in PT/INR, D-dimer, and aPTT evaluated using one reagent could be demonstrated for up to 24 hours. Changes in fibrinogen, and FV were significant but differences had no clinical relevance with mean bias below the recommended limits of Ricos et al. A time-dependent decline in FVIIII:C results could be demonstrated (ANOVA), with a mean bias, calculated according to Bland-Altman, above the limit recommended by Ricos et al. after a 3 hour-storage, but remaining below the recommended value of the GFHT until 6 hours. FIX was stable for up to 12 hours, with mean bias below the maximum limit recommended by the GFHT.

Discussion/Conclusion: These results suggest that FVIII:C could be validly evaluated in centrifuged citrated tubes left capped in vertical position at room temperature for up to 6 hours, whereas the delay should be extended o 12 hours for FIX. However, routine coagulation tests such as PT/INR, aPTT, fibrinogen, FV, and D-dimer could be validly evaluated within a 24 hour-delay.

Disclosure of Interest: None declared.

P247 | Results from a phase 3B, open-label, multicenter, continuation study of rurioctocog alfa pegol for prophylaxis in previously treated patients with severe hemophilia A: Analysis by age group

P. Chowdary[1,*]; E. Mullins[2]; O. Stasyshyn[3]; J. Zhang[4]; W. Engl[5]; S. Tangada[4]

[1]Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Hospital, London, UK; [2]University of Cincinnati College of Medicine and Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [3]Academy of Medical Sciences of Ukraine, Lviv, Ukraine; [4]Shire, Cambridge, MA, USA; [5]Shire, Vienna, Austria

Introduction: This study investigated the long-term safety and efficacy of an extended half-life PEGylated recombinant FVIII, rurioctocog alfa pegol (SHP660, BAX 855, ADYNOVI™; Baxalta [part of Shire, Lexington, MA, USA]), for prophylaxis and treatment of bleeding episodes in patients with severe HA.

Methods: Eligible patients ≤75 years old either transitioned from a previous SHP660 study or were naïve to SHP660 but had been treated with plasma-derived or recombinant FVIII. Patients received prophylactic SHP660 in a fixed dose (FD) or a pharmacokinetic-tailored

dosing (PK) regimen, and could switch from FD to PK regimen. Co-primary endpoints were the incidence of confirmed FVIII inhibitors and the spontaneous annualized bleed rate (ABR) analyzed using a generalized linear model. Secondary endpoints included occurrence of adverse events (AEs). Data are expressed as mean (SD) unless otherwise indicated.

Results: The study (NCT01945593; initiated Oct 2013, completed Mar 2018) included 216 patients overall. Mean age was 22.8 (15.7) years; age groups analyzed were: <6 years, n = 32; ≥6 to <12 years, n = 33; ≥12 to <18 years, n = 30; ≥18 years, n = 121. 215 patients received ≥1 dose in the FD regimen and 25 received ≥1 dose in the PK regimen. Overall mean SHP660 exposure was 209.8 (108.4) days over a mean observation period of 2.20 (1.11) years/patient. None of the patients developed a confirmed FVIII inhibitor. 838 AEs were recorded in 174 (81%) patients; 20 of these AEs were investigator-assessed as related to SHP660. A total of 52 serious AEs (SAEs) were recorded in 33 (15%) patients, including 1 fatal SAE (cerebral hemorrhage); none were considered related to SHP660. AE and SAE frequencies had no clear trends across age groups. Among patients receiving twice-weekly FD and PK prophylaxis, respectively, the point estimates (95% CI) for spontaneous ABR by age group were: <6 years, 0.7 (0.4–1.1, n = 31) and 0.9 (0.2–3.8, n = 4); ≥6 to <12 years, 0.8 (0.4–1.3, n = 31) and 0.9 (0.4–1.9, n = 6); ≥12 to <18 years, 1.8 (1.1–2.9, n = 23) and 0.8 (0.1–5.8, n = 6); ≥18 years, 1.3 (0.9–1.8, n = 101) and 1.0 (0.4–2.3, n = 9).

Discussion/Conclusion: In this population of previously treated patients with severe HA, FD and PK-tailored SHP660 prophylaxis was well-tolerated and efficacious across the analyzed age groups.

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P249 | Treatment patterns, determinants and outcomes of hemophilia: Results from a multinational survey

P. Dasmahapatra[1,*]; S. Ali[1]; T. Colberg[1]; C. Johnston[2]; J. Mellor[2]; G. Milligan[2]; C. Benson[1]; D.-T. Tran[1]; A. Hamed[1]; B. Mei[1]

[1]*Sanofi Genzyme, Cambridge, USA;* [2]*Adelphi Group, Manchester, UK*

Introduction: Hemophilia is an X-linked recessive bleeding disorder due to deficient clotting factors (Factor VIII in hemophilia A [HA], Factor IX in hemophilia B [HB]). Despite clinical benefits of available therapies, challenges exist in the management of patients with hemophilia (PWH); hence, it is important to understand the treatment patterns and health outcomes for PWH in the real-world.

Methods: This study was conducted in five European (EU) countries: France, Germany, Italy, Spain, UK; and the United States (US) in 2017. Physicians responsible for the management of ≥ 5 PWH reviewed 1397 patients' medical history (males, ≥ 12 years, HA or HB, ± inhibitors). A subset of patients (18%, n = 257) completed self-reported quality of life (QoL), work productivity and activity impairment (WPAI) questionnaires.

Results: The cohort of patients represent Italy (24%, n = 332), Germany (15%, n = 203), France (14%, n = 199), Spain (14%, n = 199), UK (11%, n = 152); and the US (22%, n = 312). The mean (± standard deviation) age of patients was 34 ± 17 years; with HA (76%, n = 1056) and HB (24%, n = 341); 18% (n = 245) had inhibitors; 32% (n = 371/1152) were severe.

Among non-inhibitor patients, 45% (n = 441/983) were on prophylaxis with the highest adherence in Germany (66%, n = 110/166) and lowest in Spain (34%, n = 53/156) in this group studied. Most severe non-inhibitor patients on prophylaxis had ≥ 1 bleeding episode(s) in the past 12-months (73% HA; 77% HB).

A third (n = 457/1397) of patients had arthropathy in at least one joint. Multivariable analysis revealed that the presence of joint arthropathy was independently associated with increasing age, HA, inhibitor status, severity, and treatment strategy (prophylaxis vs on-demand). Arthropathy (vs no arthropathy) was associated with lower patient-reported outcomes measured by EQ-5D scores (mean: 0.78 vs 0.88, $P < 0.001$), % activity impairment (Mean: 39% vs 29%, $P < 0.001$) and work time missed (Mean: 7.3% vs 2.8%, $P < 0.01$) on the WPAI. A noteworthy limitation of the study is recall bias of patient clinical history.

Discussion/Conclusion: PWH have different rates of adherence to prophylaxis in EU countries and US with sub-optimal outcomes even for patients on prophylaxis. Hemophilic arthropathy has a major impact on health outcomes and QoL. There still exists an unmet need for treatments that can reduce real-world joint bleeds, improve adherence to prophylaxis, and reduce the impact on joints in PWH.

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P250 | Improving balance in hemophilia patients using specialized equipment in the hydrotherapy pool

R. Tiktinsky*; G. Kenet; on behalf of Co-Author

National Hemophilia Center, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

Introduction: Hydrotherapy has been shown to have rehabilitative effects that help improve muscle strength, balance, and reaction

time. Hydrotherapy exercises have been used to help different musculoskeletal problems such as osteoarthritis, rheumatoid arthritis, joint arthroplasty, and neurological problems.

Methods: The object of this pilot study was to show that treatment in the hydrotherapy pool using specialized equipment helped to improve balance on land for these participants.

Five Hemophilia patients ages 40-65 participated in this pilot study. It included independent ambulators with or without walking aids.

The participants underwent assessments to determine their muscle strength, range of motion, and balance using the Berg Balance test and one leg stance test. The program took place twice a week for eight weeks.

The Therapeutic Manual EWAC Obstacle Course by URS Gamper and Johan Lambeck EWAC Medical, The Netherlands was used. It consists of a balance beam, reaching pole, wobble board and hurdles of variable height. The main objective was to train the participants in order to reduce or prevent falls on land. The exercises promote improvement in weight shift and balance, standing on one leg, walking in all directions, dual tasking while standing or walking, and are performed with the eyes open and then closed. All of these activities help to improve reactive movements as well.

Results: The results showed an improvement in all aspects tested. Muscle strength and range of motion improved in lower extremities. Muscle strength improved from 4- and 4 to 4 + and 5-. Range of motion improved between 10-15 degrees in the hip and knee. Results of the Berg Balance test improved by 20% and the one leg stand test by 50%.

Discussion/Conclusion: In conclusion, it has been shown that as individuals age, their risk of falls increases. In our pilot study, the results have shown an improvement of strength, range of motion and balance on land. Our aim is to include a control group and increase the amount of participants in order to reinforce our findings.

Disclosure of Interest: None declared.

P251 | Application of global coagulation assays in dysfibrinogenemic patients: Correlation with clinical phenotype and genetic mutations

R. A. Bochicchio*; C. Santoro; M. MG; on behalf of Barone F, Baldacci E, Ferretti A, Abbruzzese R, Miulli E, Chistolini A, Aprile S, Santoro C

Hematology, Università Roma Sapienza, ROMA, Italy

Introduction: Dysfibrinogenemic (DF) patients (pts) show a variable clinical phenotype, from bleeding to thrombosis, but most of them are asymptomatic. Aim of this study is the application of global coagulation assays in DF pts in baseline conditions to look for correlation between clinical phenotype and laboratory parameters.

Methods: DF pts were enrolled from our center. Bleeding phenotype (BP) was quantified using ISTH-BAT. Thrombophilic screening tests were executed. Thromboelastography (TEG) and Calibrated Automated Thrombography (CAT) were performed in baseline conditions.

Results: 8 DF pts were enrolled: 2 males and 6 females; median age 45 years, range 24-74. No one reported a significant BP (median ISTH-BAT score 2, range 0-3). One patient was heterozygote for FVLeiden, two were heterozygote for FIIG20210A; no one reported thrombosis. The pts were studied for the genetic causative mutation: 4 presented a missense mutation in FGA gene, 1 in FGG while in the other 3 the study is ongoing. Median thrombin time (TT) is prolonged (33.7, range 25.7-45.5, nv <23.0), median fibrinogen activity is decreased in all pts (72 mg/dL, range 51-145, nv 196-440) while median fibrinogen antigen is normal (363 mg/dL, range 198-452, nv 170-350). As for TEG, median *R* is increased (6.9 min, range 5.2-8.6, nv 4.3-6.2); median K, α and MA parameters are normal (K 2.1 min, range 1.8-4.6, nv 1.3-2.1; α 62.1°, range 40.1-64.7, nv 57.2-70.7; MA 65.4 mm, range 48.7-69.7, nv 59.8-70.5 mm); lysis parameters are decreased: LY30 is 0.0% (range 0.0-0.1, nv 0.2-3.8) and LY60 is 1.2% (range 0.0-2.1, nv 3.1-14.6%). As for TGA all the median parameters are normal: Lag Time 3.00 min (range 2.50-4.67, nv 1.93-3.92); ETP 1306.15 nM/mm (range 879.90-1828.63, nv 541.64-1484.13); Peak 209.83 nM (range 114.34-329.32, nv 90.05-258.45); tt-Peak 7.00 min (range 3.67-8.50, nv 3.82-8.70). Notably ETP is increased in 2 pts, 1763.34 and 1828.63 respectively.

Discussion/Conclusion: As concerns TEG, the increased *R* is probably due to the qualitative defect of the fibrinogen molecule and it could be the equivalent of TT. As concerns TGA, the increased ETP in 2 pts seems not to be related to a thrombotic phenotype, but a prognostic value in situation at higher risk cannot be excluded. A larger patient population and longer follow-up are needed to confirm these preliminary data.

Disclosure of Interest: None declared.

P252 | Timing of treated spontaneous bleeding in persons with haemophilia A (PwHA) with inhibitors in the HAVEN 1 study

R. Kruse-Jarres[1,*]; B. Trzaskoma[2]; K. Raimundo[2]; E. Tzeng[2]; B. Perez Sanz[2]; R. H. Ko[2]

[1]Washington Center for Bleeding Disorders at Bloodworks Northwest, University of Washington, Seattle, USA; [2]Genentech, Inc., South San Francisco, USA

Introduction: HAVEN 1, a phase III study in adolescent and adult persons with haemophilia A (PwHA) with inhibitors, demonstrated that once-weekly emicizumab prophylaxis resulted in a significant reduction in treated spontaneous bleed rates by 92% ($P < 0.001$) vs no prophylaxis. In this retrospective, post-hoc analysis, we examined how treated spontaneous bleeds were distributed within the weekly emicizumab dosing interval in HAVEN 1.

Methods: PwHA receiving emicizumab in the HAVEN 1 study (NCT02622321), by either treatment assignment or switch to emicizumab following initial assignment of no prophylaxis, were included

in this analysis. Each treated spontaneous bleed was categorized as having occurred on a given day of the patient's dosing interval (e.g. 1, 2, 3, etc.) and the incidence of bleeding was compared across the days within the interval. The most recent database cut-off (September 2017) was used for this analysis in order to capture additional bleeds and longer follow-up when compared with the original data cut dated October 2016.

Results: In total, 113 patients were enrolled and received emicizumab treatment in this analysis with a total of 129.6 emicizumab-exposure years (median [range]: 1.16 [0.0–1.8] years). Of the 113 patients analyzed, 116 treated spontaneous bleeds occurred in 37 patients. The distribution of when treated spontaneous bleeds occurred within the emicizumab dosing interval appeared to be relatively similar amongst the days from the last dose of emicizumab: Day 1 = 14.7%; Day 2 = 11.2%; Day 3 = 12.1%; Day 4 = 15.5%; Day 5 = 9.5%; Day 6 = 17.2%; Day 7 = 17.2%. A few patients received emicizumab 8 or 9 days from the prior emicizumab dose with very few bleeds occurring on those days (2 and 1, respectively). Additionally, statistical tests indicated no evidence of a tendency for bleeds to occur in any particular pattern in relationship to the emicizumab dosing schedule ($P = 0.4902$).

Discussion/Conclusion: Analyses related to the timing of treated spontaneous bleeds within the emicizumab dosing schedule demonstrated no relationship with number of days from the last dose of emicizumab.

Disclosure of Interest: R. Kruse-Jarres Grant/Research support from: CSL Behring, Pfizer, Genentech, Consultant for: CSL Behring, Grifols, Genentech, NovoNordisk, Shire, B. Trzaskoma Shareholder of: Genentech, Employee of: Genentech, K. Raimundo Shareholder of: Genentech, Employee of: Genentech, E. Tzeng Employee of: Genentech, B. Perez Sanz Shareholder of: Roche, Employee of: Roche, Genentech, R. Ko Shareholder of: Genentech (employee benefit), Employee of: Genentech.

P253 | Challenges in establishing a hemophilia registry- an experience from a developing nation

R. Sudevan[1,*]; N. Sidharthan[2]; M. Raj[3]; A. Sudhakar[4]

[1]Hemato Oncology & Health System Research, Amrita Institute of Medical Sciences, Kochi, Kerala, India; [2]Haemato Oncology, Amrita Institute of Medical Sciences, Kochi, Kerala, India; [3]Pediatrics & Health System Research, Amrita Institute of Medical Sciences, Kochi, Kerala, India; [4]Pediatric Cardiology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

Introduction: Registries are the pivotal documents to quantify the epidemiology and document the health care practices in a given population. Haemophilia is a sparse and less recognized chronic disease in developing nations. In such nations, there exists an inevitable need to develop regional registries to improve patient care. Our state is devoid of haemophilia registry. We are currently in the process of developing a state wide haemophilia registry via patient organizations (POs).

Methods: There exist seven POs in our state. After the institutional ethical approval we contacted the POs. We contacted Six POs over the phone and five POs agreed to cooperate. All were briefed about the relevance of registry and methodology to collect required data. Only three POs responded to the tasks. The soft copy of proforma was mailed to each PO and the filled proforma was sent back to the institution by POs as email. A unique id was assigned to each patient with Haemophilia (PwH). We collected data from 501 patients within a period of two months. The data includes demographic details, diagnostic information, clinical history and treatment details of each participant. The data were analyzed in SPSS version 21. We present continuous variables as mean (SD) and categorical variables as frequency (%).

Results: The mean age of the patients was 23.66(SD ± 11.58) years. Among 492 PwH, 81.8% (n = 410) were of Haemophilia A. In 463 PwH who responded for severity of illness, 74.7% (n = 374) were having severe haemophilia, 12.2% (n = 61) with moderate and 5.6% (n = 28) with mild type. In 258 PwH who responded for presence of inhibitors, 3.6% (n = 18) were inhibitor positive. Data regarding annual bleed rate was provided by only 30 PwH. Among them, 0.8% (n = 4) had 0-3 bleeds, 2% (n = 10) had 4-10 bleeds and 2.8% (n = 14) had 11-20 bleeds per year. The response for type of treatment was also low (n = 266). PwH under ODT were 86.8% (n = 231) v/s PT 1.5% (n = 4). We didn't receive any conclusive data to report the annual use of CFCs.

Discussion/Conclusion: We were able to collect considerable data as an initial step forward to developing a registry in a low resource setting. There were difficulties in convincing the need of registry to POs and also in data collection. Patients were apprehensive to share their medical reports. Awareness regarding the need and usefulness of registries need to reach out to more POs and PwH.

Disclosure of Interest: None declared.

P254 | Mutations potentially associated with severe X-linked abnormalities in hemophilia A carriers with skewed X chromosome inactivation

R. Dardik; T. Livnat; E. Avishai; A. Dvir; N. Kornbrot; S. Lalezari; N. Rosenberg; G. Kenet

National Hemophilia Center, Sheba Medical Center, Ramat Gan, Israel

Introduction: Hemophilia A is an X-linked recessive disease, while females are typically asymptomatic carriers. However, in rare cases, female carriers present with hemophilia A due to skewed X-inactivation of the chromosome carrying normal F8 gene, resulting in exclusive mutant F8 gene expression. Prenatal diagnosis for prevention of hemophilia A in such women is based on exclusion of male fetuses carrying the mutant F8 gene. However, since extreme skewing is frequently associated with mutations in genes involved in severe X-linked abnormalities (e.g. X-linked intellectual disability (XLID)), selecting male fetuses with the X chromosome bearing the normal F8 gene, may be associated with a significant risk of selecting fetuses with severe X-linked abnormalities. The aim of our study was to identify mutations potentially related to X-linked

abnormalities in 2 female hemophilia A patients (obligate carriers, daughters of severe hemophilia A patients) with confirmed skewed X-inactivation (Factor 8~1%) treated and followed up at the Israeli National Hemophilia Center.

Methods: Patients' DNA was analyzed by whole exome sequencing (WES), followed by comprehensive bioinformatics analysis and direct sequencing.

Results: Patient 1: In addition to being a carrier of her paternal F8 mutation, the patient was found to be a carrier of a frameshift mutation in the PGK1 gene encoding for phosphoglycerate kinase (PGK), inherited from her mother, who also demonstrated skewed X-inactivation of the chromosome bearing the mutant PGK1 gene. PGK deficiency is an X-linked disorder commonly associated with mental retardation. Patient 2: In addition to being a carrier of her paternal F8 gene mutation, the patient was found to be a carrier of a nonsense mutation in the NKAP gene encoding for the transcriptional regulator NFKB Activating Protein, inherited from her mother, who also demonstrated skewed X-inactivation of the chromosome bearing the mutant NKAP gene. NKAP is absolutely required for hematopoietic stem cell maintenance and survival, and NKAP deficiency was reported to be lethal in mice.

Discussion/Conclusion: Hemophilia carriers with skewed X-inactivation should be analyzed for mutations associated with severe X-linked abnormalities on their inactivated X chromosome prior to being offered prenatal diagnosis and/or PGD based on exclusion of their mutant F8 gene.

Disclosure of Interest: None declared.

P255 | Results from a phase 3, randomized, multicenter study of rurioctocog alfa pegol PK-guided prophylaxis targeting 2 FVIII trough levels in patients with severe hemophilia A (propel study)

R. Klamroth[1,*]; J. Windyga[2]; V. Radulescu[3]; P. Collins[4]; O. Stasyshyn[5]; H. M. Ibrahim[6]; W. Engl[7]; S. Tangada[8]; W. Savage[8]; B. Ewenstein[8]

[1]*Department for Internal Medicine, Vascular Medicine and Haemostaseology, Vivantes Klinikum Friedrichshain, Berlin, Germany;* [2]*Department of Hemostasis Disorders and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland;* [3]*Hemophilia Treatment Center, University of Kentucky, Lexington, KY, USA;* [4]*School of Medicine, Cardiff University, Cardiff, UK;* [5]*Academy of Medical Sciences of Ukraine, Lviv, Ukraine;* [6]*Pediatric Department, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia;* [7]*Shire, Vienna, Austria;* [8]*Shire, Lexington, MA, USA*

Introduction: Prophylaxis with extended half-life recombinant FVIII rurioctocog alfa pegol (SHP660, BAX 855, ADYNOVI™; Baxalta [part of Shire, Lexington, MA]) targeting FVIII trough levels ≥1% is effective and well-tolerated in people with severe hemophilia A (Konkle et al. Blood 2015). As patients may benefit from higher trough levels, this study (NCT02585960) evaluated the safety and efficacy of SHP660 in PK-guided prophylaxis targeting 2 different FVIII trough levels in previously treated patients.

Methods: Eligible patients had FVIII activity <1%, annualized bleed rate (ABR) ≥2, and transitioned from a previous SHP660 study or were 12–65 years old with ≥150 exposure days to plasma-derived or recombinant FVIII. After initial PK assessments, patients were randomized to 12 months of PK-guided prophylaxis targeting FVIII trough levels of 1–3% (LOW) or 8–12% (HIGH) (1st 6 months: dose adjustment period). Primary outcome was the % of patients with total ABR = 0 (all bleeds) during the 2nd 6-month study period. Secondary outcomes included total ABR, spontaneous ABR and joint ABR (AJBR) (all bleeds), and adverse events (AEs).

Results: Overall, 115 male patients (57 LOW, 58 HIGH) received ≥1 SHP660 dose. Median (range) age was 28 (12–61) years; 106 patients (56 LOW, 50 HIGH) completed the study. During the 2nd 6 months, total ABR = 0 was achieved by 22/57 (39%) LOW, 38/58 (66%; $P = 0.075$) HIGH, spontaneous ABR = 0 by 35/57 (61%) and 49/58 (84%; $P = 0.141$), respectively, and AJBR = 0 by 39/57 (68%) and 52/58 (90%; $P = 0.179$). Mean (SD), median (IQR) total ABRs for the 2nd 6-month period: 3.6 (7.3), 2.0 (4.0) LOW; 1.6 (3.3), 0 (2.0) HIGH. Overall AEs and SAEs occurred in 63% and 9% of patients; 1 HIGH patient (0.9%) had an SAE considered related to SHP660: a transient 0.6 BU inhibitor without evidence of anti-FVIII binding that resolved by study end.

Discussion/Conclusion: SHP660 prophylaxis targeting 8–12% vs 1–3% trough levels was associated with trends for lower total ABR and a higher proportion of total ABR = 0, with similar results for spontaneous ABR and AJBR. AE profiles were comparable and consistent with previous SHP660 trials. There is potential for improved outcomes with higher trough levels and a need for further treatment personalization. Ongoing analyses will characterize the relationships between activity, FVIII levels and bleeding events.

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P256 | Abstract withdrawn

[Correction added on 31 January 2019, after print publication: Abstract P256 has been withdrawn and its authors are omitted from the author index.]

P257 | An introduction to CVESS: The cost of von Willebrand disease in Europe- a socioeconomic study

R. Willock[1,*]; M. Laffan[2]; J. Goudemand[3]; A. Tiede[4]; N. Skouw-Rasmussen[5]; N. Giraud[6]; R. Peake[7]; J. de Meris[8]; L. Caroll[9]; A. Finnegan[10]

[1]HCD Economics, Daresbury, UK; [2]Imperial College London, London, UK; [3]CHRU de Lille - Centre de Biologie Pathologie Génétique, Lille, France; [4]Medizinische Hochschule Hannover, Hannover, Germany; [5]European Haemophilia Consortium, Brussels, Belgium; [6]Association Française des Hémophiles, Paris, France; [7]Birmingham and Solihull Mental Health NHS Foundation Trust, Birmingham, UK; [8]Nederlandse Vereniging van Hemofilie-Patiënten, Nijkerk, Netherlands; [9]The Haemophilia Society, London; [10]University of Chester, Chester, UK

Introduction: Von Willebrand disease (VWD) is the most common inherited bleeding disorder however, there is little data regarding HRQoL, despite evidence that certain phenotypes have a HRQoL akin to severe haemophilia. In addition, there is little evidence regarding direct, indirect and societal costs across Europe.

The University of Chester (UoC) is undertaking a prevalence-based burden of illness study across Europe (France, Germany, Italy, Spain and the United Kingdom) to understand the socioeconomic burden of VWD in both adult and paediatric patients as well as their carers'.

Methods: The primary objective is to explore the impact of VWD on HRQoL and the secondary is to quantify existing VWD-related costs from a societal perspective.

The study population includes adult and paediatric patients with a known diagnosis and classification of VWD and 917 patients have been enrolled into the study thus far (70:30 adult: paediatric split).

This study follows a retrospective, cross-sectional methodology that recruits a sample of hematologists (surveyed between September and November 2018) and provides demographic and clinical information, including 12-month ambulatory and secondary care via an online questionnaire (eCRF). Each patient or carer will be invited to complete a corresponding Patient and Public and Involvement & Engagement (PPIE) questionnaire including quality of life, disability and work-related activity. Direct non-medical and indirect costs are also collected.

The study is overseen by an Expert Review Group (ERG) which includes medical experts and patient representatives. The study is governed and approved by the UoC Research Ethics Committee.

Results: This study will report on validated HRQoL measures to offer general insight into the patient and caregiver experience of VWD. This study will also enable the generation of a granular database comprehensively detailing the wide variety of costs that accompany living with VWD. Direct medical and non-medical resource costs will be collated at country level whilst indirect costs will be valued with the Human Capital approach.

Discussion/Conclusion: The CVESS study aims to add to the evidence base regarding the socioeconomic burden in VWD and this study is the largest of its kind. The study brings value to a wide range of stakeholders including academics, patients, payers and industry. Findings will be available in peer-reviewed journals by Q2 2019.

Disclosure of Interest: None declared.

P258 | Effect of fascial therapy in patients with hemophilia and ankle arthropathy: A randomized clinical trial

E. Donoso-Úbeda[1]; J. Meroño-Gallut[2]; J. A. López-Pina[3]; R. Cuesta-Barriuso[4,5,6,*]; on behalf of Group of Research and Physiotherapy in hemophilia-InHeFis

[1]*Physiotherapy, Optimus Osteopathy and Physiotherapy Clinic;* [2]*Physiotherapy, Physiotherapy service, Tu Bienestar 360°;* [3]*Department of Basic Phycology and Methodology, University of Murcia, Murcia;* [4]*Department of Physiotherapy, European University of Madrid;* [5]*Research, Real Fundación Victoria Eugenia;* [6]*Physiotherapy, Fishemo-Spanish Federation of Hemophilia, Madrid, Spain*

Introduction: Chronic pain and functional deficit are two of the main clinical manifestations of hemophilic arthropathy. Fascial therapy aims to eliminate joint restrictions, improving movement between joint structures and relieving joint pain.

Methods: Randomized, controlled trial, multicentric and intention-to-treat analysis. Sixty-five patients with hemophilic ankle arthropathy from five regions of Spain. The experimental group (n = 33) received one fascial therapy session per week for 3 weeks. The control group (n = 32) received no treatment. The primary outcome was frequency of joint and muscle bleeding measured using self-registration. Secondary outcomes were: joint pain (under load-bearing and non-load-bearing conditions) measured using *Visual Analogical Score*; joint status measured by *Hemophilia Joint Health Score* scoring from 0 to 20 points per joint. Outcomes were measured at baseline, posttreatment and after 5 months' follow-up.

Results: No joint or muscle bleeding occurred during or after intervention. The treatment through fascial therapy significantly improved ankle joint pain and joint status. Significant differences were found in the factor of repeated measures in the dependent variables. In the interaction with the experimental group, significant differences were found in the pain under load-bearing conditions and the joint state of both ankles and in the pain under non-load-bearing conditions of the left ankle.

Discussion/Conclusion: Fascial therapy does not appear to produce muscle or joint bleeding in patients with hemophilic ankle arthropathy. This physiotherapy technique improves joint pain and joint status in patients with hemophilic ankle arthropathy, maintaining improvements after a follow-up period of five months.

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P259 | Safety and effectiveness of fascial therapy in adult patients with hemophilic elbow arthropathy. A cohort study

R. Pérez-Llanes[1]; R. Cuesta-Barriuso[2,3,4,*]; E. Donoso-Úbeda[5]; J. A. López-Pina[6]; J. Meroño-Gallut[7]; on behalf of Group of Research and Physiotherapy in hemophilia-InHeFis

[1]*Department of Physiotherapy, Catholic University San Antonio-UCAM, Murcia;* [2]*Department of Physiotherapy, School of Biomedical and Health Sciences, European University of Madrid;* [3]*Real Fundación Victoria Eugenia;* [4]*Fishemo CEE, Spanish Federation oh Hemophilia, Madrid;* [5]*Department of Physiotherapy, Optimus Osteopathy and Physiotherapy Clinic;* [6]*Department of Basic Phycology and Methodology, University of Murcia, Murcia, Spain;* [7]*Physiotherapy service, Tu Bienestar 360°, San Javier, Murcia, Spain*

Introduction: Hemophilic arthropathy is characterized by loss of function and chronic pain. Fascial therapy mobilizes the connective tissue, intervening in the state of the injured fascial complex and the surrounding tissues.

Methods: Prospective and longitudinal cohort study. Twenty-eight adult patients with hemophilia from 21 to 63 years of age were recruited in four cities in Spain. The intervention consisted of three sessions of 45-minute fascial therapy for three consecutive weeks. Outcomes were measured at baseline, posttreatment and after three months' follow-up. The study variables were: joint status (assessed with *Hemophilia Joint Health Score*), joint pain (using Visual Analogue Scale) and bleeding frequency (administering self-registration of bleeding). The mean difference was calculated using the t-student test and using the Cohen formula we calculated the effect size of the dependent variables. An intention-to-treat analysis was used to analyze the results.

Results: None of the patients developed muscular or joint bleeding during the treatment and follow up period. After treatment, significant improvements in joint pain and joint condition ($P < 0.01$) were observed in both elbows. Similarly, the improvement in all variables was maintained after follow-up period ($P > 0.05$). The size effect in both elbow pain was moderate and high ($d = -0.65$ and $d = -0.85$, in right and left elbow respectively).

Discussion/Conclusion: The application of physiotherapy through fascial therapy does not produce muscle or joint hemorrhages. A treatment through three sessions of fascial therapy can improve joint pain and joint elbow condition in adult patients with hemophilic arthropathy.

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P260 | Pronounced and persistent hepatotropism with high tolerability of an AAV-FVIII gene therapy vector (BAY 2599023) for treatment of haemophilia A: A nonclinical safety and biodistribution study in mice

F. Reetz[1,*]; K. Flagella[2]; I. A. Ivens[3]; L. Stoica[4]; S. Wadsworth[5]

[1]Bayer, Berlin, Germany; [2]Ultragenyx Pharmaceutical Inc, Novato; [3]Bayer, San Francisco; [4]Ultragenyx Gene Therapy, Cambridge; [5]Ultragenyx Gene Therapy, Shrewsbury, USA

Introduction: BAY 2599023 (AAVhu37FVIII) is a non-replicating recombinant adeno associated virus (AAV)-based vector consisting of the hu37 serotype capsid and a single-stranded genome containing a B domain deleted (BBD)-FVIII expression construct under control of a liver-specific promoter/enhancer combination. This study in wild-type C57BL/6N mice with intact coagulation systems was conducted to characterize the toxicological and biodistribution profile of BAY 2599023 after a single intravenous (iv) administration.

Methods: A total of 292 mice received a single iv dose of $1x10^{13}$, $3x10^{13}$ or $10x10^{13}$ genome copies (GC)/kg or vehicle with analyses on day 4, 29 or 92. Analyses included cytokine levels, splenic T-cell response, anti-AAV capsid Abs, histopathological evaluation, FVIII protein serum levels and FVIII DNA/RNA sequence biodistribution.

Results: BAY 2599023 was well tolerated with no effects on body weight, food consumption, haematology, clinical chemistry, coagulation and histopathology, other than a minimal, transient leukopenia observed at 10×10^{13} GC/kg on day 4. hFVIII levels increased after day 4 in all dose groups. IL-1β, IL-10, and IL-12p70 were detected in 2/5 animals at 10.0×10^{13} GC/kg four hours post dose with positive IFN-g splenic T cell response at Day 29 in the IFN-γ ELISpot assay and in a further 1/5 animals at 10×10^{13} GC/kg on day 92. BAY 2599023 vector genome DNA was widely distributed at low levels in organs and tissues at all time points, with highest levels in liver. hFVIII mRNA expression was apparent in all tissues and increased from day 4 to 29 with a slight decrease by day 92. Liver showed >100-fold higher hFVIII mRNA expression compared to other tissues at day 92. The No Observed Adverse Effect Level (NOAEL) was considered to be $>10.0 \times 10^{13}$ GC/kg.

Discussion/Conclusion: BAY 2599023 was well tolerated with mild activation of the innate and acquired immune system in some mice. Vector distribution and hFVIII transgene expression analysis revealed a pronounced and persistent hepatotropism. Based on the efficacious doses of BAY 2599023 to mediate sustained hFVIII activity at therapeutic levels in preclinical models, the established NOAEL of $10x10^{13}$ GC/kg supports a clinical starting dose $5x10^{12}$ GC/kg with 20-fold safety margin. Recruitment for this Phase 1/2 study is ongoing.

Disclosure of Interest: R. Zierz Employee of: Bayer, K. Flagella Shareholder of: Ultragenyx Pharmaceutical Inc, Employee of: Ultragenyx Pharmaceutical Inc, I. Ivens Shareholder of: Bayer, Employee of: Bayer, L. Stoica Employee of: Ultragenyx Gene Therapy, S. Wadsworth Shareholder of: Ultragenyx Pharmaceutical Inc, Employee of: Ultragenyx Gene Therapy.

P261 | Genetic analysis of 9 Tunisian families with constitutional clotting factor XI deficiency

S. Kacem[1,*]; F. Megdiche[1]; S. Maalej[1]; R. Frikha[2]; M. Ghorbel[3]; O. Kassar[3]; L. Mbarek[1]; M. Elloumi[3]; H. Kamoun[2]; C. Kallel[1]

[1]Laboratory of Hematology, Hospital University Habib Bourguiba, Sfax-Tunisia, Hospital University Habib Bourguiba, Sfax, Tunisia; [2]Medical Genetics Department, Hospital University Hedi Chaker, Sfax, Tunisia; [3]Clinical Hematology Department, Hospital University Hedi Chaker, Sfax, Tunisia

Introduction: Inherited Factor XI (FXI) deficiency; the Rosenthal's disease; is a rare autosomal recessive coagulopathy characterized by a bleeding tendency. A wide heterogeneity of causative mutations has been previously reported in several countries. Currently, there is no available data about the spectrum of the factor XI gene (*F11*) mutations in Tunisia. The objective of this study was to assess the c.403G>T (E117X) type II Jewish mutation in Tunisian Rosenthal's disease in order to establish the correlation between phenotype and genotype.

Methods: Among 70 FXI-deficient patients from the South of Tunisia, 31 patients with various bleeding manifestations belonging to nine unrelated families were enrolled in this study. Biological diagnosis was based on the FXI activity assay (FXI: Act) and genotyping was carried out using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: 70 patients were evaluated: 40 women and 29 men aged between 1 and 74 years old. Consanguinity was about 65.2%. Among 20 bleeders, patients had 15 severe FXI deficiency (FXI: Act <20%) and 5 had moderate FXI deficiency (FXI: Act between 20 and 59). Among 50 non-bleeders, 30 patients had severe FXI deficiency and 20 had moderate FXI deficiency. With reference to the molecular study, the *F11* G403T mutation's prevalence was, respectively, for TT, GT and GG genotypes: 13% (4/31), 16% (5/31) and 71% (22/31). Homozygosity for the type II mutation was associated with severe FXI deficiency, whilst heterozygosity was associated with partial deficiency. However, bleeding manifestations were only found in 33% (3/9) of the mutated alleles (2 TT genotype and 1 GT genotype).

Discussion/Conclusion: Our results highlight the higher frequencies of the type II mutation (E117X) in Tunisian Rosenthal's disease and suggest a significant risk of inhibitors' development specially related to homozygosis. The bleeding tendency in patients is not clearly explained but might be related to the presence of various other mutations that can be involved in the FXI deficiency.

A whole genome sequencing (WGS) is mandatory to clarify the spectrum of *F11* mutations and the associated phenotypes.

Disclosure of Interest: None declared.

P262 | Missense variations affecting residue 413 of FVII: What is the clinical impact?

Y. Jourdy[1]; M. Daniel[1]; M. Fretigny[1]; N. Enjolras[2]; C. Vinciguerra[1]; M. Gianzily-Blaizot[3]; S. Le Quellec[1,2,4,*]

[1]*Laboratoire d'hématologie, Hospices Civils de Lyon;* [2]*EA 4609 - Hémostase et Cancer, Université Claude Bernard Lyon I, Lyon;* [3]*Département d'hématologie biologique, CHU de Montpellier, Montpellier;* [4]*Unité d'hémostase clinique, Hospices Civils de Lyon, Lyon, France*

Introduction: Congenital factor VII (FVII) deficiency is a rare autosomal recessive bleeding disorder with a prevalence of 1/500 000 individuals. More than 250 genetic variations of the *F7* gene have been recorded in disease-specific databases, and novel "unclassified variants" (UV), are regularly found. However, in the absence of direct experimental evidence, the clinical outcome of such UV is difficult to predict. The aim of this study was to characterize a novel FVII UV (p.Arg413Trp), which was found in homozygous state in a woman with low level of FVII activity level (FVII:C = 21%) in comparison to 3 previously described FVII variants affecting the same position 413 (p.Arg413Gln, p.Arg413Gly and p.Arg413Pro), and to wild-type FVII (FVII-WT).

Methods: The pathogenicity of these FVII UVs was studied using two methods: 1) the predictive *in silico* tools (Alamut 2.6.0, Interactive Biosoftware), and 2) the *in vitro* FVII UVs expression in COS-1 cells. FVII activity and antigen levels were measured in cell culture medium of transiently transfected COS-1 cells in comparison to FVII-WT expression.

Results: *In silico* analyses confirmed that p.Arg413Gln was a polymorphism with no deleterious impact and considered the 3 other FVII variants as deleterious. *In vitro*, p.Arg413Gly showed normal expression compared to FVII-WT whereas the expression of p.Arg413Gln, p.Arg413Trp, and p.Arg413Pro were significantly decreased compared to FVII-WT, with mean ± SD FVII:C levels at 77 ± 10% of FVII-WT ($P = 0.02$), 24 ± 10% of FVII-WT ($P = 0.001$), and <1% of FVII-WT ($P < 0.0001$), respectively.

Discussion/Conclusion: The combination of *in silico* analyses and *in vitro* functional study is a useful tool for the prediction of clinical outcome of FVII UV, and confirmed that the novel FVII UV p.Arg413Trp is responsible for low FVII:C level in our patient. Such investigation represents an interesting approach for the evaluation of the various clinical impact induced by the mutated residue type at a same residue position of FVII.

Disclosure of Interest: None declared.

P263 | Coagulation and platelet functions in noonan syndrome

M. Daniel[1]; J.-C. Bordet[2]; S. Girard[1]; S. Meunier[3]; S. Le Quellec[1,2,3,*]

[1]*Laboratoire d'hématologie Grand Est, Hospices Civils de Lyon, Lyon, France;* [2]*EA 4609 - Hémostase et Cancer, Université Claude Bernard Lyon I, Lyon, France;* [3]*Unité d'hémostase clinique, Hospices Civils de Lyon, Lyon, France*

Introduction: Noonan syndrome (NS) is usually associated with bleeding diathesis and abnormal bleeding test results. However, recent studies reported that bleeding diathesis was mainly related to platelet function abnormalities. The aim was to evaluate coagulation factor activity levels and platelet functions in patients with NS using various methods.

Methods: The bleeding diathesis of patients with NS was evaluated by a bleeding score, coagulation tests, and various platelet analyses including platelet morphology, light-transmission platelet aggregation, glycoprotein and platelet activation flow cytometry, and electronic microscopy. The gene mutation responsible for the NS was also investigated.

Results: A total of 10 patients were screened. Six out of 10 (60%) patients showed mild to moderate bleeding diathesis (3 with spontaneous bleedings, 3 with provoked bleedings). Platelet count was normal in 9/10 (90%) patients with NS and all of them had normal platelet morphology which suggested that patients with NS produce sufficient and normal-sized platelets. Different clotting factor deficiencies were observed for 3/10 (30%) patients. In 8/10 (80%) individuals, platelet aggregation tests showed moderate abnormalities in response to various agonists, with variations from one patient to another. Dense bodies defect was found in 4/10 (40%) patients. Flow cytometry showed abnormal PAC1 expression in response to various agonists in 4/10 (40%), which corresponded to patients having a mutation in the *SOS1* gene that translated to p.Ser548Arg missense mutation.

Discussion/Conclusion: We observed that platelet function disorders are the main expression of bleeding diathesis in patients with NS. As standard bleeding tests do not allow for sufficient screening, additional evaluation of platelet functions using of platelet function assays, electronic microscopy analysis and flow cytometry may be useful to better estimate bleeding risk in patients with NS, especially before surgery.

Disclosure of Interest: None declared.

P264 | Adherence to prophylaxis in adult patients with severe haemophilia A

S. Bonanad[1,*]; M. García-Dasí[2]; J. A. Aznar[1]; E. Mingot Castellano[3]; V. Jiménez Yuste[4]; M. Calle[5]; A. Palma[6]; M. Fernández López[7]; P. Marco[8]; M. Paloma[9]; R. Pérez Garrido[10]; N. Fernández Mosteirin[11]; B. Galmes[12]; M. Sanabria[13]; M. Álvarez[13]

[1]*Unidad de Hemostasia y Trombosis. Servicio de Hematología. Hospital Universitario y Politécnico La Fe, Valencia, Spain;* [2]*Unidad de Hemostasia y Trombosis. Servicio de Hematología. Instituto de Investigaciones Sanitarias La Fe. Hospital Universitario y Politécnico La Fe, Valencia, Spain;* [3]*Hospital Regional Universitario de Málaga, Málaga, Spain;* [4]*Servicio de Hematología., Hospital Universitario La Paz, Madrid, Spain;* [5]*Hospital de Torrecárdenas, Almería, Spain;* [6]*Hospital Juan Ramón Jiménez, Huelva, Spain;* [7]*Hospital Juan Canalejo, A Coruña, Spain;* [8]*Hospital General de Alicante, Alicante, Spain;* [9]*Hospital Virgen del Camino, Pamplona, Spain;* [10]*Hospital Virgen del Rocío, Sevilla, Spain;* [11]*Hospital Universitario Miguel Servet, Zaragoza, Spain;* [12]*Hospital Son Espasses, Mallorca, Spain;* [13]*Medical Department Hematology, Bayer Hispania S.L., Barcelona, Spain*

Introduction: Adherence in chronic diseases is around 50%, and is essential to prevent arthropathy in haemophilia. Information regarding

the factors with influence on adherence is limited in adults. *Aim:* To assess adherence in adult patients with severe hemophilia A receiving prophylaxis and investigate the factors influencing it. Given that during the development of this study no Spanish tools were available to measure adherence in haemophilia, the psychometric properties of the Spanish version of the VERITAS-Pro questionnaire to measure adherence were also assessed.

Methods: 12 month observational, prospective study including adult patients receiving factor VIII in 15 Spanish centers. Patients recorded infusion doses on a logbook. Adherence rate was the percentage of infused doses over the prescribed ones. To investigate the cognitive factors (beliefs about health) related with adherence behavior, patients responded Multidimensional Health Locus of Control Scale (MHLCS), Perceived Self-Efficacy Scale (PSE), Health Belief Questionnaire (HBQ) adapted ad hoc and Health Value Scale (HVS). The relationship between adherence and clinical status and beliefs was investigated. To assess the psychometric properties, patients responded VERITAS-Pro at baseline, month 6 and 12. Feasibility, Test-retest reliability, Construct, Convergent and Criterion Validity were evaluated.

Results: 66 patients were followed-up for 12 months. Mean adherence rate was 82.5. A total of 53 patients (80.3%) showed a moderate-to-high adherence rate (>70). Knee as target joint (-20.3; $P = 0.034$) and treatment duration (-0.7; $P = 0.027$) showed significant influence on adherence. Adherence rate was not influenced by the patient's health beliefs (MHLCS: $P = 0.369$; PSE: $P = 0.79$; HBQ: $P = 0.886$-$P = 0.169$). To assess the psychometric properties of the VERITAS-Pro, were included 83 patients. Total score was 41.8 (high adherence) (24-70). Test-retest reliability showed a high correlation (0.79-0.97). Internal consistency was good ($\alpha \geq 0.7$). Construct validity was shown by factorial analysis (6 factors), explaining 66.4% of variance. There was no clear relationship with the other 4 health scales (Convergent Validity).

Discussion/Conclusion: Adult patients in Spain have moderate-to-high adherence. Treatment duration and the knee as a target joint are factors with negative influence on adherence. Spanish version of VERITAS-Pro has been demonstrated to be reliable and valid to evaluate adherence in haemophilia.

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P265 | New subcutaneous therapies and clinical trials: A survey on patient's perspectives

S. García-Barcenilla; P. Acuña-Butta; T. Cebanu; R. Justo-Sanz; E. Monzon-Manzano; I. Fernández-Bello; N. Butta-Coll; I. Rivas-Pollmar; M. Martín-Salces; M. T. Alvarez-Román; V. Jiménez-Yuste

Hospital Universitario La Paz -IdiPAZ, Madrid, Spain

Introduction: Clinical trials (CTs) provide the basis of developing new drugs, biological products, and medical devices. However, the recruitment of patients in CT is not easy. The perspective of patients and the barriers perceived about participating in a CT might be useful for the clinical research team (CRT) to guide the clinical approach correctly. *Aims:* to assess the level of satisfaction and the perception of patients about the participation in CT with new subcutaneous molecules

Methods: Transversal descriptive study carried out in October. A total of 33 in a CT of subcutaneous administration therapy (ST) (emicizumab or concizumab molecules) were included. A survey that collected information about how they decided to participate in a CT, fears and doubts, communication of adverse events, the benefit of participating in a CT and the perception they had prior enrollment.

Results: 25 patients completed the questionnaire. Most of them (72.0%) reported that the main reason for participating in the CT was the benefits obtained from ST. Regarding fears and doubts when participating in a CT, 72.0% related potential side effects of ST. After the communication of several adverse events in CT, they found confidence continuing in CT when their physician called them and they knew first-hand the information in 40.0% of cases, a 32.0% when talked with nurses or members of CRT, 28.0% when they discussed with their physician at clinic visit. About the greater benefit of participating in the CT most of them reported an improvement of quality of life in a 76.0% of cases, in 48.0% reduction of bleeds, 40.0% improvements in administration route, 24.0% a reduction of infusion frequency and one answer to live without fears. Finally, asking about prior point of view of participating in a CT, an 84.0% reported a positive point of view.

Discussion/Conclusion: Decision of participating in a CT are most based on the benefits obtained of ST molecules and recommendations or trust in CRT. Since the more frequent fear are potential side effects, maintain patient's confidence is mandatory, as show the high percentage of patients that reported they found confidence continuing in CT when information is transmitted first-hand from physician. Patients desire an improvement in quality of life, bleeding reduction, as well improvement in the administration route.

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P266 | Pain management during intravenous treatment administration in people with hemophilia

S. García-Barcenilla[1,*]; C. Benedicto-Moreno[2]; N. Caballero-Mencía[2]; M. C. García-Martínez[3]; R. Berrueco-Moreno[2]; M. Álvarez-Román[1]

[1]Hospital Universitario La Paz -IdiPAZ, Madrid, Spain; [2]Hospital Sant Joan de Deu, Barcelona, Spain; [3]Hospital Universitario La Paz, Madrid, Spain

Introduction: Nowadays, administration and plasma activity levels after treatment with concentrates of people with hemophilia (PWH), are done by intravenous route, with the pain and discomfort that it entails, mostly in children.

Objectives: Analyse the techniques used by nurses to reduce pain and anxiety of patients caused by intravenous processes in hospital settings, and how nurses manage patient's pain in daily routine. *As secondary objectives*: obtain information about actions taken in different centers and evaluate nurses' level of perception of the importance of pain assessment.

Methods: anonymous survey of 14 questions with one-choice Likert-type answer was distributed electronically to nurses dedicated to the care of PWH in Spain.

Results: 24 answered surveys were obtained, from different Spanish centers.

95.8% thought that is important to evaluate the pain, but 37.5% considered they don't have enough time to evaluate and record it daily. About the relationship between reduction of pain referred by patient at infusion time and patient's adherence, 83.3% confirmed a direct relationship. A total of 91.7% related that applying relaxing/distraction techniques facilitates process of pain dealing during venipuncture. The experience of using vibrators or virtual reality (VR) glasses has been positive (41.7%), not available for all nurses (only for 62.5%), and with nitrous oxide was positive in 45.9% of cases but 45.8% claim to have no experience. Regarding topical anaesthetics, 70.5% consider that they reduce pain and anxiety of patient during venipuncture. A high percentage of nurses use more non-pharmacological than pharmacological procedures to reduce pain (83.3%) in daily routine, also 83% tries to use first use non-pharmacological tools, and then discuss with physician in case of patients with fear or anxiety related to venipuncture. A 66.6% reports that patients whom at pediatric age suffered fear and/or anxiety associate with venipuncture, have been able to overcome it in adulthood using distraction techniques or with pharmacological approaches.

Discussion/Conclusion: Some approaches were reported as positive but were not available in all centers (79.2% think more resources to manage pain are needed). A high percentage agree about the relevance of monitoring pain, and that has an impact on patient's adherence. Improvement of measures and protocols are needed to manage pain and anxiety during intravenous procedures in PWH.

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P267 | Going digital with clinical treatment plans

S. Mangles*; M. H. Cordial; L. Oyesiku

Haemophilia and Thrombosis Centre, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK

Introduction: New approaches to service delivery through the introduction of technology, as part of the NHS challenge to go paperless, are well underway. As technological advances in healthcare gather pace, and as hospitals develop electronic patient records (EPR), information required to ensure the appropriate treatment of patients with bleeding disorders should be readily available to all clinicians.

Prompt assessment and treatment of bleeding problems is associated with a better outcome. Delays in treatment may lead to hospital admissions, the need for prolonged therapy and long term sequelae. In the UK, patients are issued with bleeding disorder information cards to show when they present to a hospital in an emergency, which includes their diagnosis and treatment. However, we know that many patients may not carry them, or may lose them. We therefore wanted to create a way that all patients registered with our centre could have a treatment plan accessible on the EPR.

Methods: At our centre, the development of an in-house EPR by the hospital allowed us to work with the developers to create a critical treatment plan (CTP) template. This included diagnosis, baseline levels, usual treatment as well as contact numbers for the team in and out of hours and some general advice. The plan "flashes" so that it is very visible on the EPR.

Results: All patients with bleeding disorders were first tagged, using a red stick person symbol, then a CTP was created. In the first

12 months since this was developed 587 people have been tagged. Treatment plans have been written for 452 people. An audit of 88 patients attending clinic over a 3 month period showed 74 /88 (84%) had a CTP. 100% of the treatment plans were up to date and reflected current treatment.

Discussion/Conclusion: The introduction of the CTP has been a success. It has allowed on-call physicians to have quick access to the correct treatment plan. An additional benefit of the red stick person/ CTP has involved other hospital teams, e.g. radiology and general surgery contacting the haemophilia team to say a patient has been admitted or is booked for a procedure. A process is now in place to review all CTPs when a patient attends clinic, to create new plans for new patients and to review patient tags and CTPs on a bi-annual basis.

Disclosure of Interest: None declared.

P268 | The cares study focus groups-haemophilia carriers' experience study: Life choices, psychosocial needs and parenting

H. Aiston; F. Laver; W. T. Hung; R. Pink; S. Mangles*

Haemophilia and Thrombosis Centre, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK

Introduction: There is very little research looking at the experiences and psychosocial needs of haemophilia carriers. Previous research considered the needs of carriers only as they relate to parenting a child with haemophilia. Few previous studies have looked into carriers' experiences of being a patient themselves, their familial experiences of haemophilia, their decision-making around having a family and the impact of this decision on their family life, wellbeing and future.

The CARES study aims to explore the experience of being a carrier of haemophilia, in terms of mood, self-perception, relationships and general wellbeing, as well as the decision-making process that carriers face when deciding whether to have a family, or further children after a child with haemophilia.

Methods: Focus groups were set up and qualitative methods used to undertake an in-depth exploration of carriers' experiences and establish relevant themes. Carriers were invited to a semi-structured focus group or interview; their responses were recorded and transcribed. Transcripts were analysed using thematic analysis, which describes themes in the data and constructs patterns of meaning across the transcripts.

Results: 16 participants, from the UK, were consented and recruited; 11 carriers of severe haemophilia, 2 moderate haemophilia and 3 mild haemophilia. 15 had children, 10 had boys with haemophilia and 1 had a girl with low levels. 8 did not know the status of their child(ren) and 5 had children unaffected by haemophilia. Mean age 41 (range 26-62). 8 knew they were registered with a local haemophilia centre. 13 had family members with haemophilia.

Common themes across the participants included: family planning, guilt and worry, self-perception, own physical health, responses to diagnosis, early experience of haemophilia in the family, effect of having a child with haemophilia gene, family support/coping style, barriers and need for support.

Discussion/Conclusion: These themes will be used to develop a questionnaire for use in a wider group of carriers across the UK. This study is ongoing. Within our own centre the results led to discussion and learning on how we care for haemophilia carriers and the additional support we may need to provide.

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P269 | Resource use and costs of hemophilia A patients in the Netherlands

S. Broos-Bahmany[1]; T. Vo[2,*]; M. Krol[3]; D. Van der Hoeff[3]; B. V. Woerden

[1]*Market Access, Roche, Nederland;* [2]*Medical Department, Roche, Nederland;* [3]*IQVIA, Amsterdam, Netherlands*

Introduction: Hemophilia A (HA) is hallmarked by a bleeding tendency. Severity is linked to the patient's residual Factor VIII (FVIII) activity and presence of FVIII inhibitors. Severe HA patients with or without inhibitors often need medical care. This study investigated the HA related hospital resource use and costs of HA in patients without inhibitors in the Netherlands between 2012-2016.

Methods: A claims database including ~ one-third of the Dutch population was analyzed. Data contained anonymized patient ID, gender, age, diagnosis codes and claimed hospital care reimbursed by the health insurers (e.g. drugs, policlinic visits, admissions and surgery). Patients were defined as non-inhibitor patients when using FVIII-products. Within the non-inhibitor subgroup, based on clinical expert input, treatment was defined as prophylactic if i) using >100 000 international units FVIII AND ii) receiving a minimum of three FVIII prescriptions per year AND iii) having a maximum prescription interval of <100 days. Treatment with FVIII not fulfilling these criteria was defined as on demand treatment. To ease reporting, care was subdivided in 27 care clusters, such as blood/diagnostic tests, care related to bleedings, oral surgery and the use of FVIII or Bypassing Agents (BPA's)).

Results: Within the non-inhibitor group the data included per year on average 281 patients with on demand therapy and 137 patients with prophylactic therapy. Top five care consumption (in terms of number of claims) in the on demand group was: usage of FVIII, blood testing, diagnostic testing, care related to bleedings and the use of antibodies. Top five in the prophylactic patients was: FVIII usage, blood testing, care related to bleedings, diagnostic testing and oral surgery. Average annual cost of care for non-inhibitor patients with on demand therapy in a specific year was €48 118 of which €46 768 related to the costs of FVIII. Average annual costs for non-inhibitor patients with prophylactic therapy were €136 522 of which €133 763 related to the costs of FVIII products.
Discussion/Conclusion: Most HA related hospital care in the Netherlands consisted of FVIII usage, blood/diagnostic testing and care related to bleedings. Around 95% of the costs of HA related care were drug costs.
Disclosure of Interest: S. Broos-Bahmany Employee of: employee of Roche Nederland B.V., T. Vo Employee of: employee of Roche Nederland B.V., M. Krol Consultant for: Roche Nederland B.V. provided funding to IQVIA for data analysis and reporting of results., D. Van der Hoeff Consultant for: Roche Nederland B.V. provided funding to IQVIA for data analysis and reporting of results.

P270 | Difficulty differentiating lupus anticoagulants from inhibitory antibodies to coagulation factors; 2 case presentations

S. Anzej Doma*; M. Fink; I. Preloznik Zupan

hematology, University Medical Centre Ljubljana, Ljubljana, Slovenia

Introduction: Coagulation factor (F) inhibitors may develop in patients with congenital factor deficiencies in response to replacement therapy or as an autoimmune phenomenon in individuals without congenital factor deficiency (most commonly against FVIII). Lupus anticoagulants (LA) are a heterogeneous group of antibodies directed against phospholipid-binding proteins; they may interfere with APTT-based factor activity assays causing one or more spuriously low or undetectable factor activity results.
Methods: Activities of FVIII, FIX, FXI and FXII were determined with one-stage APTT test, while presence of LA was tested with silica clotting time and diluted Russell viper venom time. Both tests for LA were determined with low and high phospholipid concentration (screen and confirm test). The results were given as a ratio between screen and confirm test.
Results:
Case 1: An 81-year old woman was admitted to emergency room for severe anemia; subsequently megaloblastic anemia was diagnosed. She reported no bleeding and no signs of bruising were evident. Her coagulation test were: APTT 118 s, PT 0.81, fibrinogen 3.75 g/L, thrombin time 16.6 s, D-dimer 0.579 mg/L, FVIII 0.27 IE/mL, FIX 0.0 IE/mL, FXI 0.0 IE/mL and FXII 0.04 IE/mL. LA were strongly positive. Lupus anticoagulants' inhibitor effect in factor assays could not be diluted with saline or buffer; resulting in persistently low intrinsic factor activities.
Case 2: A 60-year old female patient was referred to a hematologist before a planned surgery because of a prolonged APTT (147s). Her PT was 0.79, FVIII 0.01 IE/mL, FIX 0.0 IE/mL, FXI 0.0 IE/mL, FXII 0.03 IE/mL. Again, correct FVIII, FIX, FXI and FXII could not be determined due to a high titre of LA. She had no signs nor history of bleeding. She had a high titre of anti-nuclear antibodies (1:640) with no obvious rheumatological disease.
Discussion/Conclusion: Laboratory distinction between LA and specific intrinsic factor inhibitors can be difficult but it si clinically important; patients with LA are potentially at an increased risk for thrombosis, while factor inhibitors generally lead to a bleeding diathesis. Antibodies against other but FVIII are extremely rarely found. In the distinction between true FVIII inhibitors and spurious positive results due to LA, chromogenic FVIII activity and ELISA-based FVIII inhibitor assays are recommended as neither assay demonstrates LA interference.
Disclosure of Interest: None declared.

P271 | Kinesiophobia (fear of movement and reinjury) in a patient with severe hemophilia A

S. Aytac[1,*]; H. Güney Deniz[2]; S. Lobet[3]

[1]*Pediatric Hematology, Hacettepe University, Ankara, Turkey;* [2]*Physiotherapy and Rehabilitation, Hacettepe University Faculty of Health Sciences, Ankara, Turkey;* [3]*Cliniques Universitaires Saint-Luc, Haemostasis and Thrombosis Unit, Brussels, Belgium*

Introduction: Recurrent intraarticular bleeding in patients with hemophilia can be severely debilitating due to joint pain and stiffness with subsequent loss of mobility and function. But in some rare hemophilia cases intraarticular/intramuscle bleeding might not the exact reason for stiffness and immobility.
Methods: An 18 y/o male with severe Hemophilia A who was on prophylaxis was admitted to our clinic with a complaint of stiffness on his both elbows. There was no previous history of inhibitor. His physical exam revealed a pain and stiffness on his both elbows and total range of motion was 35°. Joint Ultrasonography was found to be normal and HJHS Elbow Score for left was 7 and for right was 6 points, the score of functions of the arms in Pediatric Hemophilia Activity List was 6 out of 36 points (higher points defines better functioning). After a month with every other day prophylaxis regimen, no functional improvement were observed and the patient stopped going to school. Moreover, the patient's mother reports that when the patient sleeps, his elbows are extended.
Results: Elbow joint MRI were found to be normal without evidence of hemarthrosis and hematoma. Tampa Scale for Kinesiophobia results was 43 out of 68, represents a high kinesiophobia level. His symptoms resolved with the help of the exercises during the next 2 weeks period after inspiring him with confidence that he was doing well comforting the initial diagnosis of kinesiophobia.

Discussion/Conclusion: Kinesiophobia is the most extreme form of fear of movement, and is defined as an excessive, irrational and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or reinjury. Older age, lower education levels, negative coping styles, greater pain intensity, lower self-efficacy and less social support were some other known determinants of kinesiophobia. Clinicians should be aware of kinesiophobia in hemophilia and consider it in patients with functional limitation but without present evidence of structural joint damage.
Disclosure of Interest: None declared.

P272 | Life threatening recurrent gastrointestinal bleeding in a patient with type III von Willebrand disease: Successful treatment with propranolol

S. Karaman[1,*]; A. Unuvar[1]; D. Tugcu[1]; Z. Onal[2]; F. G. Soysal[3]; S. Ocak[1]; R. Tuna[1]; Z. Karakas[1]

[1]Pediatric Hematology, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey; [2]Pediatric Gastroenterology, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey; [3]Pediatric Surgery, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey

Introduction: Patients with von Willebrand disease (VWD) have an increased frequency of angiodysplasia and vessel abnormalities. Especially in their gastrointestinal tract bleeding caused by angiodysplasia, can be severe, life-threatening. Currently, the lack of optimal treatment is difficulty for physicians. We presented a patient with type 3 vWD with recurrent gastrointestinal bleeding. He was receiving regularly factor concentrate 3 times every week. We successfully treated with betablocker in addition to conventional treatment.
Methods: Case: A 10-year-old male patient was admitted to the hospital with complaints of pallor and fatigue. He was diagnosed with type 3 von Willebrand factor deficiency at the age of 2 years due to recurrent nose bleeding. At the age of 3, total gastrectomy, jejunojejunal anastomosis, esophagojejunostomy were performed despite intensive factor therapy. At that time, he had uncontrolled gastrointestinal bleeding because of the arteriovenous malformation on endoscopy. So, he received prophylactic factor therapy twice a week. Despite regular treatment for the last 2 years it has been recurrent intermittent hematemesis and melena. There was anemia in blood count. Bleeding site was not detected in the repeated endoscopy. Rectosigmoid region had a focus on the old hemorrhage on colonoscopy. During active bleeding periods, factor therapy twice daily and tranexamic acid were applied. Erythrocyte-marked scintigraphy and capsule endoscopy showed activity at the ileum level and was evaluated as a bleeding center. It was thought that the angiodysplasia and vascular anomalies were caused bleeding.
Results: Propranolol therapy has been added to factor therapy. Because of increasing bleeding frequency, factor therapy was increased to 50 U/kg/day for 3 days. The patient is good now and he follows up without bleeding for 12 months
Discussion/Conclusion: Patients with vWD have an increased frequency of vessel abnormalities, telangiectasias and angiodysplasia especially in GI tract. vWF therapy is successful in case with acute management of GI bleeding but giving prophylactic factor therapy is less effective for preventing recurrent GI bleeding. Embolization, surgical resection can be used managed bleeding. But it can be limited in cases with multiple, diffuse lesions. Propranolol may effect by suppression of vascular endothelial growth factor.
Disclosure of Interest: None declared.

P273 | The relationship between "timed-up and go test" and "6-minute walk test" in assessing functional capacity of adult hemophilic individuals

S. Önal Aykar[1,*]; F. Can[2]; S. Aksu[3]; F. Şahin[4]

[1]Faculty of Health Sciences, Physiotherapy And Rehabilitation Department, Adnan Menderes University, Aydın; [2]Faculty of Health Sciences, Physiotherapy and Rehabilitation Department; [3]Department of Internal Diseases, Hematology Subdivision, Hacettepe University, Ankara; [4]Ege Adult Haemophilia and Thrombosis Center, Ege University, İzmir, Turkey

Introduction: Functional capacity is ability to perform activities of daily living that is also used to express an individual's capacity to perform submaximal activities. Physical performance tests like 6-Minute Walk Test (6-MWT) and Timed Up and Go (TUG) Test can also be used for assessing the functional capacity. Hemophilic individuals may have decreased physical capacity resulted from flexion contracture, abnormal gait and impaired balance due to frequent musculoskeletal bleeds. Therefore, functional capacity of hemophilic patients are needed to be evaluated. For this purpose, that would also be useful to investigate whether 6-MWT and TUG test will be related each other for hemophilic individuals. The aim of this study was to investigate the relationship of TUG test with 6-MWT of adult hemophiliacs.
Methods: 19 patients aged between 22-60 years were participated to the study. The TUG test and 6-MWT were used to evaluate the functional capacity. In order to examine the relation between variables; Pearson Correlation Analysis was used.
Results: The mean age of patients was 38.84 ± 11.75 years and the mean body mass index (BMI) was 25.71 ± 3.86 kg/m². The TUG test was strongly correlated with 6-MWT ($P = 0.018/r = -0.537$). In addition, there was a moderate level correlation between BMI and 6-MWT($P = 0.033$ / $r = -0.489$), although there was no correlation between BMI and TUG test ($P = 0.234$ / $r = 0.287$).
Discussion/Conclusion: This study showed that there is a strong correlation between TUG test and 6-MWT in accordance with each other which showed the similar results to evaluate functional capacity. BMI was only related with 6-MWT. Therefore if the individuals with higher BMI may not tolerate 6-MWT, TUG test may be chosen to evaluate functional capacity of hemophilic individuals. TUG test also may be used to collect related data especially in places where it is not possible to perform 6-MWT.

Disclosure of Interest: None declared.

P274 | Does kinesiophobia correlated with quadriceps femoris and hamstring muscle strength in adult hemophilic individuals?

S. Önal Aykar[1,*]; F. Can[2]; S. Aksu[3]; F. Şahin[4]

[1]*Faculty of Health Sciences, Physiotherapy and Rehabilitation Department, Adnan Menderes University, Aydın;* [2]*Faculty of Health Sciences, Physiotherapy and Rehabilitation Department, Hacettepe University, Ankara;* [3]*Faculty of Medicine, Department of Internal Diseases, Hematology Subdivision, Hacettepe University, Ankara;* [4]*Ege Adult Haemophilia and Thrombosis Center, Ege University, İzmir, Turkey*

Introduction: Most of the bleedings of patients with hemophilia occur in the joints, especially in lower limbs, leading to increased susceptibility for further bleeds. As a consequence joint degeneration, articular distortion, muscle weakness can be observed. Kinesiophobia or fear of movement is defined as a fear to move and to make activity since individuals believe it will cause pain or injury. Fear of movement has been investigated in various patient populations and has been associated with increased pain, physical disability and psychological disability. However there is neither a study on hemophilic individuals nor a study which investigated the association of kinesiophobia with muscle strength. Thus, we aimed to investigate whether there is any correlation between kinesiophobia and Quadriceps femoris(QF) and hamstring(H) muscle strength in adult hemophilic individuals.

Methods: Twenty-three patients aged between 20-60 years were enrolled. QF and H muscles' strength were measured with a digital hand held dynamometer. Kinesiophobia was assessed by Tampa Scale of Kinesiophobia (TSK). Higher TSK total score means higher severity of kinesiophobia and total score of 37 is defined a cut-off score as a high degree of kinesiophobia(4-68 points). In order to examine the relation between variables; Pearson correlation analysis was used.

Results: The mean age of patients was 37.73 ± 12.63 years and mean body mass index (BMI) of patients was 25.49 ± 3.71 kg/m². The TSK scores of patients was between 36-51 points and only one of the patients' score was under 37 points. There were no significant correlation between QF muscle strength and TSK(right QF $P = 0.315/r = 0.219$; left QF $P = 0.101/r = 0.350$). The strength of the right H muscle ($P = 0.736/r = 0.074$) and left H muscle ($P = 0.626/r = 0.107$) were not correlated with TSK. However, QF muscles strength were positively correlated with H muscles strength ($P < 0.05$).

Discussion/Conclusion: Strength measurements of QF and H muscles seems important to determine the muscle weakness for the prevention of recurrent bleeds and disability in the hemophiliacs. According to results of this study kinesiophobia has seen to be in a substantial proportion of hemophilia patients but it seems not associated with QF and H muscles' strength. Further research is needed to determine the factors that cause kinesiophobia and to find solutions for eliminating kinesiophobia beliefs in hemophiliacs.

Disclosure of Interest: None declared.

P275 | Congenital factor XIII deficiency: Demographic and clinical description of the french cohort from the FranceCoag network

S. Bouttefroy[1,*]; V. Milien[2]; M. Boucekine[2]; K. Baumstarck[2]; L. Rugeri[1]; H. Chambost[2]; S. Meunier[1]

[1]*Centre Régional de Traitement de l'Hémophilie, Lyon;* [2]*FranceCoag, Marseille, France*

Introduction: Factor XIII (FXIII) deficiency is a rare bleeding disorder responsible for life-threatening haemorrhage, challenging to diagnose because the standard coagulation tests are normal and requiring specific FXIII assays. The aim of this study was to describe the population of patients included in the FranceCoag network for a FXIII congenital deficiency with a FXIII <10% at diagnosis.

Methods: All 33 patients from FranceCoag with a FXIII level <10% at diagnosis were included. This national retrospective cohort study described demographic, clinical characteristics, treatments and different complications that arise in those patients.

Results: Median age for diagnosis was 3.2 months (0.39 – 21.71 months) and 75.8% of patients were diagnosed before 2 years old. The patients with bleeding manifestation were diagnosed earlier than those without clinical bleeding: 3.2 months (0.39 – 21.61 months), versus 21.7 years (12.1 – 31.29 years). This deficiency was revealed in 65% of cases by umbilical bleeding, and in 31% of cases by intracranial haemorrhage. Those bleeding manifestation are life-threatening in 62% cases. Median FXIII level of our patients is 1% (1 – 5.25%). Prophylactic treatment was started directly after diagnosis for only 45.5% of the patients. For others, it was introduced after 3.4 years (1 – 17.4 years) if the patients displayed bleeding manifestations, or after 11 years if not. 67% of our patients had a life-threatening bleeding among whom of them 36% were known to suffer from congenital FXIII deficiency but not received prophylactic treatment. No bleeding episode was noted in patients treated. In the same way, among the 46% of patients who presented intracranial haemorrhage, half of them presented the FXIII deficiency but were untreated. Neurological sequelae were found in 43% cases corresponding to 9% of the entire population. 67% of the women of childbearing age had been pregnant. All of these pregnancies lead to a miscarriage if the women did not receive treatment, as opposed to only 18.8% of the pregnancies if the women were treated ($P < 0.001$).

Discussion/Conclusion: We described here a homogenous cohort of deficiency of FXIII less than 10%. That the deficiency expose to a severe haemorrhage phenotype with 67% of life-threatening bleeding. These results conduct us to recommend prophylaxis treatment as a reference treatment in FXIII deficiency with FXIII <10% at diagnosis.

Disclosure of Interest: None declared.

P276 | The relationship between HLA-DRB1 and factor VIII inhibitor formation in severe hemophilia A patients in Iran

S. Hosseini[1,*]; A. Aghaie[1]; F. Yari[1]; N. Rezaie[1]; S. Moazezi[2]; A. A. Pourfatolah[3]

[1]*Research, High Institute for research and Education in Transfusion Medicine, Tehran, Iran;* [2]*Research, Iranian Comprehensive Hemophilia Care Center, Tehran, Iran, Islamic Republic Of;* [3]*Research, Tarbiat Modares University and managing director of Iranian Blood Transfusion Organization Tehran, Iran*

Introduction: Hemophilia A is a recessive, inherited, X-linked hemorrhagic disease caused by factor VIII deficiency. In a number of hemophiliac patients treated with factor VIII, inhibitor antibodies are formed against factor VIII. Today, inhibitor formation is one of the major problems in hemophilic patients. Inhibitor is influenced by various genetic and environmental and other factors. In some studies, HLA class II has been reported as a predictor of inhibitor formation.

Methods: Fifty severe hemophilic patients with inhibitor referring to the Iranian Comprehensive Hemophilia Care Center (ICHCC) were selected and fifty patients without inhibitor were considered as controls. The Bethesda method was performed to determine the inhibitor. Genomic DNA was extracted by salting out method. Determination of genotype HLA-DRB1 alleles by multiplex PCR-SSP was performed in both groups of patients. A multiple logistic regression model was used for evaluating the odds ratio

Results: In controlling for other alleles HLADRB1* 01: 01 allele was 2.7 times higher in patients without inhibitors than in patients with inhibitors and was statistically significant, [ORadj = 2.7 (CI 95%, 1.08-6.97), (P = 0.034). In controlling for other alleles, HLADRB1*15: 03 allele was 0.94 times in patients without inhibitors than in patients with inhibitors but it was not statistically significant [ORadj = 0.94 (CI 95%, 0.38-2.35), (P = 0.94)] and in controlling for other alleles, HLADRB1*11 was 0.47 times in patients without inhibitors than in patients with inhibitors but it was not statistically significant [ORadj= 0.47(CI 95%, 0.27-1.82), (P = 0.47)].

Discussion/Conclusion: According to this study There was a negative association between HLADRB1*01:01 and factor VIII inhibitor formation. Therefore, this allele in the Iranian population with severe hemophilia can be considered as an allele having a protective effect on inhibitor formation. For further study, this study for acquired hemophilia patients seems necessary.

Keyword: Hemophilia, Inhibitor, HLA-DRB1.

Disclosure of Interest: None declared.

P277 | Intraabdominal Kaposiform Hemangioendothelioma presenting with Kasabach-Merritt Phenomenon in infancy

S. Çinar Özel[1,*]; N. G. Akyel[2]; H. Tıkıroğlu[3]; E. Ceyhun[3]; N. Çomunoğlu[4]; S. Kuruğoğlu[2]; F. Gülşen[2]; T. T. Celkan[1]

[1]*Department of Pediatrics, Division of Pediatric Hematology-Oncology, İstanbul University-Cerrahpaşa Medical Faculty, Istanbul, Turkey;* [2]*Department of Radiology, İstanbul University-Cerrahpaşa Medical Faculty, Istanbul, Turkey;* [3]*Department of Pediatrics, İstanbul University-Cerrahpaşa Medical Faculty, Istanbul, Turkey;* [4]*Department of Pathology, İstanbul University-Cerrahpaşa Medical Faculty, Istanbul, Turkey*

Introduction: Kasabach-Merritt Phenomenon (KMP) is characterized with arteriovenous malformation and life-threatening thrombocytopenia, hypofibrinogenemia, elevated fibrin split products, prolonged PT and aPTT.

Methods: We describe a case of 6-week –old boy with KMP presenting as constipation and perineal ecchymosis.

Results: Ultrasonographic evaluation revealed no tumor (taught to be either rhabdomyosarcoma or neuroblastoma) or arteriovenous malformation except bleeding. Magnetic resonance imaging pointed a large lesion which is spreading from back of bladder to rectum. Biopsy of the lesion was diagnosed as Kaposiform Hemangioendothelioma (KHE). There was response neither to propranolol nor steroid treatment, but vincristine dramatically.

Discussion/Conclusion: This case highlights difficulty of diagnosis, management, and treatment of KMP in underlying vascular tumors, specifically KHE, which if untreated may result in significant morbidity and even mortality.

Disclosure of Interest: None declared.

P278 | Online education improves healthcare providers' knowledge regarding the principles of gene therapy for hemophilia

S. Hurst[1,*]; C. Warren[1]; H. Kadkhoda[1]; E. Van Laar[1]; G. Pierce[2]; on behalf of Educational Collaborators: National Hemophilia Foundation (NHF), European Haemophilia Consortium (EHC), World Federation of Hemophilia (WFH)

[1]*Medscape Education, New York, NY, USA;* [2]*World Federation of Hemophilia, Montreal, Canada*

Introduction: Gene therapy offers the hope of a functional cure for hemophilia. To prepare healthcare providers (HCPs) for this potential paradigm shift in care, NHF, EHC, WFH, and Medscape Education collaborated to develop a multi-modal, online, continuing medical education (CME) curriculum. The current study assessed the ability of online CME to improve HCPs' knowledge regarding the scientific principles underlying gene therapy overall and its study in hemophilia.

Methods: A 15-minute, CME-certified video commentary with synchronized slides was developed and launched online on 8/3/2018. Educational effectiveness was assessed with a repeated-pairs pre-/

post-assessment study design, in which each individual served as his/her own control. Responses to 3 multiple-choice, knowledge questions and 1 self-efficacy confidence question were analyzed. A chi-squared test assessed changes pre- to post-assessment. *P* values <0.05 are statistically significant. Effect sizes were evaluated using Cramer's V (<0.05 modest; 0.06-0.15 noticeable effect; 0.16-0.26 considerable effect; >0.26 extensive effect).

Results: To date, 1634 HCPs (958 physicians) have participated in this program. This analysis presents preliminary data from the subset of hematologists/oncologists (n = 77; hem/oncs) who answered all pre-/post-assessment questions during the initial analysis period of 8/3/18-9/5/18; data collection is ongoing. Significant improvements were observed overall (*P* = 0.0007; V = 0.156) and in the following areas,

- Correct identification of transient transaminitis as the most common adverse event observed in gene therapy trials (45% vs 73% [62% relative increase]; *P* = 0.0006; V = 0.277)
- Recognition of the relatively low homology between the adeno-associated virus (AAV) vector used in gene therapy trials for hemophilia A (AAV5) and other primate AAVs (36% vs 55% [53% relative increase]; *P* = 0.023; V = 0.182)
- 39% of hem/oncs had increased confidence in their understanding of the science underlying gene therapy in hemophilia

Lastly, the findings uncovered educational needs, such as the understanding of the FIX construct currently under study in hemophilia B trials.

Discussion/Conclusion: Participation in this online activity significantly improved hem/oncs' knowledge with regard to the adverse events, viral vectors, and gene constructs in current clinical trials for gene therapy in hemophilia.

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P279 | The positive impact of CME on healthcare providers' knowledge of gene therapy studies in hemophilia

S. Hurst[1,*]; C. Warren[1]; H. Kadkhoda[1]; E. Van Laar[1]; S. Pipe[2]; on behalf of Educational Collaborators: The National Hemophilia Foundation (NHF), European Haemophilia Consortium (EHC), the World Federation of Hemophilia (WFH)

[1]*Medscape Education, New York, USA;* [2]*University of Michigan, Ann Arbor, USA*

Introduction: To educate healthcare providers (HCPs) on the potential paradigm shift that gene therapy may represent for hemophilia, NHF, EHC, WFH, and Medscape Education collaborated to develop a multi-modal, online, continuing medical education (CME) curriculum. The current study assessed the ability of online CME to improve HCPs' knowledge regarding how gene therapy is evolving in hemophilia.

Methods: A 30-minute, CME-certified, panel discussion activity was developed and launched online on 6/18/2018. Educational effectiveness was assessed with a repeated-pairs pre-/post-assessment study design, with each individual serving as his/her own control. Responses to 3 multiple-choice, knowledge questions and 1 self-efficacy confidence question were analyzed. A chi-squared test assessed changes pre- to post-assessment. *P* values <0.05 are statistically significant. Effect sizes were evaluated using Cramer's V (<0.05 modest; 0.06-0.15 noticeable effect; 0.16-0.26 considerable effect; >0.26 extensive effect).

Results: To date, 2344 HCPs (1954 physicians) have participated in this education. This analysis comprises data from the subset of hematologists/oncologists (n = 52; hem/oncs) who answered all pre-/post-assessment questions during 6/18/18-9/17/18; data collection is ongoing. Significant improvements were observed overall (*P* < 0.0001; V = 0.219) and with respect to:

- Correctly identifying the nonenveloped parvovirus vector construct (adeno-associated virus; AAV) that is currently being studied in gene therapy trials (56% vs 85% [52% relative increase]; *P* = 0.0013; V = 0.315)
- Recognizing that the University College London/St Jude trial provided the first evidence that therapeutic levels of FIX could be expressed and sustained for several years using an AAV-based system (48% vs 73% [52% relative increase]; *P* = 0.0091; V = 0.255)
- 19% of hem/oncs had increased confidence with regard to how gene therapy could be used to treat hemophilia A.

The findings also uncovered educational needs, such as the need for additional education regarding the FVIII expression levels that have been observed within AAV gene therapy trials for hemophilia A.

Discussion/Conclusion: Participation in this online educational activity significantly improved hematologists' knowledge with regard to the viral vectors that are currently being studied in hemophilia trials as well as the extent and duration of factor expression that have been observed to date.

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P280 | Emicizumab therapy leading to resolution of a massive iliopsoas haematoma and allowing removal of port-a-cath in an adolescent with severe haemophilia A, chronic high titre FVIII inhibitor and previous pulmonary embolism

S. Brown[1,*]; J. Holzmann[1]; H. Coulsen[2]; W. Poulsen[2]; J. McCosker[3]; M. Harlen[3]

[1]*Haemophilia & Haematology, Children's Health Queensland, Brisbane, Australia;* [2]*Physiotherapy, Children's Health Queensland, Brisbane, Australia;* [3]*Haemophilia Centre, Children's Health Queensland, Brisbane, Australia*

Introduction: Inhibitor formation in children with severe haemophilia A remains the most significant complication of FVIII therapy.

Treatment of bleeding episodes in individuals with a FVIII inhibitor utilises by-passing agents (BPA) such as recombinant activated factor VII and activated prothrombin complex concentrates. Recent studies have reported prevention of bleeds in patients with inhibitors using a novel monoclonal antibody, Emicizumab. We report a case where Emicizumab therapy lead to the resolution of a massive retroperitoneal haematoma originating from the iliopsoas muscle, and allowed removal of a port-a-cath.

Methods: Case report.

Results: A 15-year-old male, who had failed immune tolerisation, and had a chronic high titre FVIII inhibitor (maximum 3328 BU/mL) presented in haemodynamic shock with a massive retroperitoneal bleed (estimated 2L, nadir Hb 64 g/L) despite daily BPA prophylaxis. He had a history of recurrent musculoskeletal bleeds (ABR >30), chronic arthropathy (HJHS 25) with subsequent mobility issues, regularly missed school due to bleeds, and previously suffered a pulmonary embolus (PE) during BPA therapy. The acute iliopsoas bleed was controlled with BPA therapy, and a port-a-cath was re-inserted (complicated by a large wound haematoma) to facilitate intensified haemostatic therapy. An application for compassionate use Emicizumab was lodged a month before the bleed. Emicizumab therapy (3 mg/kg weekly sc injections for 4 weeks and 1.5 mg/kg weekly injections thereafter) was approved and commenced 14 weeks after the initial bleed. On Emicizumab the TEG normalised, the haematoma (pre-Emicizumab size 6 x 4 x 5 cm) fully resolved over 19 months, the ABR was 0, school attendance increased and the port-a-cath was removed without BPA therapy. No complications or adverse events were encountered on Emicizumab.

Discussion/Conclusion: Emicizumab is a novel monoclonal antibody that bridges FIXa with FX, activating FX and thereby bypassing FVIII. This case demonstrates the safe and effective use of Emicizumab for over 20 months in an individual with a prior history of PE complicating his severe haemophilia A with a chronic high titre FVIII inhibitor.

Disclosure of Interest: None declared.

P281 | Antimicrobial prophylaxis in patients with immune thrombocytopenia treated with rituximab: A retrospective analysis

S. Raso[1,*]; M. Napolitano[2]; M. Sardo[2]; S. Siragusa[2]; M. Carlisi[3]; F. Mansueto[3]; M. Salvatrice[2]

[1]Department of Surgical, Oncological and Oral Sciences (Di.Chir.On.S.); [2]Unit of Haematology, Biomedical Department of Internal Medicine and Medical Specialties (Di.Bi.M.I.S); [3]Department of Surgical, Oncological and Oral Sciences (Di.Chir.On.S.), University of Palermo, Palermo, Italy

Introduction: Rituximab (RTX) increases the risk of viral and fungal infections. Although antimicrobial prophylaxis (AP) is used in patients (PTs) with hematological neoplasms receiving RTX, evidence is lacking in the field of immune thrombocytopenia (ITP). We here reported the role of AP in a group of PTs with ITP under RTX.

Methods: PTs with ITP treated at our Centre from January 2013 to June 2018 were retrospectively evaluated. The following data were collected (pre and post RTX) up to last follow-up (FU): demographic, comorbidities, absolute lymphocyte count (ALC), serum protein electrophoresis (SPEP), antimicrobial prophylaxis, clinical manifestations of *Pneumocystis Jirovecii* (PJ), Herpes Zoster Virus (HZV) and Herpes Simplex Virus (HSV) infections, confirmed diagnosis of any infections.

Results: Overall, we analyzed 20 PTs with ITP treated with RTX (Table 1). All PTs had previously received first-line therapy. RTX was always administered according to "standard regimen" (4 weekly 375-mg/m2). 5 PTs did not receive AP: 2 PTs had the lower median age and 3 presented only hypertension as comorbidity. 2 PTs discontinued AP within 1 week due to allergic reaction. 11 PTs received AP for PJ with trimethoprim/sulfamethoxazole (TMP/SMX) and 10 with acyclovir (AC) for HZV. Therapy was maintained for 1 year(y) following 1st RTX. 3 PTs had ALC < 1000/mmc at the end of RTX, value turned to normal after a mean of 4 *m*. SPEP was available in 8 PTs and showed no decrease in g-globulin level up to 1y post RTX. No clinical signs of infection by PJ, HZV and HSV were reported. Hospitalization or specific assay for any suspected infection during FU was never required.

TABLE 1.

Age (mean y)	52
Comorbidities (n° pt)	
Diabetes mellitus	5
Hypertension	7
Hypotiroidism	1
Ulcerative colitis	1
GIST*	1
No comorbidities	9
Prophylaxis (n° pt)	
TMP/SMX 3 or AC 2	
TMP/SMX + acyclovir	8
Discontinued prophylaxis 2 No prophylaxis	5

Discussion/Conclusion: In our study, 55% of PTs received AP. PTs not treated with AP had a lower median age and less comorbidities. Assayed parameters did not show any persistent alteration, neither did clinically diagnosed infections occurred. This analysis shows that AP could be suitable in a subgroup of PTs with ITP having higher risk of infections as elderly PTs or those with multiple comorbidities. However prospective studies are needed to better define this indication.

Disclosure of Interest: None declared.

P282 | Usefulness of the haemophilia health joint score on an adult cohort in a Portuguese hemophilia center - What can we conclude?

S. Teixeira[1,*]; I. Machado[1]; M. Carvalho[1]; L. Gonçalves[1]; M. Ramalho[1]; M. J. Leite[2]; M. Lopes[2]; C. Koch[1]

[1]Centre of Thrombosis and Haemostasis, Centro Hospitalar São João, EPE, Porto, Portugal, Porto, Portugal; [2]Department of Orthopedic Surgery, Centro Hospitalar São João, EPE, Porto, Portugal, Porto, Portugal

Introduction: Joint bleeding in haemophilic patients may lead to arthropathy which can increase morbidity. In order to assess the impact of the disease in the musculoskeletal (MSK) system several tools have been developed, such as the Hemophilia Joint Health Score (HJHS). Our aim was to evaluate the results of the HJHS in our haemophilic patients and their relationship with patient disease characteristics regarding treatment.

Methods: In one moment in the year of 2018, the HJHS was performed on 19 male patients (mean age 44.5 ± 12.6): 9 with severe haemophilia A (HA) including 2 patients with inhibitors, 3 with moderate HA and 7 with severe haemophilia B. Joints that had been replaced with prosthesis correspond to a score of 0. A descriptive and comparative analysis between HJHS and age, diagnosis and type of treatment (prophylaxis /*on demand*) was performed. The statistical analysis was performed using *IBM SPSS Statistics 25.0*®. Significance level was set at 5%.

Results: There was a statistically significant positive correlation between score and age ($P = 0.003$). No statistical difference was found between score results and type of haemophilia, severity of disease and type of treatment. In a multivariate analysis, adjusted for age, there was no association between severity of the disease and type of treatment with HJHS score.

Discussion/Conclusion: Our study showed that age has an important impact in HJHS, since older patients started prophylaxis later on, or maintain *on demand* treatment. We did not find an association with types of haemophilia or treatment, which can be explained by the small sample size. However, it is important to pinpoint that this score may not reliably translate the true impact of the haemophilia treatment in joint health. HJHS was initially designed to be applied to children who are usually treated with primary prophylaxis leading to better joint health and fewer joints replacements. Even though this score seems useful for patient evaluation through time, when we want to analyze the efficacy of treatment and consequences of the severity of the disease, there is an underestimation of the value of the score, since a joint that has been replaced scores the same as a healthy joint. According to our study, it may be helpful to define a standard value for a joint that has been replaced or, if applicable, the use of the last known score of the joint previously to surgery.

Disclosure of Interest: None declared.

P283 | Evaluation of a haemarthrosis-simulating artificial knee in therapeutic education for patients with haemophilia: Results of GEFACET study

S. Le Doré[1,*]; N. Grinda[2]; E. Ferré[1]; V. Roussel-Robert[3]; F. Truong-Berthoz[4]; B. Frotscher[5]; P. Chamouni[6]; S. Meunier[7]; S. Bayart[8]; E. De Raucourt[9]

[1]Centre for the Treatment of Haemophilia, Hospital of Versailles, Versailles, France; [2]Regional Centre for Haemophilia, Hospital of Bicêtre (AP-HP), Kremlin-Bicêtre, France; [3]Regional Haemophilia Treatment Centre, Cochin Hospital (AP-HP), France; [4]Shire France SAS, Paris, France; [5]Haemophilia Treatment Centre, Hospital of Brabois, Vandoeuvre-Les-Nancy, France; [6]Regional Haemophilia Treatment Centre, University Hospital of Rouen, Rouen, France; [7]Regional Haemophilia Treatment Centre, GHE - Louis Pradel Hospital (HCL), Bron, France; [8]Haemophilia Treatment Centre, Regional University Hospital of Pontchaillou, Rennes, France; [9]Centre for the Treatment of Haemophilia, Centre for the Treatment of Haemophilia, Versailles, France

Introduction: One of the major haemophilia-related complications, especially in severe or moderately severe haemophilia, is recurrent joint bleedings leading to haemophilia arthropathy. In these patients, therapeutic education is performed to evolve patients' knowledge of their disease, to allow self-care and favor patients' autonomy, improving their quality of life. The study GEFACET, French acronym for "Artificial Knee and Therapeutic Education" was set up in order to evaluate the impact of a new tool on patients' knowledge: a haemarthrosis-simulating artificial knee (HSAK), developed by The French Haemophilia Treatment Centre (HTC) of Versailles.

Methods: Patients aged ≥ 6 years, with severe and moderately severe hemophilia A or B (FVIII or FIX: C ≤ 2%) were included in this prospective multicenter study, among 7 HTCs, and received therapeutic education with HSAK (HSAK-TE) at baseline. Questionnaires were administered at baseline, before and after HSAK-TE, and at 6 months. Knowledge of disease and treatment were scored and analyzed using descriptive statistics. Scoring was performed on disease and treatment-related questions. Knowledge of disease was calculated based on 4 questions and marked out of 7 points. Knowledge of treatment patterns was calculated based on 3 questions and marked out of 3 points. Evolution of score from baseline, after HSAK-TE and at 6 months was evaluated using Wilcoxon signed rank test for paired data.

Results: 93 patients participated, and 92 were eligible for analysis (84 were eligible for 6 months of data analysis). Median age was 14 years (range: 6 – 68 years). Median (mean ± SD) of knowledge of disease was 5 (4.5 ± 2.0) before HSAK-TE. It increased significantly ($P < 0.001$) after HSAK-TE to 7 (5.9 ± 1.5) and maintained at 6 months at 7 (5.9 ± 1.5). Before HSAK-TE, Median (mean ± SD) of knowledge of treatment was 3 (2.6 ± 0.7), remained at 3 (3.0 ± 0.6) after HSAK-TE and at 6 months (3.0 ± 0.7).

Discussion/Conclusion: these results suggest that HSAK-TE may improve educational program for patients with haemophilia.

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P284 | Review of haemophilia care in India

S. Bosbach[1,*]; V. Narendra[2]; S. Morampudi[2]; A. Gowda[2]

[1]Phamax AG, Zug, Switzerland; [2]s/max, Phamax Analytic Resources Pvt. Ltd, Bangalore, India

Introduction: India has the second highest number of People With Haemophilia (PWH) in the world. The Indian government is taking initiatives to provide support and care though it is not in the priority list of diseases due to its high-cost, low-volume status. This review qualitatively assesses the strengths and pitfalls in haemophilia care in the country.

Methods: The investigators performed a systematic literature review of MEDLINE and COCHRANE databases using keywords. Standard checklists were used to assess the credibility of the studies prior to inclusion for review. The investigators analysed and reported the thus extracted qualitative data. They then generated the codes and tagged similar codes under a theme.

Results: There are multiple interlinked facets related to the patient, provider, and system, posing a challenge in the provision of effective care. These facets included the 'lack of awareness', 'inadequacy in the provision of comprehensive care', 'paucity of scientific evidence', and 'cultural and economic factors' to name a few. A high proportion of patients sought care in private hospitals that is expensive. Services provided by governmental institutions are affordable but lacks expertise and facilities. Hence care is limited to those who can afford it and majority are subjected to symptomatic management. Inequity in distribution of government managed tertiary care centres was noticed limiting the availability to a small section of population in a specified geography. Financial assistance was provided by the government to PWH, however, it is restricted to in-patient care. Patients with complications or episodic patients requiring transfusions without admissions cannot avail the benefits of the scheme. Doctors' role in policy decisions was lacking.

Discussion/Conclusion: Haemophilia is gaining attention in the country but in a limited manner. Inter-sectoral co-ordination between doctors, patient advocacy groups, and governance with the sensitization of policy makers is essential to increase awareness, build capacity, and develop infrastructure. Doctors have to play a key role in evidence generation, influence, and planning and developing guidelines for care and support.

Disclosure of Interest: None declared.

P285 | Thrombin generation assay to guide replacement therapy in patients with factor XI deficiency undergoing elective surgery

S. Desage*; X. Vanhoye; S. Meunier; L. Rugeri; A. Lienhart; C. Nougier; Y. Dargaud

Unite d'Hemosatse Clinqiue, Hopital Louis Pradel, Lyon, France

Introduction: Most patients with factor XI (FXI) deficiency are mild bleeders but certain patients with similar FXI activity may exhibit different bleeding phenotype. Routine laboratory assays do not help physicians to estimate the individual bleeding risk in these patients. Our group and others reported that thrombin generation assay (TGA) may be a useful tool to predict bleeding risk in FXI deficiency. We showed that independently of their plasma FXI levels, bleeder patients exhibited delayed thrombin generation (lag time >14 min) with low thrombin peak (peak < 55 nM) and decreased thrombin generation velocity (velocity<3.5 nM/min). It has been also shown that TGA may be used to monitor FXI replacement therapy with either fresh frozen plasma (FFP) or FXI concentrate (FXIc).

Methods: We report here the first prospective clinical experience using TGA to guide replacement therapy in patients with FXI deficiency who needed elective surgeries. After obtaining informed consent, TG was systematically measured during routine clinical visits of 47 patients with FXI < 50 IU/dL between January 2014 and October 2018. TGA was performed in platelet rich citrated plasma, collected on corn trypsin inhibitor 18.3 µg/mL, using a very low concentration of tissue factor at 0.5 pM.

Results: Among these patients, 24 had elective surgeries during the study period (tooth extractions, orthopedical surgeries, mucosa surgeries and breast surgery). Four of them, presenting both 3 impaired TGA parameters (lag time, peak and velocity), received replacement therapy (FFP or FXIc); 13 who had one or two abnormal TGA parameters received tranexamic acid only and 7 patients with normal TGA had no procoagulant drugs before surgery.

Plasma FXI levels were not correlated neither with bleeding history of the patients nor with TGA. Thus four patients, with very low and delayed TGA and strong bleeding history, had FXI levels at 35 – 8 - 46 and 6 IU/dL respectively. No bleeding or thrombosis occurred during the perioperative period.

Discussion/Conclusion: Our prospective clinical surgery results suggest that TGA may help physicians to predict the individual bleeding risk of patients before surgery and to guide replacement therapy that may be associated with a certain risk of thrombosis.

Disclosure of Interest: None declared.

P286 | Do we really need plasma-derived FVIII concentrates in every PUP to minimize the risk of inhibitor development?

S. Halimeh*; H. Rott; M. Siebert; G. Kappert

[1]CRC Coagulation Research Centre GmbH, Duisburg, Germany

Introduction: Inhibitor development remains a challenge in haemophilia treatment, particularly in previously untreated patients (PUPs). They usually develop within the first 50 exposure days (EDs), with a median time of 10–15 EDs. The impact of product type on the risk of inhibitor development remains controversial. Whilst some studies have found no difference in the incidence of inhibitors between plasma-derived (pd) and recombinant (*r*)FVIII products, the prospective, randomised SIPPET study found an 87% higher incidence of inhibitors in PUPs treated with rFVIII than treated with pdFVIII products containing von Willebrand factor (VWF).

Methods: The aim of our study was to investigate an individualised treatment approach in PUPs limiting joint damage and inhibitor development. This approach included the use of intensive monitoring from an early age, tailored prophylaxis using pdFVIII products and personalised physiotherapy regimen. FVIII levels and Von Willebrand Antigen (VWF-Ag) were possibly measured after birth, before start and during prophylaxis. Inhibitor titre was measured every 3-4 EDs. Our study cohort was compared with a historical cohort treated with early prophylaxis with rFVIII or pdFVIII. 24 patients were enrolled from the historical cohort rFVIII[n = 7], pdFVIII [n = 2]) and from our study cohort (pdFVIII [14], not yet treated [1]).

Results: Since 2013 all 14 PUPs started early prophylaxis with pdFVIII/VWF with an initial dose ranging from 25 IU/kg/10 days to 60 IU/kg/week for the first 20 ED; thereafter individual dose escalation was performed. So far, no patient had developed and inhibitor. 4 patients in the historical cohort developed a high titre inhibitor (≥ 5 BU) during the first 20 EDs with rFVIII, but none of the patients with pdFVIII ($P = 0.007$).All patients who had developed an inhibitor had a VWF-Ag < 77% (n = 4), patients receiving rFVIII without inhibitor had an VWF-Ag >77% (n = 3); this difference was significant ($P < 0.001$). Inhibitor patients of the historical cohort had a lower VWF at prophylaxis start compared to the cohort without inhibitors. In our study cohort, 7 patients had low and 6 patients normal VWF-Ag.

Discussion/Conclusion: We found that individualized treatment and early prophylaxis minimized the incidence of inhibitors. It still has to be investigated in a prospective study if PUPs with a high VWF-level can be treated safely with rFVIII without an inhibitor risk.

Disclosure of Interest: None declared.

P287 | Cross-cultural differences in caregiver burden of parents of children with haemophilia

S. Von Mackensen[1,*]; L. Myrin Westesson[2]; K. Kavakli[3]; A. Klukowska[4]; C. Escuriola[5]; N. Uitslager[6]; C. Santoro[7]; M. Holland[8]; K. Khair[9]

[1]Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; [2]Coagulation Centre, Department of Medicine/Haematology and Coagulation Disorders, Sahlgrenska University Hospital, Gothenburg, Sweden; [3]Paediatric Haematology Department of Children, Haemophilia Centre, Ege University Hospital, Izmir, Turkey; [4]Department of Paediatrics, Haematology Oncology, Warsaw Medical University, Warsaw, Poland; [5]Haemophilia Centre Rhein Main (HZRM), Mörfelden-Walldorf, Germany; [6]Van Creveldkliniek, Division of Internal Medicine and Dermatology, Van Creveldkliniek, DUniversity Medical Center Utrecht, Utrecht, Netherlands; [7]Haemophilia Centre, La Sapienza University Rome, Rome, Italy; [8]Haemnet; [9]Centre for Outcomes and Experience Research in Childhood Health, Illness and Disability (ORCHID), Centre for Outcomes and Experience Research in Childhood Health, IIGreat Ormond Street Hospital for Children NHS Trust, London, UK

Introduction: Caring for children with haemophilia can cause burden to caregivers; from worries about the child's health to financial and emotional impacts on caregivers. The aim of the study was to assess differences in caregivers' burden across 7 European counties (France, Germany, Italy, Poland, Sweden, Turkey and UK).

Methods: Non-interventional study in the assessment of burden in caregivers of children with haemophilia across Europe. Consecutive enrolment of caregivers/children dyads at haemophilia treatment centres (HTC). Caregiver burden was assessed with the 'HEMOphilia associated CAregiver Burden scale' (HEMOCAB™) scale. In addition socio-demographic characteristics of the caregiver and clinical data of the child were collected.

Results: 144 dyads from Poland [n = 25], Sweden [n = 21], the UK [n = 21], Turkey [n = 20], Germany [n = 19], Italy [n = 19] and the Netherlands [n = 19] participated in the study.

In the UK 45% of caregivers reported that haemophilia has an economic impact on their family, followed by 44% in Poland and only 10.5% in the Netherlands. There was a significant difference regarding out of pocket costs ($P < 0.011$), Poland spending the highest amount and Germany the lowest.

There was a significant difference in the incidence of disability due to haemophilia in the family ($P < 0.023$), 48% in Poland, 36.8% in the Netherlands and 5.3% in Italy. Chronic pain was significantly more present ($P < 0.006$) in the UK (52.4%) compared to only 4.8% in Sweden.

Significant differences were also found for time needed for infusion ($P < 0.0001$) [in Sweden 16.08 ± 17.3 hours/month vs. Netherlands 2.97 ± 4.5] and time needed to reach HTC ($P < 0.006$) [in Turkey 16.0 ± 15.1 hours/month vs. Netherlands 2.17 ± 4.7].

A significant difference was found for home treatment ($P < 0.003$), Turkey having the lowest incidence (60%). No difference was found for treatment regimen.

42.9% of caregivers in the UK and Sweden had significantly >2 children ($P < 0.007$) compared to none in Turkey.

There was a significant difference across the countries ($P < 0.0001$) concerning caregiver burden; highest burden was reported in the

HEMOCAB total score in Turkey (39.93 ± 18.1) and lowest burden in the Netherlands (10.57 ± 8.7).

Discussion/Conclusion: Burden related to caring for a child with haemophilia is significantly different across Europe with the greatest burden in the low-income countries. These differences are not only related to economic aspects, but also to sociodemographic characteristics.

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P288 | Indications of systemic conflicts of interest regarding adherence between different stakeholders

S. Von Mackensen[1,*]; Y. Douma[2]; S. Halimeh[2]

[1]*Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany;* [2]*Coagulation Research Centre GmbH, Duisburg, Germany*

Introduction: For a successful prophylaxis not only effective and safe factor concentrates are necessary, a high degree of adherence of persons with haemophilia (PWH) is also required. According to the WHO adherence can be influenced by several factors, e.g. socioeconomics, therapy, patients, disease and health care system.

Methods: Six focus groups were performed with PWH (adults, adolescents, parents of haemophilic children), haemophilia treaters (HCP: internists, paediatricians) and representatives of statutory health insurance (HIC: Health Insurance Company). Using semi-structured interviews, participants were asked about the following topics: Framework conditions, barriers or facilitators, possible interventions, understanding of the concept of adherence and the treatment situation. In addition, participants had the opportunity to make suggestions for questions for a new adherence questionnaire. Further 50 PWH and 25 HCP were asked to formulate questions about adherence in writing. All contributions were clustered and evaluated using qualitative content analysis and mind mapping.

Results: 42 persons (13 HCP, 26 PWH, 3 HIC) participated in the focus groups; 14 HCP and 6 PWH made suggestions on adherence questions. A total of 741 statements were evaluated, 458 by PWH, 205 by HCP and 78 by HIC. This resulted in indications of systemic conflicts of interest regarding adherence. For PWH, the most important interests were "minimal restrictions in everyday life" (38.2%), "as rare as possible/painless infusions" (15.3%), "time savings" (13.8%) and "trust in HCP" (12.7%). However, for HCP 'motivating patients' (35.1%), 'complying with documentation requirements' (17.1%), 'treating effectively' (15.6%) and 'empowering patients' (14.1%) and for HIC, 'effective therapy' (42.3%), 'motivating patients' (30.8%), 'pharmaceutical industry contribution' (14.1%) and 'efficient use of resources' (11.5%) had the highest priority.

Discussion/Conclusion: The conflicts of interest that have been found are in contrast to previous legislative cost-cutting initiatives, as well as the benefit assessments carried out by G-BA/IQWiG on pharmaceuticals, in which convenience is explicitly excluded as a patient-relevant added benefit. In fact, convenience effects on treatment adherence are very pronounced for PWH. Enhancing prophylactic convenience could contribute to a more effective and efficient use of resources in haemophilia care.

Disclosure of Interest: S. Von Mackensen Grant/Research support from: SOBI, Y. Douma: None declared, S. Halimeh: None declared.

P289 | Safety and efficacy of pdVWF/FVIII in patients with von Willebrand disease undergoing surgery: Results from a non-interventional multicentre study

K. Khair[1]; M. von Depka Prondzinski[2]; M. Sholzberg[3]; M. Sol Cruz[4]; K. Decker[5]; Z. Čermáková[6]; S. Werner[7,*]; G. Rodgers[8]

[1]*Centre for Outcomes and Experience Research in Children's Health, Illness and Disability (ORCHID), Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK;* [2]*Werlhof Institute, Hannover, Germany;* [3]*St. Michael's Hospital, Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Canada;* [4]*Fundacion Hemofilia de Salta, Salta, Argentina;* [5]*McMaster University, Hamilton, Canada;* [6]*Blood Centre, University Hospital, Ostrava, Czech Republic;* [7]*Octapharma USA Inc., Hobocken;* [8]*University of Utah, Salt Lake City, USA*

Introduction: Management of perioperative bleeding in patients with von Willebrand disease (VWD) can be challenging due to the risk of FVIII accumulation with repeated dosing of VWF-containing concentrates, which may predispose to thromboembolism. WIL-20 is a non-interventional, prospective, multicentre study that collected real-life data on the use of a human VWF/FVIII concentrate with the native VWF/FVIII complex in a physiological 1:1 ratio (wilate®; pdVWF/FVIII) in routine clinical practice. Here we present a subset of the data in VWD patients who received perioperative prophylactic treatment.

Methods: The primary objective of WIL-20 was to document the safety and tolerability of pdVWF/FVIII over a 2 year observation period. Patients of any age with any type of VWD who were prescribed pdVWF/FVIII were eligible for the study. PdVWF/FVIII was administered at the study-site investigator's discretion. Data recorded included relevant demographic and clinical variables, laboratory parameters, treatment details and occurrence of adverse drug reactions. As a secondary objective, efficacy was assessed using a 4-point haemostatic efficacy scale.

Results: A total of 111 patients were enrolled in the study, and 99 surgical procedures (46 major/53 minor) were performed in 62 patients; 56% with type 1 VWD, 29% type 2 and 13% type 3 (2% type unknown). Median age was 35.5 years (range 2–77.5) and 48% of patients had not been previously treated with a pdFVIII/VWF concentrate. All but one of the surgeries were managed with pdVWF/FVIII prophylaxis. The median dose was 34.2 IU/kg (range, 6.3–679.6) for minor procedures and 110.8 IU/kg (range, 21.8–500) for major procedures. There were no thrombotic events despite 25% of surgeries

being orthopaedic. No VWF neutralising inhibitors were observed. Two patients reported symptoms of hypersensitivity that were mild and moderate in severity. Efficacy of pdVWF/FVIII was rated 'excellent' or 'good' in 100% (46/46) of major and 98% (50/51) of minor surgeries with available assessments.

Discussion/Conclusion: In patients treated for perioperative prophylaxis as part of routine clinical practice pdVWF/FVIII was well tolerated and there were no thrombotic events despite the use of intensive treatment. PdVWF/FVIII demonstrated efficacy in VWD patients in this notoriously challenging clinical setting.

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P290 | Living with haemophilia: The development of an APP

T. Cebanu; P. Acuña-Butta; S. García Barcenilla; R. Justo-Sanz; E. Monzon-Manzano; M. Martín Salces; M. Rivas-Pollmar; I. Fernandez-Bello; H. de la Corte; N. Butta-Coll; V. Jiménez-Yuste; M. Álvarez-Román

Hospital Universitario La Paz-IdiPaz, Madrid, Spain

Introduction: Patients with haemophilia may have many doubts about their pathology and in some situations they can have incidents that they do not know how to solve without certain advice. So we thought that the creation of an application for mobile devices would allow didactic disclosure of haemophilia for children and adolescents, without neglecting their parents and caregivers. In this way they would be able to solve the doubts about their pathology.

We created a multiplatform APP iOS and Android for the informative divulgation of the haemophilia to show in a visual and attractive way everything concerning this pathology and its implications in daily life.

Methods: Based on the analysis of updated information available to patients, we created an APP accessible to the general public.

Health team from Hospital Universitario La Paz responsible for the care of haemophilia patients met with the company responsible for design and development of APP (Simed Software SL), creating a living ecosystem and around it, the most suitable teaching materials for adults and children. These materials will be updated throughout the life of the APP in an automatic way.

Results: We developed an APP that is able to show multiple file formats (PDF, HTML, Video and Audio) and that has a Tablet version and a "lite" version for mobile.

Specific sections were included:

- Information about characteristics of haemophilia.
- Material for haemophilia carriers and advices for their pregnancy.
- Prophylaxis regimen explained on the basis of pharmacokinetics.
- Counsel to travellers.
- Contact data for emergencies.
- Recommended physical exercise.
- Patient associations data.

The APP has not yet been made public and is in BETA phase. It is being tested by the health team and the company responsible for its development. We introduced it to 100 persons chosen within haemophilia patients and their families to get their comments after using this APP. Their feedback was taken into account to optimize the APP.

The impact of the use of this APP or the analysis of the demographic characteristics of its users cannot be reported yet because it has not been released to stores.

Discussion/Conclusion: We consider that this APP examines effective strategies to improve health behaviors in haemophilia patients and their families. We are very satisfied with the work done and we will continue to be involved in the creation of content to give life to the APP for a long time.

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P291 | The anti fibrinolytic effect of bypassing agents in hemophilia A patients with inhibitors- an ex vivo ROTEM study

T. Livnat*; E. Avishai; R. Dardik; G. Kenet

The Israeli National Hemophilia Center, Sheba Medical Center, Tel Hashomer, Israel

Introduction: In patients with hemophilia A (HA) clots may be more susceptible to fibrinolysis. Rotational thromboelastometry (ROTEM) was used as a complimentary global assay enabling evaluation of clot formation and strength in HA patients. *Aim*: We used tPA-induced ROTEM assays in order to define the anti-fibrinolytic effect of rFVIIa, FEIBA alone or in combination on blood of HA patients.

Methods: Blood samples were obtained from 10 severe HA patients, 6 severe HA patients with inhibitor (0.5-21BU), and 11 healthy controls for ROTEM assays with additional increasing concentrations of tPA. Ex-vivo spiking with rFVIIa (1.25 and 3.75 μg/mL) and FEIBA (0.25 and 0.5U/mL) alone or in combination was simultaneously performed. Fibrinolysis was evaluated by lysis index (LI) and clot firmness parameters.

Results: Preliminary evaluations indicated that EXTEM reagent (containing CaCl2 + tissue factor) and tPA at final concentration of 130 ng/mL were the most sensitive conditions for evaluation of fibrinolysis in HA patients' blood.

HA clots were more susceptible to tPA-induced fibrinolysis as compared to controls (LI30: 38.5 ± 31.6 control vs. 11.33 ± 18.9 HA). Individual anti-fibrinolytic responses to ex- vivo bypassing agents spiking were noted in HA patients with inhibitor. In 3/6 patients, high concentration of FEIBA (0.5U/ml) induced the most prominent anti-fibrinolytic effect. In 2/6 patient the combination of low concentrations of FEIBA+rFVIIa achieved the highest anti-fibrinolytic effect whereas in 1/6 patient similar effect was induced by the 2 former options. In all our inhibitor patients' samples the anti-fibrinolytic effect of high concentration of rFVIIa was less prominent than any other option tested.

Discussion/Conclusion: Our results indicate the beneficial anti-fibrinolytic effect of either FEIBA or combined bypassing agents. Further laboratory assessments with clinical response correlation may enable future individually tailored optimal treatment for HA patients with inhibitors.

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P292 | Incidence of coronary artery disease in patients with congenital bleeding disorders

T. Kanellopoulou[1,*]; G. Kampelos[2]; A. Apostolopoulou[2]; M. Bellia[2]; V. Tsevrenis[2]; E. Nomikou[2]

[1]*Department of Clinical Haematology-Blood Bank-Hemostasis, Onassis Cardiac Surgery Centre, Athens, Greece;* [2]*Blood Bank and Haemophilia Unit, Hippokration General Hospital, Athens, Greece*

Introduction: The life expectancy of patients with congenital bleeding disorders (CBD) has increased and as a result, age-related diseases including coronary artery disease have become even more common. Despite the hypocoagulable state it is generally accepted that patients with CBD are not protected against atherosclerosis. Similarly to the recommended approach in the general population, percutaneous coronary intervention (PCI) and coronary artery bypass (CABG) surgery should be proposed when another approach is not indicated.

Methods: A retrospective analysis of the adult patients with CBD that successfully underwent PCI ± CABG in a single haemophilia unit was performed.

Results: Eight patients were diagnosed with CAD that represented 1.2% of all patients. Cardiovascular risk factors were present at diagnosis and included smoking (75%), hyperlipidemia (87.5%), diabetes (50%), hypertension (50%), low physical activity due to arthropathy or obesity (25%). All patients had more than one factor present. The underlying CBD were von Willebrand disease (vWD) type-I in 3 patients, mild platelet function disorders (PFD) in 3 patients, mild haemophilia-B in 1 patient and mild F-XI deficiency in 1 patient. None patient with haemophilia-A or other CBD was identified. Stent insertion was necessary in six patients (1-vessel in 2 patients, 2-vessels in 4 patients) and 1 patient was referred for CABG. Preprocedure single bolus infusions of factor concentrates were given in two patients with vWD and FXI deficiencies that had a history of bleeding events in the past. All patients underwent PCI with standard heparinization and then were treated with single antiplatelet treatment 2 patients, double antiplatelet 2 patients, combination of single antiplatelet and anticoagulation 1 patient without bleeding complications. CABG was performed with bolus F-IX concentrate infusion with no complications.

Discussion/Conclusion: No general recommendations exist concerning which coagulation factor levels are acceptable before PCI or CABG or whether platelet transfusions are needed in patients with PBD. Moreover, acute coronary syndromes are reported to be provoked after the administration of factor concentrates or desmopressin and treatment approach is challenging. In most patients with CBD with no history of severe bleeding events no factor replenishment is proposed before PCI and treatment with antiplatelets appear to be safe.

Disclosure of Interest: None declared.

P293 | Associated impact of treatment adherence on health-related quality of life and work impairment in severe haemophilia A

J. O'Hara[1,2]; M. Jain[3]; C. Camp[3]; T. Burke[2,*]

[1]*Faculty of Health and Social Care, University of Chester, Chester, UK;* [2]*HCD Economics, Daresbury, UK;* [3]*BioMarin Europe Ltd, London, UK*

Introduction: Severe haemophilia (<1% normal factor levels) is characterised by spontaneous (non-trauma related) bleeding episodes into the joint space and muscle tissue, leading to progressive joint deterioration and chronic pain in the affected individual. In developed countries, severe haemophilia A (HA) is often managed by prophylactic infusions of replacement factor VIII. Adherence to the prescribed prophylactic factor regimen is essential to minimise bleeding episodes. This study evaluates the relationship between adherence to factor replacement therapy, health status and work impairment in severe HA, using real-world observational data.

Methods: Data were drawn from the 2015 'Cost of Haemophilia across Europe – a Socioeconomic Survey' (CHESS) dataset, a cost-of-illness assessment in severe haemophilia A and B in five European countries. Physicians provided clinical and sociodemographic

information on 996 adults with HA, 426 of whom completed corresponding questionnaires. Physician-reported adherence was captured using a 3-level Likert scale (1 = low, 2 = moderate, 3 = high); overall work impairment (WI) was reported among employed patients via the General Health version of the Work Productivity and Activity Impairment questionnaire (WPAI:GH), calculated as a percentage function of absence from work (absenteeism) and reduced productivity while at work (presenteeism). Health status was assessed using the EQ-5D-3L tool.

Multiple linear regression was used to assess the relationship between treatment adherence, WI and EQ-5D-3L index scores, adjusting for age, treatment strategy, history of joint damage, and inhibitor status.

Results: EQ-5D-3L index scores were calculated in 418 patients (mean 0.72; SD 0.28). WI was calculated in 190 employed patients (mean 29.8%; SD 24.7). Suboptimal adherence (pooled score of 'low' or 'moderate' adherence) was associated with a 0.103 decrease in EQ-5D-3L index score (n = 168; 95% CI 0.055-0.151; $P < 0.001$), and a 12.8 percentage-point increase in WI (n = 70; 95% CI 5.7-19.8; $P < 0.001$).

Discussion/Conclusion: Results of this research indicate suboptimal treatment adherence is associated with a decrement in health status, and an increase in overall work impairment score in adults with severe haemophilia A.

Disclosure of Interest: J. O'Hara Grant/Research support from: BioMarin Europe, M. Jain Employee of: BioMarin Europe, C. Camp Employee of: BioMarin Europe, T. Burke Grant/Research support from: BioMarin Europe.

P294 | An introduction to 'the cost of haemophilia across Europe - a socioeconomic survey (CHESS): Paediatrics' study

T. Burke[1,*]; K. Khair[2]; L. Carroll[3]; L. Ruiz[4]; G. Pedra[1]; J. O'Hara[1,5]

[1]*HCD Economics, Daresbury, UK;* [2]*Great Ormond Street Hospital, London, UK;* [3]*The Haemophilia Society, London, UK;* [4]*HCD Economics, Madrid, Spain;* [5]*Health and Social Care, University of Chester, Chester, UK*

Introduction: In 2017, the 'CHESS: paediatrics' study was developed – a comprehensive, 'bottom-up' cost-of-illness study in moderate and severe haemophilia across France, Germany, Italy, Spain, and the UK (EU5). The objective was to quantify direct and indirect costs of severe haemophilia A (HemA) and B (HemB) in infants, children, and adolescents. This would be achieved through the retrospective capture of 12-month resource use and subsequent extrapolation of the results to population level.

Methods: A cross-section of paediatric haemophilia specialists (surveyed December 2017-March 2018) provided demographic and clinical information and 12-month ambulatory and secondary care activity for up to 16 consulting patients, via an online survey. In turn, those patients (or caregivers by proxy) were invited to provide direct and indirect non-medical cost information via a paper-based self-completion (PSC) questionnaire. This covered impact on schooling and lifestyle/activity level, caregiver work loss and out-of-pocket expenses, as well as data on quality of life, and therapy adherence. A corresponding cost database was developed for each participating country, with a comprehensive cost profile for each patient. The study was governed by a steering committee consisting of charity representatives from participating countries, plus clinicians and health economists. The research was conducted in accordance with relevant European guidelines, approved by the University of Chester Ethics Committee, and analysis conducted by the university and HCD Economics.

Results: A total of 101 physicians participated in the study from across the EU5, capturing information on 992 patients (785 HemA and 206 HemB). There was an even split across children and adolescents (48%, 1-10 yrs; 52%, 11-17 yrs). A total of 256 patients/caregivers completed corresponding PSC questionnaires, with over 200 variables captured on each patient.

Discussion/Conclusion: 'CHESS: paediatrics' has enabled the production of a granular database from which the research team will be able to achieve the objective of producing a comprehensive burden of disease study on a larger scale. This evidence base will help the community understand costs and wider societal burden associated with living with moderate and severe haemophilia in the paediatric population.

Disclosure of Interest: None declared.

P295 | Key findings from an expert validation workshop to establish an appropriate modelling framework in severe haemophilia A

J. O'Hara[1,2]; T. Burke[1,*]; P. Chowdary[3]; K. Khair[4]; M. Laffan[5]; P. McLaughlin[3]; J. Pasi[6]; M. Stevenson[7]; J. Willan[8]; C. Hawes[9]; M. Jain[9]; C. Camp[9]

[1]*HCD Economics, Daresbury, UK;* [2]*Faculty of Health and Social Care, University of Chester, Chester, UK;* [3]*Royal Free London NHS Foundation Trust, London, UK;* [4]*Great Ormond Street Hospital, London, UK;* [5]*Imperial College London, UK;* [6]*Barts and the London School of Medicine and Dentistry, London, UK;* [7]*University of Sheffield, Sheffield, UK;* [8]*Oxford University Hospitals NHS Foundation Trust, Oxford, UK;* [9]*BioMarin Europe Ltd, London, UK*

Introduction: Despite broader access to prophylactic factor VIII replacement, breakthrough bleeding and haemophilic arthropathy (HArth) continue to represent a significant burden to persons with severe haemophilia A (PwSHA) and challenges for health systems. There is also considerable heterogeneity in bleeding patterns and manifestation of HArth in PwSHA, which has yet to be fully captured in published modelling frameworks. This issue is especially pertinent with the advent of novel therapies that suggest a future of zero (or very few) bleeding events.

Methods: In April 2018, a workshop with clinical and health economic modelling experts was held to establish an appropriate modelling framework that reflects both the current, and future treatment

paradigm for PwSHA in the UK. The workshop included six clinical experts (n = 4 haematologists; n = 1 specialist physiotherapist; and n = 1 nurse specialist) and an expert in health economic modelling. A theoretical modelling framework was presented and the data and assumptions on which it was based were presented to the expert group. The relevance and validity of each element was critiqued and alternative approaches were discussed for further exploration.

Results: The expert group considered the proposed modelling framework appropriate for projecting current and future outcomes for PwSHA. However, it was recognised with zero (or very few) bleeding events, monitoring joint deterioration and chronic morbidity (i.e., HArth) will be vital in determining optimal care to PwSHA. Consequently, the planned approach to utilise published evidence on the relationship between bleeding events and joint deterioration was considered too simplistic. It was agreed that a holistic, yet pragmatic approach to defining and measuring joint deterioration was needed. Consequently, the expert group agreed on the term 'problem joint', reflecting clinical and patient-centric factors, such as joint pain and functional mobility, which can be accumulated and measured over time.

Discussion/Conclusion: Discussion with clinical and modelling experts highlighted the importance of measuring long-term outcomes for PwSHA. Expert opinion on the future disease trajectory for PwSHA – both in the presence and absence of bleeding events – will aid in developing measures to capture and evaluate the lifetime benefits and costs of current and future novel therapies.

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P296 | Use of pharmacokinetics-pharmacodynamics modeling and simulation to support early phase dose selection for PF-06741086, an anti-TFPI monoclonal antibody

T. Zhu[1,*]; C. N. Lim[1]; P. Dua[2]

[1]*Pfizer Inc, Cambridge, USA;* [2]*Pfizer Inc, Cambridge, UK*

Introduction: Tissue factor pathway inhibitor (TFPI) is a protease inhibitor of tissue factor-activated coagulation factor VII (FVIIa) and activated factor X (FXa). PF-06741086 is a monoclonal antibody that targets TFPI with the intent to reduce inhibition of the extrinsic coagulation pathway and increase clotting activity in bleeding disorders such as hemophilia. The objective was to develop population pharmacokinetic-pharmacodynamic (PKPD) models for PF-06741086 with data from healthy subjects and use these to support internal decision making and dose selection for the Phase 1b/2 study. PD biomarkers of interest included ex vivo coagulation endpoints such as diluted prothrombin (dPT), peak thrombin generation (PKT) and in vivo biomarker prothrombin fragment 1 + 2 (PF1 + 2).

Methods: Nonlinear mixed effects modeling approach was taken to describe PF-06741086 PK, total TFPI and coagulation biomarkers data from a randomized, placebo-controlled Phase 1 single ascending dose study. Various models were explored for PK and total TFPI (including quasi-steady-state approximation of a target mediated drug disposition model, parallel linear and Michaelis-Menten elimination) and PKPD (direct Emax, indirect response). Modeling and simulations were performed using NONMEM.

Results: Data following intravenous (150 to 440 mg) and subcutaneous (30 to 300 mg) administration of PF-06741086 in healthy subjects was included in the analysis. PF-06741086 PK was adequately characterized by a two-compartment model with first-order absorption and parallel linear and Michaelis-Menten elimination from the central compartment. PK-dPT and PK-PKT relationships were described with direct effect Emax model, and PK-PF1 + 2 relationship by indirect response model with stimulatory effect on PF1 + 2 input. Based on simulations utilizing the PKPD models, a certain dosing regimen was predicted to produce robust changes in the biomarkers, with projected steady-state trough concentrations above the estimated EC90 for all the biomarkers.

Discussion/Conclusion: Modeling and simulations was used to facilitate dose selection for the Phase 1b/2 study using Phase 1 data.

Disclosure of Interest: T. Zhu Shareholder of: Pfizer, Employee of: Pfizer, C. Lim Shareholder of: Pfizer, Employee of: Pfizer, P. Dua Shareholder of: Pfizer, Employee of: Pfizer.

P297 | Individualizing prophylactic treatment with the use of albutrepenonacog alfa: Case reports

M. Economou[1]; A. Teli[1]; V. Gourtsa[1,*]; A. Adramerina[1]; E. Platokouki[2]

[1]*1st Pediatric Department of Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki;* [2]*Haemostasis and Thrombosis Unit, Aghia Sophia Children's Hospital, ATHENS, Greece*

Introduction: Treatment with the new longer-acting FIX products promises increased trough levels and effective prophylaxis with fewer injections. It is widely accepted that prophylaxis with longer-acting products should be individualized according to each patient's clinical profile.

Methods: The aim of the present report was to describe the use of albutrepenonacog alfa (IDELVION, CSL Behring), a new recombinant coagulation factor IX with prolonged half-life that is achieved by fusion with recombinant albumin, in non-inhibitor patients with moderate hemophilia B. IDELVION has been licensed for treatment and

prophylaxis of bleeds in patients with hemophilia B based on clinical data mainly involving patients with the severe form of the disease.

Results: The first case concerns a 13 year old patient presenting with a mild bleeding phenotype during the first years of his life. At the beginning of puberty the child started presenting with repeated traumatic bleeds. The family could not control the child's physically intense life-style and subsequent bleeds –approximately 10 a year–, so tertiary prophylaxis with standard recombinant factor IX was initiated (30-40 IU/kg, once weekly). Even though number of bleeds only slightly decreased (~8/year) and a target joint developed, the family did not agree on increasing prophylactic FIX dosing intervals. IDELVION initiation at 35 IU/kg once weekly was proposed. In the subsequent 6 months the child has remained free of bleeds, while fully maintaining previous physical activity. The second case concerns a 12 year old boy also with a moderate genotype but a severe phenotype. His record showed an ABR of ~10 while on twice weekly prophylaxis at ~35 IU/kg with a standard recombinant factor IX, mainly as a result of traumatic bleeds due to intense physical activity. IDELVION was proposed at 35 IU once weekly. During the subsequent 6 months the boy has presented with only 1 traumatic joint bleed, while retaining previous physical activity.

Discussion/Conclusion: Bearing in mind that bleeding phenotype is not always consistent with genotype, and that in certain age groups physical activity is usually not a matter of discussion but has to be considered as a given, extended half-life products such as IDELVION offer the opportunity of extending effective prophylaxis to more patients, with limited number of monthly infusions.

Disclosure of Interest: None declared.

P298 | Exergames for home rehabilitation in children with hemophilia

V. Begnozzi*; G. Dallari; E. Boccalandro

IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Introduction: The aim of this study was to the test the efficiency of two different home exercise programs, in order to understand which one is more suitable for children with haemophilia. According to the guidelines for the treatment of chronic diseases exercises programs, to be effective must be funny and challenging. In the project HERO we used exergames to entertain children with hemophilia and control them remotely, in the frame of a rehabilitation program carried out at home, thus being able to observe them and modify accordingly the planned exercises.

Methods: We have compared two different groups (experimental and control), each formed by 10 boys. Each group did a daily routine program, from Monday to Friday, for two months. The workout did last 10 minutes daily. Children were evaluated before and after the program by means of the scoring tool HJHS, a statistic postural evaluation and the baropodometric platform. The experimental group used an exergame program designed in collaboration with the faculty of informatics of the University of Milano, while the control group did the prescribed exercises as described by the physiotherapist in the playbook Libro dei Gormiti.

Results: We investigated in both groups the imbalance between the weight put alternatively on the left and right side with open and closed eyes. We analyzed them with the t-Student, which proved that none of the before vs after differences were statistically significant (open eyes – *P* value: 0.18; closed eyes – *P* value: 0.27). We also analyzed the improvement in the LFS score, tested both with open and closed eyes. They were found to be both statistically significant (open eyes – *P* value: 0.04; closed eyes – *P* value: 0.02).

Discussion/Conclusion: Both the experimental (exergames) and control groups have shown improvements after rehabilitation, but the experimental group was more markedly improved in comparison with the control group, especially for the LFS score, both with open and closed eyes. This experience with rehabilitation using exergames should be considered as a pilot study, experience to the limitations of the short duration of the follow up. However, the enthusiasm shown by the boys involved in the exergames prompt us to design another protocol based upon a much longer follow-up.

Disclosure of Interest: None declared.

P299 | A case of founder effect in Russian patients with hemophilia A

V. Salomashkina[1,*]; O. Pshenichnikova[1]; F. Perina[2]; V. Surin[1]

[1]*Laboratory of genetic engineering, National Research Center for Hematology, Moscow, Russian Federation (Russia), Moscow;* [2]*Sverdlovsk region Regional Clinical Hospital for Children №1, Ekaterinburg, Russian Federation*

Introduction: A founder effect is reported for some human genetic disorders like ataxia-telangiectasia (Gilad et al., 1996), glomuvenous malformations (Brouillard et al., 2005), Wilson disease (Loudianos et al., 1999), Pompe's disease (Shieh et al., 1998), Tay-Sachs disease (Mitchell et al., 1996). It was also reported for hemophilia A and B (Li et al., 2014; Lasalle et al., 2018), although independent de novo mutations are considered to be much more common for these diseases.

Methods: We conducted a mutation analysis by Sanger sequencing of all functionally significant F8 gene fragments for patients with no inv22 or inv1 found. Total DNA was extracted from whole blood using the phenol–chloroform method. We also constructed haplotypes using four variable loci: two SNPs located in introns 1 and 19 and two extragenic microsatellite loci HA472 (STS REN 90200) and HA544 (near STS sWXD2469), each consisting of two independent blocks of trinucleotide DNA motifs (Surin et al., 2007). The SNPs were analyzed using the restriction analysis followed by electrophoresis in PAAG; microsatellite loci were sequenced.

Results: During our work on the mutation spectrum research for Russian Hemophilia A patients, we discovered a new mutation His634Arg that was found in 7 patients with mild Hemophilia A (F8 activity 10-30%). No other nucleotide substitutions were found for those patients. All of them originated from Sverdlovsk Oblast – a federal subject in

the Ural Mountains region in Russia; its area is around 200 thousand square km and population is around 4 million people. We constructed four-loci haplotypes for those patients and for 10 other patients with Hemophilia A from the same region carrying different mutations. All patients with the reported mutation shared the same unique haplotype Alu(-) Hind(-) HA472:(CTT)24(CTT)20 HA955:(CCT)13(ATT)7. All other patients had different haplotypes, which indicates founder effect for this new mutation.

Discussion/Conclusion: Our results show that for mild Hemophilia A the founder effect is quite a frequent event. It can be found even in ethnically mixed region with complex population history, provided the mutation leads to FVIII deficiency mild enough to provide carriers survival during the historical times before supplemental FVIII treatment became available.

Disclosure of Interest: None declared.

P300 | Implementation of a web-based platform for articular monitoring in patients with hemophilia in the French database NHEMO

V. Horvais[1,*]; N. Grinda[2]; M. Gérard[2]; B. Gillet[3]; A. Fouasson-Chailloux[4]; M. Dauty[4]; R. D'Oiron[2]; M. Trossaërt[3]; T. Lambert[2]

[1]Clinical Research, University Hospital of Nantes, Nantes; [2]Haemophilia Treatment Centre, Kremlin-Bicêtre University Hospital, Kremlin-Bicêtre; [3]Haemophilia Treatment Centre, University Hospital of Nantes, Hôtel-Dieu; [4]Physical Medicine and Rehabilitation Centre, University Hospital of Nantes, Saint-Jacques, Nantes, France

Introduction: With the development of electronic medical records, web-accessible and mobile applications have become the new standard for caregivers. Therefore, the French Haemophilia Treatment Centres (HTC) have a free access to a web-based database "NHEMO" to record clinical, biological and treatment data. Nevertheless, NHEMO was lacking a specialized tool designed for physiotherapists to monitor the articular follow-up of Patients with Haemophilia (PwH), for whom the intra-articular and intramuscular bleedings may conduce to a terminal degeneration of the joints.

Methods: This project aims to develop a web formulary to record all episodes, articular scores (Haemophilia Joint Health Score HJHS) or treatments related to muscular and articular bleedings in PwH, on Personal computers (PC) or mobile devices, via NHEMO. Physiotherapy experts and Information Technology staff members of two French constitutive HTC lead the project. The major steps were the following: review of the literature / statement of requirements to identify the critical items and define the process workflows, collegial consultation process to define the global design of the appliance and operational acceptance tests / implementation.

Results: The deployment on PC is already effective. The formulary meets the World Federation of Haemophilia's demands about the regular standardized evaluation of joints and allows collecting via NHEMO: the musculoskeletal status (HJHS) and the assessment of long-term outcomes (haemarthrosis, muscles' strength and circumferences, balance, back statics), the sites & types of bleeds (hematomas, haemorrhages), the imaging evaluations, the types & doses of treatment and the surgical procedures & hospitalizations. Summary reports permit to synthesize the articular condition from one evaluation to the next. The tests 'results are on read-only access for any NHEMO users.

Discussion/Conclusion: The decision to implement an articular follow-up appliance in the NHEMO database has fixed some key demands about the data governance and has ended up in a user-friendly formulary, consistent with the needs of the ultimate users. New lines of approach can be explored, such as a satisfaction survey to ameliorate the apparatus, the implementation of an Anglo-Saxon version and, of course, the very first research protocols on haemophiliac physiotherapy.

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P301 | Management of acquired von Willebrand syndrome in the setting of a patient with Dieulafoy's lesion

V. Higuero Saavedra[1,*]; A. Avendaño Pita[1]; E. Sobejano Fuertes[1]; D. Presa Morales[1]; H. M. Prieto Marcos[2]; J. R. González Porras[1]; J. M. Bastida Bermejo[1]

[1]Hematology, University Hospital of Salamanca; [2]Gastroenterology, Hospital Universitario de Salamanca, Salamanca, Spain

Introduction: Acquired von Willebrand syndrome (aVWS) is a rare hemorrhagic syndrome with the biological abnormalities found in hereditary von Willebrand disease, but associated to an underlying condition. We report a case of aVWS in the setting of a MGUS and Dieulafoy's lesion.

Methods: A 51-year-old woman was admitted to the ER due to hemorrhagic stools. She referred a 6-year history of hemorrhagic syndrome. Previous history did not show clotting times alteration or familiar history of bleeding.

Results: At her arrival blood analyses showed prolonged aPTT and anemia. Endoscopic studies showed Dieulafoy's lesion in gastric mucosa that was treated with hemoclip and cauterization.

Further analysis showed low levels of factor VIII:C (21%), FVW antigen (20%) and activity (<15%). Desmopressin test showed no response. Genetic studies for VWF and Rendu-Osler syndrome were negative.

Full body CT did not show data of lymphoproliferative disorders and autoimmune disorders were discarded. Serum protein electrophoresis showed a monoclonal component of 0.3 mg/dL. Bone marrow aspirate was performed with 1% plasma cells, 73% pathological by flow cytometry immunophenotyping. The patient was diagnosed with MGUS, known to be a cause of aVWS. The pathophysiology is immune-mediated, with production of antibodies directed against VWF, forming complexes that are cleared from circulation.

Management of this pathology varies depending of the underlying cause. Studies demonstrate the efficacy of intravenous immunoglobulin (IVIG) during the bleeding episodes; in case of no response, VWF containing concentrates or recombinant factor VIIa are an alternative treatment. In our patient, on-demand-only IVGV was decided initially; however, due to Dieulafoy's lesion, she suffered various episodes of digestive bleeding with severe anemia after the diagnosis. At this point, monthly IVIG was established. With this approach we overcome a decrease in the number of bleeding episodes and an improvement in quality of life. Nevertheless, treatment adherence was an issue and the patient missed IVGF in several occasions which resulted in new severe bleeds.

Discussion/Conclusion: aVWS is a significant under-diagnosed bleeding disorder which can occur in different diseases. Diagnosis is complex due to the many tests that have to be obtained. The management varies depending on the underlying condition, but there is little evidence coming from big studies.

Disclosure of Interest: None declared.

P302 | Low dose prophylaxis therapy in severe pediatric hemophilia A patients

V. Shah[1,2,*]; P. R. bambharoliya[3]; H. M. Radadiya[4]; on behalf of Dr Vijay B Shah, Dr Praful Bambhroliya, Dr Haresh Radadiya

[1]Government Medical College, Pediatrics, Surat, India; [2]Hemophilia Care Center, Surat, India; [3]Pediatrics, New Civil Hospital, Surat, India; [4]Hemophilia Care Center, New Civil Hospital, Surat, India

Introduction: Though prophylaxis can prevent joint damage, most of the PWHA from west India (Gujarat) used to receive on demand factor replacement until recently when Gujarat State Government started providing factors to PWH free of cost. We started patient education workshops, Hemophilia Clinics, awareness programs and motivational activities for family members. This was followed by initiation of low dose prophylaxis treatment in eligible candidates.

Methods: Out of 162 pediatric patients of PWHA registered, 10 severe PWHA were eligible and consented for prophylaxis. They were assessed with ABR, HJHS, FISH, Patterson score, MRI both knee score before and 1 year after starting prophylaxis. PWHA were started prophylaxis with 15 IU/kg (recombinant factor VIII) twice a week, supplemented with physiotherapy, patient education programs and one on one interactions with family members to address various medical & non-medical issues. In PWHA with break through bleeds were treated as per WFH 2012 guideline. Factor infusion technique was taught to parents, to pave a road to home therapy in future.

Results: There was 80.64% reduction in ABR, 80% reduction in HJHS and 28.22% increase in FISH, 37.5% reduction in Pettersson score and 7.1% reduction in MRI score after 1 year of low dose prophylaxis in PW Hemophilia A.

Discussion/Conclusion: Low dose prophylaxis therapy was very effective in our pediatric severe PWHA (<1%) to improve the joint health and functional status, in patients who were previously receiving on demand therapy, that too infrequently. The overall Functional improvement was seen in our patients. Probably with time, we will see more improvement in functional scores. There was no deterioration on FISH score of any patient. The overall joint health improvement was seen in our patients. Probably with time and physiotherapy we will see more improvement in joint health scores. Decreased Pettersson score and MRI of both knee score was seen suggesting improvement in our patients at the end of 1 year.

Overall, low dose prophylaxis with factor VIII, along with patient education programs and regular physiotherapy in severe PWH A showed improvement in their bleed rates (ABR), joint health score (HJHS) and functional assessment (FISH) and Pettersson score and MRI score at the end of 1 year, in those, who were previously receiving on demand factor replacement.

Disclosure of Interest: None declared.

P303 | Avoiding accumulation of FVIII when treating vwd patients with normal baseline FVIII levels by using a high ratio von Willebrand concentrate

V. J. M. Hortensius*; P. van der Valk; K. P. M. van Galen; K. Fischer; R. E. G. Schutgens; E. P. Mauser

Haematology (Van Creveldkliniek), University Medical Center, Utrecht, Netherlands

Introduction: In von Willebrand disease (VWD) patients, accumulation of plasma factor VIII levels (FVIII) after the administration of exogenous FVIII in low von Willebrand factor (VWF)/FVIII ratio products (LRP) has been reported. However, data on accumulation of FVIII after repetitive bolus administrations of the plasma derived high ratio VWF-product (HRP) Wilfactin® is lacking.

Methods: In this monocentre retrospective study, all VWD patients (VWF:RCo levels ≤50 IU/dL) with FVIII levels ≥50 IU/dL treated with the HRP Wilfactin® from 2011 to 2018 were included. FVIII and VWF activity (VWF:Ristocetin, VWF:RCo) levels were extracted from electronic medical records (median [IQR]). Accumulation of FVIII was defined as FVIII levels >150 IU/dL after repetitive injections, in combination with a >50% increase in FVIII activity level.

Results: 34 VWD patients (22 type 1, 5 type 2A, 4 type 2B and 3 type 2M) with 58 HRP treatment episodes were included. Indications for treatment were: surgical procedure (n = 38), bleeding episode (n = 5) or other (n = 15). Mean age was 53.3 ± 16.3 years. Median baseline VWF:RCo and FVIII levels at t = 0 were 29 [20-48] and 77 [63-106] IU/dL, respectively. A median of 3 HRP infusions were given (range 1-15) with a median first dose of 31 [21-43] IU VWF:RCo/kg. 30 minutes after the first dose mean VWF:RCo recovery was 1.72 ± 0.60 IU/dL per IU kg^{-1} (n = 41). VWF:RCo recovery was similar in patients with type 1 and 2 VWD (mean difference 0.04 IU/dL per IU kg^{-1}). As expected, hardly any FVIII increase occurred 30 minutes after the first dose (mean recovery 0.03 ± 0.31 IU/dL per IU kg^{-1}). After two HRP infusions, the median increase in VWF:RCo and FVIII levels was 43 IU/dL [29-66] and 33 IU/dL [20-63] respectively, at *t* = 24 hours (n = 24)

Accumulation of FVIII was documented in 3/24 (13%) treatment episodes. In 4 of 32 treatment episodes, FVIII levels exceeded 200 IU/dL at some point after repeated injections. No thrombotic events were reported. Four mild secondary bleedings (oozing from surgical wounds) occurred in 3 individual patients. For 3 of these bleedings, additional infusions with the HRP were given with good clinical effect.

Discussion/Conclusion: In the majority (87%) of treatment episodes in VWD patients with baseline FVIII levels ≥50 IU/dL FVIII accumulation did not occur after repeated bolus injections with HRP von Willebrand concentrate.

Disclosure of Interest: None declared.

P304 | Extracts from Malian herbal plants could modify in vitro hemostasis parameters using blood from severe hemophilia A patients?

Y. Diallo[1,*]; S. D. Nathalie[2]; D. S. I. Boubacar[3]; K. Bourama[4]; T. D. Adiaratou[2]; D. Mamadou[4]; S. S. Djeneba[1]; K. Massama[1]; N. Doumbia[1]; O. Nouhoum[1]; T. S. Boubacar[5]; K. B. Aphou Salle[6]; D. Adama[6]; K. M. Halidou[3]; S. T. Assa[1]; M. Jonnhy[7]; D. Drissa[2]; S. Rokia[2]

[1]Service de Médecine, Hopital du Mali; [2]Dapartement de Médecine Traiditionnelle, Faculté de Pharmacie; [3]Laboratoire de Biologie; [4]Pediatrie, Hopital du Mali, Bamako; [5]Service de Médecine, Hopital Somino Dolo, Sevare; [6]Radiotherapie, Hopital du Mali, Bamako, Mali; [7]Bleeding Disorders Unit/ Haemophilia Comprehensive Care Centre-Charlotte Maxeke Johannesburg Academic Hospital Johannesburg, University of the Witwatersrand and NHLS, Johannesburg, South Africa

Introduction: We have postulated that some plants used for their hemostasis properties could modify hemostasis parameters using blood from severe hemophilia A patients. Our objective is to study the effect of twelve extracts from ten herbal plants known for their capacity to stop bleed in non-hemophiliac patients, which could reduce the coast of hemophilia A patients treatment.

Methods: Twelve extracts from ten plants were incubated with five milliliters of whole blood from volunteers severe hemophilia A. The blood sample was incubated at the room temperature with extract solution at the final concentration of 0.25 g/L. The platelet poor plasma was prepared by centrifugation at 4000 g for 15 minutes at 20°C. Phosphate buffered saline (PBS) was used as a control.

Activated Prothrombin Time (aPTT) and Prothrombin Time (PT) were measured immediately (T0) and following 30 minutes (T30) incubation using a *STA satellite®*, reagents (Stago). The aPTT results were expressed as a ratio and were compared to aPTT for all patients before incubation with extracts. The PT results were expressed as a percentage. All tests were performed in the laboratory of Hopital du Mali. Each experimental point was performed in duplicate. Results from at least 3 experiments were expressed as mean ± SEM and range between minimum and maximum values.

Results: After testing the 12 extracts, we have found that 4 extracts modified aPTT, and 6 has a probably effect on PT.

We have found for aPPT values at T0 and T30, respectively following results with extracts: Annona senegalensis (0.98 ± 0.12 vs 1.01 ± 0.11), Entada africana (0.98 ± 0.07 vs 0.94 ± 0.05), Carica papaya (1.03 ± 0.16 vs 0.91 ± 0.18), Detarium microcarpum (1.03 ± 0.18 vs 0.89 ± 0.17). The mean result for the pure condition at T0 without any extracts was (2.67 ± 0.67).

The means values for PT at T0 and T30, were respectively (81.2 ± 22.6 vs 89.5 ± 21.6) for the pure condition, (91.8 ± 36.1 vs 93.7 ± 35.6) for Cassia sieberiana, (93.6 ± 28.5 vs 106.3 ± 34.1) for Pteleopsis myrtifolia (roots), (101.0 ± 31.0 vs 106.0 ± 23.9) for Pteleopsis myrtifolia (barks), (87.7 ± 20.2 vs 95.0 ± 22.4) for Erythrina senegalensis (roots), (85.0 ± 21.2 vs 102.3 ± 27.6) for Erythrina senegalensis (barks) and (80.0 ± 18.1 vs 97.1 ± 20.3) for Carica papaya.

Discussion/Conclusion: Some extracts from Malian herbal plants could modify in vitro, PT and aPTT using blood from severe hemophilia patients in Mali.

Disclosure of Interest: None declared.

P305 | Assessment of the quality of life, anxiety and depression in children and adolescents with haemophilia and their mothers' in Turkish sample

M. Cikili Uytun[1]; F. Cetin[1]; R. Yilmaz[1]; S. Uytun[2]; Z. Babadagi[1]; M. Karadogan[3]; F. T. Mutlu[3]; Y. Altuner Torun[3,*]

[1]Child and Adolescent Psychiatry, Medical Health Sciences, Kayseri, Turkey; [2]Pediatrics, Medical Health Sciences, Kayseri, Turkey; [3]Pediatric Hematology, Medical Health Sciences, Kayseri, Turkey

Introduction: Due to the improvements in the management of haemophilia, it can still have psychological and social effects which can impact on the quality of life (QoL), not only for a child who has the condition, but also for their parents. It was aimed to study the assessment of psychological problems in children and adolescent with hemophilia and their parents. Additionally we explored the influence of mothers' psychological states on their children.

Methods: A total of 20 children and adolescents with haemophilia A or B and 20 healthy controls, aged 6–16 years old were included. Firstly, Kiddie-Schedule for Affective Disorders and Schizophrenia, present and life time version (K-SADS-PL) was applied to parents. However, sociodemographic questionnaire, Child Depression Inventory, The Spielberger State-Trait Anxiety Inventory and KINDL^R Questionnaire was used for children and adolescents in both groups. Beck Depression Inventory, Beck anxiety inventory and KINDL parent form was used for mothers in both groups. Burden interview, The Level of Expressed Emotion scale and MOS SF-36 scale was used mothers only in patient group.

Results: Our results demonstrated higher anxiety scores and increased anxiety disorder diagnosis among children and adolescents with hemophilia. However, mother's anxiety scores, depression scores are higher than control group and QoL of their children also show lower scores in parents' KINDL forms. Mothers' depression and anxiety are associated with children's depression, anxiety and QoL scores.

Discussion/Conclusion: Our study emphasis that psychiatric factors should not be ignored in the treatment and follow-up of children and adolescents with hemophilia and their parents.

Disclosure of Interest: None declared.

P306 | Significance of birth and family histories for hemophilia

Z. Salcioglu*; G. Aydogan; F. Akıcı; C. Bayram; G. N. Özdemir; G. Ersoy; T. N. Güçer; Z. Başlar

Pediatric Hematology and Oncology Clinic, İstanbul Kanuni Sultan Süleyman Education and Research Hospital, İstanbul, Turkey

Introduction: Both hemophilia A and B are X linked recessive disorders, which are seen familial in 70% of cases and others are seen sporadically. However, the few number of cases that are diagnosed prenatally is remarkable. This study is planned to evaluate family and birth histories of our patients.

Methods: Family and birth histories of 153 hemophilia A and B patients who have been followed in our outpatient clinic between 1990 and 2017 are evaluated retrospectively from patient reports and parents information.

Results: All the patients were male except for a girl who have diagnosed as hemophilia A. 114 of patients were hemophilia A and 39 were hemophilia B. Factor activities in hemophilia A group were <1% for 77 patients (67.5%), 1%-5% for 27 patients (23.7%); >5% for 10 patients (%8.8). Delivery types of 95 patients (83.3%) were normal spontaneous way and 19 patients (16.7%) were c-sections. 66 of patients (58%) have family history of relative with hemophilia but none has preferred prenatal diagnosis. Factor activities in hemophilia B group were <1% for 16 patients (41%), %1-5 for 9 patients (23%); >5% for 14 patients (36%). Delivery types of 28 patients (72%) were normal spontaneous way and 11 patients (28%) were cesarian section. 24 of patients (62%) have family history of relative with hemophilia but none has preferred prenatal diagnosis, like hemophilia A group. There were 12 parents who have more than one child with hemophilia A, whereas there were 4 parents who have more than one child with hemophilia B. Inhibitors are detected in 7 patients with hemophilia A. There were 12 refugee patients, 7 hemophilia A and 5 hemophilia B. There were 2 deaths from hemophilia during 27 years, one from sepsis and one from traffic accident. When all patients were analyzed, in 90 patients (58.8%) there family history of hemophilia but none was directed for prenatal diagnosis. 123 patient (80.4%) has normal spontaneous delivery where as 30 patients (19.6%) has been delivered by c-section. The decision for c-section was taken because of conditions except hemophilia.

Discussion/Conclusion: Overall, it is obvious that taking a detailed family history in hemophilia patients is very important. Evaluation of hemophilia carriers to have genetic counseling and follow up during pregnancy, is consequential to decrease morbidities caused by hemophilia.

Disclosure of Interest: None declared.

P307 | Iliopsoas hematoma in patients with hemophilia: A five year experience of a single center

Z. Karakas; S. Celilova; R. Tuna; D. Tugcu; S. Ocak; A. Hasdemir; S. Aydogdu; A. O. Karagenc; A. Unuvar; S. Karaman

Pediatric Hematology-Oncology, Istanbul University Istanbul Medicine Faculty, Istanbul, Turkey

Introduction: Iliopsoas hematoma is a rare but especially dangerous complication of severe hemophilia. The presenting symptoms are hip, groin, thigh, or low back pain and may mimic a variety of etiologies ranging from benign to life threatening such as hemarthrosis of the hip joint, osteonecrosis of the femoral head, appendicitis, kidney stone, or incarcerated hernia.

Methods: Four cases of iliopsoas hematoma were diagnosed in 50 patients with severe and moderate hemophilia over the last 5 years at our hemophilia center. We retrospectively reviewed these cases to determine the incidence and precipitating factors of iliopsoas hematoma in hemophilia.

Results: Of the 4 patients, 2 had severe hemophilia A and 2 had moderate hemophilia A. No patients had a history of inhibitors to factor VIII concentrates. The age range was 10 to 20 years (median: 16 years). At the time of the hematoma, 1 patient was receiving long-term prophylactic factor VIII concentrate therapy. The hematoma was posttraumatic in 3 cases and spontaneous in 1 case. Diagnosis was made by ultrasound and MRI in all patients, Femoral nerve compression developed in 1 case. The treatment consisted of 3 recombinant, 1 plasma derived factor VIII concentrate, and rehabilitation therapy. There was one recurrence and no pseudotumor developed in any of the patients. Two patients with moderate hemophilia underwent Factor VIII prophylaxis for 3 months. Lifelong prophylaxis program initiated for the severe hemophiliac.

Discussion/Conclusion: Although prophylactic use of FVIII and compliance with treatment is expected to reduce the risk of serious bleeding in patients with hemophilia, sports and other activities in adolescent patients may lead to the development of iliopsoas hemorrhage. Prophylaxis in adolescent patients should be planned considering the patient's activity.

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