EXTENDED REPORT

FMF50: a score for assessing outcome in familial Mediterranean fever

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ABSTRACT

Background Colchicine is the main treatment for familial Mediterranean fever (FMF). However, biological agents and other treatments are available for patients who are unable to receive optimal treatment.

Objective To develop outcome criteria that define response to treatment.

Methods Two rounds of Delphi exercise were followed by a consensus conference enabling the definition of the criteria to be employed. Data for patients with FMF responding and resistant to their treatment were obtained from the FMF Arthritis Vasculitis and Orphan disease Research in paediatric rheumatology (FAVOR) website. The suggested criteria were analysed and validated in this patient cohort. Sensitivity/specificity measures and the ability of the score to discriminate between patients with active and inactive disease via the best cut-off score were calculated by a receiver operating characteristic analysis.

Results Compliance with the maximum dose of the drug was considered essential for evaluation of the patients. Seven criteria were suggested in the consensus conference. The performance of each criterion, in differentiating between resistant and responsive patients, was tested. The final set of criteria was defined as at least 50% improvement in five of six criteria, without worsening in any one defined response to treatment with a very high sensitivity and specificity. The items of this FMF50 included:

1. Percentage change in the frequency of attacks with the treatment.
2. Percentage change in the duration of attacks with the treatment.
3. Patients/parents' global assessment of disease severity (10 cm visual analogue scale (VAS)).
4. Physicians' global assessment of disease severity (10 cm VAS).
5. Percentage change in arthritis attacks with the treatment.
6. Percentage change in C-reactive protein, erythrocyte sedimentation rate or serum amyloid A level with the treatment.

Conclusions The FMF50 produced is a user-friendly measurement tool to guide physicians and can be used in clinical trials.

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease.[1 2] It is characterised by recurrent and 1–3-day febrile attacks affecting peritoneal or pleural serosa, synovial tissues and skin. Untreated patients have the early and long-term complications of ongoing inflammation and may develop secondary amyloidosis.[3] Colchicine is effective in both controlling the attacks and preventing the development of the most devastating complication of amyloidosis. Colchicine treatment is safe, effective and well tolerated in the large majority of patients with FMF. However, 5–10% of patients do not respond to colchicine treatment[2 4] and another 2–5% do not tolerate the drug well.[4] Untreated or inadequately treated patients are at risk of developing complications and have a poor quality of life. Biological agents have been effective in a considerable number of these patients.[5–7] However, we do not have standardised measures to assess response to treatment in patients with FMF, nor in any of the autoinflammatory diseases.

Many problems of FMF management are not standardised for optimal disease control and follow-up.[8] Performing clinical trials in patients with FMF is challenging, mainly owing to the small number of patients resistant to treatment and the heterogeneity of disease manifestations. Standardised disease-specific outcome scores are required to assess the performance of new drugs, by using variables that are sensitive to change over time.

We therefore aimed to develop a set of criteria that will help to assess treatment response in patients with FMF to be used both in clinical practice and in drug trials.

PATIENTS AND METHODS

The project was conducted using the Delphi technique and nominal group technique (NGT), specifically designed to combine judgements from a group of experts in a particular field. These two well-known techniques have been used previously to develop outcome instruments in rheumatic diseases.[9]

The first consensus panel was held in Ankara on 25 November 2011, to define the items necessary for a set of criteria to be used for the evaluation of response to treatment in FMF. The consensus was organised by FMF Arthritis Vasculitis and Orphan disease Research in paediatric rheumatology (FAVOR). Members of the Turkish Rheumatology Association, Turkish FMF study group, Turkish Society for Paediatric Nephrology and Paediatric Rheumatology Association were invited for this step.

Consensus formation methodology was designed so that each step was based on the results of the previous steps.

Step 1: web-based Delphi collection

Two sequential questionnaire-based surveys were carried out to select and rank the variables used in routine clinical practice to assess the response of a patient with FMF to a given treatment. At the first Delphi round, four open-ended questions were sent to 120 experts/doctors practising in paediatric rheumatology, nephrology and adult rheumatology, with special interest in FMF, through FAVOR (http://www.favor.org.tr).

In the second survey, physicians were asked to select up to 10 variables that they judged as clinically most important. Based on the results of the first Delphi round, a second Delphi form was developed with five questions. This latter set of questions aimed to define complete response, partial response and non-response. Mail, email, fax or telephone reminders were used to ensure a response rate of at least 80% for both surveys.

Step 2: data collection

Doctors who were running a dedicated outpatient clinic for FMF were invited to register their patients for the study. Registered patients were required to be diagnosed as having FMF according to Tel-Hashomer[10] or paediatric FMF[11] criteria and to have no other accompanying inflammatory disease.[10 11] All patients had been receiving colchicine at stable doses for at least 6 months. The response to treatment was based on the subjective clinical assessment of the senior FMF expert in each centre. Subsequently, another doctor was asked to complete the online registration forms for each patient. The experts were interviewed beforehand, to harmonise their assessment of the patients.

The six-page, case report form included demographic data, clinical manifestations (presence of signs/symptoms related to FMF), laboratory findings (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, serum amyloid A level (SAA)) and response to treatment. Demographic data included age, gender, date of disease onset and diagnosis, date of first and last visit to the referring centre. Information about molecular analysis was also collected, including the mutations found (according to the Infever database, http://fmf.igh.cnrs.fr/ISSAID/infevers/).

Detailed information about the attacks was collected: (i) characteristics of fever episodes (duration, frequency, triggers, etc); (ii) presence and frequency (always or often/sometime) of the clinical manifestations.

The electronic forms contained some predefined rules to avoid errors and missing data, and were also reviewed for consistency by a dedicated FAVOR research assistant.

The study was approved by local ethics committees, and informed consent was obtained from parents/guardians if the participant was younger than 18.

Step 3: consensus panel for defining criteria

NGT is a structured face-to-face meeting designed to facilitate reaching consensus through round robin discussion. After the surveys, and data collection a 1-day consensus conference was held in Ankara, Turkey, May 2013. Participants (listed as coauthors) were Turkish doctors who were experts in management of FMF and hereditary periodic fever syndromes. Two moderators with expertise in NGT (CA and ED) oversaw the implementation of this meeting. The goal of the meeting was to reach a consensus about the domains and variables (see below for definitions) that should be included in the FMF core set (the outcome measure to define the response to treatment in FMF). Before the meeting, participants received a booklet containing relevant articles and previous results of the Delphi round. The seven domains included in the final core set of variables for the evaluation of response to treatment in FMF and the related suggested variables for measuring each domain are shown below. Consensus (≥80%) was reached for the final statements.

Step 4: validation

Validation of the core set measures was conducted with the use of the OMERACT filter for outcome measures in rheumatology.[12] The applicability and practicality of the measures were determined by considering their briefness, simplicity, ease of scoring and the percentage of missing values.

Face and content validity were based on the results of the previous Delphi study and the consensus meeting. To determine responsiveness, the standardised response mean (SRM) was used to detect clinically important change between baseline and 6 months. The SRM was the average difference between the paired measurements, divided by the SD—that is, SRM=(value after treatment−value before treatment)/SD; 95% CIs were also provided. An absolute value for the SRM of 0.2 is considered a small effect, a value of 0.5 a moderate effect and a value of 0.8 a large effect.

We used the physician assessments as the 'gold standard'. Doctors who evaluated patients at baseline and at 6 months assigned them to the resistant or adequate response group.

Discriminative qualification was determined by evaluating the ability to distinguish between patients with or without improvement. A Student t test was used to compare the mean values of adequate and inadequate response groups. For Spearman's rank correlation coefficient, a value >0.7 was considered high, a value of 0.4–0.7 moderate, and a value of <0.4 low).

To determine measurement validity of the new scale, Spearman's correlation coefficient was calculated between scale score and percentage of reduction between the sixth month and baseline. To determine the best cut-off points for each item, receiver operating characteristic (ROC) analysis performed. We performed univariate logistic regression analysis for all the initially suggested criteria. The items that remained significant were used for the final criteria set (total items 6). Subsequently, the coordinates of the ROC were calculated and ROC curves were drawn to evaluate different set and weighting options. Sensitivity, specificity, negative predictive values and positive predictive values were calculated for different cut-off points:

PPV: probability of patient being drug sensitive while number of recovered criteria more than cut-off point.

NPV: probability of patient being drug resistant while number of recovered criteria less than cut-off point.

Sensitivity: detected proportion of true drug-sensitive patients.

Specificity: detected proportion of true drug-resistant patients.

Statistical analysis were performed using SPSS for Windows V.15.0.

RESULTS

Results of the Delphi exercises and consensus conference

In the first Delphi round, the frequency, severity and duration of inflammatory episodes ranked the highest for defining response to treatment. Elevated acute phase response (in order of frequency: CRP, ESR, SAA and fibrinogen) was the best laboratory indicator of resistance to treatment.

In the second Delphi round, 59 experts reported the frequency of attacks, 40 experts reported the duration of attacks and 36 reported the severity of the inflammatory episodes as

best indicators for the assessment of response to colchicine treatment. For a complete response, normal CRP levels were required by 54 experts while 43 experts reported that 50% decrease in CRP levels was acceptable as 'response' to treatment. Thirty-three experts stated that the patient should be attack free for a complete response to colchicine treatment. For defining the partial response to treatment, a 50% decrease in attack frequency was the preferred choice.

At the final consensus conference the requirements for assessing the outcome of the disease were defined as:

Compliance should be ascertained.

Efficacy of the treatment should be assessed after 3–6 months of treatment.

The dose of colchicine should be 2 mg/day for adults and it should be the appropriate maximum dose for the age and weight of a child.[13]

If the patient was unable to tolerate the required dose owing to side effects they were considered to be intolerant to the treatment.

A criteria set of seven items were defined to assess outcome or treatment response:

1. Percentage change in the frequency of attacks with the treatment.
2. Percentage change in the duration of attacks with the treatment.
3. Patients/parents' global assessment of disease severity (10 cm visual analogue scale (VAS)).
4. Physicians' global assessment of disease severity (10 cm VAS).
5. Percentage change in arthritis attacks with the treatment.
6. Percentage change in exertional arthralgia, myalgia, leg pain with the treatment.
7. Percentage change in acute phase reactants with the treatment (at least 2 weeks after the last attack).

Subsequently, each of these items was evaluated on the registry for their performance in differentiating between patients who were responding to treatment from those who were resistant.

The registry

A total of 289 patients with FMF for a median of 6.5 years were included. Of the 289 patients, 136 (47.1%) were male and 153 (52.9%) were female, and 147 (50.9%) were under the age 18. The mean age of the patients was 20.7 ± 12.91 and the mean age at diagnosis was 14.3 ± 10.9 years. The caring physician reported that 71 (24.6%) of these patients were resistant to the treatment they were receiving. All patients were receiving colchicine. None of the patients included were receiving anti-interleukin 1 (anti-IL-1) treatment at the time they were included in this registry.

For all patients, the number and duration of attacks decreased after treatment. The acute phase reactants decreased for all (see online supplementary table 1). The pattern of attacks was irregular in 63.6% of patients. Before treatment, 117 patients (40.5%) had had at least three attacks a month on average, whereas after treatment only 24 patients (8.3%) still this number of attacks.

The change in outcome parameters was more pronounced among the group of patients who had an 'adequate' response to treatment.

Finalising the criteria set for measuring outcome in FMF

The performance of each item defined by the consensus group was evaluated in the patient registry. The item 'percentage change in exertional arthralgia, myalgia, leg pain' performed poorly in differentiating between patients responding to treatment and those who were resistant. After the exclusion of this item the remaining six items were evaluated (table 1). At least 50% improvement in at least five of these six items, without worsening in any one, was defined as an adequate response to treatment in all of the registered patients (100% sensitivity)—that is, FMF50 (box 1). Any patient who did not satisfy FMF50 by 3–6 months of treatment was classified as not having an adequate response. Furthermore, 96.3% of the patients with resistant disease improved in only one item (table 1).

We then sought correlations between each item. Moderate to high correlations were found between patient VAS, physician VAS, percentage change in the frequency of attacks and change in the duration of attacks with treatment (all $p<0.005$). There were also significant correlations between ESR, CRP and SAA (table 2). Since all performed similarly in the validation process, the laboratory item was kept as ESR or CRP or SAA.

Finally the ROCs were assessed to analyse whether a 50% or 70% response defined the responding patients better. Although at the highest specificity the ROC curve for 70% response may be better, the overall area under the curve (AUC) for 50% response was found to be better than for the 70% response (AUC=0.817 (95% CI 0.761 to 0.874) vs AUC =0.784 (95% CI 0.721 to 0.830)) (figure 1). However, the difference between the two AUCs was not statistically significant (difference 0.033 (95% CI −0.019 to 0.103), p=0.182). We chose the 50% response mainly because it would be easier to achieve in practice.

Table 1 Sensitivity and specificity of the criteria for different threshold points

Number of recovered items	Number of patients with adequate response (TP/FP)	Number of patients with inadequate response (TN/FN)	Sensitivity	Specificity	PPV	NPV
0	218/0	3/68	100.0	4.2	76.1	100.0
≥1	210/8	20/51	96.3	28.2	80.4	71.4
≥2	190/28	45/26	87.1	63.4	87.9	61.6
≥3	146/72	57/14	67.3	80.3	91.3	44.5
≥4	92/126	65/6	42.4	91.5	93.9	34.2
≥5	36/182	71/0	16.6	100.0	100.0	28.2
6	0/218	71/0	0	100.0		24.7

FN, false negative; FP, false positive; NPV, probability of drug resistant while number of recovered criteria less than cut-off point; PPV, probability of drug sensitive while number of recovered criteria more than cut-off point; Sensitivity, detected proportion of true drug-sensitive patients; Specificity, detected proportion of true drug-resistant patients; TN, true negative; TP, true positive.

Box 1 Final domains in the core set for the evaluation of response to treatment in familial Mediterranean fever (FMF): an FMF50 response is required which shows at least 50% improvement in at least five of these parameters with no worsening in one

Outcome measures to define the response to treatment in FMF

1. Percentage change in the frequency of attacks with the treatment
2. Percentage change in the duration of attacks with the treatment
3. Patients/parents' global assessment of disease severity (10 cm VAS)
4. Physicians' global assessment of disease severity (10 cm VAS)
5. Percentage change in arthritis attacks with the treatment
6. Percentage change in CRP, ESR or SAA level with the treatment (at least 2 weeks after the last attack)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; SAA, serum amyloid A; VAS, visual analogue scale.

DISCUSSION

The introduction of colchicine was a major breakthrough in the treatment of FMF. Subsequent studies have shown that an efficient dose of colchicine decreases attacks and prevents the major complication of secondary amyloidosis.[2 4 13 14] However, we have found that some patients were intolerant or became intolerant over time to colchicine.[4] We also found that at least 5% were resistant to the drug and were at risk of developing secondary amyloidosis. New drugs and biological agents have become available. A range of drugs have been used for FMF, including thalidomide, interferon α, anti-tumour necrosis factor, anti-IL-6 and all the available anti-IL-1 formulations.[4 6 7 15] Initial small series and trials, particularly with anti IL-1 drugs, have shown that these drugs completely control inflammation in FMF.[6 7] However, the choice of biological drug depends on many factors, including documenting its efficacy by accepted and validated outcome measures allowing it to be licensed and the cost reimbursed by authorities.

To achieve this goal, we chose to work with experts in a country where FMF is common, with a prevalence of at least 1/1075.[16] This was to ensure that the doctors had a vast experience with the disease and could also gather a reasonable number of patients who were resistant to the standard of care. We applied a well-established methodology with an epidemiologist experienced in the structure. The consensus panel agreed on seven items that were also well-recognised features of previously published activity and severity criteria for the disease.[17 18] Subsequently, we assessed the performance of these seven criteria in differentiating between responsive and resistant patients. This analysis provided us with six criteria and the 50% response rate as cut-off value. Our main aim was to have a high specificity, since defining a 'non-responsive' patient as 'responsive' would put the patient in danger of the complications of chronic inflammation, including amyloidosis. The disadvantage of this approach was a lower sensitivity; however, we considered this acceptable, given that our main aim was to define 'adequate response'.

The proposed criteria include the patient's perspective with a VAS assessment as well as acute phase reactants, offering objective laboratory responses. Although SAA is regarded as the most sensitive measure of inflammation it was not chosen to be the sole marker because it is not available everywhere.

Until now there has been no formal way of assessing treatment response in FMF, or in any of the autoinflammatory diseases. Doctors dealing with patients with these diseases judged response based on the clinical features and laboratory results, but no guidelines were available. We herein present a user-friendly measurement tool to guide doctors and which can be used in clinical trials. The structure was designed to be similar

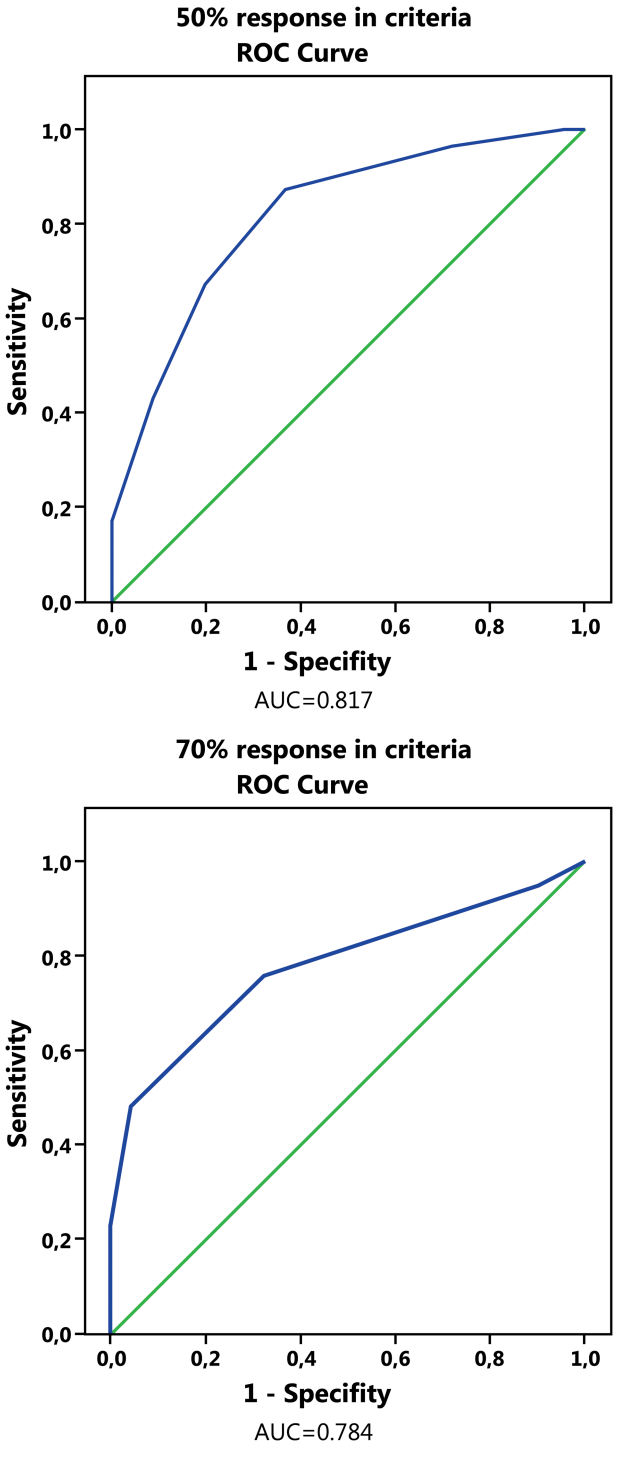

Figure 1 Receiver operating characteristic (ROC) curves for the performance of outcome criteria: the area under the curve is greater for a 50% response in the selected criteria than for a 70% response.

to ACR50. We hope that these criteria will be used to define response to all potential drugs, that they will be validated in other autoinflammatory diseases and also that FMF50 will become a definition used by health authorities. Subsequently, we suggest that the FMF50 tool might serve as a generic outcome measure accepted by all authorities. We await the performance of this tool in other populations.

This study had a number of limitations. All the 'treatment-resistant' patients were receiving colchicine, and the performance of FMF50 was not assessed in patients resistant to biological agents. We think that these outcome measures are not colchicine-specific and that the same set of criteria could be applied to measure response to biological agents. Another limitation was that we aimed to form a tool for both paediatric and adult patients. As a result some disease manifestations might be important for defining disease severity in one of the subgroups —for example, myalgia is a more pronounced clinical finding in adults, but this was omitted because of this combined aim.

In conclusion, the FMF50, defined as at least 50% improvement in five of the six criteria by 3–6 months with no worsening in any one (box 1), can define resistant disease in FMF. We hope that this will guide doctors in their management of the disease.

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Contributors All authors took part in the conception and design, acquisition of data or analysis and interpretation of data. Additionally, SO, ED and AD drafted the article or revised it critically for important intellectual content. CA also contributed to the design and drafting as our clinical epidemiologist.

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