

## Off-Label Dermatological Uses of Intravenous Immunoglobulin Treatment

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Published:

*J Turk Acad Dermatol* 2015; **9** (4): 1594r2.

This article is available from: <http://www.jtad.org/2015/4/jtad1594r2.pdf>

**Keywords:** Intravenous immunoglobulin, off-label, treatment

### Abstract

**Background:** Intravenous immunoglobulin (IVIG) was originally licensed as antibody replacement therapy in patients with primary immunodeficiencies. Subsequent experimental use of IVIG during the last several decades, however, has shown that it is effective in numerous medical conditions. Currently there are six United States, Food and Drug Administration approved clinical indications for IVIG including: the treatment of primary immunodeficiencies, the prevention of bacterial infections in patients with hypogammaglobulinemia caused by B-cell chronic lymphocytic leukemia, the prevention of coronary artery aneurysms in Kawasaki disease, the prevention of infections, pneumonitis, and acute graft-versus-host disease after bone marrow transplantation, the reduction of serious bacterial infections in children with HIV, and the increase of platelet counts in patients with idiopathic thrombocytopenic purpura. IVIG treatment have been reported in the following dermatologic diseases: autoimmune blistering diseases, toxic epidermal necrolysis, Stevens Johnson syndrome, drug-induced hypersensitivity syndrome, pyoderma gangrenosum, pityriasis rubra pilaris, atopic dermatitis, dermatomyositis, scleromyxedema, nephrogenic fibrosing dermopathy, vasculitis, lupus erythematosus, psoriasis, polymorphous light eruption, urticaria, Behçet's disease, scleroderma, Mucha-Habermann disease, hidradenitis suppurativa, acne vulgaris, streptococcal and staphylococcal toxic shock syndrome. The vast majority of these reports are in the form of individual case reports and small case series. A growing number of published reports suggest that IVIG treatment may be effective in the treatment of numerous inflammatory skin disease outside their currently approved indications. The following article provides a summary of the salient points in relation to the clinical use of intravenous immunoglobulin in dermatology.

### Introduction

IVIG has been used in the treatment of various dermatological conditions, including toxic epidermal necrolysis, bullous pemphigoid and pemphigus vulgaris. The new criteria have formalized the eligibility requirements for several dermatological conditions. This may increase access to intrave-

nous immunoglobulin for treatment for these conditions. However, there remain stringent eligibility criteria with which dermatologists need to be acquainted. In some conditions, dermatology review is mandated by these criteria while in other conditions with skin manifestations, referral to other specialists is required. Intravenous immunoglobulin is a fractionated blood product manufactured

from pooled human plasma. Introduced in the late 1970s, IVIG rapidly overtook the use of intramuscular preparations as a replacement therapy in primary and secondary immunodeficiencies.

Intravenous immunoglobulin is increasingly important as replacement therapy in immunodeficiency and as an immunomodulatory agent in autoimmune diseases and transplantation. In general, replacement therapy is indicated for patients who have primary or secondary immunodeficiency diseases with a history of recurrent or severe infection and deficient or absent antibody production. When used as immunomodulatory therapy, IVIG can interrupt the pathological immune responses that result in a wide range of human diseases, including various disease processes which involve the immune system, the nervous system, the blood and blood-forming organs, and the skin. There is a continuing increase in the clinical indications for IVIG resulting in double-digit annual increases in the volume used over the last 10 years [1, 2, 3, 4].

### Composition of IVIG

Since the early 1980s, immunoglobulin products approved for intravenous administration have been available in the United States. Typical plasma pools for yielding IVIG range from 4000 L to more than 50,000 L and contain plasma from between 1000 and 15,000 donors. Thus, each aliquot of IVIG contains a polyclonal mixture of antibodies from multiple donors that, by definition, contain antibodies with a multitude of antigenic specificities. The pooled preparations of immunoglobulin are made up of more than 90% IgG and small amounts of IgM and IgA. There are multiple commercial preparations of human immunoglobulin available for purchase in the United States. These products are distributed as either lyophilized powders or liquid concentrates. Lyophilized powders require reconstitution, whereas liquid concentrates do not. Sugars are often added to IVIG preparations to stabilize the product and prevent re-aggregation. Because IVIG is a blood product it carries an inherent risk of transmitting infectious diseases. Multiple steps are taken to minimize this risk during preparation, beginning with careful donor selection.

The second line of defense is screening of single plasma donations for HCV, HBV, HIV, and HBs antigen. In addition, PCR testing on plasma mini-pools or on the entire pool for fractionation has now been introduced. Processing of pooled donations then consists of a variety of viral inactivation or removal steps including treatment with solvent/detergent, polyethylene glycol, enzymatic treatment with pepsin or trypsin, pasteurization, acidification, nanofiltration, treatment with caprylate, and depth filtration. It is crucial for clinicians to understand that commercial IVIG products are not generic or identical. Differences in production methodologies impact the product's pharmacologic and physiologic profile and these, in turn, impact tolerability and efficacy. Important aspects of individual products that may affect clinical tolerability include volume load, osmolality, sodium content, sugar content, pH, and IgA content. Thus, the decision to use one product over the others is not trivial, as small differences may affect individual clinical outcomes [2, 3].

### Mechanism of Action of IVIG

The mechanism of action of IVIG is complex and is not fully understood at the present time. In many autoimmune bullous diseases, administration of IVIG has been shown to be associated with a decrease in serum levels of pathogenic autoantibodies, with undetectable levels being reached within 8–10 months and remaining undetectable. This has been demonstrated for antibodies to desmoglein 1 and 3 in pemphigus vulgaris, desmoglein 1 in pemphigus foliaceus, BPAG 2 in bullous pemphigoid, and anti- $\beta$ 4 integrin and anti- $\alpha$ 6 integrin autoantibodies in mucous membrane pemphigoid. In all of the dermatologic diseases presented in this article, however, IVIG likely produces its therapeutic effects via a combination of the following pathways: Functional blockade of Fc receptors, auto-antibody neutralization and inhibition of auto-antibody production, complement inhibition, modulation of cytokine and cytokine antagonist production, activation or functional blockade of the death receptor Fas, modulation of dendritic cell properties, increased expression and signalling through the inhibitory Fc-re-

**Table 1.** Off-Label Applications of IVIG in Skin Diseases

<b>A-Autoimmune Connective Tissue Disease</b>
1-Systemic and cutaneous lupus erythematosus
2-Dermatomyositis
3-Scleroderma
4-Mixed connective tissue disease
<b>B-Autoimmune Blistering Diseases</b>
1-Bullous pemphigoid
2-Cicatricial pemphigoid
3-Pemphigus vulgaris
4-Pemphigus foliaceus
5-Epidermolysis bullosa aquisita
6-Herpes gestationis
7-Linear IgA bullous disease
<b>C-Systemic vasculitis</b>
1-Wegener's granulomatosis
2-Polyarteritis nodosa
3-Microscopic polyangiitis
4-ANCA-negative vasculitis
5-Anti-neutrophil antibody syndromes
6-Livedoid vasculopathy
7-Cutaneous polyarteritis nodosa
8-Churg–Strauss syndrome
9-Behçet's disease
<b>D-Infectious diseases:</b>
1-Staphylococcal and streptococcal toxic shock syndrome
2-Necrotizing fasciitis
<b>E-Drug eruptions</b>
1-Stevens–Johnson syndrome
2-Toxic epidermal necrolysis
<b>F-The other inflammatory skin diseases</b>
1-Atopic dermatitis
2-Pyoderma gangrenosum
3-Hidradenitis suppurativa
4-Polymorphous light eruption
5-Pityriasis rubra pilaris
6-Nephrogenic fibrosing dermopathy
7-Psoriasis
8-Scleromyxedema and pretibial myxedema
9-Chronic urticaria
10-Kaposi sarcoma

ceptor, Fc gamma RIIB, enhancing steroid sensitivity [1, 2].

**Recommendations For Administration and Monitoring**

When initiating IVIG therapy, a dose of 2 g/kg per cycle is generally recommended, although a 3–4 g/kg total dose is recommended in patients with toxic epidermal necrolysis. A cycle consists of the total dose divided into three equal doses, each given on 3 consecutive days. Some clinicians prefer to give 400 mg/kg/day over 5 days. Each infusion is given slowly over 4–4.5 hours. Aggressive topical therapy and/or intralesional corticosteroids are essential supportive therapies in conjunction with IVIG in many diseases, especially autoimmune blistering diseases. The initial frequency is generally one cycle of IVIG every 3–4 weeks. In patients with aggressive ocular cicatricial pemphigoid, the infusions are given every 2 weeks. The initial frequency should be continued until there is effective control of the disease, which is defined differently depending on the condition. For autoimmune blistering diseases, this generally takes between 5 and 8 months. Thereafter a slow reduction in the IVIG treatments may be attempted. In patients who do not respond optimally, some clinicians sequentially add dapsone 100–200 mg daily. If this does not improve response within 3–4 months then 25 mg methotrexate weekly is also added. If there is still no response, rituximab 375 mg/m<sup>2</sup> is added. These medications are then discontinued once the patient has clearing for a number of months. Unlike in other diseases, there is a defined endpoint when treating autoimmune blistering diseases with IVIG. Once control of disease is achieved (absence of new lesions for about 10 weeks) the consensus statement group recommends maintaining the same dose but increasing the time intervals between infusions gradually to 6, 8, 10, 12, 14, and 16 weeks. The proposed endpoint is two infusions each given 16 weeks apart. If the disease remains under control after the endpoint is reached, attempts to discontinue IVIG may be pursued. The beginning of the remission period is defined as the absence of clinical disease after cessation of all systemic therapy, including

IVIg. If there is a disease recurrence during the tapering period the recommendation is to increase the frequency of cycles to every 3–4 weeks until the recurrence is over and then begin tapering again. Strict adherence to the protocol for slow tapering of IVIg therapy is recommended and seems to be important as disease recurrence can result from a rapid reduction in the frequency of infusions, not completing the protocol, or terminating it early. In one study of 16 PV patients who initially responded to IVIg, all eight patients who abruptly discontinued IVIg developed recurrences, whereas all eight patients who adhered to the tapering protocol eventually discontinued IVIg, went into remission, and none have had recurrence of the disease since completing the last infusion of the protocol (mean follow-up 21 months). In a second study of patients with severe bullous pemphigoid, similar results were obtained. Thus, it is strongly recommended that once IVIg therapy is initiated every attempt should be made to complete the protocol [3].

#### **Off-Label Dermatological uses of IVIg**

The off-label use of IVIg in dermatology includes treatment of a wide variety of conditions. No large, multicenter, randomized controlled studies have been performed to support these off-label uses of IVIg, yet the list of diseases which have reportedly been successfully treated with IVIg is still expanding. A comprehensive review of these off-label uses is beyond the scope of this article and has been published elsewhere. The efficacy of IVIg is best documented in patients with graft-versus-host disease, Kawasaki's disease and dermatomyositis; however, its utility in dermatology continues to grow. A number of case series have found IVIg effective in the treatment of patients with pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid, herpes gestationis and epidermolysis bullosa acquisita. A consensus statement was recently published on the use of IVIg in patients with autoimmune mucocutaneous blistering diseases. For autoimmune bullous disease the recommended guidelines for IVIg are as follows: failure of conventional therapy; significant adverse effects from conventional

therapy; contraindications, relative or absolute, to the use of high-dose long-term systemic therapy; progressive disease despite conventional therapy; uncontrolled, and rapid debilitating disease. The evidence for the use of IVIg in toxic epidermal necrolysis has been recently the subject of debate. No consensus has been reached due to the lack of randomized clinical trials. The anecdotal results differ from one center to another. Yet, IVIg remains commonly used as initial therapy for toxic epidermal necrolysis. Current findings are insufficient to recommend the routine administration of IVIg in patients with pyoderma gangrenosum, atopic dermatitis, chronic urticaria and Steven-Johnson syndrome. For a review of the major off-label dermatological uses of IVIg, refer to Tables 1. A brief review of the literature regarding the off-label use of IVIg in dermatologic conditions will be presented here [1, 2, 3].

#### **A-Autoimmune Blistering Diseases**

There are no United States, FDA-approved therapies for the autoimmune blistering diseases. Conventional therapy for autoimmune blistering diseases during the past several decades has been high-dose, long-term systemic corticosteroids and immunosuppressive agents. In a significant majority of patients conventional treatment controls the disease and produces long-term remission. However, there are numerous dose-related adverse effects, some irreversible, that occur in patients with autoimmune blistering diseases treated with long-term corticosteroid therapy, including severe infection, diabetes mellitus, osteoporosis, and psychological changes. Similarly, each immunosuppressive agent is associated with common and serious adverse effects, making the current autoimmune blistering diseases treatments less than perfect. Pemphigus is an autoimmune bullous disease characterized by IgG antibodies to desmoglein 1 and desmoglein 3. However, occasionally deposition of IgA is found to coexist on direct immunofluorescence with an intradermal intercellular pattern. The role of IgA and its antigenic role in this setting remain unclear.

As such the role of IVIG in treatment of this subset of pemphigus is unknown [5, 6].

### 1-Bullous Pemphigoid

Bullous pemphigoid (BP) is a subepidermal blistering disease with auto-antibodies directed against 180 or 230 kDa BP antigens that are components of dermoepidermal hemidesmosomal adhesion complexes. It is a rare acquired blistering skin disease characterized clinically by large, tense blisters or bullae, which are often present on the surfaces of the extremities, such as the ankles, the palms, also in the axilla, groin, and abdomen with a prominent inflammatory component. Mucosal lesions are extremely rare in typical BP. Biopsy of an early lesion reveals a subepidermal blister with a dermal infiltrate. This dermal infiltrate may be rich in eosinophils or polymorphonuclear leukocytes and histiocytes or contain a mixed infiltrate. Direct immunofluorescence performed on perilesional skin will demonstrate IgG and C3 at the basement membrane zone (BMZ). Although it is considered a disease of elderly people, it can also affect children. The autoantibodies in BP recognize two very distinct autoantigens present in the hemidesmosome within the basal keratinocytes. The BP antigen 1 is a 230-kDa protein and is considered to be a desmoplakin protein. BP antigen 2 is a hemidesmosomal 2180-kDa protein, which has a cytoplasmic and intracellular component. Lesions result from a failure of basal keratinocytes to adhere to the epidermal basement membrane. BP is traditionally treated with systemic or topical steroids with or without other immunosuppressive medication. Not infrequently, it is resistant to this therapeutic approach. Published data show a positive response of BP to IVIG in 35 reported cases. In these patients IVIG was used at 2 g/kg per monthly cycle over 3 months or initially as an adjunctive treatment. Once conventional therapy was tapered and withdrawn, IVIG could be used as a monotherapy to sustain the remission. In most patients, BP is not a life-threatening disease and usually responds rapidly to treatment. The disease usually spontaneously clears within 6 years and all medication can be stopped. The mortality rate for bullous pemphigoid has been reported to

be between 11% and 40%, and an estimated 25% of bullous pemphigoid patients do not respond to standard treatment with immunosuppressive therapies. There are reports of over 35 patients with bullous pemphigoid who have been successfully treated with IVIG in the literature. In most of these cases, patients were not responsive to conventional therapy and IVIG administration resulted in significant clinical improvement. In the only prospective study, 15 patients with bullous pemphigoid who were unresponsive to conventional therapies were treated with IVIG (2 g/kg) and all cleared, were able to discontinue prednisone, and achieved a sustained remission. There are also published case series and case reports reporting the successful use of IVIG in the treatment of BP. There have been two reported treatment failures. IVIG lowers autoantibody titers to both BP Ag 1 and 2. In the only prospective study, *Ahmed* et al treated 15 patients with BP with IVIG (2 g/kg every 4 weeks). The interval between IVIG treatments was then gradually lengthened to every 16 weeks after patients cleared. All 15 patients cleared after a mean of 2.9 months and were able to discontinue prednisone after mean of 3.3 months. IVIG was used as monotherapy thereafter. All 15 patients achieved sustained remission with a mean duration of follow-up off IVIG of 22.9 months. Indication for IVIG use includes the bullous pemphigoid resistant to topical and systemic glucocorticoids and immunosuppressive therapy. If the moderate to severe disease diagnosed by a dermatologist and corticosteroids or immunosuppressive agents are contraindicated; or the condition is unresponsive to corticosteroids and immunosuppressive agents; or presenting with severe side-effects of therapy, IVIG treatment can be started. Efficacy dose was demonstrated with doses of at least 2 g/kg per monthly treatment cycle. To assess the effectiveness of IVIG use, dermatologist should revise the response demonstrated at review at 6 months. Improvement to be demonstrated for continuation of supply; reduction in recurrence of disease or relapse; ability to reduce dose or discontinue other therapies; improved quality of life; resolution of blisters and healing of affected skin; resolution of pruritis must be obtained [6, 7, 8, 9].

## 2-Pemphigus Vulgaris

Pemphigus vulgaris (PV) is a rare but potentially fatal condition accounting for approximately 70% of pemphigus cases. Pemphigus vulgaris can develop at any age, but is most commonly diagnosed in the fourth to sixth decades of life. In PV, blisters develop just above the basal-cell layer and are associated with autoantibodies to desmoglein 3, a keratinocyte cell surface adhesion molecule. The binding of desmoglein 3 by these antibodies results in disruption of calcium-sensitive adhesion function and resultant splitting of the desmosome occurs with mechanical stress. Skin biopsies from early lesions demonstrate a characteristic intact layer of basal cells with loss of adhesion between epidermal cells (acantholysis), which are often seen floating in the cavity of the blister. Direct immunofluorescence is essential in the diagnosis of PV and demonstrates deposition of IgG on keratinocyte cell surfaces in almost all patients. While the cause is unknown, an immunogenetic predisposition is well established. Individuals with certain HLA allotypes are predisposed to the disease, though the susceptibility gene differs dependent on ethnic origin with, HLA-DRB1\*0402 associated with the disease in Ashkenazi Jews and DRB1\*1401/04 and DQB1\*0503 in non-Jewish patients of European or Asian descent. Pemphigus vulgaris may also be drug-induced. Drugs reported to be most significantly associated with PV include penicillamine, captopril and other thiol-containing compounds. Only about 30% of patients with pemphigus vulgaris enter a sustained medication-free remission and the mortality rate is between 5% and 10%. The cause of death in these patients is usually opportunistic infection secondary to prolonged immune suppression. Over 60 patients with pemphigus vulgaris have been successfully treated with IVIG. In the two largest prospective studies, which are from one institution, 42 patients with severe mucocutaneous disease unresponsive to conventional therapies were treated with IVIG (2 g/kg). This led to a clinical remission in all 42 patients and was sustained in many. In 2009, the first multicenter, randomized, placebo-controlled, double-blind trial of IVIG for pemphigus was conducted in Japan. This clinical trial has proved that 400 mg/kg per day for 5 days administration of

IVIG is effective as an adjuvant therapy with systemic steroid therapy and/or immunosuppressive agents. IVIG lowers antibody titers to dsG 1 and dsG 3, often making them undetectable. IVIG has been shown to be effective in the treatment of PV in numerous studies. In the two largest studies, which are from one institution, 42 patients were treated with IVIG (2 g/kg every 4 weeks) until control was achieved, as defined by healing of old lesions and no new lesions. The interval between IVIG treatments was then gradually increased to every 16 weeks. Prednisone and immunosuppressive agent were tapered off during this time in all patients; IVIG was used as monotherapy thereafter. Treatment with IVIG led to a clinical remission in all patients [10,11]. In the study by Ahmed, control was achieved after a mean of 4.5 months, prednisone was tapered off after a mean of 4.8 months, and immunosuppressive agents were tapered off after a mean of 2.9 months [12]. Both studies were prospective, but uncontrolled. There have been an additional two case series and 6 case reports of the successful treatment of 23 patients with PV with IVIG. However, 9 case reports of treatment failures from other institutions have been reported. In one case, the patient only received one cycle of IVIG. Among the several mechanisms to explain the mode of action of IVIG, several lines of evidence have suggested that neonatal Fc receptor for IgG (FcRn) plays an important role for rapid clearance of pathogenic antibody in pemphigus induced by IVIG. Additionally, the long suppression of IgG production induced by IVIG has been observed in some cases. Taking these characteristics into consideration, IVIG, which leads to decreased pathogenic IgG, is recommended to use in combination with oral corticosteroids or other immunosuppressants, which suppress the production of pathogenic IgG. Once a fatal illness, severe pemphigus vulgaris can now be treated successfully with high-dose systemic steroids and the addition of immunosuppressive drugs including azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate. In some cases, however, patients cannot tolerate high-dose steroids; in others tapering of the steroids causes disease flare-ups. Long-term high-dose steroid treatment does lead to significant side-effects. In certain patient subsets, there is a need for an

alternative therapeutic modality. Over the years, although the first-line treatment of PV was systemic corticosteroids, IVIG has been reported in several interesting uncontrolled studies to serve as an adjuvant corticosteroid-sparing regimen in recalcitrant [1, 2]. *Bystryn* et al. and *Baum* et al. separately reported in 6 and 12 therapy-resistant patients with PV, respectively, that IVIG resulted in a rapid improvement of disease, and a steroid-sparing effect in over 80% of their patients [13,14]. Several studies performed by *Ahmed* and colleagues have also shown very high rates of response to IVIG, and moreover, in their treatment protocol, patients are tapered off immunosuppressive drugs and can sustain long-term remission using long-term IVIG monotherapy. The treatment scheme proposed for PV is 2 g/kg over 3–5 days (1 cycle) every month. Side-effects were minor in these studies and, as far as cost is concerned, a recent study suggests that IVIG is a cost-effective treatment compared with conventional immunosuppressive therapy in patients who are non-responders to first-line therapy [12]. Recently, IVIG in combination with rituximab has been successfully used to treat 11 patients with severe refractory PV who did not respond well to IVIG alone. *Ahmed* et al studied patients with refractory pemphigus vulgaris involving 30% or more of their body-surface area, three or more mucosal sites, or both who had inadequate responses to conventional therapy and IVIG. They treated the patients with two cycles of rituximab once weekly for 3 weeks and IVIG in the fourth week. This induction therapy was followed by a monthly infusion of rituximab and IVIG for 4 consecutive months. Titers of serum antibodies against keratinocytes and numbers of peripheral-blood B cells were monitored. Of 11 patients, 9 had rapid resolution of lesions and a clinical remission lasting 22 to 37 months. All immunosuppressive therapy, including prednisone, could be discontinued before ending rituximab treatment in all patients. Two patients were treated with rituximab only during recurrences and had sustained remissions. Titers of IgG4 antikeratinocyte antibodies correlated with disease activity. Peripheral-blood B cells became undetectable shortly after initiating rituximab therapy but subsequently returned to normal values. Side effects that have been associated

with rituximab were not observed, nor were infections. They concluded that the combination of rituximab and IVIG is effective in patients with refractory pemphigus vulgaris. The mechanism of action of IVIG in PV is still to be determined precisely. It has been suggested that IVIG decreases serum levels of pemphigus auto-antibodies by increased catabolism, and recent evidence in an animal model provides evidence that IVIG can inhibit the binding of anti-desmoglein-3 antibodies to recombinant desmoglein-3 in a dose-dependent manner in vitro, as well as blistering in vivo in experimentally-induced PV in newborn mice [12].

### 3-Pemphigus Foliaceous

Pemphigus foliaceus (PF) is an autoimmune blistering disorder characterized by autoantibodies to dsG 1. The superficial variant of the pemphigus family, pemphigus foliaceus can be resistant to conventional therapy and, here too, IVIG has shown benefit in widespread disease. Furthermore, in certain patients long remissions have been observed after discontinuation of IVIG. It is a rare autoimmune blistering skin disease characterized by loss of cohesion of cells in the superficial layers of the epidermis. It accounts for approximately 25% of all cases of pemphigus. The cutaneous involvement in PF is often more extensive than in PV and involves the scalp, face, chest, back and upper extremities, but can extend to areas below the umbilicus. The lesions are generally well demarcated and do not coalesce to form large eroded areas. The histology of an early lesion would demonstrate a subcorneal intra-epidermal vesicle with acantholysis, while direct immunofluorescence demonstrates deposition of IgG in the upper stratum malpighii. Pemphigus foliaceus is mediated by an autoantibody that targets desmoglein 1, a cell-to-cell protein molecule that binds the desmosomes of neighbouring keratinocytes in the epidermis. Similar to the binding of desmoglein 3 in PV, the binding of antidesmoglein 1 antibody in PF results in disruption of adhesion function and splitting of the desmosome occurs with mechanical stress. As with PV, the cause of PF is unknown; however, an immunogenetic predisposition is well established. Sporadic and endemic forms of PF exist. The sporadic form is most common

in Europe and the USA in association with HLA DRB1\*0102 and 0404. An endemic variant of PF (also known as fogo selvagem and Brazilian pemphigus foliaceus) is frequently diagnosed in certain regions of Brazil and other underdeveloped areas of the world, including Tunisia and Colombia. The susceptibility genes for endemic pemphigus are HLA DRB1\*0102, 0404, 1402s and 1406 [15]. At least 25 patients with pemphigus foliaceus resistant to conventional therapies have been successfully treated with IVIG [2]. In two prospective studies of 11 and 8 patients with extensive treatment-resistant pemphigus foliaceus, respectively, patients were successfully treated with high-dose IVIG (2 g/kg), allowing previous therapies to be discontinued and IVIG to be used as monotherapy thereafter. In both studies the patients remained in clinical remission for a 3–5-year period after discontinuation of IVIG. There are a few case series and numerous case reports reporting the successful use of IVIG in the treatment of PF. IVIG lowers antibody titers to dsg 1, often making them undetectable [16, 17]. Sami et al conducted a prospective study of 8 patients with severe steroid-resistant PF. Patients were treated with IVIG (2 g/kg every 4 weeks) until they were completely healed. The interval between IVIG treatments was then gradually lengthened to every 16 weeks. All patients attained clinical control after a mean of 4 months. Prednisone was tapered off in a mean of 2.9 months; IVIG was used as monotherapy thereafter. Ahmed and Sami reported 11 patients with PF who were treated with IVIG (2 g/kg every 4 weeks) until they were completely healed. The interval between IVIG treatments was then gradually lengthened to every 16 weeks. All patients cleared after an average of 5.3 months of therapy. Prednisone was tapered off in a mean of 4.5 months and other immunosuppressive agents after a mean of 2.6 months; IVIG was used as monotherapy thereafter. All 11 patients maintained remission after discontinuation of IVIG for a mean follow-up time of 18.6 months [17]. Indication for IVIG use includes the patients with pemphigus foliaceus resistant to corticosteroids and immunosuppressive therapy or when these agents are contra-indicated. Qualifying criteria for IVIG therapy are severe widespread PF, defined as disease involving 30% or more of body surface

area, diagnosed by a dermatologist; and corticosteroids or immunosuppressive agents is contraindicated; or condition is unresponsive to corticosteroids and immunosuppressive agents; or presenting with severe side-effects of therapy. Efficacy dose is at least 2 g/kg per monthly treatment cycle. To review criteria for assessing the effectiveness of IVIG use, dermatologist should evaluate the response demonstrated at review at 6 months; improvement to be demonstrated for continuation of supply; clinical progression: treatment is stopped when patients are clinically free of disease and have a negative finding on direct immunofluorescence; autoantibody titres reflect the response to systemic therapy [1, 2, 3].

#### **4-Mucous Membrane Pemphigoid (Cicatricial Pemphigoid)**

Cicatricial pemphigoid or mucous membrane pemphigoid (MMP) is a rare, acquired chronic, subepithelial autoimmune disease, which predominantly involves mucosal surfaces although there is involvement of the skin in 25–35% of cases. The typical bullae, vesicles or erosions, heal with scar formation in most. While scarring is significantly less common in the oral cavity, scarring is often the major problem when the disease involves the conjunctiva. Scarring is also common in the nasopharyngeal, laryngeal, anogenital, vaginal, penile and oesophageal mucosa. The significant morbidity and irreversible sequelae seen in MMP patients are associated with the scarring process. Biopsies of MMP demonstrate a subepithelial blister with an inflammatory infiltrate that can be a mixed but predominantly neutrophilic or eosinophilic picture. Direct immunofluorescence of perilesional tissues typically reveals linear deposition of IgG and complement at the epithelial BMZ. However, immunoglobulin A (IgA), immunoglobulin M and/or fibrin are found in some patients. Efforts have been made to identify the antibodies involved in MMP. It has been shown that the sera of MMP patients bind to human  $\beta$  4 integrin. Sera of patients with only oral pemphigoid bind to  $\alpha$ 6 integrin. Other studies have shown that the sera of MMP patients contain antibodies that bind to BP180 and BP230; however, the antibody levels do not correlate with disease activity or severity when studied

over a long duration. Although the antibody involved in most cases of MMP is still yet to be clearly identified there is a subset of MMP patients referred to as anti-epiligrin cicatricial pemphigoid who produce an antibody to lamina 5 and 6. The aim of long-term treatment is cessation of the autoimmune process. Failure to do so results in invariable progression of the disease, culminating in progressive scarring. At least 25% of patients with ocular involvement of mucous membrane pemphigoid, despite the most aggressive therapy, progress to blindness. Other mucous membrane pemphigoid patients develop laryngeal stenosis, esophageal stenosis, anal stenosis, and/or vaginal stenosis. Over 68 mucous membrane pemphigoid patients who have obtained a significant benefit from IVIG therapy in terms of halting disease progression, clinical control, and induction of long-term clinical remission have been reported [18]. In one study of 10 patients who were already blind in one eye and had progression of disease despite conventional treatment, high-dose IVIG (2 g/kg) every 2–3 weeks arrested the patients' disease and stabilized vision in the unaffected eye. IVIG has been shown to lower titers of beta4-integrin and alpha6-integrin in patients with MMP. IVIG has been shown to be effective in the treatment of MMP in several prospective studies from one institution [19]. There have been two additional case reports of treatment successes and one treatment failure from other institutions. Patients were initially treated with corticosteroids and other immunosuppressive agents, which were tapered off in all cases. Remission was generally attained in 4 to 5 months and treatment with IVIG led to prolonged remissions that persisted after treatment with IVIG was discontinued [20]. One study of 16 patients with stage 2 ocular MMP compared IVIG with Standard treatment with corticosteroids and immunosuppressive agents. Randomization was based on whether insurance would pay for IVIG. Eight patients were treated with IVIG until control was achieved. The interval between IVIG treatments was then gradually lengthened to every 16 weeks and corticosteroids and other immunosuppressive agents were tapered off. The other 8 patients were treated with corticosteroids and other immunosuppressive agents. The median time to remission for groups was 4 and 8.5 months,

respectively. There were no recurrences for 1st group, whereas 5 of 8 patients in 2nd group experienced a recurrence. No patients in 1st group experienced progression, whereas 4 of 8 patients in 2nd group progressed to stage 3. In MMP, IVIG given at 2g/kg/cycle initially every 2–3 weeks is a therapeutic option if aggressive first-line immunosuppressive therapy is unable to halt disease progression or the scarring process in vital structures such as the eye [18].

### **5-Epidermolysis Bullosa Acquisita, Linear IgA Bullous Disease, Pemphigoid Gestationis**

Epidermolysis bullosa acquisita is a very rare bullous skin condition. It is a difficult-to-treat autoimmune blistering disease characterized by circulating and skin basement membrane-bound IgG auto-antibodies against type VII collagen. In the majority of epidermolysis bullosa acquisita patients, there is a non-inflammatory blister which occurs at sites of trauma, particularly on the knuckles of the hands, elbows, knees and ankles. The involvement of mucous membranes is not uncommon. The blisters heal with milia formation and scarring. The histological examination of an early intact vesicle, usually demonstrates a subepidermal blister. The infiltrate present will depend upon whether the epidermolysis bullosa acquisita is of an inflammatory subset or non-inflammatory subset. In the non-inflammatory type a few, if any, cells are seen. In the inflammatory type, which resembles BP or MMP, inflammatory cells will be seen in the upper dermal area. Perilesional tissues demonstrate deposition of IgG at the BMZ very similar to that seen in BP and MMP. Epidermolysis bullosa acquisita results from an autoantigen to type VII collagen, a 290-kDa protein, which is present in the anchoring fibres of the upper dermal area very close to the BMZ. Clinically, EBA can be differentiated from BP by indirect salt-split skin immunofluorescence with the IgG antibody of BP labeling the epidermal roof whereas the IgG antibody for epidermolysis bullosa acquisita labels the dermal side of the fractured lamina lucida zone. Epidermolysis bullosa acquisita is felt by some clinicians to be the most difficult of the autoimmune blistering diseases to treat, as most patients are corticosteroid re-

sistant and achievement of long-term remission is uncommon. There are reports describing a total of nine patients with epidermolysis bullosa acquisita unresponsive to other therapies who have been treated with IVIG. Eight of these 9 experienced significant clinical improvements in their mucocutaneous lesions. IVIG was given as monotherapy in 5 cases and in conjunction with corticosteroids or other immunosuppressives in the others. The dose used ranged from 1 to 2 g/kg. Treatment was successful in 8 of these cases with resultant decrease in formation of new blister formation and healing of old lesions. IVIG should be considered for severe epidermolysis bullosa acquisita cases refractory to conventional immunosuppressive therapy. Because of the exceptionally rare nature of this disease there is little literature defining the appropriate IVIG dose in this clinical setting. EBA is a disorder that is often difficult to treat. Therapy of EBA consists mainly of combinations of systemic steroids and immunosuppressants. Recently, an increasing number of case reports point to a possible benefit of IVIG in helping achieve disease control, usually in association with previously introduced immunosuppressive therapy. Further data are needed to establish the real potential of IVIG in EBA [21, 22, 23].

Linear IgA bullous dermatosis is also a rare autoimmune bullous skin disease, characterized by subepidermal blister formation and linear IgA deposits along the basement membrane zone. A few case reports, again requiring further clinical confirmation, suggest that IVIG in this setting may be useful in patients who do not respond to dapsone and immunosuppressive treatment regimens. There have been 7 patients with linear IgA bullous dermatosis who have been successfully treated with IVIG. There have also been reports describing a total of seven patients with linear IgA bullous disease and one patient with pemphigoid gestationis who were successfully treated with IVIG [24].

There has been a case report of a 17-year-old girl with pemphigoid gestationis that persisted 1.5 years after delivery. This patient had a diffuse bullous eruption and the authors were unable to reduce her prednisone below 40 mg. She received one cycle of IVIG (2 g/kg) with prednisone (20 mg), which led to a re-

mission and a marked reduction in ant basement membrane zone IgG and C3. Her disease returned 5 weeks later at which time she received a second course of IVIG with concomitant cyclosporine (100 mg/d). She again responded and her disease remains quiescent on 10 mg/d of prednisone. Gan, Doiron and Rodrigues also treated their patients with IVIG treatment successfully [25, 26, 27, 28].

## 6- Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a very rare, painful mucocutaneous intraepithelial blistering disease associated with occult or confirmed malignancy. Patients with paraneoplastic pemphigus show severe, progressive mucocutaneous disease with a high mortality rate, because of drug-induced infectious complications. The patients sometimes benefit from high doses of oral corticosteroids. However, pulse therapy with high doses of prednisolone (or dexamethasone) in combination with other immunosuppressants induces variable and inconstant results. IVIG has been applied in different cases of paraneoplastic pemphigus with encouraging results. Rossum et al reported a case of paraneoplastic pemphigus responding IVIG treatment. Plasmapheresis or plasma exchange in combination with corticosteroids and/or cyclophosphamide or azathioprine showed similar rapid and beneficial results in association with decreasing autoantibody levels in this group of refractory pemphigus. Plasma exchange leading to prompt depletion of autoreactive antibodies combined with immunosuppressants or synchronisation of plasma exchange with IVIG seems the best treatment modality for this refractory group [29, 30].

## B-Autoimmune Connective Tissue Disease 1-Dermatomyositis and Polymyositis

Dermatomyositis is a disease mainly of skin and muscle that may affect the lung and other tissues. It is a pathogenetically heterogeneous disease characterized by muscle inflammation and weakness, and cutaneous manifestations. Muscle involvement without skin manifestations is called polymyositis (PM). Subsets of patients may have an underl-

ying malignancy, autoantibodies and/or additional autoimmune diseases, or no humoral autoimmunity. It is an auto-immune disease that affects the skin and muscle as a consequence notably of a complement-mediated microangiopathy and T-cell mediated muscle destruction. Proximal or generalized weakness or skin rash are the typical presenting features. Muscle pathology in typical DM is quite distinct, with perivascular inflammatory cells that include plasmacytoid dendritic cells, abnormal capillaries and perimysial perifascicular myofibres. The classic dermatological manifestation of DM is cutaneous Gottron's papules which are found over bony prominences, particularly the metacarpophalangeal joints, the proximal interphalangeal joints and/or the distal interphalangeal joints. There is often a characteristic periorbital heliotrope, and violaceous erythema of upper trunk and extremities. Other skin manifestations have been noted with active disease including bullous and erosive lesions, exfoliative erythroderma, panniculitis, urticaria, and hyperkeratosis of the lateral fingers and palms. The evidence remains strong that DM is a disorder with capillary pathology but precise pathogenic mechanisms remain uncertain and debated. However, a recent evaluation indicates that in DM, genes induced by interferon- $\alpha$  and - $\beta$  were highly over-expressed, and immunohistochemistry for interferon- $\alpha$  and - $\beta$ -associated protein Myxovirus-resistance protein A showed dense staining of myofibrils and capillaries. This may indicate that the innate immune response in addition to an adaptive immune response contribute to the pathogenesis of DM. While the factors that initiate the autoimmune process in DM or juvenile DM has not been established, there is the suggestion that the onset of some cases is seasonal and in children disease may follow a viral infection. The classic manifestations of DM are easily recognized when present. However, early diagnosis remains a challenge, especially prior to manifestation of characteristic rash or in cases where crossover with other connective tissue disease is present. Many treatment options exist to treat DM including systemic corticosteroids, methotrexate, cyclosporin and IVIG. Treatment of DM with high-dose systemic steroids (1 mg/kg) alone or in association with other immunosuppressive drugs such as

cyclosporine, azathioprine, methotrexate, and cyclophosphamide is effective, but the associated side-effects are severe and some patients are partially or completely resistant to such therapy. Skin and muscle inflammation in this disease has been shown to be associated with an early microvascular injury mediated by the membrane attack complex of complement. Patients with refractory disease or poor prognostic factors, such as progressive disease despite other immunosuppressant therapies, malignancy and dysphagia affecting nutrition, intensive immunosuppressant therapy, for example with IVIG, should be considered. However, while IVIG has been suggested for treatment of calcification secondary to juvenile DM. IVIG (2 g/kg) appears to be a promising treatment for a subset of patients with dermatomyositis and/or polymyositis resistant to conventional therapies and has reported efficacy in dermatomyositis in both controlled and open-label studies. In a randomized, double-blind, placebo-controlled trial, 11 of 13 patients who received IVIG had clinical improvement. Moreover, multiple case series and open-label studies in which IVIG has been used to treat dermatomyositis also show efficacy of this treatment. IVIG has been shown to prevent the formation of the membrane attack complex by scavenging C3 fragments, and their therapeutic potential in DM has therefore been studied intensely [31, 32, 33]. Peake et al also reported a case of cutaneous ulcers of refractory adult dermatomyositis responsive to IVIG [34]. Recently, data showing that IVIG also down-regulates ICAM-1 expression on blood vessels and certain muscle fibres provides a basis whereby IVIG could limit the migration of activated T cells from capillaries towards the muscle fibres [35]. Several case reports, uncontrolled trials and a placebo-controlled crossover trial conducted by Dalakas et al. provide evidence for a benefit of IVIG in patients with DM. In the latter double-blind placebo-controlled study performed in 15 patients with treatment-resistant DM, IVIG at a dose of 2 g/kg per month was shown to be very effective in improving both skin involvement and muscle strength as early as following the second infusion. IVIG has been used to treat both DM and PM. Evidence strongly suggests that IVIG is effective in improving muscle weakness. Of 133 patients with DM or

PM, 103 had improvement in muscle strength in 11 case series including 11 of 12 patients in a randomized, placebo-controlled, crossover trial. However, caution should be used because comparison across studies is difficult as a result of differences in severity of disease, efficacy variables, and outcome measures. Moreover, most patients in these reports were on various combinations of corticosteroids and other immunosuppressives. The effectiveness of IVIG on cutaneous manifestations of DM is less clear. Reports on the treatment of DM with IVIG have been exclusively in neurologic and rheumatologic journals, often with little to no attention paid to the cutaneous response to IVIG. However, in those reports that did discuss the cutaneous response, a resolution of the rash usually correlated with an improvement in muscle strength. Most patients tend to relapse after IVIG is discontinued. The mechanism of action of IVIG in the treatment of DM has been elucidated in several studies [32]. Basta and Dalakas examined sera and muscle biopsy specimens in 13 patients from their double-blind, placebo-controlled crossover study and concluded that IVIG exerts its beneficial effects by intercepting the assembly and deposition of membrane attack complex on the endomysial capillaries through the formation of complexes between the infused immunoglobulins and C3b [36]. Dalakas et al have demonstrated that IVIG leads to a decrease in major histocompatibility complex-1 and intracellular adhesion molecule-1 in muscle suggesting that IVIG binds Fc receptors on macrophages, leading to decreased production of pathologic cytokines [32]. Taken together, favourable responses can be expected after 2–4 months in approximately 80% of the patients treated, but the effect does not seem to be permanent, and maintenance treatment is often required. Recognizing certain limitations to the interpretation of the published data, such as the heterogeneous composition of patients included in the studies, and the generally low number of patients in each study, high-dose IVIG does appear to have significant efficacy in the treatment of dermatomyositis. It should be considered as a second-line treatment in association with corticosteroids for patients who do not respond completely to first-line therapy with corticosteroids. IVIG use has also been shown to result in clinical improve-

ment in children with refractory juvenile dermatomyositis. Indication for IVIG use includes the patients with DM with significant muscle weakness unresponsive to corticosteroids and other immunosuppressive agents. Diagnosis made by a neurologist, rheumatologist, or immunologist of: patients with DM who have significant muscle weakness or dysphagia and have not responded to corticosteroids and other immunosuppressive agents. Induction dose of IVIG is 2 g/kg in 2–5 divided doses for DM and maintenance doses are 0.4–1 g/kg 4–6 weekly. IVIG should be used for 3–6 months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIG therapy should be abandoned. Regular review by a neurologist is required: frequency as determined by clinical status of patient. For stable patients on maintenance treatment, review by a neurologist is required at least annually. Clinical documentation of effectiveness is necessary for continuation of IVIG therapy [32].

## **2-Cutaneous and Systemic Lupus Erythematosus**

Current therapies for systemic lupus erythematosus (SLE) are targeted at immunosuppression and at reducing inflammation. Topical agents and first-line systemic treatment options including systemic steroids, azathioprine, cyclophosphamide, cyclosporine, and methotrexate have been used for cutaneous lupus erythematosus. Further second-line treatment includes retinoids, dapsone, and mycophenolate mofetil. Because of severe side effects or high costs, other agents, such as thalidomide or high-dose intravenous immunoglobulins, are reserved for severe recalcitrant cutaneous lupus erythematosus. Multiple retrospective studies, uncontrolled studies, and case reports have reported the successful treatment of systemic lupus erythematosus patients with high-dose IVIG, including improvement or resolution of cutaneous manifestations and resolution of organ-specific complications of SLE. In addition, IVIG has been used to successfully treat patients with cutaneous lupus, including subacute cutaneous lupus erythematosus. The current therapies are broad-spectrum and include steroids and cytotoxic agents that are

counterbalanced by toxicity and side effects of the medications. Methotrexate can be utilized to reduce steroid requirements in mild to moderate SLE. Manipulation of the hormonal axis includes DHEA and bromocriptine. Mycophenolate mofetil is an immunosuppressive agent that is being investigated for SLE renal disease. Autologous stem cell transplantation or high-dose cyclophosphamide may be an option for severe refractory SLE. The aim of the future is to target therapies by altering specific known mechanisms of inflammation and autoimmunity. Although the inciting antigen is still unknown in SLE, it may be possible to alter the regulation of the immune response by targeted molecular therapy. Methods to do so would include manipulation of idiotypes, manipulation of second signal stimulation of the immune response, manipulation of cytokines, and the induction of tolerance by administration of blocking peptides. IVIG is an immunomodulator that has been successful in the treatment of SLE [37,38]. Goodfield et al describe 10 patients with cutaneous LE who were treated with IVIG (1 g/kg for two cycles followed by 400 mg/kg/mo until disease resolution or for 6 months). Five patients had complete or near complete clearing of their skin disease, two had partial but helpful improvement, and 3 had limited responses [39]. Levy et al reported a case series of 20 patients with various manifestations of systemic LE who were treated with IVIG (2 g/kg). The 4 patients with cutaneous manifestations experienced resolution or marked improvement [40]. Schroeder et al treated 12 patients with SLE with IVIG (120 g over 4 days for two cycles) in an uncontrolled study. Five patients had facial erythema, of which 3 experienced partial remissions. Two of 4 patients with Raynaud's phenomenon showed marked improvement [41]. Francioni et al treated 12 patients with SLE with IVIG (2 g/kg once/mo for 6-24 cycles) in an uncontrolled study. The authors report that the majority of patients with rash, vasculitis, and cutaneous and buccal mucosa ulcerations experienced regression; specifics were not provided [42]. Genereau et al described one patient with cutaneous lupus who was successfully treated with IVIG (2 g/kg) [43]. Krueter et al described one patient with severe, recalcitrant subacute cutaneous lupus erythematosus who nearly cleared after

IVIG (3 g/kg) [44]. However, the patient later progressed to systemic LE and died. In contrast, two patients with subacute cutaneous lupus erythematosus described by De Pita et al did not respond to IVIG therapy [45].

### 3-Systemic Sclerosis, Mixed Connective Tissue Disease, Hyper-IgE Syndrome

There are two reports describing clinical improvement in patients with scleroderma after high-dose IVIG (2 g/kg), including one open-label study with 15 patients who experienced a mean decrease in Rodnan skin score of 35%. The same authors previously reported 3 patients with scleroderma who responded to IVIG [46, 47, 48, 49, 50]. Reports of patients with both mixed connective tissue disease (2 g/kg) and Hyper-IgE syndrome who experienced significant clinical improvement after treatment with high-dose IVIG have also been reported [51, 52]. Ulmer et al described a patient with mixed connective tissue disease manifested by macular erythema and acral cyanosis, and other systemic manifestations. The patient responded after two monthly cycles of IVIG (2 g/kg), cleared after 16 weeks, and has maintained remission with IVIG cycles every 6 weeks [51]. Wetter et al described a patient with widespread ulcerations, Raynaud's phenomenon, and myositis who experienced complete healing of his ulcerations within 3 weeks of treatment with two cycles of IVIG (2 g/kg), prednisone, and mycophenolate mofetil. The patient had previously failed 6 months of treatment with prednisone and mycophenolate mofetil [53].

### 4-Behçet's Disease

Seider et al reported the successful use of IVIG in the treatment of ocular Behçet's disease in 4 patients resistant to corticosteroids and cyclosporine. In this report, 6 eyes of four patients with ocular Behçet's disease refractory to steroids and cyclosporin A were treated with a course of IVIG and followed up for their response to treatment. Patients were treated with IVIG (0.4 g/kg/d) for 5 days, followed by 3 infusions over that month. Infusions were then repeated every 3 weeks for 3 cycles, followed by infusions every 6 weeks for 1 year. All 4 patients responded to treatment.

All six eyes of all four patients showed good response to IVIG therapy. They concluded that IVIG could have a role in treating refractory ocular Behçet's disease. They suggested that a wide range of controlled studies with longer follow up was needed to substantiate this impression [54]. Gastrointestinal involvement in Behçet's syndrome may be relatively rare, but may be the cause of significant morbidity. Treatment may be difficult; a recent experience with a case of Behçet's colitis suggests IVIG may be beneficial [55, 56]. Shetty et al also described the optimal use of IVIG in a patient with Behçet syndrome and common variable immunodeficiency [57].

### C-Drug-Eruptions

#### 1-Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are now considered to be distinct clinical entities within a spectrum of adverse cutaneous drug reactions of increasing severity based on their surface of skin detachment. Both SJS and TEN are characterized morphologically by the rapid onset of keratinocyte cell death by apoptosis, a process that results in the separation of the epidermis from the dermis. Recent evidence is supportive of a role for inflammatory cytokines and the death receptor Fas and its ligand FasL in the pathogenesis of keratinocyte apoptosis during TEN. TEN is a rare, life-threatening hypersensitivity reaction to certain medications, such as sulphonamides, antibiotics, non-steroidal anti-inflammatory drugs and anticonvulsants. Drug-induced epidermal apoptosis has been proposed as a possible pathogenesis. SJS is considered as a less extensive manifestation of the same phenomenon. Clinically, TEN and SJS are characterized by a severe bullous reaction with extensive destruction of the epidermis, and morphologically by ongoing apoptotic keratinocyte cell death that results in the separation of the epidermis from the dermis. It is believed that IVIG inhibits TEN by blocking the interaction of Fas receptor (FasR) with its natural membrane-anchored ligand, Fas ligand (FasL). While FasR is normally expressed in keratinocytes, high levels of soluble FasL were observed in the sera of patients with TEN. The observed beneficial effect of

IVIG in TEN is believed to be due to the presence of naturally occurring antibodies against FasR in IVIG that block FasR-FasL interaction. TEN remains an unpredictable, life-threatening disease process associated with 30% mortality rate. While optimal treatment of this condition is still yet to be classified, discontinuation of the presumed offending drug and careful symptomatic relief are considered mainstays. The use of IVIG in TEN is in debate as it does not always limit the progression of TEN. However, as IVIG has minimal toxicities and the given the gravity of the underlying clinical condition, the risk/benefit ratio remains favourable for the early administration of IVIG to treat TEN. The average mortality of patients with TEN ranges between 25% and 35%, whereas the mortality of SJS is about 1%. Current treatment options are essentially limited to supportive care in intensive care or burn units, although there is some evidence that cyclosporine, cyclophosphamide, and plasmapheresis may be beneficial. Treatment with corticosteroids and other immunosuppressive agents is controversial because of a possible increased risk of sepsis [58, 59, 60, 61].

Randomized controlled studies have not been performed in the treatment of TEN, likely because it is rare and associated with high rate of mortality. The evidence supporting or refuting IVIG in the treatment of SJS and TEN consists of multiple open-label, prospective studies, retrospective case series, and case reports. More than 70% of the case series conclude that toxic epidermal necrolysis patients benefit from treatment with IVIG, although in only one of the studies using a comparator group was the benefit statistically significant [58, 59, 60]. Of note, Prins et al. found survival correlated with relatively high doses of IVIG (mean total dose of 2.8 g/kg in survivors versus 2 g/kg in those who died) and when IVIG treatment began earlier in the course of disease (6.8 days after onset in survivors vs. 10.2 days in those who died) in their retrospective review [62]. One prospective, open-label study and two retrospective studies did not find IVIG to be beneficial in the treatment of TEN. In one of the retrospective studies, 67% of the patients treated with IVIG also simultaneously received corticosteroids. In the other retrospective study, relatively low doses of IVIG (mean total dose of 1.6 g/kg) were

used and the time between onset of symptoms to treatment initiation was 9.2 days in the IVIG group versus 5.6 days in the historic control group, although this difference was not statistically significant. Although randomized, controlled, multicenter studies are lacking, the results from the majority of case series supports the use of IVIG in the treatment of TEN and TEN/SJS overlap. Prins et al. recommend a total dose of 3 g/kg given over 3 days. Of the 11 studies, 8 concluded that IVIG was beneficial in the treatment of TEN, although in only one of the studies using a comparator group was a statistically significant result achieved [58, 59, 60]. Shortt et al concluded that IVIG was not beneficial in their retrospective series, because although patients receiving IVIG experienced a lower mortality compared with historic control subjects, the difference was not statistically significant [63]. There was also a trend toward less progression of skin sloughing in the IVIG-treated group compared with historic control subjects. A prospective, open-label study by Bachot et al and a retrospective study by Brown et al also did not find IVIG to be beneficial in the treatment of TEN. The study by Bachot et al included patients with SJS [64]. The study by Brown et al was confounded by the fact that 67% of the patients treated with IVIG also received concomitant corticosteroids. Brown et al also used lower doses of IVIG than most other studies. This is important, because Prins et al found a higher mortality with lower doses in their retrospective review. Moreover, the days from onset of symptoms to treatment was 9.2 in the IVIG group versus 5.6 in the historic control group, although this difference was not statistically significant. Again, Prins et al found a higher mortality when treatment was delayed. Because several studies did not include a comparator group, a compilation of mortality benefit from IVIG across studies is not possible [58, 59, 60]. Prospective, randomized, multicenter, controlled trials are needed, however, before treatment with IVIG can be considered the standard of care. Over the past 8 years we have been using a protocol for TEN patients at Cedars Medical Center (Miami, FL), which includes IVIG administration at 1 g/kg daily for 4 days (total dose 4 g/kg). Of the 24 patients treated with this protocol only one has died, suggesting high

efficacy. The use of IVIG in the treatment of SJS is not warranted given the low associated mortality and lack of evidence for efficacy. Indication for IVIG use includes to limit progression of TEN or TEN/SJS overlap when administered in early stages. The qualifying criteria for IVIG therapy consist the TEN or TEN/SJS overlap of the following: diagnosis by a dermatologist; and body surface area (erythema and/or erosions) of 10% or more; and evidence of rapid evolution. IVIG should be initiated as early as possible, preferably within 24 hours of diagnosis; urgent skin biopsy should be performed for confirmation but should not delay IVIG therapy if indicated; adverse Drug Reactions Advisory Committee should be notified of the inciting medication. IVIG dose is 2 g/kg, preferably as a single dose, or divided over three consecutive days. To date, no specific therapies for TEN have reached evidence-based medicine standards of acceptance. Numerous case reports and 9 non-controlled clinical studies containing 9 or more patients have analysed the therapeutic effect of IVIG in TEN. Taken together, although each study has its potential biases, 7 of the 9 studies point towards a benefit of IVIG used at total doses greater than 2 g/kg over 3–4 days on the mortality associated with TEN. Detailed analysis of studies published to date, also suggests that total doses of 2 g/kg or lower may be insufficient to obtain optimal therapeutic effect.

## 2-Drug-induced Hypersensitivity Syndrome

Drug-induced hypersensitivity syndrome (DIHS) is a severe multi-organ system reaction caused by specific drugs. Many reports have revealed that human herpesvirus 6 (HHV-6) reactivation contributes to the development of DIHS. In addition, recent articles have shown that reactivation of other herpesviruses such as human herpesvirus 7 (HHV-7), Epstein-Barr virus (EBV), cytomegalovirus (CMV) might be also implicated in the development of DIHS. These observations suggest that not only HHV-6 but also other herpesviruses might reactivate from the latency and play an important role in the appearance of clinical manifestations of DIHS. Several patients with DIHS were treated with IVIG in addition to systemic corticosteroids by Kano et al. The re-

sults have been encouraging although virus reactivation could not be suppressed. Although the pathomechanism of IVIG treatment in patients with DIHS remains unknown, the therapeutic effects of IVIG could be dependent, in part, on functional capabilities of anti-virus IgG contained in IVIG. Mostella et al reported a patient with anticonvulsant hypersensitivity syndrome. The patient was treated with one infusion of 30 g of IVIG in conjunction with pulse methylprednisolone. These treatments resulted in rapid improvement of her illness, but it is not possible to discern whether the IVIG played a role [65].

#### D-Vasculitis

Treatment with IVIG has been reported to clinically improve or resolve a variety of vasculitides, including antineutrophil cytoplasmic autoantibody-positive vasculitides (such as Wegener's granulomatosis and microscopic polyangiitis, Churg–Strauss Syndrome, cutaneous polyarteritis nodosa, antineutrophil cytoplasmic antibody–negative nonleukocytoclastic vasculitis, leukocytoclastic vasculitis, and Behçet's disease. Among these reports, IVIG has been used to successfully treat 12 patients with rapidly progressive glomerulonephritis from antineutrophil cytoplasmic autoantibody-positive vasculitides. In one report describing 15 patients with Churg–Strauss Syndrome, treatment with 2 g/kg of IVIG in addition to corticosteroids with or without cyclophosphamide improved motor neuropathy in 13 of 15 patients and cardiac function (in terms of improved left ventricular ejection fraction) in all five patients with heart failure [66].

#### 1-Kawasaki Disease

It is an acute, self-limited vasculitis that occurs predominately in infants and young children. It is characterized by an acute febrile illness, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa associated with fissured lips, strawberry tongue and injected pharynx, distinctive changes in extremities with erythema and oedema of hands and feet and later the typical acral desquamation, a polymorphous exanthem, and cervical lymphadenopathy. The polymor-

phous exanthema itself is non-specific and has been described as morbilliform, annular, urticarial and erythema multiforme-like targetoid lesions. Coronary aneurysms and ectasia develop in 20–25% of untreated children and may lead to myocardial infarction, sudden death and ischaemic heart disease. The aetiology of Kawasaki disease remains unknown, although an infectious agent is suspected because the syndrome has many of the clinical features similar to those of other infectious diseases, such as adenovirus infection and scarlet fever, as well as a well-documented seasonal peak in the winter and spring months in most geographical areas. There are significant variations in the rates of Kawasaki disease in different ethnic groups with Asian and Pacific Islanders having higher rates of incidence than Caucasians. The peak incidence in the toddler age group with only rare cases in infants under 3 months of age and in adults suggests a role for transplacental antibodies conferring protection as well as the development of protective immunity as a result of asymptomatic infection in most individuals. Up to 20% of cases of Kawasaki disease will require re-treatment due to evidence of ongoing inflammation or failure to respond to initial therapy with IVIG and aspirin. The goal of treatment in Kawasaki disease is to reduce inflammation and prevent the formation of coronary aneurysms. The American Heart Association (AHA) recommends treatment with high-dose aspirin (80–100 mg/kg/day) and IVIG (2 g/kg) within the first 10 days of disease. Approximately 10–15% of patients fail to respond to initial IVIG therapy; failure is defined as persistent fever or recurrence of fever within 36 hours of IVIG therapy. Persistent or recurring fever is concerning because it likely indicates on-going inflammation and is associated with an increased risk of developing coronary aneurysms. In a small multicenter randomized prospective trial of a second IVIG infusion versus infliximab, an anti-TNF- $\alpha$  agent (5 mg/kg), for refractory Kawasaki disease there were no statistically significant differences between the two treatment groups in recurrence of fever, coronary artery outcomes, or laboratory markers of inflammation. However, current AHA guidelines recommend re-dosing IVIG at least once in the event of IVIG failure. If two or more doses of IVIG are ineffective then corti-

costeroid pulse therapy (30 mg/kg for 1–3 doses) or treatment with infliximab (5 mg/kg) should be considered. For uncomplicated Kawasaki disease, an echocardiogram should be performed at diagnosis, at 2 weeks, and then again at 6–8 weeks to assess treatment efficacy for the prevention of aneurysm formation. The diagnosis of recurrent cases in 3–5% of affected children in Japan suggests either a failure to mount a protective immune response in a subset of patients after the first exposure to the causative agent or exposure to multiple agents that cause the same syndrome. While the classic manifestations of typical Kawasaki disease are easily recognized when present, diagnosis of this syndrome remains a challenge, especially prior to manifestation of characteristic rash and oedema of extremities or in cases where only some of the diagnostic criteria are present, sometimes called incomplete or atypical Kawasaki syndrome. Clinical suspicion, prompt diagnosis and referral for institution of IVIG therapy at a dose of 2 g/kg remains essential, with evidence that early initiation of therapy within 10 days of the onset of symptoms associated with a decreased risk of late cardiac complications. Indication for IVIG use includes the early in Kawasaki disease to prevent coronary artery pathology. IVIG dose is 2 g/kg in a single dose over 10–12 hours unless cardiac function necessitates the administration of a prolonged or divided treatment dose, usually once only. Re-treatment with 2 g/kg in a single dose may be given when there is ongoing inflammation [67, 68].

## 2-Polyarteritis Nodosa

There are 5 case studies reporting the successful use of IVIG in the treatment of cutaneous polyarteritis nodosa, although improvement could not be maintained in two patients. In addition, 3 patients with parvovirus B19 associated cutaneous polyarteritis nodosa who were successfully treated with IVIG have been described. *Asano* et al describe a 58-year-old Japanese female who developed polyarteritis nodosa. Her skin disease and systemic symptoms were resistant to dapsone, high-dose oral prednisone and azathioprine, and intravenous cyclophosphamide pulse therapy. She was ultimately treated with infusion of IVIG at a dose of 0.1 g/kg/ daily for five con-

secutive days weekly for a period of 12 weeks, resulting in remission of his cutaneous and systemic symptoms and successful tapering of his prednisone and azathioprine dose. Twelve months later, relapsing fever and polyarthrits recurred, and eventually, 24 months later, indurated erythema and punched-out ulcers appeared on the lower legs. These symptoms were reduced after increasing the dose of oral prednisone. Their case indicated that the IVIG infusion therapy could be useful for controlling polyarteritis nodosa in certain periods since the long-term observation revealed deterioration of symptoms [69]. *Balbir-Gurman* et al reported similar cases [70]. In polyarteritis nodosa NSAIDs and corticosteroids are the mainstay of therapy. In cases of persistent or relapsing disease steroid-sparing agents like IVIG have been used.

## 3-Livedoid Vasculopathy

Livedoid vasculopathy is a thrombotic vasculopathy of the skin of unknown origin. No treatment has been validated in this indication, but case reports suggest the successful use of IVIG in livedoid vasculopathy. *Bounfour* et al treated 5 treatment-resistant ulcerated livedoid vasculopathy patients with IVIG. Treatment with IVIG induced complete remission (based on clinical evaluation and a pain-related visual analog scale) in four patients but was ineffective in one patient. Three patients relapsed; the median time to relapse was 10.7 months. Re-treatment with IVIG in these three patients was successful. Their cases confirmed previous reports that IVIG seems to be a rapid, effective, and safe treatment for patients with idiopathic refractory ulcerated livedoid vasculopathy. They concluded that a placebo-controlled study was mandatory to confirm these results. *Krueter* et al reported an open-label, prospective trial of IVIG in the treatment of 9 patients with livedoid vasculitis. IVIG (1-1.5 g/kg once/mo for a mean of 7.6 cycles) resulted in improvement of skin lesions and pain, and a significant decrease in the clinical score. Case reports of an additional 6 patients with livedoid vasculitis who were successfully treated with IVIG have been reported. These cases confirm that IVIG seems to be a rapid, effective, and safe treatment for patients with idiopathic refractory livedoid vasculopathy. However, a

placebo-controlled study is mandatory to confirm these results [71, 72, 73].

#### 4-Urticarial Vasculitis

Hypocomplementemic urticarial vasculitis is a type of urticarial vasculitis with multisystemic involvement and poor prognosis, sometimes associated with systemic lupus erythematosus. Several therapies have been attempted with no consensus on an effective therapeutic regimen. IVIG has been used in severe manifestations of systemic lupus erythematosus and recently in hypocomplementemic urticarial vasculitis. Yamazaki-Nakashimada reported IVIG therapy for hypocomplementemic urticarial vasculitis associated with systemic lupus erythematosus in a 7-year-old child. Shah et al also reported a case of hypocomplementemic urticarial vasculitis associated with non-Hodgkin lymphoma and treatment with IVIG [74, 75].

#### 5-Antineutrophil Cytoplasmic Antibody Associated Vasculitis

Jayne et al have shown that IVIG is effective in treating antineutrophil cytoplasmic antibody associated systemic vasculitis, but do not specifically remark on the response of skin manifestations. Richter et al reported a clinically significant benefit of IVIG in the treatment of 6 of 15 patients with antineutrophil cytoplasmic antibody associated systemic vasculitis who were poor responders to conventional therapy. Three patients had skin manifestations, of which two improved. Ito-Ihara et al successfully treated 12 patients with rapidly progressive glomerulonephritis from antineutrophil cytoplasmic antibody associated systemic vasculitis with IVIG. One patient had cutaneous involvement, but the response to treatment was not provided. Additional small case reports support the use of IVIG in the treatment of antineutrophil cytoplasmic antibody associated systemic vasculitis including one additional case of a patient with palpable purpura. In this vasculitis, methotrexate and corticosteroids are used for induction in milder cases. Maintenance therapy is typically with mycophenolate mofetil or azathioprine for 18 to 24 months. IVIG

(2g/kg/month) is an option for refractory disease [76, 77, 78].

#### 6-Antineutrophil Cytoplasmic Antibody Negative, Nonleucocytoclastic Vasculitis

Altmeyer et al treated 7 patients with recurrent necrotizing antineutrophil cytoplasmic antibodynegative nonleucocytoclastic vasculitis with IVIG. Complete clearance of disease was observed in 5 of 7 patients within 6 months while receiving IVIG (0.5 g/kg every 4 weeks for 1 year). Two of the 5 responders healed completely and therapy could be stopped after 6 months [79].

#### 7-Leukocytoclastic Vasculitis

Two cases of leukocytoclastic vasculitis successfully treated with IVIG have been reported in the literature. Ong and Benson successfully treated a patient with recalcitrant leukocytoclastic vasculitis with IVIG (2g/kg for 9 cycles). IVIG resulted in complete healing of the patient's ulcer and enabled discontinuation of prednisone, cyclosporine, and azathioprine. Sais et al successfully treated a patient with common variable immunodeficiency and leukocytoclastic vasculitis manifested by confluent palpable purpura with IVIG (300 mg/kg every 3 weeks). The purpura resolved in 10 days. Wetter et al noted a PR in one patient [53, 80, 81].

#### E-Infectious diseases

##### 1-Streptococcal and Staphylococcal Toxic Shock Syndrome

Pyrogenic toxin superantigens comprise a large family of exotoxins made by Staphylococcus aureus and group A streptococci. These toxins include toxic shock syndrome toxin-1, the staphylococcal enterotoxins, and the streptococcal pyrogenic exotoxins, all of which have the ability to cause toxic shock syndromes and related illnesses. These toxins have a similar three-dimensional structure that allows them to interact with relatively invariant regions of major histocompatibility complex class II molecules on the surface of antigen-presenting cells and with certain variable regions of the T-cell receptor-beta chain. The consequence of these interactions

is the exaggerated release of bioactive cytokines. The latter molecules are responsible for the clinical signs of illness associated with these toxins. Both in vitro and in vivo studies have suggested that IVIG inhibits the activity of streptococcal antigens and superantigens, and numerous reports suggest benefit from IVIG in patients with streptococcal toxic shock syndrome. The use of IVIG in treating streptococcal toxic shock syndrome in one case-control series provided an odds ratio for survival of 8:1. Schlievert indicated use of intravenous immunoglobulin in the treatment of staphylococcal and streptococcal toxic shock syndromes and related illnesses [82].

## 2-Necrotizing Fasciitis

Multiple studies have also examined clinical use of IVIG in necrotizing fasciitis. Currently at least one major United States hospital (Massachusetts General Hospital) patients are candidates for IVIG if they are sufficiently ill to require intensive care units support and have documented evidence of fasciitis and microbiologic data consistent with invasive streptococcal infection [83].

## F- Other Inflammatory Dermatoses

A variety of other dermatologic disorders have reportedly improved or resolved after treatment with IVIG, including pretibial myxedema and Graves' ophthalmopathy, psoriasis, atopic dermatitis, livedoid vasculopathy, nephrogenic fibrosing dermopathy, pyoderma gangrenosum, hidradenitis suppurativa, Kaposi sarcoma secondary to immunosuppression, anticonvulsant hypersensitivity syndrome, and polymorphous light eruption.

## 1-Pyoderma Gangrenosum

Pyoderma gangrenosum is a neutrophilic dermatosis of unknown aetiology characterized by typical skin ulcers with an undermined border. In 50% of affected patients, pyoderma gangrenosum is associated with systemic disease, including inflammatory bowel disease, autoimmune arthritis and haematological malignancies. It is an inflammatory disease characterized by painful ulcerations. It does not have characteristic serologic or histologic

features. Therefore, other potential causes such as malignancy, vasculitis, infection, and coagulation disorders should be ruled out. In addition, patients often have aggressive disease that is refractory to immunosuppressive therapy, but there is only a paucity of clinical data to help direct therapy. There are several lines of evidence to support an immunologic etiology of pyoderma gangrenosum. Although the pathogenesis is still not well understood, it is clear that pyoderma gangrenosum is associated with the upregulation of several cytokines including IL-8, TNF, IL-1 $\beta$ , IL-6, and interferon gamma, among many others. TNF and IL-1 $\beta$  are of particular interest, because some biologic medications that target these cytokines have been effective in treating pyoderma gangrenosum. Immunosuppressive treatment is central to the management of pyoderma gangrenosum once specific treatment of the underlying systemic disease has been initiated. Response to immunosuppressive treatment is variable, and a few reports concerning a total of 6 patients suggest that IVIG (2 g/kg/cycle) may be of use in an adjunctive setting in cases that have failed to respond to immunosuppressive therapy alone. There have been 6 reports about patients with pyoderma gangrenosum who have been successfully treated with IVIG [84, 85, 86]. The first describes a 35 year old woman with no identifiable underlying cause for PG who received multiple other treatments including: oral, intravenous, and intralesional steroids, dapsone, and cyclosporine with no sustained benefit. The ulcer continued to enlarge and IVIG was given at 0.4 g/kg/d for 5 days with improvement within 2 weeks. A second cycle of IVIG was given at 1 g/kg/d for 2 days and sustained benefit was observed, in that the ulcer gradually healed and cyclosporine and prednisolone were reduced. Eight months later the ulcer had not recurred. The second report describes a 37 year old woman with large painful PG ulcers on her feet and distal legs for 15 years, who failed to respond to high-dose oral steroids and cyclosporine. The cyclosporine was discontinued due to renal side effects and IVIG was introduced as adjunctive therapy with prednisolone at 60 mg/d. Improvement was noted after 1 week and monthly cycles of IVIG were continued for 4 months resulting in complete healing. During this time it was also possible to taper the

prednisolone to 10 mg/d. In a further report, a 45 year old female patient with a preexisting IgG monoclonal gammopathy developed post-traumatic pyoderma gangrenosum following a cardiac bypass procedure and was treated with combination IVIG and high-dose steroids, which rapidly halted progression of the disease [84]. Gupta et al first reported a patient with pyoderma gangrenosum who experienced marked improvement within 2 weeks of IVIG (2 g/kg). After a second course, the ulcer completely healed [87]. Dirschka et al treated a patient with pyoderma gangrenosum with monthly infusions of IVIG (2 g/kg), which resulted in complete healing after 4 months [88]. Hagman et al described a patient with multiple ulcers who had objective improvement within 2 weeks of one infusion of IVIG (2 g/kg). A second infusion induced a dramatic clinical improvement of one ulcer and healing of the others. They described a patient with pyoderma gangrenosum leg ulcers who was treated with 2 g/kg IVIG over 5 days and subsequently over 2 days. This resulted in the onset of ulcer healing within 2 weeks. The final case describes the development of annular crystalline keratopathy in association with IVIG treatment in a 6 year old boy who's pyoderma gangrenosum had responded to 5 cycles of 0.4 g/kg/d for 5 days in combination with dapsone and methylprednisolone [89]. Dobson et al reported a patient with superficial granulomatous pyoderma who completely healed in 3 months. Improvement was observed in all patients. He reported an 85 year old man with superficial pyoderma gangrenosum which had failed to respond to topical and oral steroids, anti-tuberculous chemotherapy, minocycline, and topical tacrolimus. A single cycle of 2 g/kg adjunctive IVIG given over 5 days resulted in complete healing over 3 months allowing the cessation of oral steroids [90]. Cummis et al treated ten pyoderma gangrenosum patients with IVIG at Johns Hopkins Department of Dermatology. In this study, all patients had severe mutilating and/or refractory disease requiring multi-agent therapy. The charts were reviewed retrospectively. Seven of the ten patients had clearance of pyoderma gangrenosum lesions in the setting of IVIG and six of these patients maintained efficacy with repeated IVIG treatment. Five patients complained of nausea with treatment, and in one

case nausea was severe and intractable. One patient developed an immune reaction requiring diphenhydramine and methylprednisolone and another experienced aseptic meningitis. They concluded that IVIG could be an effective adjuvant in the treatment of pyoderma gangrenosum and has an acceptable side-effect profile. Randomized, placebo-controlled, double-blinded trials are needed to confirm this hypothesis [84]. Meyer et al reported on two patients with pyoderma gangrenosum for whom immunosuppressants could not be prescribed and who were treated with high-dose intravenous immunoglobulins. One patient was a 58-year-old man who presented with a 6-year history of pyoderma gangrenosum. He was initially treated with prednisone. The 20 mg/day dosage of prednisone could not be reduced and treatment had to be discontinued after 1 year because of serious adverse effects. Minocycline treatment led to improvement but had to be discontinued after 6 years because of facial skin hyperpigmentation. The other patient was a 66-year-old man who presented with a 3-year history of pyoderma gangrenosum. Different therapeutic procedures for pyoderma gangrenosum including prednisone, topical tacrolimus or betamethasone had failed. IVIG was administered monthly at a dose of 2 g/kg for 6 months. They observed that the treatment induced stabilisation of the disease and made it possible to reduce corticosteroid use in both patients. The authors concluded that IVIG represent a therapeutic alternative for pyoderma gangrenosum, but the efficacy of this treatment should be confirmed in further studies. Finally, pyoderma gangrenosum associated with hypogammaglobulinaemia has been described to respond to replacement therapy with IVIG. Multiple drugs are available to help control pyoderma gangrenosum. Biologics, IVIG, and conventional immunosuppressive drugs have been reported to be effective. Multidrug therapies should be considered for refractory cases. Pyoderma gangrenosum is a complex inflammatory disease with multiple involved pathways. IVIG represent a significant advancement in treatment options. The majority of cases reported were treated adjunctively with IVIG and responded over several weeks where other therapies had failed. It was also clear that it was possible to reduce other treatments when the lesions had

healed and to discontinue IVIG. Improvement of pyoderma gangrenosum in the setting of hypogammaglobulinemia has also been described with replacement IVIG. The mechanism of action is not clear; however, it is possible that effects of IVIG on the local cytokine environment particularly at the active edge of the ulcer where a vasculitic histology is observed and modification of cellular recruitment into the ulcer may play a role [86].

## 2-Atopic Dermatitis

Atopic dermatitis (AD) is a common disease with worldwide prevalence, affecting up to 20% of children and 6% of adults. Recent evidence regarding pathogenesis has implicated epidermal barrier defects deriving from filaggrin mutations with resulting secondary inflammation. Most cases of AD will benefit from emollients to enhance the barrier function of skin. Topical corticosteroids are first-line therapy for most cases of AD. Topical calcineurin inhibitors are considered second line therapy. Several novel barrier-enhancing prescription creams are also available. Moderate to severe cases inadequately controlled with topical therapy may require phototherapy or systemic therapy. The most commonly employed phototherapy modalities are narrow-band UVB, broadband UVB, and UVA1. Traditional systemic therapies include short-term corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, leflunamide and most recently IVIG therapies. Since cumulative toxicity and lack of efficacy can limit the immunosuppressive drugs use, IVIG has been tested in this indication. About 40 patients, including both children and adults, with atopic dermatitis treated with IVIG have been reported in the literature. All nine children treated with IVIG as monotherapy clinically improved. On the other hand, none of the 13 adults treated with IVIG as monotherapy exhibited significant improvement. Ten of 17 adult patients treated with IVIG plus corticosteroids or other immunosuppressive agents, though, did clinically improve. Thus, IVIG may be effective as monotherapy for children with atopic dermatitis, but it appears that adults may require simultaneous treatment with immunosuppressive agents [91, 92]. Lamb et al used IVIG for treatment atopic dermatitis. IVIG (2 g/kg in di-

vided doses) has widened to include a number of inflammatory diseases, including atopic eczema. The published experience in severe childhood atopic dermatitis to date suggests that IVIG can improve skin scores, and thus objective skin involvement, when used as monotherapy; 9 of 10 studied children improved when given 2 g/kg IVIG. In adults, monotherapy with IVIG does not appear to have the same effect, as confirmed by a small randomized study of 9 patients treated with one cycle of IVIG monotherapy and evaluated for skin scores 60 days later [92]. Some patients with AD treated with IVIG have been reported in the literature. Additional studies conducted by Noh et al are not discussed as patients received very low doses of IVIG [93]. Paul et al conducted the only controlled study. In this randomized, parallel-group, evaluator-blinded trial of 10 patients with severe AD, patients were randomized to immediate or delayed (by 1 month) treatment with one infusion of IVIG (2 g/kg over 2 days). There was a statistically significant, but modest, decrease in the severity scoring index of AD of 22% at 60 days after IVIG infusion. Paul et al concluded that IVIG treatment was not associated with clinically significant improvement of AD signs and symptoms [94]. Jolles et al conducted an open-label study of 6 patients with severe AD. The mean age was 36 years (range 18-53). Patients received IVIG (2 g/kg once/ mo for 6 cycles) with a 3-month follow-up period. Of 6 patients, 4 had major improvements in skin scores and the overall reduction was significant [95]. Huang et al treated 5 infants with monthly infusions of IVIG (2 g/kg for 3 cycles) as monotherapy. The severity scoring index of AD was significantly reduced compared with a control group treated with topical corticosteroids. In addition, patients attained a prolonged remission of greater than 6 months [96]. This finding was similar to another case series of IVIG for AD in children in which 4 children attained a remission of 6 months with IVIG monotherapy. An additional 15 patients with AD have been treated with IVIG. Six improved, whereas 9 had insignificant improvement or none at all. In summary, of 9 children treated with IVIG as monotherapy, all improved. In contrast, none of 13 adults treated with IVIG as monotherapy had significant improvement. However, 10 of 17 adult patients treated with IVIG as an adjunct to

corticosteroids or other immunosuppressive agents responded. The 7 patients who did not respond received lowdose corticosteroids. In conclusion, IVIG may be helpful as monotherapy for some patients with AD, particularly children. It appears that adults may need concomitant immunosuppression. The results of published case reports are mixed suggesting that larger, controlled studies are needed before the use of IVIG in the treatment of severe AD can be justified. IVIG does; however, seem to have a positive effect in 50–60% of adult patients suffering from severe atopic dermatitis when used as adjunctive therapy. High-dose IVIG has been noted to be beneficial in the treatment of AD anecdotally, in case reports, and small trials. As yet, no double blind, placebo controlled studies have been performed. There are now 10 children and 30 adults in the literature with AD who have been treated with IVIG, 17 of these had adjunctive high-dose IVIG. A further study using variable lower dose IGIV with short follow-up is not included in this analysis. Summarizing this small number of patients, 9 out of 10 children improved on monotherapy. The child who failed to respond suffered from Wiskott–Aldrich syndrome. Seventeen of the adult patients were treated with adjunctive therapy and 10 improved (59%); however, of the 7 who did not respond, adjunctive treatment amounted to less than 7 mg of prednisolone per day. None of the adults treated with monotherapy responded. The only randomized study of 9 patients used a single cycle of IVIG monotherapy and the authors concluded that the results did not support the use of IVIG in atopic dermatitis they did; however, note a significant reduction in skin scores at 60 days. When all reports of IVIG for dermatological indications are analyzed, the success of monotherapy versus adjunctive therapy is approximately 40% and 80% respectively, in spite of a likely reporting bias for successful outcomes. In the small number of reports of the use of IVIG in AD, the benefit of adjunctive therapy is obvious only in the adults, while in children, under 6 years of age, 90% responded to monotherapy. Drug costs may be reduced by closely monitoring disease indices and increasing the interval between cycles when remission has been achieved. This addresses the question of duration of immunomodula-

tion rather than the dose required to immunomodulate. Dose reduction may be possible where a lowering in steroid dose has led to weight loss and therefore, the overall dose of IVIG required. In-patient costs can be reduced by using outpatient infusion centers and by making use of an accredited IVIG home infusion program, as is the case for primary antibody deficiencies. Home infusion therapy has also been successfully used in patients with chronic neurological disease. Adjunctive IVIG may offer a useful therapeutic approach in the small group of adults with severe treatment resistant AD. Appropriately designed double blind, placebo controlled trials of at least 4 months adjunctive IVIG are required to decide if this form of treatment has a place in the management of this subset of patients with AD. The mechanism of IVIG anti-inflammatory action has yet to be fully understood. Proposed mechanisms include modulation of IgE responses and a reduction in inflammatory cytokines with a reduction in T-cell proliferation. Antibacterial and antitoxin effects may also play a role. Further controlled studies are needed to define the role of IVIG in the therapeutic approach to severe atopic dermatitis [1, 3, 91].

### 3-Psoriasis/Psoriatic Arthritis

Psoriasis is characterized by chronic scaly symmetrical plaques which may be itchy. It may also affect the hair, nails, and joints with a destructive seronegative arthropathy. Approximately, 2% of the population is affected. There is a single case report describing IVIG therapy for psoriasis and psoriatic arthritis. Treatment with 2 g/kg IVIG in three patients led to dramatic improvement in arthritis with a decrease in erythrocyte sedimentation rate and C-reactive protein levels. Treatment led to dramatic improvement in arthritis after one infusion, although monthly maintenance therapy was required. One patient had severe psoriasis, which cleared after 3 infusions, and another had mild psoriasis, which cleared after one infusion. A third patient with severe psoriasis had minimal improvement, but only received one infusion of IVIG [97]. *Taguchi et al* reported a case of psoriasis improved by IVIG therapy. They concluded that IVIG therapy could be an effective treatment for intractable psoriasis. The authors speculated

that the mechanism of IVIG could involve effects on TNF- $\alpha$ , as some inhibitors of this cytokine have been shown to have efficacy in the treatment of psoriasis [98].

#### **4-Scleomyxedema and Other Disorders Scleromyxedema**

Scleromyxedema is a chronic, idiopathic disorder characterized by cutaneous dermal mucin deposition in association with increased dermal collagen and absence of thyroid disease. It is a rare cutaneous mucinosis of unknown cause characterized by widespread symmetric 2–3 mm, firm, waxy, closely spaced papules localized especially on the head and neck, dorsum of the hands, accompanied elsewhere by hardened skin causing reduced mobility. The clinical lesions involve sclerosis of skin with numerous, 2–3 mm, firm, waxy, papules in a symmetrical distribution pattern. The skin lesions may progress to widespread and indurated plaques resulting in patient disability via decreased mobility, sclerodactyly and microstomia. Abnormalities in the muscular, neurologic, rheumatologic, pulmonary, renal and cardiovascular systems may accompany the cutaneous lesions. Restrictive disease is also observed in other organs, such as heart, lung, oesophagus, and joints. The most common extracutaneous manifestation of scleromyxoedema is a benign plasma cell dyscrasia. A number of treatments have been tried such as cytotoxic drugs, cyclosporine, interferon alpha, retinoids, plasmapheresis, extracorporeal photopheresis, thalidomide and PUVA therapy with limited efficacy and significant adverse side-effects. Currently there is no consensus on optimal treatment of this potentially fatal disease because of the lack of randomized controlled trials and limited number of case reports. It is not clear what role the paraprotein plays in the pathogenesis of scleromyxedema; however, there are precedents for the use of IVIG in conditions with paraproteins. The first is when replacement doses of IVIG are used to prevent infection when a paraprotein is associated with immune paresis and significant hypogammaglobulinemia. In the second, IVIG is used at high-dose in the demyelinating neuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP), which may be associated with paraproteins.

In CIDP, associated with a monoclonal paraprotein, the benefit of IVIG appeared similar to CIDP without a paraprotein, suggesting that the presence of a paraprotein is not necessarily a contraindication to IVIG treatment [99, 100, 101, 102].

There are now seven interesting publications reporting a total of 13 patients with scleromyxoedema treated with IVIG 2 g/kg over 5 days. A majority of patients were treated with IVIG as monotherapy, and the remainder in association with prednisolone, thalidomide or melphalan. Improvement in cutaneous and systemic manifestations of the disease was observed in all patients reported within a period of 6 months, and could be maintained in 11 of 13 patients with IVIG maintenance therapy. Controlled study data will be difficult to generate in this rare disease, but it is hoped that small studies or case series will continue to be reported and thus help to strengthen the preliminary but novel evidence suggesting that IVIG is an effective therapeutic option in scleromyxoedema. A total of 24 patients with scleromyxedema have been successfully treated with high-dose IVIG (2 g/kg). All patients received 2 g/kg every 4 to 6 weeks. Improvement was generally seen after 2 to 12 weeks and was sustained after several cycles [99, 100]. Sroa et al reported a case of scleromyxedema successfully treated with IVIG [99]. Rey et al. reported a case scleromyxedema associated with the dermatoneuro syndrome successfully treated with IVIG [100]. Majeski et al reported a case of scleromyxedema treated with low-dose oral prednisone and IVIG [101]. Shergill et al reported a case of dementia associated with scleromyxoedema reversed by IVIG. They described a patient with scleromyxoedema who presented with novel central nervous system manifestations of chronic cognitive impairment and dementia, which improved within a week after treatment with IVIG with full restoration at 2 months [102].

There are now 5 reports, totalling 10 scleromyxedema patients who have been treated with IVIG following the first report by Lister and colleagues. All were given a dose of 2 g/kg/month given over 5 days and improvement was noted in all patients. The majority were treated with monotherapy and improvements in both cutaneous and systemic mani-

festations of their disease were observed. The onset of improvement was gradual in some, and cycles of 6–8 weeks were generally needed to maintain remission [103]. One patient with multiple sclerosis treated with interferon beta-1a developed scleromyxedema which responded to thalidomide and IVIG. One of the most serious aspects of scleromyxedema is encephalitis which is associated with a high mortality. It is of particular interest that IVIG was observed to improve encephalitis, and it is possible that inflammation involving the blood brain barrier may make the central nervous system more accessible to IVIG. Although reductions were observed in some patients, there were no consistent overall reductions in the level of paraprotein. A minority of the patients had a long-lasting benefit from IVIG, while in most; the treatment interval could be increased. In view of the lack of understanding of the pathogenesis of scleromyxedema, it is only possible to speculate at the mechanism of action of IVIG. It seems likely that serum factor stimulate fibroblasts to divide and produce excessive matrix components and that IVIG may interfere either with the production or action of these putative factors. The rarity of this condition makes it difficult to envisage controlled studies; and therefore, it will be important to glean as much information from the increasing number of cases treated with IVIG to allow informed therapeutic decisions to be made. Given the lack of other effective therapeutic options, it is likely that IVIG will play an increasing role in scleromyxedema [101].

**Lichen myxedematosus:** It is a rare idiopathic disorder characterized by papules, plaques, and/or nodules in the skin secondary to mucin deposition and variable dermal fibrosis in the absence of thyroid disease. No standard treatment regimen exists, and the response to treatment varies. Macnab and Kenny reported a case of successful IVIG treatment of atypical lichen myxedematosus. They reported an unusual case of atypical lichen myxedematosus associated with hypothyroidism, central nervous system disturbances, and atrial fibrillation in a 64-year-old male. The patient experienced remarkable improvement within 3 months of beginning IVIG treatment; however, he required repeat therapy due to the recurrence of central nervous system symptoms 3 months after treatment. They concluded

that IVIG was an effective treatment, particularly in the setting of systemic complications or acute worsening of lichen myxedematosus [104].

### **Pre-Tibial Myxoedema**

These are localized edematous and thickened pretibial plaques which rarely develop in patients with hyperthyroidism due to Graves' disease. Three clinical types are recognized: nodular, diffuse, and elephantiasic forms. Histology reveals an excessive dermal and subcutaneous deposition of glycosaminoglycans, the mechanism of which is not understood. There is, however, some in vitro evidence that anti-thyroid stimulating hormone receptor antibodies (anti-TSH receptor) may be directed against thyroid antigens on pretibial skin fibroblasts and adipocytes stimulating them to secrete large amounts of glycosaminoglycans. It is a cutaneous mucinosis typically associated with Graves' disease and high serum concentrations of thyroid-stimulating hormone receptor antibodies. Certain forms of pre-tibial myxoedema are associated with elephantiasis. In severe cases of pre-tibial myxoedema, systemic immunomodulation may be necessary, although long-term efficacy of such therapy is non-existent. Two contradictory reports of the use of IVIG in pre-tibial myxoedema have been published. The first, and larger report, suggests a clear benefit of IVIG at a dose of 2 g/kg in 3-week cycles for a total of 7–15 cycles. All 7 patients with pre-tibial myxoedema (4 nodular pre-tibial myxoedema, two diffuse pretibial myxoedema and one elephantiasic pre-tibial myxoedema) treated with IVIG showed clinical improvement of the skin lesions, ophthalmopathy, and a reduction in circulating auto-antibody levels, whereas 2 pre-tibial myxoedema patients treated with systemic steroids alone showed no improvement. In this report, 7 patients with Graves' ophthalmopathy and pretibial myxedema (4 with nodular, 2 with diffuse, and 1 with elephantiasic types) were treated with IVIG. EndobulinR was given to 6 patients at 2 g/ kg over 5 days, every 3 weeks, the same dose was then subsequently given over 1 day for 7 to 15 cycles. The remaining female patient with elephantiasic pretibial myxedema was given VenoglobulinR S, using the same proto-

col. Clinical improvement of pretibial myxedema and Graves' ophthalmopathy was noted in all patients (in 4 patients, the lesions disappeared) with a reduction of pretibial skin thickness by ultrasonography. Four patients had a reduction in the mucopolysaccharide level in skin; in 3, lymphocytic skin infiltration disappeared; and in 2, IgG deposition decreased. A parallel reduction in the titer of circulating autoantibodies (antithyroglobulin, anti-microsomal, anti-TSH receptor, antinuclear, anti-smooth muscle, and anti-mitochondrial) was observed. Two control patients with Graves' ophthalmopathy and pretibial myxedema treated with systemic corticosteroids did not show any improvement in the skin [105].

The second report, of a single case of long-standing elephantiasic pre-tibial myxoedema, describes no response to 2 g/kg IVIG after 6 monthly cycles, but a reduction in anti-TSH receptor antibody titres. Antonelli et al reported 7 patients with Graves' ophthalmopathy and pretibial myxedema who were treated with IVIG (2 g/kg every 3 weeks for 7-15 cycles). Both the ophthalmopathy and pretibial myxedema improved in all 7 patients. This group later reported the result of a prospective, nonrandomized, evaluator-blinded, comparator trial of methylprednisolone to IVIG (2 g/kg every 3 weeks) in 65 patients with Graves' ophthalmopathy. Improvement in soft-tissue involvement, diplopia, and proptosis was nearly identical between the two treatment groups. Kahaly et al obtained similar results in a randomized trial comparing IVIG (2 g/kg every 3 weeks for 6 cycles) with prednisolone (100-mg starting dose for 20 weeks). Neither report discusses the effect of IVIG on pretibial myxedema. The second report describes a lack of response with perhaps a disease stabilizing effect of IVIG (2 g/kg/ month for 6 cycles) in a 36 year old female with longstanding elephantiasic pretibial myxedema. There was no major change in the levels of hexuronic acid in the skin 1 month after treatment and a 50% reduction in anti-TSH receptor antibodies was achieved after 5 cycles. At the 1 year follow-up, the anti-TSH receptor antibody titer had returned to slightly higher than pretreatment levels without disease progression. The authors suggest that this reduction may have been insufficient to have a greater effect on the di-

sease process and that long-standing elephantiasic pretibial myxedema remains a therapeutic challenge [106]. Dhaille et al described an elephantiasic pretibial myxoedema with upper-limb involvement responding to low-dose intravenous immunoglobulins [107]. Taken together, although more data is needed in this indication, it appears that the potential for response to IVIG therapy in pre-tibial myxoedema may depend on the type of pre-tibial myxoedema and the duration of disease.

### Sclerema Neonatorum

It is a rare neonatal panniculitis that typically develops in severely ill, preterm newborns within the first week of life and often is fatal. It usually occurs in preterm newborns with delivery complications such as respiratory distress or maternal complications such as eclampsia. This condition remains a poorly understood and difficult to treat neonatal disorder. Few clinical trials have been performed to address potential treatments. Successful treatment has been achieved via exchange transfusion, but its use in neonates is declining. Similar to exchange transfusion, IVIG enhances both humoral and cellular immunity and thus may decrease mortality associated with sclerema neonatorum. Buster et al. reported a case of sclerema neonatorum treated with IVIG. This patient was a case of sclerema neonatorum in a term newborn who subsequently developed septicemia. Biopsy showed subcutaneous, needle-shaped clefts without associated necrosis, inflammation, or calcifications. Treatment with IVIG led to notable but short-term clinical improvement [108].

### 5-Hidradenitis Suppurativa, Folliculitis Decalvans, Furunculosis and Folliculitis

Hidradenitis suppurativa (HS) is a common inflammatory skin disease. Medical treatment is often disappointing and in severe disease surgery remains the therapy of choice. Extensive surgery may be effective but also mutilating. Patients experience a significant reduction in quality of life and the need for new treatment modalities are urgent. Intramuscular human immunoglobulin (HIG) may

provide a therapeutic option as an independent or combined treatment for recalcitrant suppurative skin diseases such as hidradenitis suppurativa, folliculitis decalvans, or chronic recurrent furunculosis or folliculitis. Goo et al studied the efficacy and safety of intramuscular HIG for chronic and recalcitrant suppurative skin diseases. In this study the patients who had received HIG for hidradenitis suppurativa, folliculitis decalvans, furunculosis or folliculitis at Severance Hospital, Seoul, Korea, between January 2000 and May 2005 were identified from medical/pharmacy records. All records were analysed retrospectively. In this study, 63 patients were identified. After treatment, 37 patients (59%) showed overall improvement and were rated as having an 'excellent response' or 'good response' by the attending physician. No improvement or worsening was seen in only three patients (5%). A period without new lesions (PWNL) was achieved in 46 patients (73%). The number of times HIG was administered to achieve PWNL ranged from 1 to 12 (mean  $\pm$  SD 2.15  $\pm$  1.69). There was no significant difference in the rating score between the independent intramuscular HIG and the combined treatment groups. Pain at the injection site was the major side-effect, which led to the discontinuation of treatment in five patients. No other significant systemic side-effects were observed. The authors concluded that HIG could be used for the treatment of recalcitrant suppurative skin diseases as an independent or combined treatment [109].

## 6-Urticaria

Urticaria can be a chronic and debilitating affliction and is a relatively common disorder affecting between 10- 20% of the population. Common causes include reactions to medication, food allergen, physical stimuli and venoms. Urticaria can be acute or chronic. Chronic urticaria lasts for more than 6 weeks and is commonly difficult to treat. Chronic urticaria is a common skin disorder characterized by recurrent, transitory, itchy wheals with individual lesions lasting less than 24 h and affecting patients for 6 weeks or longer. Chronic urticaria is a common condition that can be very disabling when severe. A cause for chronic idiopathic urticaria is only infrequently identified. Potential causes include

reactions to food and drugs, infections and, apart from an increased incidence of thyroid disease, uncomplicated urticaria is not usually associated with underlying systemic disease or malignancy. In adults it has been shown that approximately 40% of patients with chronic urticaria have autoimmune urticaria, with demonstrable antibodies to IgE or the IgE receptor. It is a recurrent vascular reaction of the skin that can result from numerous etiologies, with up to one-third of affected patients having an autoimmune disease. The diagnosis is based on patient history and it is vital to spend time documenting this in detail. Extensive laboratory tests are not required in the vast majority of patients. Chronic urticaria resolves spontaneously in 30-55% of patients within 5 years, but it can persist for many years. Treatment is aimed firstly at avoiding underlying causative or exacerbating factors. The use of immunosuppressive agents for this disorder when antihistamines fail can result in significant morbidity. Histamine antagonists remain the mainstay of oral treatment for all forms of urticaria. The newer low-sedating antihistamines desloratadine, fexofenadine, levocetirizine and mizolastine should be tried first. Sedating antihistamines have more adverse effects but are useful if symptoms are causing sleep disturbance. Low-dose doxepin is effective and especially suitable for patients with associated depression. There is controversy as to whether the addition of an histamine or a leukotriene antagonist is helpful. For chronic urticaria, second-line agents include ciclosporin, short courses of oral corticosteroids, intravenous immunoglobulins and plasmapheresis, although the last two were found to be beneficial in small trials only. Cyclosporine is often the most effective but has some unique adverse effects that may prevent it from being used in some patients. Reports describing the successful treatment of chronic urticaria caused by a variety of phenomena with IVIG are numerous, including delayed pressure urticaria (2 g/kg), solar urticaria, chronic idiopathic urticaria, autoimmune urticaria, and angioedema with hypereosinophilia. In one report of 10 patients with autoimmune chronic urticaria treated with IVIG (2 g/kg), remission was noted in 9 of 10 patients, and 3 patients' experienced long-term remissions (3-year follow-up).

To date, there are four reports in the literature, with a total of 23 chronic urticaria patients treated with IVIG. The largest study included 10 patients treated with 2 g/kg over 5 days. Nine patients responded clinically, 3 of which achieved rapid, complete and prolonged remission. A remaining 6 out of 10 patients had either a rapid but less prolonged remission lasting 6–21 weeks, or an incomplete but persistent improvement. Patients with a positive autologous serum test evolved towards a weaker or negative test after IVIG treatment in 70% of cases. This non-controlled study and the other reports referenced suggest that a small percentage of patients with chronic urticaria may benefit significantly from IVIG. Furthermore, a positive autologous serum test does not appear to be predictive of a response to IVIG, but further characterization of the different forms of autoimmune chronic urticaria is likely to help define which will respond best to IVIG. In the above studies patients were given only one cycle of IVIG, and the data should therefore be interpreted in this light [110, 111, 112, 113, 114, 115].

### Chronic Idiopathic Urticaria

IVIG has also been used for chronic idiopathic urticaria, in both children and adults. Kroiss et al treated a 63-year-old woman with chronic idiopathic urticaria with IVIG (200 mg/kg) with maintenance infusions every 4 weeks. Treatment resulted in a decrease of her urticaria score from 8 to 1 [116]. Wetter et al treated one patient with urticaria resistant to multiple immunosuppressives and antihistamines. The patient responded within 1 day to one infusion with IVIG (2 g/kg) and remained 95% improved during the next 3 months [53]. Jandus describe the clinical course of 6 patients who received IVIG to treat mild antibody deficiency with refractory idiopathic chronic urticaria. Their report provided data on the response to treatment of chronic urticaria with low-dose IVIG. They concluded that low-dose IVIG could only be used as an alternative treatment of chronic urticaria if triggers such as recurrent infections can be eliminated. In autoimmune and inflammatory disorders, IVIG preparations are administered at doses of 1-3 g/kg. Since chronic urticaria is thought to have an autoimmune basis in 30% to

40% of patients with the presence of IgG targeting the Fc receptor  $\alpha$  subunit, high-dose IVIG (2 g/kg every 4-6 weeks) was tried in a small study of 6 patients with severe chronic urticaria. Remarkably, symptoms improved, thus enabling concomitant medication to be reduced after the first cycle. Another approach consisted of IVIG infusions of 0.4 g/kg/day for 5 days in patients with severe chronic urticaria; however, the effect of this treatment was less successful in another study. In contrast, low-dose IVIG replacement therapy (0.2-0.5 g/kg) is recommended in primary immunodeficiency disorders such as common variable immunodeficiency. IVIG (0.15 g/kg every 4 weeks for a minimum of 6 months and a maximum of 51 months) proved to be an effective option in patients with severe chronic urticaria refractory to conventional treatment in which an autoimmune mechanism was involved. Efficacy persisted for at least 12 months after treatment [111]. Mitzel-Kaoukhov and others used high dose IVIG (2g/Kg every 4-6 weeks) in 6 patients with chronic spontaneous urticaria resistant to other therapies. Four of 6 patients had complete remission after 2-4 cycles and symptoms such as itching, hives, and edema were greatly reduced soon after the first treatment [113]. Dodig and colleagues reported on 3 children with chronic autoimmune urticaria who required high dose IVIG. In this study, neither age of the patient or severity of the disease correlated with a serum-induced basophil histamine release test, used as a surrogate measure of autoantibody [117]. Pereira C et al. studied a group of 29 patients with chronic autoimmune urticaria. The patients were given low dose IVIG (150 mg/Kg every 4 weeks) for anywhere between 6 and 51 months. Twenty-six out of these 29 patients demonstrated improvement measured by decreased severity of urticarial lesions and decreased medication usage. Nineteen of the 26 patients achieved complete remission of symptoms, which appears quite remarkable given the low dose of IVIG used in this study. Twenty of 26 patients went into sustained remission up to 12 months after cessation of therapy [114]. Wetter and colleagues reported on the Mayo Clinic experience in the use of IVIG in various dermatological diseases. Of these, one patient with chronic urticaria had complete remission following treatment. The

role of high dose IVIG (0.4 mg/kg given daily over 5 days) in chronic urticaria was evaluated in a group of 10 patients with severe disease unresponsive or poorly responsive to conventional therapies. Urticarial activity was measured using wheal and itch scores and a visual analog score as well as objectively monitored using the autologous serum skin test. Clinical benefit was noted in 9/10 patients with 3 patients in continued prolonged remission. A reduced wheal and flare response to autologous serum was also observed post-treatment. Minimal adverse effects were experienced by the subjects enrolled in this study [53].

### Autoimmune Urticaria

There are 3 reports on the use of high doses IVIG with a total of 14 patients. The largest study by O'Donnell et al. looked at 10 autologous serum test positive patients with basophil histamine releasing activity in their serum. They treated 10 patients with autoimmune chronic urticaria from histamine-releasing autoantibodies with one cycle of IVIG (2 g/kg). Clinical benefit was noted in 9 of 10 patients: 3 patients experienced prolonged complete remissions, two had temporary CRs, and symptoms in 4 patients improved subsequent to treatment. There was significant improvement in the urticaria activity scores and visual analog scores at 2 and 6 weeks post-IVIG compared with the baseline values. Patients were given 0.4 g/kg/day IVIG for 5 days and assessed using an urticaria activity score. Two patients had rapid (2 weeks), complete, and durable responses lasting more than 3 years; 3 patients had rapid, complete responses lasting between 6 and 21 weeks; 4 patients had gradual, though incomplete improvement, beginning within 2 weeks which persisted; and the final patient had transient improvement only. Post treatment sera showed a reduced or virtually absent autologous serum test in 7 of 10 patients. The authors noted an above average frequency and severity of side effects from IVIG, generally developing on days 2 and 3; which included: headaches, nausea, low grade pyrexia, flu-like symptoms, lethargy, phlebitis, and transient elevation of liver transaminases [118]. Asero treated 3 patients with autoimmune chronic urticaria with one infusion of

IVIG (2 g/kg). One patient experienced a 3-week remission. The other two patients had no or a minimal response to IVIG. Three patients were treated in the study by Asero with 0.4 g/kg/day IVIG for 5 days, 1 patient with positive basophil histamine release had a complete remission, 1 had improved control of disease, and the third with no basophil histamine release had no change in their urticaria [119]. Kroiss et al. treated an autologous serum test negative patient with low-dose IVIG (0.2 g/kg for 1 day repeated monthly) with improvement in the urticaria. In a study on delayed pressure urticaria IVIG was administered at a dose of 2 g/kg over 2–3 days. The response to treatment was assessed subjectively and recorded as remission, improved, or unchanged. Three of 8 patients achieved remission, 2 after 1 infusion and 1 after 3 infusions. Two patients improved and 3 patients remained unchanged. Thus, IVIG induced remission or improved symptoms in 5 of 8 DPU patients with severe unremitting disease who had failed to respond to other therapies or were controlled only with systemic corticosteroids. Those who responded did so with 3 or fewer infusions. Four of 7 patients had a positive autologous serum test, 3 of whom responded to IVIG. The authors concluded that this was not a reliable predictor of response to IVIG [116]. Klote et al successfully treated one patient with IVIG with remission of disease within 48 hours. However, the patient's disease recurred and only partially responded to a second treatment [115]. Pereira et al observed the efficacy of low-dose IVIG in the treatment of severe autoimmune urticaria. They assessed the efficacy of IVIG treatment in patients with evidence of autoimmune urticaria. In this study, a group of 29 patients (with the diagnosis of autoimmune urticaria) were selected from the outpatient department. All the patients showed daily symptoms of urticaria and/or angioedema, with unsatisfactory response to conventional therapy and a positive intradermal autologous serum test. They were submitted to low dose of IVIG treatment each 4 weeks (0.15 g/kg), for a minimum of 6 months and a maximum of 51 months. They were evaluated for clinical scores, need of oral medication and AST results, before and after treatment. A clinical improvement was observed in 26 patients, with reduction of urticaria or

angioedema complaints and decreasing need for oral antihistamine medication. A reduction of histamine-releasing activity was found in the majority of the patients, documented by the decrease of reactivity in autologous serum test at the end of the treatment. Twenty patients remained without symptoms during 12 months after the active treatment, and the other 6 only reported non-severe complaints. They thought that IVIG was an effective therapeutic option in patients suffering from severe urticaria refractory to conventional treatment, in which autoimmune mechanism was involved. The efficacy persists for at least 12 months after treatment. They concluded that the number of infusions needed to achieve clinical control, showed great range between patients [114].

Delayed pressure urticaria: *Dawn* et al reported 8 patients with delayed pressure urticaria who were treated with IVIG. Of the 8, 5 remitted or improved after 3 or fewer infusions. There has been one report of IVIG use in delayed pressure urticaria (DPU), a frustrating and difficult-to-treat disorder. They evaluated the efficacy of IVIG in 8 patients with DPU. IVIG was administered at doses of 2g/kg over a 2-3 day period. Autologous serum testing was performed on the majority of the patients. Five out of the 8 cases responded favorably to IVIG infusion [120].

### Solar Urticaria

IVIG has been used in solar urticaria. Solar urticaria is characterized by development of urticarial eruption within a few minutes of exposure to ultraviolet radiation. This photodermatosis commonly results in itching and burning, but in some patients systemic manifestations may occur, including wheezing, hypotension and syncope. It is a rare idiopathic photodermatosis induced immediately after sun exposure. This disorder may considerably restrict normal daily life and management is extremely difficult when treatment with oral H1 antihistamines and sun avoidance are ineffective. Clinical control of the symptoms was optimized when this was combined with antihistamines and PUVA. A further report describes an improvement in solar urticaria in a woman treated with 2.5 g/kg of IVIG over 3 days. Two patients with solar urticaria successfully treated with IVIG have been reported in the literature [121, 122,

123]. *Darras* et al successfully treated a patient with IVIG (2.5 g/kg) in conjunction with PUVA. PUVA therapy alone resulted only in a PR [124]. *Puech-Plottova* et al treated a patient with severe solar urticaria with IVIG. The minimal urticarial dose to UVA was increased from 0.025 to 27 J/cm<sup>2</sup>. One year after treatment, the solar urticaria completely resolved [125]. *Adamski* et al reported the effectiveness of IVIG in severe solar urticaria. They performed a retrospective multicentric study via the mailing of a questionnaire to the French photodermatology units to analyze all cases of patients with solar urticaria who were treated with IVIG. In this study 7 patients with a mean age of 40 years and a mean disease duration of 5 years received IVIG. The administration schedule differed from one patient to another: 1.4 to 2.5 g/kg were infused over 2 to 5 days. Five of 7 patients obtained a complete remission. The number of courses necessary to obtain clinical remission varied from 1 to 3 courses. Complete remission was maintained during 4 to more than 12 months but antihistamines were still required. In one case, psoralen plus ultraviolet A photochemotherapy was administered. Retrospective study design, limited number of patients, and variations in the IVIG administration schedule could limit the interpretation of the results. They suggested a beneficial effect of IVIG in severe solar urticaria but additional prospective trials including a larger number of patients were needed to demonstrate the effectiveness of IVIG and to specify the optimal modalities of their administration in this disease [121]. However, *Llamas-Velasco* reported a poorer response of IVIG treatment in solar urticaria [122]. *Mitzel-Kaoukhov* et al assessed the efficacy and safety of high-dose IVIG as a treatment option in patients with therapy-resistant chronic spontaneous urticaria. In this study, 6 patients with severe chronic spontaneous urticaria unresponsive to other treatment options according to the newest guidelines for several weeks were treated with IVIG as 2 g/kg every 4-6 weeks. The response to treatment was observed on the basis of clinical signs and reduction of co-medications using a special treatment score. Patients were studied during the treatment period and were followed up for an average of 16 months. Patients showed an improvement in symptoms and a reduction in co-medica-

tion use just after the first cycle. Symptoms such as itching, wheals, and edema were reduced after the first or second cycle of IVIG treatment. Four of 6 patients had complete remission after 2 to 4 cycles. One patient needed a longer continuation of treatment to reach a stable state of improvement, and another patient had a slight relapse after the seventh cycle. The authors concluded the IVIG represents an important therapeutic option in patients with severe chronic spontaneous urticaria. *Hughes et al* reported a patient with solar urticaria successfully treated with IVIG. They presented 2 cases of severe, idiopathic solar urticaria, which were resistant to conventional treatment. Both patients achieved remission after administration of IVIG and have remained in remission at 13 months and 4 years, respectively. They proposed IVIG given at a total dose of 2 g/kg over several 5-day courses about a month apart was an effective treatment option for severe idiopathic solar urticaria. They concluded that it was also generally safe, even if certainly subject to significant theoretical risks, such as induction of viral infection or anaphylaxis. IVIG was infused at the dose of 2g/kg over 5 days and both patients achieved prolonged remission after several courses [113]. One case of severe solar urticaria remitted completely following a single infusion of IVIG administered in the dose of 2g/kg. *Correia et al.* and *Darras et al.* also reported on remission of severe solar urticaria in single patients following high dose IVIG infusion. While the poor response seen in the one report by *Llamas-Velasco et al* may have been due to differences in product or dosage protocol, it is also quite possible that solar urticaria is a heterogeneous disease, with some forms being responsive to IVIG and other forms being resistant [121, 122, 123, 124, 125].

#### **Angioedema with Hypereosinophilia**

Orson treated a 54-year-old man with angioedema and hypereosinophilia with prednisone (40mg/d) and IVIG (400 mg/kg every 3 weeks). The patient had a marked decrease in symptoms and eosinophil count after 6 weeks and prednisone was tapered off in 6 months. Interestingly, when the brand of IVIG was changed from Panglobulin to Gamimune N, the patient's illness recurred. Retreatment

with Panglobulin led to remission once again. This case report emphasizes the biologic variability that may exist between brands of IVIG [126].

**Urticarial vasculitis:** In a few instances, IVIG has also been used in some forms of urticarial vasculitis, a complement-mediated inflammatory disorder characterized by leukocytoclasia [74, 75].

These results with IVIG are promising particularly in the light of some complete remissions; and suggest that accurate characterization of the type of chronic urticaria is important; and that those patients with autologous serum test positive, autoimmune antibody mediated chronic urticaria with basophil histamine releasing activity may be the most likely to benefit. The Yin-Yang effect of IGIV in autoimmune urticaria- balancing immunoregulation and immune reconstitution with selective immunosuppression (autoantibody expression)- may provide one attractive rationale for use in refractory or difficult-to-control urticariaas opposed to the more potent immunosuppressive and toxic agents such as glucocorticoids, cyclosporine or mycophenolate. Future randomized controlled studies of the use of IVIG in this subset of chronic urticaria in the first instance are warranted [111].

#### **7-Mucha-Habermann Disease and Pityriasis Lichenoides Chronica**

Febrile ulceronecrotic Mucha-Habermann disease is a rare subtype of pityriasis lichenoides et varioliformis acuta, characterized by an acute onset of ulceronecrotic papules, rapidly coalescing into large ulcers with necrotic crusts, associated with high fever and severe systemic symptoms [127, 128, 129]. *Meziane et al* treated a case of febrile ulceronecrotic Mucha-Habermann disease with IVIG. Their case is a 65-year-old woman with a resistant form of febrile ulceronecrotic Mucha-Habermann successfully treated with a tumor necrosis factor- $\alpha$  inhibitor as infliximab. After 1 year of treatment, because of the recurrence of lesions and -occurrence of severe sepsis, they decided to change the therapeutic procedure by introducing IVIG witch induced a spectacular improvement. Only few cases of febrile ulceronecrotic Mucha-Habermann

treated with intravenous immunoglobulin have been reported to date. They concluded that IVIG could be useful, particularly in resistant cases. They suggested that further reports were required to confirm this potential therapeutic option [127]. *Marenco* et al also described a case of High-dose immunoglobulins and extracorporeal photochemotherapy in the treatment of febrile ulceronecrotic Mucha-Habermann disease. They reported a case of a 23-year-old man with a steroid-resistant febrile ulceronecrotic Mucha-Habermann treated by IVIG combined with methotrexate. IVIG proved to be effective in inducing a dramatic improvement of ulceration and in arresting the appearance of new lesions. They decided to perform a maintenance treatment with extracorporeal photochemotherapy. *Pyrpasopoulou* et al also reported a similar case [128].

*Garcia* et al used IVIG treatment in a case with pityriasis lichenoides and idiopathic thrombocytopenic purpura. Pityriasis lichenoides is an inflammatory skin disorder characterized by erythematous, desquamative papules and plaques. An acute form, pityriasis lichenoides et varioliformis acuta, and a chronic form, pityriasis lichenoides chronica, represent the two ends of the spectrum of this disorder. Most commonly seen in children and young adults, its etiology is unknown. *Garcia* et al described a young patient with concurrent pityriasis lichenoides and idiopathic thrombocytopenia purpura, a previously unreported association. They used successfully IVIG treatment for this patient [130].

### 8-Pityriasis Rubra Pilaris

Pityriasis rubra pilaris (PRP) is an uncommon dermatosis of unknown etiology. It is a rare chronic papulosquamous disorder with clinical and histological parallels with psoriasis. *Kerr* et al reported a case of type II adult-onset pityriasis rubra pilaris successfully treated with IVIG. They suggest that its immunomodulatory effect probably occurs as a result of several mechanisms, including antiproliferative actions, alteration of cytokine levels and inhibition of deposition of activated complement [131].

### 9-Nephrogenic Fibrosing Dermopathy

*Chung* and *Chung* reported a patient with nephrogenic fibrosing dermopathy who was treated with monthly infusions of IVIG (2 g/kg). The patient had mild improvement after 1 month, but no further improvement with additional infusions [132].

### 10-Kaposi's Sarcoma

*Carmeli* et al reported a 45-year-old man with polymyositis who had developed Kaposi's sarcoma from immunosuppressive therapy. Reduction in the dose of his immunosuppression did not lead to resolution of the sarcoma. IVIG (2 g/kg) was instituted to treat the polymyositis. Within 2 weeks, the Kaposi's sarcoma began to regress, and after 3 cycles, had nearly resolved [133].

### 11-Polymorphous Light Eruption

*Creamer* et al report a 55-year-old woman with common variable hypogammaglobulinemia with coincident polymorphous light eruption. Treatment of her hypogammaglobulinemia with replacement IVIG (500 mg/kg every 4 weeks) led to complete resolution of her polymorphous light eruption [134].

### Adverse Effects of IVIG

Mild and serious adverse effects are known to be associated with infusion of IVIG. Adverse reactions to IVIG can be classified as systemic or organ specific. Systemic reactions lead to constitutional symptoms which include fatigue, malaise, fever, flushing, chills, anorexia, myalgia/arthralgia, 'flu-like' symptoms and anaphylactoid symptoms, and may or may not be associated with effects on one or more organ systems. Premedications may be administered to minimize the risk of infusion-related side effects, such as headaches, myalgias and rigors. Analgesics, nonsteroidal anti-inflammatory agents, antihistamines and even low-dose intravenous corticosteroids may be of benefit to a subset of individuals. The majorities of adverse reactions is mild and include headache, low-grade fever, flushing, chills, rhinitis, myalgias, wheezing, tachycardia, back pain, abdominal pain, nausea, and

vomiting. Of these, headache is the most common reported adverse event and tension headache appears to be the single most common side effect from IVIG therapy, with an incidence reported to be as high as 56% in one series. The occurrence of headaches during IVIG infusion is reportedly often related to elevated blood pressure. Thus, therapeutic intervention to control blood pressure prior to infusion may prevent this adverse event in some patients. Many patients fortunately seem to develop headaches only during/after the first few cycles of IVIG. Migraine headaches are also a common occurrence in patients with a previous history of migraines, especially premenopausal women with such a history. Such patients should be advised to take their migraine headache medication 2 days prior to the infusion, during the infusion, and postinfusion. A number of skin eruptions secondary to IVIG infusion have also been noted and include eczematous reactions, urticaria, lichenoid reactions, pruritus of the palms, and petechiae. Of these, urticarial reactions seem to be the most common. Most reactions are minor but urticarial reactions can become severe and generalized. In the case of most of the mild adverse reactions mentioned, slowing the infusion often suffices to resolve them. Some practitioners premedicate all patients with 650 mg acetaminophen  $\pm$  50 mg diphenhydramine to minimize mild adverse reactions. Another important consideration is that IVIG may interfere with the efficacy of live vaccines, such as measles-mumps-rubella, yellow fever, and varicella. Thus, administration of such vaccines should be deferred until 6 months after treatment is complete. Also, although not a direct effect of IVIG, particular care must be exercised when using maltose-containing products in patients with diabetes because some glucose meters might falsely report high blood glucose readings as a result of interference by the maltose. A number of rare serious side effects are also seen with IVIG infusion, including hypotension, cytopenia, serum sickness, disseminated intravascular coagulation, aseptic meningitis, alopecia, acute renal failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, stroke, myocardial infarction, deep venous thrombosis, anaphylaxis, Stevens-Johnson syndrome, hemolysis, seizure, syncope, acute respiratory distress, pul-

monary edema, pulmonary embolism, acute bronchospasm, and transfusion-associated lung injury. The most common organ-specific IVIG reactions are neurological. Headache is the most reported symptom, occurring in 5–20% of infusions and up to one-third or more of patients overall. Most headaches begin during or within 1 day of the infusion and respond to non-prescription analgesics. However, an aseptic meningitis syndrome has been reported in up to 11% of neurological patients receiving IVIG. This can begin any time within 72 hours after infusion and is associated with all of the clinical features of aseptic meningitis, including a lymphocytic cerebrospinal fluid pleocytosis. Other neurological manifestations are rarer and idiosyncratic, including muscle or bone pain, dysesthesia and subjective weakness. At least 30 patients have been reported in the literature to have developed aseptic meningitis in association with IVIG therapy. No deaths have been reported and the majority of patients recover within 5 days of symptom onset. It has been reported that a history of migraine headaches predisposes patients to developing aseptic meningitis from IVIG therapy, so a careful medical history will alert the physician to monitor for this. Over 100 patients have been reported to have developed either acute renal failure or renal insufficiency associated with IVIG therapy. Many of these patients had baseline renal insufficiency and/or risk factors for renal disease. Perhaps more importantly, approximately 90% of the patients who developed renal dysfunction received an IVIG product that contained sucrose as a stabilizer. Sucrose is a disaccharide that cannot be enzymatically broken down when administered intravenously and is known to cause renal dysfunction as a result of osmotic nephrosis. Although the majority of these patients required less than 2 weeks of renal dialysis, deaths have occurred as a result of this side effect. Rarely acute renal failure due to osmotic nephrosis may occur in patients receiving IVIG. This is especially important in those patients with pre-existing renal insufficiency. Renal function should be monitored before and during therapy in all patients. Thrombotic events, including stroke, myocardial infarction, deep venous thrombosis, and pulmonary embolism also have been reported in association with IVIG administration. Most

patients who developed stroke did so within 24 hours of infusion, indicating a direct temporal relationship to the administration of IVIG. Many patients had significant risk factors for stroke including a history of prior stroke or transient ischemic attack, carotid artery stenosis, chronic hypertension, arrhythmias, and hypercoagulable states. Several patients died from direct complications of the stroke. In most patients who suffered a myocardial infarction in association with IVIG therapy, it was associated with the first cycle of IVIG therapy and developed within 24 hours of receiving an infusion. Again, the majority of patients had significant cardiac risk factors such as prior myocardial infarctions, hypertension, recent coronary artery bypass grafting surgery, and diabetes mellitus. Six patients died after developing a myocardial infarction. Multiple cases of deep venous thromboses and pulmonary emboli have also been reported in association with IVIG therapy. Several patients had a history of prior clots or were not mobile. Of interest, lyophilized products have been associated with more than 70% of thrombotic events. This may be the result of increased serum osmolality associated with reconstitution of lyophilized products. Administration of IVIG has been reported to provoke thromboembolic events such as strokes, acute myocardial infarction and even central retinal vein occlusion because of increased serum viscosity post transfusion. However, the true incidence of this is yet to be determined. IVIG is a fractionated blood product made from pooled human plasma and used in the treatment of a range of medical conditions. Anaphylactic reactions can occur in IgA deficient recipients who have anti-IgA antibodies of the IgE subclass in their serum (approximately 30–40% of IgA deficient individuals have anti-IgA antibodies in their serum). Although the IgA content of the different IVIG brands varies between less than 0.4 µg/mL and 720 µg/mL, the choice of IVIG brand may not be critical in preventing this side effect as only very small amounts of IgA are required to cause anaphylaxis and the reaction is probably not dose related. Screening for anti-IgA antibodies in IgA deficient patients may help predict risk of anaphylaxis when IVIG is felt to be an important therapeutic option. Immunoglobulin G anti-IgA antibodies have been associated

anecdotally with anaphylactic IVIG reactions. While the actual risk of such a reaction has not been determined, it has been estimated to occur in approximately 1 per 50 000 transfusions. The pathomechanism of this reaction is poorly understood but it appears to be dependent upon the IgA concentration present in the IVIG preparation, anti-IgA activity in the patient, infusion speed and the interval between each treatment. Therefore, caution should be taken with IgA-deficient patients when using IVIG in case their relative IgA deficiency is the result of anti-IgA antibodies. Clinically significant haemolysis associated with IVIG administration is rare. While mild to moderate haemolysis can be easily missed clinically, mild haemolytic reactions may be of little clinical significance and are outweighed by the benefits of IVIG. The risk factors identified include high-cumulative-dose IVIG therapy, females, and non-O blood group patients. The reason for the preponderance of female recipients is not known. However, multiparous females are more likely to develop antibodies from exposure to fetal DNA which has been linked to transfusion-associated acute lung injury, a potentially severe complication from blood transfusions. Transmission of hepatitis C virus has been reported and was likely a result of inadequate viral inactivation steps. Two IVIG preparations were voluntarily withdrawn from the market in 1994 as a result of suspected cases of hepatitis C transmission. Transmission of hepatitis B virus and HIV has not been reported. Although both mild and serious side effects are known to occur in association with IVIG therapy, these should not deter the clinician from using IVIG in appropriate clinical situations, as IVIG is safer and better tolerated than conventional therapies. For example, patients on long-term immunosuppressive therapy have an increased risk of developing malignancies, especially lymphomas and aggressive cutaneous squamous cell carcinomas. Of note, many of the patients with disease severity warranting IVIG therapy are older and thus often have a number of comorbid diseases that may put them at higher risk for the serious adverse effects. This reiterates why a careful matching of patient risk factors with the attributes or deficiencies of a given IVIG product becomes important. Even attributes such as the concentration of the IVIG solution

may be important, as the higher the concentration, the less volume is required for a given dose and this may be a critical issue for patients sensitive to fluid overload, such as those with congestive heart failure or renal insufficiency. Furthermore, fluid balance would need close monitoring in such patients, as they may require the addition of oral or IV diuretics during infusions to prevent adverse events. The serious side effects known to be associated with IVIG therapy, although rare, emphasize the importance of obtaining a comprehensive medical history and conducting a thorough physical examination on patients who are being evaluated for IVIG therapy. Particular attention should be placed on evaluating for the presence of risk factors for the serious side effects mentioned previously. For example, as hyperviscosity may explain some of the serious adverse events, one should inquire about risk factors for developing hyperviscosity such as low cardiac output, preexisting vascular disease, hypergammaglobulinemia, cryoglobulinemia, and hypercholesterolemia. Relative contraindications to IVIG use include hypersensitivity to IVIG, IgA deficiency, sensitivity to thimerosal, renal dysfunction, pregnancy (IVIG is pregnancy class C), need for administration of a live vaccination, or presence of multiple risk factors for serious adverse events. General guidelines have been established to minimize the incidence of acute renal failure from IVIG. If further administration of IVIG is given to a patient who developed acute renal failure from a sucrose-containing IVIG preparation, it should be with a nonsucrose based product. The development of urticaria is not an absolute contraindication for receiving additional cycles of IVIG therapy, but all patients who develop urticaria should be premedicated. Careful monitoring by nursing staff for signs of adverse reactions, including vital signs every 30 minutes, is critical during infusions and patients should be repeatedly asked about any symptoms they develop during infusions. During evaluation of candidates for IVIG therapy, baseline laboratory assessment of liver function, renal function (including urinalysis), CBC with differential, IgA levels, HIV, hepatitis A/B/C, serum immunoglobulins, rheumatoid factor, and cryoglobulins should be performed. Also, assessment of liver function, renal function, and

CBC with differential should be measured before each subsequent infusion. Annual HIV and screening for hepatitis A/B/C is recommended. The risks and benefits of IVIG therapy should be discussed with all patients. If patients are at risk for hyperviscosity syndromes, the administration of higher doses of IVIG and faster rates of infusion should be avoided. Intravenous IG is probably best administered to patients at high risk for adverse events as inpatients. Patients with lower risk for such events can be treated in infusion suites where they can be monitored by a physician. Some suggest that patients with autoimmune blistering diseases be infused in an ambulatory environment with equipment to handle emergencies and quick access to an emergency room and not as inpatients if at all possible as these patients have denuded skin surfaces or mucosal epithelia, which are easily capable of being infected. Moreover, these patients are at high risk for developing infections with multidrug resistant bacteria in hospital environments and any infection can delay wound healing. The placement and use of indwelling central venous catheters for the sole purpose of providing IVIG has been discouraged by some groups as a result of the inherent risks of thrombosis and infection associated with these devices. Generalized IVIG reactions vary in severity ranging from mild reactions that do not require cessation of therapy through to severe reactions require stopping the infusion and possibly resuscitation. Severe reactions occur in less than 1% of patients. However, at some point during the course of therapy, 20% or more of patients experience such reactions. Although the mechanisms of action of IVIG are still to be clearly understood, it is evident that IVIG has a role in treatment of certain autoimmune mediated dermatological conditions [1, 2, 3].

### **Future Implication**

Since January 2007 there has been medical coverage for IVIG by Medicare for all 50 states. Currently the high cost makes it difficult to get approval for IVIG therapy from insurance companies. However, when the total cost of therapy includes the sum of the cost of the drug plus the cost of the treatment of the side effects it produces, IVIG was found to be statistically more cost-effective than con-

ventional immunosuppressive therapy both during the total duration of therapy and on an annual basis, even though the initial cost of drugs used in conventional immunosuppressive therapy is low compared to IVIG. Thus IVIG is a safe, beneficial, and cost-effective alternative in patients who are unresponsive to conventional immunosuppressive therapy or who have developed significant side effects from conventional immunosuppressive therapy. In cases where side effects from conventional immunosuppressive therapy develop, IVIG may significantly improve quality of life. If there is difficulty getting insurance approval for IVIG a letter of medical necessity should be written. It is a good idea to cite papers that demonstrate efficacy of IVIG in the specific disease and the cost effectiveness of IVIG. For autoimmune blistering diseases it is pertinent to note that there are currently no FDA approved treatments, so all treatments are off-label. The future may see the advent of subcutaneous administration of IVIG. Advantages over IV infusions include a more benign side effect profile, better sustained levels of IgG in the blood, improved quality of life, and possibly decreased occurrence of adverse reactions in IgA-deficient patients who have anti-IgA antibodies. In January 2006 a polyclonal immunoglobulin product was licensed by the FDA specifically for subcutaneous administration for the treatment of patients with primary immunodeficiency (Vivaglobin; ZLB Behring, Melbourne, Australia). However, there is currently limited information concerning subcutaneous administration of IVIG for other diseases<sup>2</sup>.

### Summary

IVIG constitutes a valuable and potentially life-saving agent in managing patients with a variety of dermatologic disorders under the appropriate circumstances. Multicenter trials are needed to provide further objective data on a larger cohort of patients related to the efficacy of IVIG therapy on the clinical course of dermatologic diseases. The biggest drawback in the consideration of IVIG therapy in dermatologic disorders is the lack of randomized controlled trials. In addition, a single institution is responsible for a considerable amount of the work describing successful treatment of the autoimmune blistering diseases

with IVIG. Nevertheless, there is a significant body of evidence demonstrating the efficacy of IVIG in patients with dermatologic disorders that are resistant to treatment with standard agents. Perhaps what is more impressive is that most studies show that IVIG proved efficacious even when in the majority of patients it was given as a treatment of last resort. Importantly, trials and case reports describing failure to improve after IVIG treatment have also been described for many of the above disorders. But some, if not the majority, of these treatment failures involved doses less than 2 g/kg, patients who were treated only briefly, and occurred in patients in whom no therapy was successful. Recently a consensus statement was issued by members of the dermatology community on the use of IVIG for treating autoimmune blistering diseases. In this statement it is suggested that IVIG be considered for treating autoimmune blistering diseases in several situations, including if there is failure of conventional therapy to control the disease, the patients experience significant adverse effects as a result of conventional therapies, and there are significant contraindications to the use of standard therapies. Until randomized controlled studies are performed, we believe that these recommendations should be considered for use of IVIG in all diseases in which it has been shown to be efficacious. However, immediate IVIG use should be considered in situations where the disease is rapidly progressive and/or life-threatening, such as with toxic epidermal necrolysis. IVIG was originally licensed as antibody replacement therapy in patients with primary immunodeficiencies and there are currently six FDA-approved uses for this agent. Despite a current lack of FDA approval, off-label treatment of a multitude of dermatologic disorders with IVIG has shown exciting potential for this unique treatment modality. The diseases successfully treated with IVIG include autoimmune bullous diseases, connective tissue diseases, vasculitides, toxic epidermal necrolysis, and infectious disorders like streptococcal toxic shock syndrome. Currently the biggest drawback in the consideration of IVIG therapy in dermatologic disorders is the lack of randomized controlled trials. Nevertheless, there is a significant body of evidence demonstrating the efficacy of IVIG in

patients with dermatologic disorders that are resistant to treatment with standard agents. In summary, IVIG constitutes a valuable and potentially life-saving agent in managing patients with a variety of dermatologic disorders under the appropriate circumstances.

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