High-dose intravenous immunoglobulins: An approach to treat severe immune-mediated and autoimmune diseases of the skin

Anita Rütter, MD, and Thomas A. Luger, MD *Muenster, Germany*

Adjuvant high-dose intravenous immunoglobulins (IVIgs) are being used increasingly in a range of immune-mediated and autoimmune diseases. Although numerous immunomodulatory mechanisms have been suggested, the exact mechanisms of action are poorly understood. The efficacy of IVIg in certain diseases has been proven in clinical trials, insofar as IVIg is approved as the therapy of choice for Kawasaki syndrome or idiopathic thrombocytopenic purpura. IVIg treatment has been shown to be safe, without the many drug-related adverse effects, including systemic immunosuppression, that are related to corticosteroids and other immunosuppressive agents. Current dermatologic uses of IVIg are increasing, which calls for adequately controlled clinical trials. This review focuses on experiences with IVIg therapy for skin diseases and discusses current opinion concerning its potential immunomodulating mechanisms. (J Am Acad Dermatol 2001;44:1010-24.)

Immunoglobulin products for intramuscular application were developed 40 years ago for prophylaxis and the treatment of viral diseases and primary antibody deficiency syndromes. The introduction of immunoglobulin preparations suitable for intravenous application in the early 1980s led to a broader therapeutic use and allowed the administration of larger doses. Intravenous immunoglobulin (IVIg) is a sterile, high purified IgG preparation made from pooled human plasma and typically contains more than 95% unmodified IgG, which has functionally intact Fc-dependent effector functions and only trace amounts of IgA or IgM.[1-4]

Historically, treatment with IVIg began as a supplement for patients with X-linked agammaglobulinemia and extended to therapeutic use in primary and secondary immunodeficiencies with suppression of humoral immunity, including hypogammaglobulinemia, multiple myeloma, and chronic lymphocytic leukemia. In addition to the supplementation of immunoglobulins in these diseases, prevention of infection caused by the administration of specific antibodies is believed to play a role.[5-9] Another use of IVIg preparations was established in the provision of antibodies in diseases with multifactorial host defense defects, such as immunodeficiency occurring after immunosuppressive therapy, AIDS,[10-13] and graft-versus-host disease (GVHD).[14-16] The Food and Drug Administration first licensed IVIg in 1981 and approved its use for 6 conditions: primary immunodeficiencies, immune-mediated thrombocytopenia, Kawasaki syndrome, recent bone marrow transplantation in patients 20 years of age or older, chronic B-cell lymphocytic leukemia, and pediatric HIV type 1 infection.[17]

Abbreviations used.

AD:	atopic dermatitis
BMT:	bone marrow transplantation
BP:	bullous pemphigoid
DM:	dermatomyositis
EBA:	epidermolysis bullosa acquisita
GVHD:	graft-versus-host disease
HIES:	hyperimmunoglobulinemia E syndrome
IL:	interleukin
ITP:	idiopathic thrombocytopenic purpura
IVIg:	intravenous immunoglobulin
PBMC:	peripheral blood mononuclear cell
PF:	pemphigus foliaceus
PM:	polymyositis
PV:	pemphigus vulgaris
SLE:	systemic lupus erythematosus
SSc:	systemic scleroderma
TEN:	toxic epidermal necrolysis
TNF:	tumor necrosis factor

From the Department of Dermatology, University of Münster.
Reprint requests: T. Luger, Department of Dermatology, University of Münster, Von-Esmarch-Str 56, D-48149, Münster, Germany. E-mail: luger@uni-muenster.de.

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The anti-infectious functions of immunoglobulins are supposed to be mediated by specific binding of the Fab portion of the immunoglobulin to microbial antigens. High-affinity binding of anti-IgG antibodies plays a primary role in antimicrobial effects such as the neutralization of viruses and bacterial toxins. On the other hand, antigen-specific functions of IgG are induced and complemented by secondary functions of the Fc portion, such as the activation of complement by the classical pathway leading to bacterial cell lysis. The Fc-mediated secondary functions may also include conditioning for antibody-dependent cell-mediated cytotoxicity, which plays an important role for the defense against intracellular particles and the induction of FcR-mediated phagocytosis.[3,18-20]

POSTULATED MECHANISMS OF IVIG

High intravenous doses of immunoglobulins are thought to exhibit numerous immunomodulatory properties that are particularly mediated by the Fc portion of IgG and by the spectrum of variable (V) regions contained in the immunoglobulin preparations.[21] An already discussed hypothesis suggests the functional blockade of Fc receptors on splenic macrophages by IVIg, which leads to the reduction of the clearance of autoantibody-coated targets. One of the most important observations was the finding that the IVIg treatment of childhood idiopathic thrombocytopenic purpura (ITP) led to a rapid rise in platelet counts.[22] The mechanisms responsible for this effect of IVIg are complex and most likely involve the elimination of circulating immune complexes or microbial antigens by IgG, the competitive or steric inhibition or adsorption of plasma IgG or immune complexes to the platelet surface, and the competitive inhibition of the Fc receptor–mediated binding of platelets by macrophages.[23] It is supposed that increased levels of IgG saturate Fc receptors present on immunocompetent cells and thus prevent the removal of antibody-coated platelets.[24] According to another investigation, low doses of Rh-negative immunoglobulins caused a significant increase in platelet counts when given to Rh-positive patients with ITP, whereas no effect in Rh-negative patients was observed.[25] It is assumed that this effect occurs because of Fc receptor blockade by erythrocytes that are coated with anti-D.[23,25,26] There is also evidence that IVIg could possibly act by anti-idiotypic suppression of autoantibodies caused by IgG dimers occurring in therapeutic immunoglobulin preparations.[27] Moreover, in patients with antibodies to factor VIII who are receiving IVIg therapy, almost 95% of the antibodies disappeared from the serum within 36 hours.[28] This may be explained by a possible interaction between the V region of IVIg with factor VIII antibodies and their subsequent neutralization.[18] This was further supported by the finding of the presence of anti-idiotypes in immunoglobulin preparations to a variety of autoantibodies.[29] On the basis of in vitro and in vivo investigations, it has been suggested that the inhibition of complement-mediated damage could be dependent on the ability of IgG to bind C3b and C4b complement components, which would lead to a decreased number of activated complement fragments. In that context IgG is thought to down-regulate the available C3b with a rapid onset and duration within the half-life of IVIg.[30,31]

Furthermore, IVIgs are capable of modulating the synthesis and release of cytokines and cytokine antagonists.[32] Accordingly, both intact IgG and Fc fragments were found to down-regulate the production of the proinflammatory cytokines interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α) by lipopolysaccharide-stimulated macrophages.[33-35] In another study, inhibition of IL-6 production by human monocytes in the presence of IVIg was noted, whereas TNF-α release was not affected.[36] Moreover, staphylococcal enterotoxin B–treated human peripheral blood mononuclear cells (PBMCs) in vitro produced less IL-4. However, the release of interferon γ or TNF-α was not altered.[37] Several IgG preparations as well as IVIg have been reported to up-regulate monocyte production of the IL-1 receptor antagonist.[38-40]

Furthermore, IVIg preparations may have additional regulatory effects on cellular immune response by containing soluble molecules such as soluble CD4, CD8, human leukocyte antigens class I and class II determinants, and soluble intercellular adhesion molecule 1.[41,42] Soluble cell surface molecules are believed to interfere with antigen presentation because they appear to block the interaction between HLA class II and membrane-bound CD4 on T cells as well as the interaction between HLA class I and CD8 on cytotoxic T cells.[43,44] Preparations of IVIg also appear to contain peptide antibodies that bind to soluble and membrane-associated HLA class I antigens and thus inhibit CD8-mediated cytotoxicity of an influenza virus–specific human T-cell line. In addition, IVIg preparations were also found to contain antibodies to CD4 that are able to bind to $CD4^+$ T cells.[44]

Cytokine levels of commercially available IVIg preparations were also investigated. In a total of 238 examined samples, no evidence of IL-6, IL-10, or TNF-α was found, whereas high concentrations (≥ 10 ng/mL) of the immunosuppressive cytokine transforming growth factor β (TGF-β1 and TGF-β2) could be detected in all samples tested. In addition, an increase in latent and biologically active TGF-β plasma concentrations during IVIg infusions was observed.[45]

Table I. Possible mechanisms of action of IVIg therapy

Functional blockade of Fc receptors
Elimination of circulating immune complexes
Anti-idiotypic suppression of autoantibodies
Inhibition of complement-mediated damage
Modulating effects on the production and release of cytokines/cytokine antagonists
IL-1 ↓
TNF-α ↓
IL-4 ↓
IL-6 ↓
IL-1ra ↑
IL-10 ↑
TGF-β ↑
Regulatory effects of cellular immune response
Blockade of FasL (CD95L)

Because in animal models of autoimmune diseases the administration of TGF-β caused immunosuppression and alleviation of the disease, TGF-β present in substantial amounts in commercially available IVIg preparations could contribute to the therapeutic effects of IVIg in autoimmune diseases.[45] Moreover, there is preliminary evidence of an increase of plasma IL-10 levels occurring after IVIg administration (Rütter et al, unpublished observation).

Recently, another possible mechanism of action of IVIg has been proposed. Accordingly, a specific blockade of the cell-surface death receptor Fas and its specific ligand (FasL, CD95L) appear to be critically involved. Therefore FasL presented in pooled human IVIg could block Fas-mediated keratinocyte death in vitro. On the basis of these results, a pilot study in 10 patients with clinically and histologically confirmed toxic epidermal necrolysis (TEN) was performed, which demonstrated a highly beneficial effect of IVIg treatment[46] (Table I).

SIDE EFFECTS OF IVIG

Immunoglobulin preparations usually are well tolerated. General side effects arising from treatment with IVIg preparations tend to be mild and self-limited. A variety of vasomotor symptoms, including headache, myalgia, flushing, nausea, changes in blood pressure, and tachycardia, often occur within the first hour after onset of the infusion. These symptoms are thought to be due to aggregated immunoglobulins, antigen-antibody complex formation, and subsequent complement activation and rapidly resolve on stopping or slowing down of the infusion rate.[47]

Severe and anaphylactic reactions may occur in patients with IgA deficiency after IVIg treatment. The risk of anaphylactic shock depends on the presence of IgA autoantibodies in the patient's serum.[48] Deficiency of IgA will be detected in approximately 1 of 700 normal individuals. There is also evidence that patients with autoimmune diseases have an increased prevalence of selective IgA deficiency.[49,50] If IgA antibodies are detected, the possibility of IVIg preparations with very low amounts of IgA being used may be a beneficial alternative in these patients.[47,51]

The amount of infused IVIg strongly correlates with blood viscosity and the potential risk of cardiovascular and thus thromboembolic complications should also be considered a possible adverse reaction.[47,52] A few cases have been reported on the association of acute renal failure with IVIg therapy. However, in most of these reports, a sucrose-containing IgG preparation was believed to be the cause of renal injury.[53] Sugar additives such as sucrose, maltose, and glucose are added to stabilize the immunoglobulin preparation.

Intravenous infusion of sucrose has been reported to induce a form of "osmotic nephrosis," which has been associated with acute renal failure.[54,55] In addition, marked swelling and vacuolization of the renal tubular epithelium in the kidneys of 2 patients in whom acute renal failure developed during IVIg therapy were demonstrated.[56] Moreover, a case has been reported of a 39-year-old woman with lymphoma and mixed IgM/IgG cryoglobulinemia.[57] In this patient, acute renal failure developed 72 hours after a single IVIg infusion for an intractable pulmonary infection associated with hypogammaglobulinemia. In this case the role of cryoglobulins in initiating renal damage has been documented by renal biopsy findings. In conclusion, there is evidence that IVIg preparations containing sucrose may cause acute renal failure, which, according to most reports, is completely reversible.

Hematologic complications with clinical features of hemolysis were noted in a few patients with autoantibodies against blood group antigens of the ABO and Rh systems.[58,59] Neurologic adverse effects are rarely noted; the most serious of neurologic side effects is aseptic meningitis, which appears within 1 week after IVIg administration.[60,61] Because of recently developed purifying and virus-inactivating procedures, there should be no risk of transmission of known hepatitis virus or HIV in currently licensed IVIg preparations (Table II).

EFFICACY OF IVIG THERAPY FOR AUTOIMMUNE-MEDIATED SKIN DISEASES (Table III)

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune-mediated systemic disease, affecting multi-

Table II. Side effects of IVIg therapy

Vasomotoric symptoms
Anaphylactoid reactions correlated with IgA deficiency
Cardiovascular and thromboembolic complications
Renal failure ("osmotic nephrosis")
Hematologic complications (hemolysis)
Aseptic meningitis

ple organ systems. The complex pathomechanisms involve B-cell hyperactivity and autoantibody production to nuclear antigens and others. Autoantibody-antigen complexes cause vasculitis and may form immune complexes in the glomeruli, thereby leading to renal involvement.[62-65] Treatment usually includes systemic corticosteroids in combination with other immunosuppressive agents, such as azathioprine or cyclophosphamide.[66] Many reports on the use of IVIg in the treatment of SLE have been published; most show the efficacy and safety of this treatment.[67-80] According to two short open studies IVIg appears to have the ability to reduce clinical as well as serologic markers of disease activity temporarily.[77] There is evidence that pooled human immunoglobulins contain anti-idiotypic antibodies with reactivity against the SLE-associated 4B4 cross-reactive idiotype.[81]

The efficacy of IVIg compared with that of cyclophosphamide in the treatment of proliferative lupus nephritis was investigated in a pilot randomized trial. Patients with proliferative lupus nephritis who had received cyclophosphamide (1 g/m^2 once a month for 6 months) and prednisone (0.5 mg/kg daily) were randomly assigned to receive cyclophosphamide every 2 months for 6 months, and then every 3 months for 1 year or intravenous IVIg (0.4 g/kg monthly for 18 months). Out of a total of 14 patients, 5 received IVIg and 9 were assigned to receive standard intravenous cyclophosphamide treatment. In both groups the dose of prednisone was allowed to increase if relapse or deterioration of kidney involvement occurred. Patients in the cyclophosphamide group had used marginally more prednisone than those in the immunoglobulin group, whereas before randomization the adjustment for the amount of prednisone used in the first 6 months did not differ between the two groups. Thus IVIg was deemed to be safe and efficacious therapy for lupus nephritis.[82] In addition, the successful treatment of SLE cerebritis with IVIg was reported.[83] One case of antiphospholipid syndrome with thrombocytopenia and cerebral infarctions in a patient with SLE also was reported to have responded well to IVIg (0.4 g/kg per day for 2 days) in combination with prednisone (75 mg/day) and chlorambucil (4-8 mg/day).[69] Moreover, the successful

Table III. IVIg in the treatment of skin diseases

Diseases	Reference No.(s)
SLE	67, 68, 81, 82
Dermatomyositis/polymyositis	91, 97, 98, 104
Scleroderma	108, 109
Autoimmune blistering diseases	121, 133, 135
TEN	46, 141
AD	148
HIES	153
Allergic asthma	156, 158, 159
Chronic autoimmune urticaria	165
Kawasaki syndrome	170
Pyoderma gangrenosum	179-180
GVHD	15,16

administration of IVIg in compromised pregnancies associated with antiphospholipid antibodies and SLE has recently been shown.[84-86] In 1999, the successful treatment of cutaneous lupus erythematosus with IVIg was reported.[87] IVIg was administered at a dosage of 2 g/kg per month in combination with hydroxychloroquine sulfate (400 mg/day) and topical betamethasone dipropionate. An almost complete healing of the cutaneous lesions could be observed after 6 months (Table IV).

Dermatomyositis, polymyositis, and inclusion body myositis

Dermatomyositis (DM), polymyositis (PM), and inclusion body myositis are autoimmune-mediated diseases with skin and muscle involvement. All 3 forms show a characteristic myopathy, and muscle weakness is generally symmetric in the proximal muscle groups. In PM and inclusion body myositis, sensitized CD8$^+$ T cells are believed to cause muscle destruction.[88-91] DM is a distinct clinical entity, with a typical skin involvement such as heliotrope rash, edema on the upper eyelids, and rash on the face and upper trunk. The pathologic mechanisms, which are not fully understood, involve a complement C5b-9 membranolytic attack complex, leading to intramuscular microangiopathy, which results in fibronecrosis and atrophy.[90,92]

Standard therapy regimens include combinations of corticosteroids, methotrexate, azathioprine, cyclosporine, and cyclophosphamide. However, in many cases this disease is difficult to manage because many patients become refractory to most of the treatment modalities.[93-95] Therefore several clinical trials have been performed with IVIg used to treat DM or PM; in most of the reported cases, significant alleviation of the disease has been reported.[61,91,96-101] Accordingly, in one study 6 patients with DM and 14 patients with

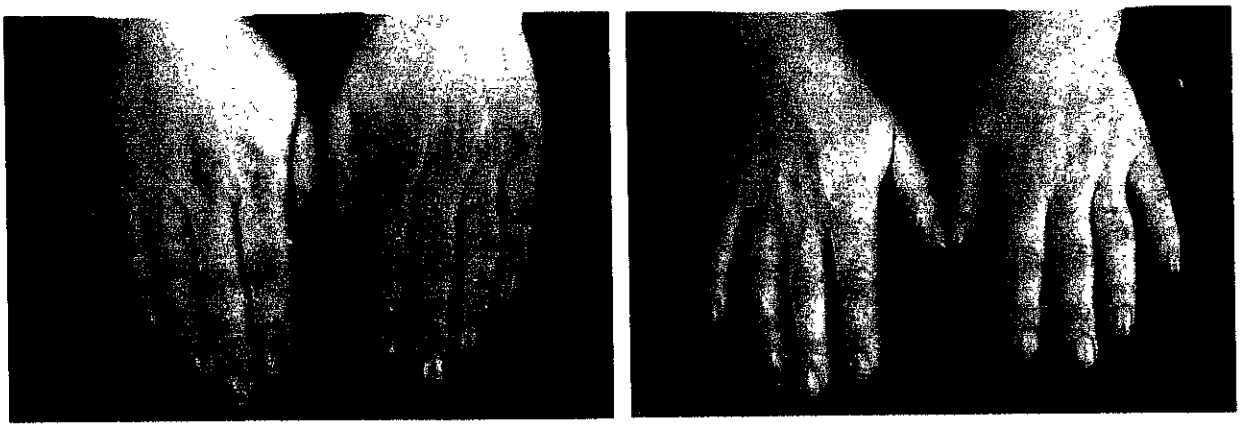

Fig 1. Acute dermatomyositis. **A,** Before treatment. **B,** After 6 IVIg courses (2 g/kg per month).

Table IV. IVIg therapy for SLE

Authors	No. of patients	Adjuvant therapy	Dosage	No. of courses (IVIg)	Results
Schroeder et al[70] (1996)	12 → IVIg	None	120 g/3 wk	2	Systemic Lupus Activity Measure ↓, antibody titer ↓
Pirner et al[71] (1993)	6 → IVIg	None	2 g/kg/mo	1	Long-term remission in 2 patients
Francioni et al[81] (1994)	12 → IVIg	None	2 g/kg/mo	6-24	Clinical and serologic improvement in 11 patients, antibody titer ↓

PM were treated with IVIg either with 0.4 g/kg for 5 days or with 1 g/kg per day for 2 consecutive days. In all of these patients a remarkable improvement and increase in muscle strength have been reported.[97] In a placebo-controlled, double-blind, crossover study, a total of 12 patients received IVIg, 2 g/kg per month. Most patients showed a significant improvement in muscle strength, which was related to an increase in the number of muscle fibers and muscle fiber diameter[91] (Fig 1).

Other reports confirmed the favorable response to IVIg in patients with juvenile-onset DM[98,102] or DM associated with panniculitis.[101] A beneficial effect of IVIg on cutaneous ulcers in patients with refractory adult DM has been reported.[103] In another open trial 19 patients with DM received IVIg at a monthly dosage of 2 g/kg over a 6- to 12-month period.[104] Most patients showed remarkable clinical improvement. A significant decrease of serum IL-2R appeared to correlate with clinical improvement (Table V).

Scleroderma

Scleroderma is a chronic disease that affects the microvascular as well as connective tissue and is characterized by fibrosis and obliteration of vessels in the skin. It may occur in a localized form (morphea) or as systemic sclerosis (systemic scleroderma [SSc]) that shows involvement of internal organs. In SSc, antibodies against topoisomerase I (Scl-70) are present in approximately 30% of patients. Treatment with immunosuppressive agents is difficult, and the disease is often progressive.[105,106] A few case reports have appeared to indicate that IVIg may be used as an alternative treatment in cases of SSc overlapping with DM.[107,108] In 1998 Wollina et al[109] reported that IVIg was beneficial in the treatment of disabling morphea of childhood. In our experience we can report significant clinical improvement with IVIg therapy in a patient with long-standing SSc/DM overlap syndrome. The patient had generalized fibrosis and hyperpigmentation of the skin, sclerodactyly, Raynaud's phenomenon, and esophageal sclerosis. In addition, there was evidence of myositis and decrease of muscle strength, which correlated with specific laboratory abnormalities. IVIg was administered at a dosage of 2 g/kg per month in combination with low-dose prednisolone. After 4 courses of IVIg therapy, a significant increase of muscle strength could be noted. After 10 courses of IVIg, sclerosis of the skin showed remarkable improvement, and the esophageal dysfunction was significantly alleviated.

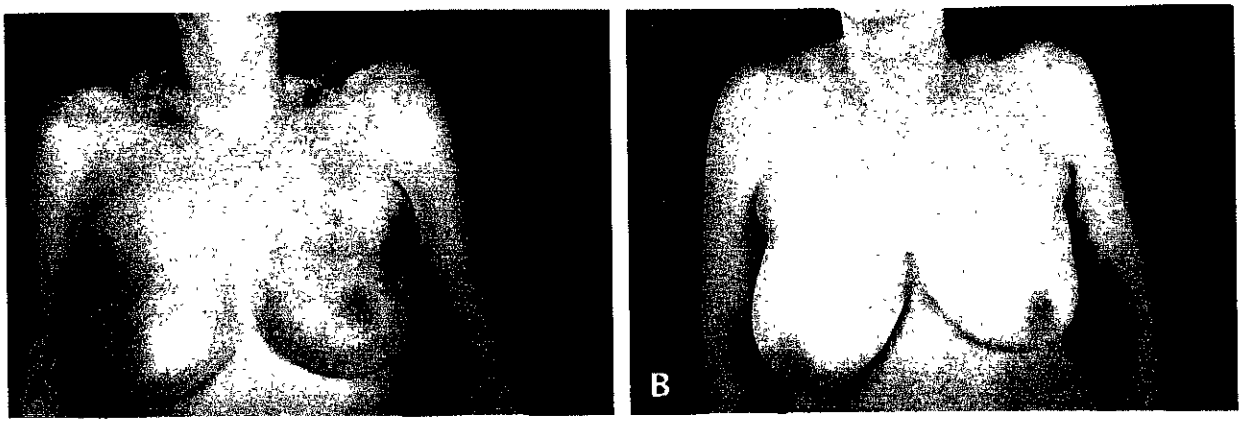

Fig 2. Patient with systemic sclerosis. **A,** Before treatment. **B,** After 10 IVIg courses (2 g/kg per month).

Table V. IVIg therapy for dermatomyositis (DM) and polymyositis (PM)

Authors	No. of patients	Adjuvant therapy	Dosage	No. of courses (IVIg)	Results
Dalakas et al[91] (1993)	15 DM; 8 → IVIg, 7 → placebo	Prednisone (25 mg/d); cross over 4 patients	2 g/kg/mo	3	Muscle strength ↑; no effects in placebo group
Cherin et al[97] (1991)	15; 12 PM, 3 DM	Steroids, MTX (variable dosage)	2 g/kg/mo		Muscle strength ↑; CPK ↓ with adjuvant therapy
Gottfried et al[104] (2000)	19 DM → IVIg	Steroids/ azathioprine/ MTX/chloroquine (variable dosage); no placebo group	2 g/kg/mo	6-12	Muscle strength ↑; sIL-2R ↓ with adjuvant therapy

The prednisolone dosage could then be tapered, without disease relapse during a 6-month period (Fig 2).

Autoimmune blistering diseases

Autoimmune blistering diseases are considered to be a group of chronic autoimmune diseases characterized by blister formation and erosions of the skin and mucous membranes in association with autoantibodies against defined cell surface components. Autoantibodies to desmoglein 3 are found in pemphigus vulgaris (PV), which results in suprabasal blister formation with acantholysis. Pemphigus foliaceus (PF) is characterized by scaly lesions caused by superficial blister formation because of the predominant expression of autoantibodies against desmoglein 1 in the upper layers of the epidermis.[110] Bullous pemphigoid (BP) is a subepidermal blistering disease, usually occurring in the elderly and occasionally in association with malignancy. Autoantibodies detected in BP bind to 2 hemidesmosomal antigens.[111-113] Another variant of pemphigus is paraneoplastic pemphigus.[114]

Therapeutic management of autoimmune blistering diseases usually includes high-dose, long-term corticosteroids in addition to other immunosuppressive drugs, such as azathioprine, cyclophosphamide, and cyclosporine.[114,115] Several studies have reported the successful use of IVIg for the treatment of autoimmune blistering diseases. Initial studies of IVIg therapy for patients with BP have shown temporary relief.[116] These patients were treated only with one course of IVIg (0.4 g/kg per day for 5 days) without additional therapy. A subsequent study showed a beneficial response of IVIg treatment in combination with alternating application of a cyclophosphamide-dexamethasone pulse regimen in 2 patients with severe BP.[117] After 5 courses of IVIg

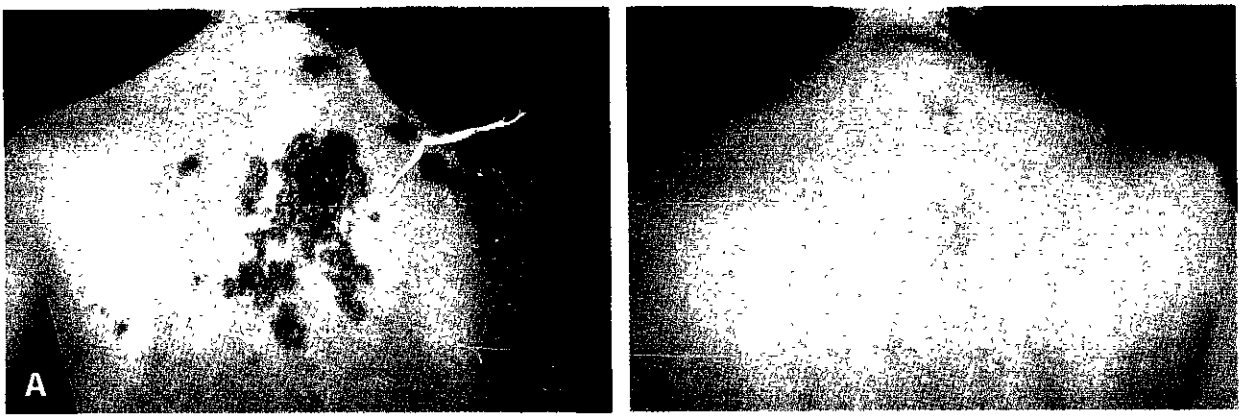

Fig 3. Dorsal lesions of PV. **A,** Before treatment. **B,** After 2 IVIg courses (2 g/kg per month).

(0.5 g/kg per day for 5 days per month), total remission has occurred in both patients. According to another report,[118] 3 patients with PV, one patient with PF, and 2 patients with BP were treated with adjuvant IVIg. In each patient, disease activity was suppressed, which allowed a reduction in the prednisone dose. In one study,[119] there was also evidence of a rapid response in one patient with severe PV, who received IVIg as monotherapy. However, subsequent courses of IVIg appeared to be less effective. In contrast with these reports, another study[120] describes treatment failure with the use of IVIg monotherapy in 3 patients with PV and BP.

More recently, the successful treatment of one case of recalcitrant penicillamine-induced PF by low-dose IVIg therapy has been described.[121] The beneficial effects of IVIg in 6 patients with PV and PF, who exhibited only a poor response to conventional immunosuppressive therapy regimens, have been reported. In all patients stabilization of their disease developed within 6 to 9 courses of an adjuvant regimen with IVIg. Reduction of corticosteroids and other immunosuppressive agents did not result in relapse.[122] The experience with IVIg therapy in a retrospective study of 14 patients with autoimmune blistering diseases was published in 1999.[123] The use of IVIg had a steroid-sparing effect in 10 patients with PV, BP, and pemphigoid gestationes. Therapy with IVIg showed a rapid effect in 2 patients with severe, progressive PV and in one patient with BP. The clinical improvement was transient and required repeated courses of IVIg (0.4 g/kg per day for 5 days). However, in two patients with nodular pemphigoid, which is a rare clinical variant of pemphigoid, no clinical improvement could be determined, despite a decrease in the titer of basement membrane zone autoantibodies after IVIg treatment in one case.[123] These results were supported by several other observations, all considering IVIg as an effective steroid-sparing agent restoring the response to conventional therapeutic regimens, when it was given at 2 to 4 weekly intervals and for a minimum of 3 courses.[124-127] In addition, IVIg appears to have a greater benefit with longer remissions when given as an adjuvant drug (Fig 3). In conclusion, it should be noted that most of these studies are preliminary in nature, and controlled randomized clinical trials proving the therapeutic efficacy of IVIg have not been done.

Pemphigoid gestationes

Pemphigoid gestationes usually occurs in the second or third trimester of pregnancy or occasionally postpartum. Clinical features are similar to those of BP, and autoantibodies to a hemidesmosomal antigen can be detected. The disease may be self-limited; it may also occasionally have a more persistent and refractory course. Conventional therapy for pemphigus gestationes in advanced stages of pregnancy is systemic corticosteroids.[128,129]

Hern et al[130] in 1998 reported on IVIg treatment in a patient with severe prolonged pemphigoid gestationes that proved refractory to corticosteroids. Adjuvant to a regimen of prednisolone (20 mg/day), IVIg was given at a dosage of 0.4 g/kg per day for 5 days. After the prednisolone had been reduced to 8 mg/day, the disease relapsed after 5 weeks; a second course of IVIg in combination with cyclosporine was administered, which reinduced remission.

Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita (EBA) is an acquired, chronic bullous dermatosis, in which clinical features resemble those of inherited epidermolysis bullosa dystrophica. Autoantibodies to the carboxyl-terminus of type VII procollagen within the

anchoring fibrils at the dermoepidermal junction have been identified as the cause of this disease.[131,132] EBA is difficult to treat, especially the inflammatory variant resembling BP. However, encouraging results were reported on adjuvant IVIg treatment in a patient with long-standing EBA.[133] This patient's disease had been resistant to dapsone, corticosteroids, and plasmapheresis. Therapy with IVIg was initiated at a dosage of 0.4 g/kg per day for 4 days and repeated every 2 weeks. Additional treatment including prednisolone (0.5 mg/kg per day) and cyclosporine (10 mg/kg per day) was continued. Rapid clearance of bullous skin lesions was noted after one course of IVIg; relapse of blistering occurred 10 days after the last infusion of IgG. Within 4 courses of IVIg, circulating autoantibodies were no longer detectable. The efficacy of IVIg in the treatment of severe EBA was further supported by another case report.[134] In this case IVIg (0.4 g/kg per day) was administered for 5 days, and treatment was repeated every 4 weeks. In addition, the previous treatment of prednisone (12 mg/day), azathioprine (100 mg/day), dapsone (100 mg/day), and colchicine (2 mg/day) was maintained. After 9 courses of IVIg all lesions were healed, and there was a marked reduction of new blister formation. According to another report of a patient with long-standing EBA, the administration of 7 courses of lower dose IVIg (0.4 g/kg per day for 5 days) led to a favorable clinical outcome and the disease stabilized for a 10-month period after the therapy was initiated.[135] Finally, two patients with refractory EBA improved after regular courses of IVIg given as monotherapy.[123]

Linear IgA bullous dermatosis

Linear IgA bullous dermatosis is a blistering autoimmune disease, which is characterized by deposition of IgA along the basement membrane zone.[136,137] The efficacy of IVIg treatment in a patient with linear IgA bullous dermatosis, which was associated with chronic renal failure, has been reported.[138] This patient had already experienced significant adverse effects from conventional therapies to which he did not respond. A total monthly dosage of 4 g/kg was used, and the infusion cycle was repeated every 2 weeks for the first 4 months, and subsequently increased to 3-week intervals. After 3 cycles, complete clearing of all lesions could be observed, and adjuvant corticosteroid therapy was withdrawn. Within the first 6 months after initiation of IVIg therapy, complete remission of the disease was noted. The disease relapsed when the interval was prolonged to 3 or 5 weeks in the initial phase of treatment. Clinical improvement was associated with decrease of the IgG autoantibody titer.

Toxic epidermal necrolysis

TEN is a severe, life-threatening, drug-induced skin disease, in which large areas of epidermis separate from the dermis. Treatment in most cases is difficult because the efficacy of corticosteroids is controversial and the benefit of other therapies (eg, plasmapheresis) has not been fully approved.[139,140] In 1998 Viard et al[46] reported an open, noncontrolled pilot study in which IVIg treatment was performed in 10 patients with histologically confirmed TEN. IVIg was administered at dosages ranging from 0.2 to 0.75 g/kg per day in a 4-day protocol. A significant improvement within 48 hours was observed in all patients, and in none of the cases was there evidence of a relapse. Programmed cell death (apoptosis) of keratinocytes, which is mediated by the interaction of cell surface receptors and their specific ligands such as Fas and FasL and is responsible for the destruction of the epidermis, is believed to play a crucial role in the pathogenesis of TEN. The mechanism responsible for this significant response to IVIg appears to be due to the presence of Fas-blocking antibodies contained in the IVIg preparations. This is further supported by the finding of high levels of FasL in the sera of patients with TEN. A recent study reported the favorable outcome with IVIg added to basic symptomatic therapy in one case of severe TEN.[141]

Atopic dermatitis

Atopic dermatitis (AD) is an eczematous inflammatory skin disease occurring in genetically predisposed persons, which is characterized by the role of type 2 helper T cells in the elevation of IgE levels and eosinophilia. In addition, several environmental and intrinsic factors may trigger the disease. Despite a variety of available treatment modalities, including corticosteroids, phototherapy, immunomodulators (interferon gamma), and immunosuppressive drugs such as cyclosporine, severe cases often are difficult to treat and tend to relapse.[142-145]

A few studies have reported on the efficacy of IVIg as an alternative therapy in resistant cases of AD and steroid-dependent asthma.[146,147] In one recent case of AD, which could not be controlled by various different immunosuppressive agents, stable improvement, which led to a significant decrease in skin score, was reached within 10 courses of IVIg treatment (0.4 g/kg per day, 5 days, every 4 weeks). Additional medication included prednisone (10 mg/day) and hydroxychloroquine (200 mg/day). Intracellular cytokine analysis in the PBMCs of this patient revealed a decrease in IL-4–positive cells on day 4 of a 5-day treatment course. No significant change was observed in IL-2–positive or interferon

gamma–positive cells. Therefore suppression of IL-4 is suggested as a potential mechanism of action for IVIg in AD.[148]

In 4 patients with severe, therapy-resistant AD (2 with Kawasaki disease and 2 with ITP), treatment with IVIg resulted in a marked reduction of the skin lesions.[146] Patients were treated with IVIg at a dosage of 0.4 g/kg daily for 5 days. In all patients receiving this IVIg monotherapy, AD was significantly alleviated without relapse of the disease over a 6-month period. The clinical features of Kawasaki disease and ITP also improved. Finally, there is still a lack of controlled, randomized clinical trials to prove the therapeutic benefit of IVIg therapy, especially in AD.

Hyperimmunoglobulinemia E syndrome

Hyperimmunoglobulinemia E syndrome (HIES) is an inflammatory skin disease that is difficult to treat, characterized by severe dermatitis, recurrent staphylococcal infections of the skin and respiratory tract, cold subcutaneous abscesses, and extremely high serum IgE levels.[149-152] In two patients with HIES and Kawasaki disease, IVIg monotherapy with one course of 0.4 g/kg daily for 5 days resulted in improvement of severe eczema.[153] Subsequently, the same regimen was used in patients with HIES alone, AD, Kawasaki disease, or ITP. Treatment with IVIg remarkably improved eczema in patients with HIES with or without Kawasaki disease and in patients with AD. Moreover, a decrease of serum IgE levels in these patients was observed, but not in patients with Kawasaki disease or ITP without AD. Supplementary in vitro studies show that the addition of high concentrations of IgG to PBMCs from patients with HIES or AD decreases spontaneous and anti-CD40–induced production of IL-4.[153-155] These data provide additional evidence of a role played by IVIg in down-regulating IL-4 release and IL-4–mediated IgE production and thus ameliorating the course of these diseases.

Allergic asthma

Like atopic eczema, allergic asthma is a T_H2-driven disease affecting the respiratory tract. A clinical trial was carried out to determine the efficacy of IVIg in severe steroid-dependent asthma.[156] Eleven adolescent and adult patients were treated with IVIg at a dosage of 2 g/kg monthly; a total of 7 IVIg courses were given. Steroid requirements, pulmonary function, symptom scores, bone densitometry, and airway reactivity were evaluated over a 7-month period. The results indicated a significant decrease in steroid use, whereas an airway reactivity, monitored by metacholine challenge, appeared to be unaffected by IVIg treatment. The results of 2 earlier small clinical studies revealed a similar response to IVIg treatment in children with asthma.[157,158] In an open-label study performed in children, a slight inhaled steroid-sparing effect on IVIg treatment was observed (0.8 g/kg monthly over a 5-month period). The effect of IVIg on steroid consumption in patients with severe asthma was investigated in a double-blind, placebo-controlled, randomized trial.[159] Among 28 patients who completed the study, 16 patients received IVIg therapy at a dosage of 2 g/kg initially and 0.4 g/kg every 3 weeks thereafter for a total of 9 months. The results of the study indicate that IVIg therapy appears to decrease the oral steroid consumption in a subpopulation of steroid-requiring patients with asthma who suffer from extreme respiratory symptoms that require larger doses of oral steroids.

Chronic autoimmune urticaria

The complex pathogenetic mechanisms of chronic autoimmune urticaria, which is frequently resistant to therapy, are poorly understood.[160] However, there is evidence from recent studies that suggests a role for autoantibodies directed against various domains of IgE or the high-affinity FcεRI receptor.[161] The autoimmune etiology of this disease is further supported by recent observations suggesting a beneficial effect of immunomodulating therapeutic strategies including corticosteroids and cyclosporine.[162-164] Therefore the potential effect of IVIg in 10 patients with chronic urticaria as well as IgE autoantibodies was investigated. Clinical improvement could be noted in 9 patients receiving 0.4 g/kg per day for 5 days. Although the mechanism of action of IVIg in this disease is not clear, a role of anti-idiotypic antibodies capable of suppressing IgE autoantibodies has been suggested.[165]

Kawasaki syndrome

Kawasaki syndrome is an acute systemic vasculitis of childhood that mainly involves the medium-sized and large arteries and thus represents the leading cause of acquired heart disease in children.[166,167] Clinical and epidemiologic data support an infectious cause, but the origin of Kawasaki disease is not completely understood. However, a role of IgA-producing cells within the vascular wall has been suggested.[168,169] Several clinical studies have demonstrated that IVIg together with acetylsalicylic acid given within the first 10 days of the disease leads to a significant reduction in the prevalence of coronary artery abnormalities.[170-172] In this well-accepted regimen, IVIg usually is applied as a single 2 g/kg per day course in combination with acetylsalicylic acid (80-100 mg/kg per day). There is evidence that down-regulation of cytokine production is responsible for the beneficial effect of IVIg in Kawasaki syn-

drome.[169,173] Accordingly, the secretion of IL-1 by PBMCs from patients with acute Kawasaki disease was found to be significantly down-regulated in those patients who responded well to IVIg therapy.[174]

Pyoderma gangrenosum

Pyoderma gangrenosum is a rare vasculitis of unknown origin sometimes associated with autoimmune disease. The chronic and often relapsing ulcerations may be resistant to various high-dosage immunosuppressive therapy regimens.[175-177] However, there are some case reports that indicate a favorable response of pyoderma gangrenosum to IVIg therapy. Marked alleviation of pyoderma gangrenosum in a patient undergoing IVIg treatment (0.4 g/kg per day for 5 days) in addition to prednisone (60 mg/day) and cyclosporine (6 mg/kg per day) has been reported.[178] After a second course of IVIg (1 g/kg per day for 2 days), the additional prednisone/cyclosporine treatment could be tapered off without any sign of relapse during a follow-up period of 8 months. In another study, the total remission of pyoderma gangrenosum in a patient receiving IVIg (1 g/kg daily for 2 days every 4 weeks) in addition to prednisone (60 mg/day) was described.[179] After 4 months, complete healing was achieved and prednisone was tapered to 10 mg/day. A recent study reported the beneficial outcome of IVIg administration as adjuvant therapy in one case with posttraumatic pyoderma gangrenosum.

Erythema exudative multiforme

Within the clinical spectrum of erythema exudative multiforme, the subgroup of recurrent erythema multiforme, in which frequent clinical episodes occur over a period of several years, is often refractory to therapy.[181-183] In one report of 65 patients with recurrent erythema multiforme undergoing a variety of therapeutic regimens, a total of 13 patients were treated with intramuscular injections of human immunoglobulin (750 mg/mo). In 11 patients a significant decrease of disease activity was observed; one patient did not show any sign of relapse over a 7-year period, and in 2 patients no beneficial effect was noted.[184] However, the mode of action may differ when immunoglobulins are administered intramuscularly.

Graft-versus-host disease

GVHD is commonly observed as a condition occurring after allogeneic bone marrow transplantation (BMT), but may also develop after syngeneic BMT or blood transfusion and reinfusion of autologous marrow.[185] Originally IVIg treatment after BMT was believed to be useful in the prevention of infections, such as cytomegalovirus-induced pneumonia.[186] It is not clear whether the phenomenon is due to a direct antiviral activity or whether it is the result of a specific immune modulation by IVIg being able to suppress GVHD.[14,15] In a controlled, randomized, long-term study, IVIg (0.5 g/kg) was administered monthly from day 90 to day 360 after BMT. The study included 250 patients; 123 patients received IVIg, and 127 were a randomized control group. The results of this clinical trial revealed that the administration of IVIg had no effect on survival or the incidence of chronic GVHD.[16] The total rate of infections in the second year was less in the control group. Thus IVIg appears not to be beneficial in the treatment of GVHD.

OUTLOOK

There is evidence that administration of IVIg is of significant efficacy in autoimmune diseases as well as in immunocompromised conditions.[7,16,20,61] Standard therapy regimens in autoimmune diseases are associated with a variety of potential long-term complications and severe side effects related to immunosuppressive agents. Establishing IVIg as adjuvant treatment may result in a steroid-sparing effect as well as in the reduction or withdrawal of additional immunosuppressive drugs. The fact that IVIg itself usually causes rare (and mild) side effects appears to be of primary importance in this context.[47,51]

The dosage regimens for IVIg vary considerably within the different studies. The effective given dosages range between 0.2 and 2 g/kg monthly, administered on 2 or 5 consecutive days. The most commonly used regimen for treatment of autoimmune diseases is 2 g/kg divided over 5 days and was introduced because of its beneficial effect in the treatment of ITP. However, it has not yet been proven that this regimen is optimal. The administration generally is repeated every month because of the half-life of IgG, which is 18 to 32 days. This may also explain the generally transient clinical benefit of IVIg treatment. In conclusion, adequately controlled long-term clinical trials are required to determine guidelines concerning duration, dose, frequency, and mode of application. The increasing knowledge concerning the underlying mechanisms responsible for the beneficial effects of IVIg in the treatment of autoimmune disease will ultimately help to optimize the use of this promising therapeutic approach. The fact that IVIg therapy is very expensive should lead to critical use in selected cases of autoimmune and inflammatory diseases.

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