Use of IGIV in the Treatment of Immune-Mediated Dermatologic Disorders

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Immunoglobulin (Ultravenous, IGIV) is now used in a variety of immune-mediated diseases. Its presumed mechanism of action involves both anti-inflammatory and immunomodulatory activities. A number of dermatologic conditions are believed to be immune mediated and in these disorders, IGIV has shown benefit in reducing symptoms and the need for cortecosteroids or cytotaxic drugs. In many of these diseases, the initial benefits seen in open-labeled trials must be confirmed in controlled clinical trials. ***Key words: IGIV, determatology, anti-inflammatory immunomodulatory. J Investig Dermatol Symp Proc 9:92–96, 2004***

INTRODUCTION

Administration of immunoglobulin (Ig) was initiated for the treatment of antibody deficiency disorders five decades ago. With the advent of significant changes in manufacturing, Ig products became available for intravenous use in the 1980s. This allowed for much broader therapeutic application because of the ability to deliver higher doses. Whereas Ig replacement in antibody deficiency disorders was begun at 100 mg/kg body weight, IGIV (immunoglobulin intravenous, human), treatment of the wider range of disorders appeared to require doses exceeding 1 g/kg body weight. The first indication of the therapeutic potential of IGIV beyond simple Ig replacement was the successful treatment of patients who had concomitant primary immune deficiency and thrombocytopenia purpura. Here, IGIV was administered at a dose of 400 mg/kg body weight for 5 consecutive days (Imbach *et al*, 1981).

In fact, indications of and support for the broader potential of Ig products was seen by a number of clinicians managing patients with primary immunodeficiency. Even doses of intramuscular Ig of 100 mg/kg body weight had surprising consequences of replacement therapy that went well beyond simple prevention of infection through provision of antibodies. Some of these responses are summarized in **Table 1**. They include reversal of significant immune-mediated cytopenias, including neutropenia and thrombocytopenia (Gelfand, 1988), lymphoid hyperplasia, reactive airway disease, growth attenuation, diarrhea, arthritis (Stuckey *et al*, 1978), concentration deficits, and—pertinent to this discussion—a number of dermatologic abnormalities that accompany some immunodeficiency disorders. In this regard, Ig replacement therapy has been shown to impact the cutaneous lesions of eczema, alopecia totalis, or nondescript rashes (Ipp and Gelfand, 1976). For each of these conditions, when seen in patients with primary antibody deficiency, monthly injections of IgG resulted in a normalization of the skin condition and even reappearance of fine hair in patients with alopecia. In many of these patients, the condition recurred when Ig therapy was stopped or delayed, only to respond again on reinstitution of therapy.

It was these clinical observations that spurred the consideration and expansion of IGIV use in a wide variety of disorders. A partial list of potentially responsive conditions is included in **Table 2**. It should be recognized that in some but not all of these conditions placebo-controlled trials have been carried out to provide validation. In many, a series of isolated reports, often anecdotal, are the basis for inclusion in the list.

MECHANISM OF ACTION OF IGIV

A major deficit in rationally and appropriately administering IGIV to this wide range of disorders with seemingly different pathophysiologies is the lack of knowledge on how and why IGIV may work. Depending on the disease target, IGIV has been shown to exhibit anti-inflammatory and/or immunomodulatory activities. The anti-inflammatory potential of IGIV is perhaps best seen in the treatment of Kawasaki syndrome (KS), an acute systemic vasculitis, primarily in infants, that mainly involves the medium and large arteries. Although clinical and epidemiological findings suggest an infectious etiology, this remains to be proved. IGIV therapy has profound effects in KS, rapidly reducing fever, irritability, cutaneous manifestations, and, importantly, reducing the prevalence of coronary artery abnormalities. As summarized in **Table 3**, all of the clinical and laboratory findings support a potent anti-inflammatory effect of IGIV in KS, but the exact mechanism of action is not defined.

Equal to the number of diseases potentially responding to IGIV are the suggested mechanisms of action (**Table 4**). Some of these are speculative, whereas others have received some experimental support. A few of the mechanisms pertinent to the dermatologic diseases are discussed below.

FC receptor interactions Following the successful treatment of immune-mediated thrombocytopenia, IGIV was postulated to act by blocking Fc receptors on phagocytic cells—for example, on splenic macrophages—preventing antibody (IgG)-coated platelets from interacting with these cells and enhancing platelet survival. In fact, in direct testing, survival of IgG-coated

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Abbreviations: Ig, immunoglobulin; KS, Kawasaki syndrome; TNFα, tumor necrosis factor α; IL-1Ra, IL-1 receptor antagonist; FasL, Fas ligand; GLR, glucocorticoid receptor; EBA, epidermolysis bullosa acquisita; OCP, ocular cicatricial pemphigoid; TH2, T helper 2; AD, atopic desmatitis.

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Table 1. Additional Benefits of Ig Replacement in Antibody-Deficient Patients

- Reversal of *autoimmune cytopenias*
  - Neutropenia
  - Thrombocytopenia
- Improvement in *skin disorders*
  - Eczema
  - Alopecia totalis
  - Undefined rashes
- Diminution of *lymphoid hyperplasia*
- Resolution of *arthritis*
- Decrease in *diarrhea*
- Improvement of *reactive airway disease*
- Acceleration of linear *growth*
  - Increase in growth hormone production
- Increase in mental *concentration*

Table 2. Diseases that Respond to IGIV Therapy

Diseases Responding to IGIV Therapy in Controlled Trials
Antibody deficiency diseases*
Idiopathic thrombocytopenia purpura*
Pediatric HIV disease*
Kawasaki syndrome*
Dermatomyositis
Guillain-Barre syndrome
Chronic inflammatory demyelinating polyneuropathy
Multifocal motor neuropathy
Stiff man syndrome

*FDA approved indication.

Diseases Which Appear to Respond in Clinical Trials But Need Further Verification Steroid-dependent asthma ANCA-positive vasculitis Multiple sclerosis Myasthenia gravis Lambert-Eaton syndrome Toxic shock syndrome

Table 3. Anti-Inflammatory Effects of IGIV in Kawasaki Syndrome

Decreased temperature
Decreased white blood cell count
Decreased serum levels of acute phase reactants
alpha1-antitrypsin
fibrinogen
c-reactive protein
Decreased serum soluble IL-2 receptors

red cells was significantly enhanced in individuals receiving IGIV (Fehr *et al*, 1982).

Recently, a murine model of ITP was used to delineate the molecular basis for IGIV (Samuelsson, 2001). In these studies, administration of clinically protective doses of intact antibody or monomeric Fc fragments to wild-type or Fcγ receptor–humanized mice prevented platelet consumption initiated by injection of a platelet-directed antibody. Of importance, the inhibitory (signaling) Fc receptor, FcγRIIB, was required for this protection. Any interference with this inhibitory receptor reversed the therapeutic benefit of IGIV. The protective effects were associated with the ability of IGIV to upregulate the expression of FcγRIIB on splenic macrophages. This demonstration of the modulation of an inhibitory signaling pathway may provide an important foundation for the therapeutic applications of IGIV in attenuating or reversing (auto)antibody-mediated diseases.

Reduction in pathogenic autoantibody titers A number of disorders in which IGIV exhibits immunomodulatory/anti-inflammatory effects are associated with autoantibodies that may

Table 4. Immunoregulatory Actions of IGIV

Inflammation
- Attenuation of complement-mediated damage
- Decrease in immune-complex-mediated inflammation
- Induction of anti-inflammatory cytokines
- Inhibition of activation of endothelial cells
- Neutralization of microbial toxins
- Reduction in corticosteroid requirements

Cell growth
- Regulation of apoptosis pathways
- Inhibition of lymphocyte proliferation

T cells
- Regulation of the production of T-cell cytokines
- Neutralization of T-cell superantigens

B cells and antibodies
- Control of emergent bone marrow B-cell repertoires
- Negative signaling through inhibitory Fcγ receptors
- Selective down-regulation or up-regulation of antibody production
- Neutralization of circulating autoantibodies by anti-idiotypes

Fc receptors
- Blockade of Fc receptors on macrophages and effector cells
- Induction of antibody-dependent cellular cytotoxicity
- Induction of inhibitory Fcγ receptors IIB
- Saturation of FcRn

be pathogenic. Thus, reducing the levels of these autoantibodies, either by limiting production or enhancing catabolism, could prove beneficial. Several studies have shown that IGIV, at least *in vitro*, can interfere with Ig synthesis. This could be the result of the activation of FcγRIIB, the inhibitory signaling pathway on B lymphocytes.

A number of possible mechanisms could trigger enhanced catabolism or degradation of serum autoantibody levels. There is evidence that IGIV contains an array of anti-idiotypes and that it may act through idiotypic suppression of autoantibody formation. Idiotypic suppression could directly modify B cell function, limiting antibody synthesis, or it could do so by neutralizing the autoantibody following interaction with the idiotype. In addition, anti-idiotypic antibodies may combine with idiotypes on the autoantibodies, thus forming complexes and so further enhancing catabolism (Rossi *et al*, 1989; Kazatchkine and Kaveri, 2001).

An interesting mechanism that may be responsible for enhanced catabolism involves the interactions between IGIV and FcRn receptors (Yu, 1999). Normally, IgG binds to FcRn that are found in many tissues, including skin and muscle, and that are highly expressed on vascular endothelial cells. FcRn is a protective receptor that prevents the catabolism of IgG. IgG binds to FcRn in endocytic vesicles, preventing its degradation by lysosomes; as a result, it returns intact to the circulation. Increasing the amounts of IgG—for example, by administration of IGIV, may saturate FcRn, thereby accelerating the rate of catabolism of pathogenic IgG autoantibodies.

Induction/suppression of cytokines There are numerous reports that IGIV modulates the synthesis and release of certain cytokines and cytokine antagonists. Thus, administration of IGIV or inclusion of IGIV in *in vitro* culture systems has been shown to downregulate the production of the pro-inflammatory cytokines IL-1 and tumor necrosis factor α (TNF-α), at the same time up-regulating monocyte production of the anti-inflammatory proteins IL-1 receptor antagonist (IL-1Ra) and IL-10. Following IGIV infusion, soluble TNF-α receptor, IL-6, IL-4 receptor, and IL-10 levels may increase, as do levels of TGF-β (Anderson, 1984; Shimozato *et al*, 1991; Arend and Leung, 1994; Campbell *et al*, 1999; Ruetter and Luger, 2001).

Table 5. IGIV Treatment of Immune-Mediated Skin Diseases

Autoimmune Blistering Diseases	Efficacy of IGIV
Pemphigus	
Bullous pemphigoid	+
Pemphigus vulgaris	+
Pemphigus foliaceus	+
Oral pemphigoid	(+)
Ocular cicatricial pemphigoid	(+)
Epidermolysis bullosa acquisita	(+)
Pemphigoid gestationes	(+)
Linear IgA bullous dermatosis	(+)
Dermatomyositis	+
SLE cutaneous	(+)
Scleroderma	(+)
Toxic epidermal necrolysis	+
Stevens-Johnson syndrome	(+)
Atopic dermatitis	+
Hyperimmunoglobulinemia E syndrome	(+)
Chronic autoimmune urticaria	+
Pyoderma gangrenosum	(+)
Erythema exsudativum multiforme	(+)
Graft versus host disease	(?)

+: Series of studies, reports
(+): Limited studies, reports, patient numbers
(?): No obvious benefit

IGIV may itself contain a number of cytokines, cell surface molecules, and antibodies that can regulate immune/inflammatory activities. They include CD4, CD5, T cell receptor Vβ regions, MHC class I and II, CD40, IL-1α, IFN-α, and GM-CSF (Kazatchkine *et al*, 1994; Aukrust *et al*, 1994; Hurez *et al*, 1994; Kaveri *et al*, 1996; Prasad *et al*, 1998; Viard *et al*, 1998).

Effects of IGIV on apoptosis Alterations in the control of apoptosis can result in the development of a number of diseases. Defective regulation of apoptosis has been associated with many autoimmune diseases. Apoptosis is tightly regulated, principally by one of two pathways: interaction between the death receptor TNFR1 and Fas with its ligand, and the participation of mitochondria. These pathways are tightly regulated by members of the BCL-2 family.

IGIV contains both agonistic and blocking antibodies to Fas (CD95), the receptor for Fas-Ligand (FasL), which transduces apoptotic signals into cells. Such antibodies can induce apoptosis of FasL-expressing lymphocytic cells and monocytic cells (Prasad, 1998; Viard, 1998). Death of cells involves caspases 1 and 3. However, not all cell death mediated in this way may be Fas mediated.

In KS, IGIV-induced apoptosis of KC neutrophils *in vitro* and *in vivo* decreases the numbers of circulating neutophils by accelerating apoptosis. This appeared to be Fas independent (Tsujimoto *et al*, 2002).

Neutralization of bacterial toxins A number of bacterial exotoxins can act as "superantigens," activating a large fraction of T lymphocytes and thus causing the release of numerous cytokines. The different exotoxins show different specificities for the β chain of the T cell receptor. IGIV contains antibodies to a number of bacterial exotoxins, preventing their interaction with T lymphocytes. As a result, IGIV can prevent T cell stimulation and proliferation induced by these toxins. Moreover, the antibodies in IGIV can prevent binding or presentation of toxins by antigen-presenting cells (Takei *et al*, 1993).

Alteration in steroid sensitivity For many of these immune-mediated inflammatory disorders, corticosteroids are a mainstay of therapy. It is now increasingly appreciated that inflammation may be associated with corticosteroid insensitivity or resistance. In part, this may be mediated by T lymphocytes as the cytokines, IL-2 and IL-4 play a major role in reducing human T cell sensitivity to corticosteroids. These cytokines induce changes in corticosteroid receptor (GCR)–binding affinities; the number of receptors remains the same. To some extent, the resistance to steroids may also reflect an increase in the expression of the inactive isoform of the receptor GCR-β (Leung *et al*, 2002). Both *in vitro* and *in vivo*, IGIV has been shown to normalize or reverse corticosteroid insensitivity (Spahn *et al*, 1999), a response that may in fact be attributable, at least in part, to its effects on cytokine production. In fact, IGIV is a potent suppressor of T cell production of IL-2 and IL-4 *in vitro* (Modiano *et al*, 1997). This improvement in steroid sensitivity with IGIV may underlie some of the responses seen in the wide variety of immune-mediated diseases where IGIV has shown benefit.

Use of IGIV in dermatological conditions A number of presumed immune-mediated skin diseases has been the target of IGIV therapy (**Table 5**). Although IGIV is emerging as a major treatment for this group of disorders, few reports of controlled trials are available. In the majority, dosages of IGIV of 1–2 g/kg body weight were used on a monthly basis for induction of remission and at greater intervals once remission was achieved.

Autoimmune blistering diseases The major group of autoimmune blistering disorders, pemphigus, is associated with circulating IgG autoantibodies against cell surface molecules on keratinocytes. Diseases within the pemphigus group are usually treated with systemic corticosteroids plus/minus immunosuppressive drugs. In pemphigus vulgaris, desmoglein 3 serves as a target antigen expressed on basal keratinocytes (Thivolet, 1994; Stanley, 1997). A number of clinical reports have demonstrated the successful use of IGIV therapy in pemphigus patients (Harman and Black, 1999; Messer *et al*, 1995; Bewly and Keefe, 1996; Weaver *et al*, 1996; Colonna *et al*, 1998; Engineer *et al,* 2000; Ahmed 2001a). Although not universal, the responses appeared rapidly with stabilization of the disease. Improvement lasted from 6 weeks to 14 months and in most cases enabled reduction of corticosteroids or immunosuppressive/cytotoxic drugs. Improvement in the skin condition was associated with decreases in pemphigus antibody titers (Bystryn *et al*, 2002), including specific antibodies to desmoglein 3 and 1.[1] The decline in antibodies did not appear to be due to interference with synthesis but resulted from increased IgG catabolism (Bystryn, 2002).

In pemphigus foliaceus, the target antigen appears to be desmoglein 1, an epidermal cadherin molecule predominantly expressed in the upper layers of the epidermis (Thivolet, 1994; Stanley, 1997). A report of IGIV as monotherapy in 11 patients with foliaceus suggested a favorable response in all and a sustained clinical remission of 18 months after discontinuation. (Ahmed and Sami 2002). After 4 months of IGIV therapy, reductions in titers of antibodies to desmoglein 1 were detected; the titers disappeared by 13 months.[2] Other studies have shown similar benefit (Enk and Knop, 1998).[3]

Bullous pemphigoid is characterized by deposition of IgG and C3 at the basement membrane. The target antigens are BPAg1 and BPAg2 within hemidesmosomes (Amagal, 1995). In different reports of more than 40 patients, and despite the use of different protocols, IGIV appeared to be a promising alternative, especially

[1]Sami N, Ali S, Bhol KC, Ahmed AR: Influence of intravenous immunoglobulin therapy on autoantibody titers to BP Ag1 and BP Ag2 in patients with bullous pemphigoid. Submitted, 2002

[2]Sami N, Bhol KC, Ahmed AR: Influence of intravenous immunoglobulin therapy on antibody titers to desmoglein 3 and desmoglein 1 in patients with pemphigus vulgaris. Submitted, 2002

[3]Sami N, Bhol KC, Ahmed AR: Influence of IVIG therapy on autoantibody titers to desmoglein 1 in patients with pemphigus foliaceus. Submitted, 2002

in patients for whom conventional therapy had failed (Ruetter *et al*, 1994; Ahmed, 2001b). Antibody levels to BPAg1 and BPAg2 were shown to progressively decrease and ultimately reach levels that indicated a serological remission (Sami *et al*, 2002d).

Epidermolysis bullosa acquisita (EBA), a chronic severe disease, involves subepithelial blister formation of the skin and mucous membranes. A target antigen has been identified: the c-terminus of type VII procollagen within the anchoring fibrils at the dermal–epidermal junction (Shimizu *et al*, 1990). Although only a handful of treated patients have been reported, IGIV appears to arrest the disease and allow ancillary medications to be reduced (Mohr *et al*, 1995; Koller *et al*, 1997). Autoantibody titers may not have decreased despite the clinical response.

Pemphigoid gestationes is a blistering disorder restricted to the second or third trimester of pregnancy. Autoantibodies to a hemidesinosomal antigen have been described. Reports of treatment with IGIV are very limited (Hen *et al*, 1998; Engineer and Ahmed, 2001).

Linear IgA bullous dermatosis is a blistering autoimmune disease characterized by IgA deposition along the basement membrane. Two reports of successful use of IGIV are noted (Khan *et al*, 1999; Kroiss *et al*, 2000).

Oral pemphigoid is a chronic autoimmune disease involving the oral cavity, characterized by a homogenous linear deposition of Ig and complement along the basement membrane and subepithelial blister formation. The α6/β4 integrin heterodimer may be a target, as autoantibodies to α6 can be detected. In a study of seven patients with severe disease, treatment with IGIV induced a clinical response after four months. This resulted in a prolonged and sustained remission associated with a reduction in anti-α6 antibody titers (Sami *et al*, 2002e).

Ocular cicatricial pemphigoid (OCP) is another blistering autoimmune disease with autoantibodies to β4 integrin, affecting the eye, skin, and mucous membranes. Serum IL-1 levels are markedly elevated in these patients. In eight patients, IGIV therapy resulted in a marked decrease in conjunctival inflammation, decreases in titers of anti-β4 antibodies, lower IL-1 levels, and increased IL-1 receptor antagonist levels (Letko *et al*, 2000; Kumari *et al*, 2001).

Toxic epidermal necrolysis This rare but severe exfoliative, often drug-induced, disorder is associated with high mortality. Alterations in control of keratinocyte apoptosis may play a role. Upregulation of keratinocyte FasL expression may be the critical trigger of cell destruction (Viard, 1998). Several reports in open trials have documented impressive and life-saving improvement with IGIV in the majority of patients treated (Viard, 1998).

Dermatomyositis This systemic autoimmune disease is characterized by a chronic skeletal-muscular inflammatory response and significant muscle weakness. There is no known cause. Of note, a major pathological feature besides the inflammatory cell infiltration along the basement membrane of the muscle fibers is the deposition of complement, the membrane attack complex C5b-C9, in intramuscular capillaries. In a number of clinical trials, IGIV has shown efficacy in returning muscle strength, reducing creatin kinase levels, and reducing the need for corticosteroids (Roifman *et al*, 1987; Dalakas *et al*, 1993; Collet *et al*, 1994; Sabroe *et al*, 1995; Furuya *et al*, 1998). Both muscle and cutaneous (ulcer) manifestations respond. In keeping with the reported activity of IGIV in preventing membrane attack complex formation, deposition of C5b-C9 was markedly reduced, as was muscle ICAM-1, TGF-β, and MHC class I expression (Dalakas, 1993).

Atopic dermatitis Atopic dermatitis is an eczematous inflammatory skin disease occurring in genetically predisposed individuals, prone to develop atopic disease. It can be triggered by a number of environmental factors, foods, and allergens, and is characterized by a T helper 2 (TH2)–biased response with elevated serum IgE levels, eosinophilia, and elevated TH2 cytokine levels, including IL-4. Often, there is marked superinfection with Staphylococcus infection. In part, the disease may be aggravated by bacterial exotoxins triggering cytokine release.

In a number of open trials, IGIV has proved beneficial in patients requiring oral corticosteroids. It can result in a rapid resolution of pruritus and restore TH cell subset balance, and it can reduce the frequency of IL-4–producing cells while increasing IFN-γ secreting cells as well as modifing skin test reactivity, thus improving symptom scores and reducing the need for corticosteroids (Gelfand *et al*, 1996; Jolles *et al*, 1999). A significant benefit of IGIV in AD may be attributable to the neutralization of bacterial exotoxins ("superantigens"), as discussed above.

As indicated in **Table 5**, there are a number of other cutaneous disorders where IGIV has shown benefit, albeit in open trials. In these diseases, IGIV may offer some promise as an alternative therapy where conventional approaches are either not effective or associated with significant toxicity.

SELECTION OF AN IGIV PREPARATION

As discussed above, in most instances, IGIV was used at a total dose of ~2 g/kg body weight on a monthly basis. This is the typical way IGIV is used in the treatment of most immune-mediated diseases. The fact that few if any direct comparisons of different products have been carried out does not infer that all IGIVs are the same. The different manufacturing processes, the formulation, and the composition of the final product all may contribute to convenience, tolerability, safety, and efficacy. In general, liquid preparations of IGIV are favored over lyophilized products. The higher the concentration of the solution, the more convenient in terms of time for infusion and safety: A 10% solution requires half the volume and likely half the time to infuse. Products that are hyperosmolar, contain sugars to prevent aggregate formation, or contain significant salt concentrations have been associated with an increase in adverse events, especially at the high doses used in the treatment of these autoimmune disorders.

SUMMARY

As with other immune-mediated diseases, IGIV is emerging as an important alternative in the treatment of a number of immune-mediated skin diseases. Where conventional therapies of these disorders—corticosteroids and immunosuppressive drugs—have failed or proved too toxic to continue treatment, IGIV has provided sustained clinical remission, especially in the group of autoimmune blistering diseases. The underlying mechanisms of action are not clear but may reflect a combination of immunomodulatory and anti-inflammatory activities, enhancement of steroid sensitivity, and catabolism of pathogenic autoantibodies. Optimization of IGIV therapy in these diseases must await further delineation of the mechanism of action. This is essential, as therapy is expensive and utilizes blood products that are not in unlimited supply. For these reasons, carefully controlled clinical trials are necessary not only to establish efficacy but also to provide needed guidelines for dosing, frequency, and even selection of the best product for specific patients.

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