

REVIEW ARTICLE

Intravenous Immunoglobulin: Properties, Mode of Action and Practical Use in Dermatology

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Since they were first administered to patients with antibody deficiency disorders over 50 years ago, human intravenous immunoglobulin preparations have been used successfully to treat a rapidly increasing number of autoimmune and inflammatory disorders, among which are a series of cutaneous autoimmune and inflammatory diseases. These include dermatomyositis, Kawasaki's disease, a number of autoimmune bullous diseases, severe adverse drug reactions, and other autoimmune and/or allergic conditions, such as atopic dermatitis. Although only a minority of these indications (dermatomyositis, Kawasaki's disease) are officially registered or based on double-blind, placebo-controlled clinical studies, the observed efficacy and safety profile of currently available intravenous immunoglobulin sometimes makes this a treatment of choice for initiation of therapy or for replacement of more toxic alternatives, such as systemic immunosuppressive medications. The increasing use of intravenous immunoglobulin has been associated with further understanding of its mechanism(s) of action, clinical manipulation and associated side-effects, as well as the introduction of improved or new types of intravenous immunoglobulin. This paper reviews the current knowledge of the mode of action of intravenous immunoglobulin, its reported therapeutic effects in cutaneous disease, its mode of administration and safety profile, and compares the currently available intravenous immunoglobulin preparations. **Key words:** *intravenous immunoglobulin; review; mechanism of action; side-effects; dermatomyositis; Kawasaki's disease; skin disease; dermatology.*

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PRODUCTION OF COMMERCIAL INTRAVENOUS IMMUNOGLOBULINS

Intravenous immunoglobulin (IVIG) is not manufactured, but is purified from pooled human plasma from healthy donors, using a procedure that varies somewhat

between manufacturers, but results in an end-product that is a relatively pure concentrate of IgG (small amounts of IgA and IgM) with intact function and the minimal presence of aggregates.

In order to achieve the required high level of product quality and guarantee an optimal level of product safety, the manufacturing process includes important measures such as the careful selection of plasma donors, who are usually volunteers, preventive "screening" of plasma samples for all currently known transmissible infectious agents, and the use of modern viral inactivation techniques. The processes of purification have the potential, however, to adversely affect the final quality or biological activity of IVIG. Thus, the fractionation and purification processes have to aim for an "ideal", ensuring that the purified immunoglobulin (Ig) that will be used to treat patients is physiologically and pharmacologically the same as that taken from the human body, in order to guarantee optimal safety and efficacy (1).

Four purification processes currently exist for commercial IVIG. The Cohn-Oncley process (cold ethanol precipitation) was developed in the 1940s and has been modified slightly since, but this core process, which is used by most companies today, remains the same. The Kistler-Nitschmann process, was developed in the 1950s by the Swiss Red Cross Laboratory, now known as ZLB-Behring, and is a variation of the cold ethanol precipitation process. Chromatography as the sole separation procedure has also been used, but with little success, and last but not least, a completely newly engineered purification process combining caprylate precipitation/viral inactivation and double anion exchange chromatography has been developed recently by Bayer HealthCare (plasma business recently acquired by Talecris Biotherapeutics, North Carolina, USA). The latter procedure has enabled the purification under less harsh conditions of better yields of a highly purified product within a shorter overall production time in which protein denaturation is minimized. The resulting product is now marketed under the name Gamunex®.

As a consequence of continuing to improve the quality of commercial IVIG preparations and their compliance with the final product purity criteria of the WHO, the therapeutic use of IVIG is now associated with a low incidence of side-effects. These safety parameters have

certainly contributed to the increasing clinical use of IVIG despite a still-limited number of indications for which evidence-based data are available.

COMPOSITION AND HALF-LIFE OF INTRAVENOUS IMMUNOGLOBULIN

Preparations of IVIG consist of intact IgG molecules with a distribution of IgG subclasses corresponding to that of normal serum. Subclass distribution may vary between preparations, with some products having less than physiological levels of IgG₃ and/or IgG₄. IVIG also contains small, but variable, amounts of other proteins and products, notably, and depending on the commercial preparation, albumin, IgA (content varying from less than 5 µg/ml to more than 700 µg/ml), IgE, IgM, sugars, salts, solvents (trace amounts), detergents (trace amounts) and buffers (trace amounts). Also, the monomer and/or dimer content may vary between preparations and up to 3% non-active polymers may be found. Several of these proteins and products may affect the tolerability of IVIG infusions, notably salt, sugar and/or IgA content; volume, pH, osmolality and rate of infusion (Table I). The half-life of IVIG after intravenous infusion or intramuscular injection is approximately 2–3 weeks. This can, however, vary depending on the immune status of the patient.

Finally, the final commercial IVIG products are most often licensed to be used as 50 mg/ml (5%) or 100 mg/ml (10%) solutions for infusion. Importantly, despite the generic term for all products as IVIG, it should be realized that they are not all the same (Table I).

MODE OF ACTION OF INTRAVENOUS IMMUNOGLOBULINS

IVIG has an immunomodulatory activity that is based on the modulation, via selective and distinct molecular mechanisms, of biological processes that are implicated in innate or acquired immune responses (Table II).

The biological effects of IVIG include:

- *Functional blockade of Fc receptors.* Fc receptors are implicated in the clearance by phagocytes of particles or cells that are opsonized by IgG. This process is of great physiological importance, for example, in the mechanisms of defence against certain infectious agents, but can also contribute to the pathogenesis of certain auto-antibody-mediated diseases. This is the case, for example, in peripheral autoimmune cytopenias (e.g. idiopathic thrombocytopenic purpura). In such situations, the saturation of Fc receptors by IVIG leads to decreased cellular destruction as a consequence of Fc-mediated phagocytosis of antibody-coated cells (2).
- *Auto-antibody neutralization and inhibition of auto-antibody production.* IVIG preparations contain anti-idiotypic antibodies, i.e. antibodies that are able to interact specifically with the variable region (antigen recognition site) of auto-antibodies. This interaction has the potential to neutralize an auto-antibody and to hamper its production via binding to autoreactive B lymphocytes. Such a neutralizing or inhibitory activity has been shown, amongst others, for auto-antibodies directed against factor VIII, DNA, intrinsic factor, thyroglobulin and anti-neutrophil cytoplasmic antibodies (ANCA) (2, 3).
- *Complement inhibition.* The Fc portion of IVIG can bind the C3b and C4b fragments of complement, and thereby inhibit their tissue deposition as well as the generation of the C5 convertase (C4b2a3b), an enzyme that is required for the subsequent formation of the membrane attack complex (4–6). This cascade of events has been shown to occur in dermatomyositis and thereby contributes to the therapeutic effect of IVIG in that disease.
- *Modulation of cytokine and cytokine antagonist production.* Experimental work has shown that IVIG significantly modulates the production of several cytokines (including IL-1, -2, -3, -4, -5, -10, TNF-α, and GM-CSF) and cytokine antagonists (IL-1 receptor antagonist) by monocyte-macrophages and lymphocytes (7). Although quite complex, it appears that the resulting biological anti-inflammatory effects implicate both the F(ab)₂ and Fc portions of IgG, are associated with an inhibition of lymphocyte proliferative responses, and a modulation of T helper 1 (Th1) and Th2 cytokine production.
- *Activation or functional blockade of the death receptor Fas (CD95).* More recently it has been shown that IVIG can either inhibit or activate cell death by binding to the death receptor Fas (8, 9). IVIG contains IgGs that bind to several distinct epitopes on the extra cellular portion of Fas and are in fact naturally occurring anti-Fas antibodies. It has been shown that these can be divided into agonistic anti-Fas IgG and antagonistic anti-Fas IgG (10). Why IVIG preparations in which both agonistic and antagonistic anti-Fas antibodies coexist and either trigger or protect from cell death is unclear at present, but appears in part to depend on the cell type concerned.
- *Modulation of dendritic cell properties.* Recent work suggests that IVIG affects the differentiation, maturation and functional status of dendritic cells (DC). DC appear to be a primary target for the immunosuppressive effects of IVIG on T-cell activation. This effect of IVIG is mediated notably by inhibition of the differentiation and maturation of DC *in vitro*, with down-regulation of the expression

Table 1. Characteristics of selected commercialized intravenous immunoglobulin products including properties and excipients that may account for side-effects (sugar and sodium content, osmolality, pH and IgA content)

Category	Manufacturer or distributor	Carimune NF/ Redimmune NF/ Sandoglobulin	ZLB Bioplasma	Grifols	Gammagard® S/D		Gammar® PIV	ZLB Behring	Gamunex® Biotherapeutics Corporation	Iveegam EN® Baxter Division	American Red Cross	Polygam S/D		Octagam®	Octapharma	ZLB Bioplasma	Redimmune NF Liquid	Intraglobin F
					5%	10%						5%	10%					
Formulation		Lyophilized	Liquid	Liquid	Lyophilized	Lyophilized	Lyophilized	Lyophilized	Liquid	Lyophilized	Lyophilized	Lyophilized	Lyophilized	Liquid	Liquid	Liquid	Liquid	Liquid
Reconstitution time (min)		Several	None (liquid solution)	None (liquid solution)	<20	<5 at room temperature; >20 if cold	<20	<20	None (liquid solution)	≤10 at room temperature	Several	5 at room temperature; >20 if cold	5 at room temperature; >20 if cold	None (liquid solution)	None (liquid solution)	None (liquid solution)	None (liquid solution)	None (liquid solution)
Available concentration (%)	3–12		5	5	10	5	5	10	10	5	3–12	5	10	5	12	5	5	5
Maximum recommended infusion rate (ml/kg/h)	>2.5		6	4	8	3.6	3.6	4.8	4.8	1.8	>2.5	4	8	4.2	1	1	1.9	1.9
Time to infuse (h)	<3.3 (6% solution)	1.7	2.5	2.5	0.6	2.8	2.8	1.0	1.0	5.6	<3.3 (6% solution)	2.5	0.6	2.4	4.2	5.3	5.3	5.3
Sugar content	1.67 g sucrose/g protein	50 mg/ml D-sorbitol	20 mg/ml glucose	20 mg/ml glucose	50 mg/ml sucrose	40 mg/ml glucose	50 mg/ml sucrose	None	None	50 mg/ml glucose	1.67 gm sucrose/g protein	20 mg/ml glucose	40 mg/ml glucose	100 mg/ml maltose	None	None	25 mg/ml glucose	25 mg/ml glucose
Sodium content	<20 mg/g protein	<3.2 mEq/l	8.5 mg/ml	8.5 mg/ml	5 mg/ml	17 mg/ml	5 mg/ml	Trace amounts	Trace amounts	3 mg/ml	<20 mg/g protein	8.5 mg/ml	17 mg/ml	1.75 mg/ml	<10 mmol/l	<10 mmol/l	78 mmol/l	78 mmol/l
Osmolality	192–1,074 mOsm/kg	240–350 mOsm/l	636 mOsm/l	636 mOsm/l	309 mOsm/l	1,250 mOsm/l	309 mOsm/l	258 mOsm/l	258 mOsm/l	≥240 mOsm/l	192–1,074 mOsm/kg	636 mOsm/l	1,250 mOsm/l	310–380 mOsm/kg	360 mOsm/kg	360 mOsm/kg	≥240 mOsm/l	≥240 mOsm/l
pH	6.4–6.8	5.0–6.0	6.4–7.2	6.4–7.2	6.4–7.2	6.4–7.2	6.4–7.2	4.0–4.5	4.0–4.5	6.4–7.2	6.4–6.8	6.4–7.2	6.4–7.2	5.1–6.0	5.3	5.3	6.4–7.2	6.4–7.2
IgA content	720 µg/ml	<50 µg/ml	<2.2 µg/ml	<2.2 µg/ml	<2.5 µg/ml	<2.2 µg/ml	<2.5 µg/ml	46 µg/ml	46 µg/ml	<10 µg/ml	720 µg/ml	<2.2 µg/ml	<2.2 µg/ml	≤100 µg/ml	≤100 µg/ml	≤100 µg/ml	2.5 mg/ml	2.5 mg/ml

Table II. *Mode of action of intravenous immunoglobulin*

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- 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 (CD95)
 - Modulation of dendritic cell properties
 - Increased expression and signalling through the inhibitory Fc-receptor, Fc gamma RIIB
 - Enhancing steroid sensitivity
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of co-stimulatory molecules, thus impairing the ability of mature DC to produce IL-12, and enhancing their ability to produce IL-10. The consequences of this have been shown to be inhibition of auto- and alloreactive T-cell activation and proliferation (11, 12).

- *Signalling through the inhibitory Fc receptor, Fc gamma RIIB.* The molecular basis of anti-inflammatory properties of IVIG has been investigated in a murine model of immune thrombocytopenia by Samuelsson et al. (13). In this model administration of clinically protective doses of intact antibody or monomeric Fc fragments prevented platelet consumption triggered by a pathogenic auto-antibody, and the inhibitory Fc receptor, Fc gamma RIIB, was shown to be required for protection, because disruption either by genetic deletion or with a blocking monoclonal antibody reversed the therapeutic effect of IVIG. IVIG were also shown to induce the expression of this inhibitory receptor on monocytes.
- *Enhanced steroid sensitivity.* Work by Spahn and colleagues (14) in asthmatic patients has shown that the action of IVIG, which is used as an oral glucocorticoid-sparing agent in patients with steroid-dependent asthma, is due to an enhancement in glucocorticoid receptor-binding affinity, subsequent enhanced glucocorticoid sensitivity, and synergistic suppression of lymphocyte activation when combined with glucocorticoids. In an open-label study, IVIG was shown to result in significant reductions in oral glucocorticoid dose, and both patients with glucocorticoid-insensitive and -sensitive asthma responded equally well to IVIG (14).

INDICATIONS FOR INTRAVENOUS IMMUNOGLOBULIN

Generally speaking, the currently licensed indications for IVIG therapy include: substitution in the context of primary or secondary hypogammaglobulinaemias; idiopathic thrombocytopenic purpura (ITP); paediatric HIV infection; Guillain-Barré syndrome, Kawasaki disease, chronic B-cell lymphocytic leukaemia, bone marrow

transplantation, multiple myeloma, and chronic inflammatory demyelinating polyneuropathy (CIDP) (15, 16).

Despite this limited list, 50–60% of world sales result from the use of IVIG in indications that are “off-label”, or not officially licensed, and based in general on data from non-controlled clinical trials or case reports (16, 17). These indications often involve rare diseases, thus rendering validation through well-controlled clinical trials particularly challenging.

Table III lists the dermatological diseases for which reports concerning the use of IVIG exist. In many instances beneficial effects were observed, although several indications are still controversial due to the lack of controlled clinical trial data. The most convincing clinical data are in the use of IVIG as an adjuvant in the treatment of dermatomyositis, either with the aim of inducing a clinical remission, or in order to enable a decrease and sparing of immunosuppressive drugs such as corticosteroids or cyclosporine. The other potentially useful dermatological indications for IVIG therapy, all of which require confirmation in appropriately designed clinical trials, include: pemphigus vulgaris and foliaceus; bullous pemphigoid; mucous membrane (cicatricial) pemphigoid; pemphigoid gestationis; epidermolysis bullosa acquisita; linear IgA dermatosis; toxic epidermal necrolysis (Lyell's syndrome); atopic dermatitis; pyoderma gangrenosum; chronic urticaria; scleromyxoedema, and pre-tibial myxoedema. Existing published experience concerning the therapeutic effects of IVIG in these dermatological diseases is discussed below.

Dermatomyositis

Dermatomyositis (DM) 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. Treatment of DM with high-dose systemic steroids (1 mg/kg) alone or in association with other immunosuppressive drugs (cyclosporine, azathioprine, methotrexate, cyclop-

Table III. *Dermatological diseases treated with intravenous immunoglobulin*

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- Kawasaki's syndrome
 - Dermatomyositis
 - Pemphigus vulgaris and foliaceus
 - Bullous pemphigoid
 - Mucous membrane (cicatricial) pemphigoid
 - Pemphigoid gestationis
 - Epidermolysis bullosa acquisita
 - Linear IgA dermatosis
 - Toxic epidermal necrolysis (Lyell's syndrome)
 - Atopic dermatitis
 - Pyoderma gangrenosum
 - Chronic urticaria
 - Scleromyxoedema
 - Pre-tibial myxoedema
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hosphamide) 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 (C5b-9) (6). 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. 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 (for review, see 18).

Several case reports, uncontrolled trials and a placebo-controlled crossover trial conducted by Dalakas et al. (27) provide evidence for a benefit of IVIG in patients with DM (19–27). 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 (27). 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.

Pemphigus vulgaris and foliaceus

Once a fatal illness, severe pemphigus vulgaris (PV) can now be treated successfully with high-dose systemic steroids and the addition of immunosuppressive drugs (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

PV. Bystryn et al. (28) and Baum et al. (29) 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. Several studies performed by Ahmed and colleagues (30, 31) 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 (32).

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 (28, 33).

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 (34–37).

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. 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 27 out of 32 reported cases (38–41). 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 (42).

In mucous membrane (cicatricial) pemphigoid, 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 (43–48).

Epidermolysis bullosa acquisita and linear IgA dermatosis

Epidermolysis bullosa acquisita (EBA) is a rare, difficult-to-treat autoimmune blistering disease characterized by circulating and skin basement membrane-bound IgG auto-antibodies against type VII collagen. 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 (39, 49–56). Further data are needed to establish the real potential of IVIG in EBA.

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 (57–61).

Stevens-Johnson syndrome and toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN, Lyell's syndrome) 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.

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 (Table IV) (8, 62–69). 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 (70).

Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by dysregulated immune responses, which affects approximately 20% of children and persists in approximately 6% of adults, some of whom have severe disease. Severely affected patients often require immunosuppressive treatment. Since cumulative toxicity and lack of efficacy can limit the immunosuppressive drugs use, IVIG has been tested in this indication. The literature reveals several anecdotal case reports and series reporting over 40 patients with AD treated with IVIG, of which 10 were childhood cases (71–77; reviewed in 78). The published experience in severe childhood AD 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 (75). IVIG does, however, seem to have a positive effect in 50–60% of adult patients suffering from severe AD when used as adjunctive therapy (109). Further controlled studies are needed to define the role of IVIG in the therapeutic approach to severe AD.

Pyoderma gangrenosum

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis of unknown aetiology characterized by typical skin ulcers with an undermined border. In 50% of af-

Table IV. *Compilation of studies of intravenous immunoglobulin and toxic epidermal necrolysis*

1 st author (Ref.) year	Viard (8) 1998	Prins (62) 2003	Trent (63) 2003	Bachot (64) 2003	Campione (65) 2003	Shortt (66) 2003	Brown (67) 2004	Al-Mutairi (68) 2004	Tan (69) 2005
Study type	Prosp Non-cont	Retros Non-cont	Retros Non-cont	Prosp Non-cont	Prosp Non-cont	Retros Non-cont	Retros Non-cont	Prosp Non-cont	Retros Non-cont
Patients (n)	10	48	16	34	10	32	45	12	12
Mean age (years)	39	43	43	47	49	53	45	27	50
Detachment	28.5	45	43	19	49	65	49	58	NR
Dose IVIG	3 g/kg	3 g/kg	4 g/kg	2 g/kg	2 g/kg	2.8 g/kg	1.6 g/kg	2–5 g/kg	2 g/kg
Predicted deaths (SCORTEN)	–	–	5.8 (36%)	8.2 (24%)	3.5 (35%)	6 (38%)	6 (28.6%)	–	–
Actual mortality	0 (0%)	6 (12%)	1 (6%)	11 (32%)	1 (10%)	4 (25%)	10 (41.7%)	0 (0%)	1 (8%)

Prosp: prospectively; Retros: retrospectively; Non-cont: uncontrolled; NR: not registered; IVIG: Intravenous immunoglobulin.

fectured patients, PG is associated with systemic disease, including inflammatory bowel disease, arthritis and haematological malignancies. Immunosuppressive treatment is central to the management of PG 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 (79–84). Improvement was observed in all patients. Finally, PG associated with hypogammaglobulinaemia has been described to respond to replacement therapy with IVIG (85, 86).

Chronic urticaria

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. 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.

To date, there are four reports in the literature, with a total of 23 chronic urticaria patients treated with IVIG (87–91). 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 (87). 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.

Scleromyxoedema

Scleromyxoedema 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. 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 (cytotoxic drugs, cyclosporine, interferon alpha, retinoids, plasmapheresis, extracorporeal photopheresis, thalidomide and psoralen plus ultraviolet light A (PUVA) therapy) with limited efficacy and significant adverse side-effects.

There are now seven interesting publications reporting a total of 13 patients with scleromyxoedema treated with IVIG 2 g/kg over 5 days (91–97). 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.

Pre-tibial myxoedema

Pre-tibial myxoedema (PM) is a cutaneous mucinosis typically associated with Graves' disease and high serum concentrations of thyroid-stimulating hormone receptor antibodies. Certain forms of PM are associated with elephantiasis. In severe cases of PM, systemic immunomodulation may be necessary, although long-term efficacy of such therapy is non-existent. Two contradictory reports of the use of IVIG in PM 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 PM (4 nodular PM, 2 diffuse PM and one elephantiasic PM) treated with IVIG showed clinical improvement of the skin lesions, ophthalmopathy, and a reduction in circulating auto-antibody levels, whereas 2 PM patients treated with systemic steroids alone showed no improvement (98). The second report, of a single case of longstanding elephantiasic PM, describes no response to 2 g/kg IVIG after 6 monthly cycles, but a reduction in anti-TSH receptor antibody titres (99). Taken together, although more data is needed in this indication, it appears that the potential for response to IVIG therapy in PM may depend on the type of PM and the duration of disease.

MODE OF ADMINISTRATION OF IVIG

All the different preparations of IVIG are formulated for intravenous administration, in either a lyophilized or liquid form. Lyophilized formulations have to be reconstituted with water, saline or 5% glucose in water just before treatment to achieve concentrations of 3–12%, as indicated by the manufacturer. Liquid preparations have

the advantage of being "ready to use", thus eliminating the time required for reconstitution and, theoretically, limiting the risk of error. As shown in Table I, most liquid IVIG preparations are available in concentrations of 5% (0.05 g/ml or 1 g/20 ml) or 10% (0.1 g/ml or 1 g/10 ml). The rate of infusion must be adapted for each individual patient and the recommended rates vary according to the IVIG product used (Table I).

In practice, before initiating therapy with IVIG one should check liver function, renal function (to exclude patients with progressive renal disease), perform a complete blood cell count and a viral hepatitis screen. It is also important to measure Ig levels to exclude an IgA deficiency, as well as exclude high titres of rheumatoid factor and cryoglobulinaemia. On the day of infusion, patients are monitored (blood pressure, heart rate, temperature) before infusion, every 15 min for the first hour of infusion, and every 30 min for the rest of the infusion. Initial IVIG infusions are usually initiated at a slow rate, if tolerated, then increased every 15 min, and then progressively accelerated in the absence of side-effects. After 2–3 successful infusions, the initial rates are often accelerated.

The dose of IVIG infused depends on the underlying medical condition, but in general the doses administered for anti-inflammatory/immunomodulatory indications are 3–5 times those given for Ig replacement therapy, administered every 3–4 weeks (cycles). Thus 2 g/kg bodyweight are given every 3–4 weeks when seeking anti-inflammatory/immunomodulatory effects, as opposed to 400–600 mg/kg body weight in replacement therapy. Depending on the type of IVIG and the patient's tolerance, the time to infuse a total dose of 1 g/kg to a 70 kg patient can be as short as 2.5 h (maximum rate of perfusion 28 g/h) or as long as 8 h (maximum perfusion 9 g/h).

DRUG INTERACTIONS

No drug interactions have been reported so far with IVIG products. IVIG products should not, however, be administered at the same time as attenuated live vaccines (German measles, mumps, or measles) since they may inhibit or delay the desired immune response. When high-dose IVIG is administered, there should be a 3–6 month period between the planned vaccination and the last IVIG infusion.

SIDE-EFFECTS

As a consequence of the constant efforts invested by manufacturers to improve the safety and quality of IVIG, severe side-effects of IVIG infusion have become rarer and in most cases the adverse events are minor (100, 101) (Table V). No comparative data exist concerning the incidence of side-effects among the different brands

Table V. Side-effects of intravenous immunoglobulin

Side-effects	% of cases ^a
<i>Minor side-effects</i>	
Headache	72
Nausea	38
Fever, chills	33
Shortness of breath	23
Cough	14
Sore throat	12
Malaise/fainting	4
Myalgias, arthralgias	
Flushing	
Abdominal pain	
Leukopaenia	
<i>Severe side-effects</i>	
Aseptic meningitis	
Acute renal failure	
Stroke	
Myocardial infarction	
Deep venous thrombosis/pulmonary embolism	
Anaphylactic shock	

^aAccording to International Diabetic Federation survey (see also 100, 101). There are no figures in the lower part of the table as they are rare side effects and their exact frequency is unknown.

of IVIG. However, salt and sugar content, osmolality, total volume infused, rate of infusion, concentration, and total dose of IVIG infused appear to be associated to some extent with the likelihood of side-effects (102).

There are a number of "minor" side-effects associated with IVIG infusion. These are usually transient and self-limited, and often arise during the first hours of infusion, but can occur up to 72 h following an infusion. They include headache, low-grade fever, muscle, back and joint pain, nausea, vomiting, abdominal pain, flushing, bronchospasm, variations in heart rate and blood pressure, and urticaria. These side-effects are considered to be possible consequences of low-level aggregation of the IgG, immune complex formation and complement activation or, in certain cases, to the sugar content of the IVIG product. These side-effects are usually overcome easily by reducing the rate of infusion, administering corticosteroids, antihistamines, NSAIDs, and/or acetaminophen before beginning the infusion.

In rare cases, side-effects are severe. Many of them occur in patients who have underlying risk factors or diseases that are considered to predispose to such side-effects. Importantly, the majority of these severe adverse events occur on the first infusion. It is thus important to obtain a complete medical history and to perform a medical work-up before initiation of IVIG therapy.

Aseptic meningitis may occur after the first 24–72 h of a high-dose IVIG treatment, particularly in patients with a history of migraine headaches. This side-effect appears to be dose-related since it has been reported almost exclusively, but not entirely, in patients treated with high-dose IVIG (103). Aseptic meningitis is rarely seen following the use of replacement doses. Symptoms

of aseptic meningitis can last for up to a week. Although reducing the rate of IVIG infusion has been reported to decrease the incidence of aseptic meningitis, several patients have been reported to develop this side-effect despite slow infusion (104). Oral fluid loading and antihistamines have been anecdotally reported to be helpful in this instance. Corticosteroids do not seem to shorten the course of the side-effect, which is self-limited, but in predisposed patients, headache treatment administered before IVIG infusion can be of benefit.

Acute renal failure can occur following IVIG infusion as a consequence of proximal tubular dysfunction. This side-effect is reversible in almost all cases, and in most cases this dysfunction is characterized only by a transient increase in blood creatinine levels. However, patients may rarely develop oliguria or anuria and subsequently require supportive haemodialysis. The majority of such patients recover their renal function completely within days or weeks after the end of the IVIG treatment. Only in exceptional cases has chronic renal failure requiring long-term haemodialysis been reported. Most authors attribute acute renal failure to the osmotic pressure caused by the stabilizing agent included in formulating the IVIG (albumin, sucrose, glucose, maltose, sorbitol, glycine). High osmotic pressure can indeed cause renal damage and lead to acute or chronic renal failure. Renal monitoring is thus mandatory during IVIG treatment. Risk factors for renal failure are male sex, age above 65 years, pre-existing renal disease, diabetes, high blood pressure, hypovolaemia, and obesity. The risk is also increased when the infusion rate is high. In patients with one or several risk factors, low IVIG concentrations (5% rather than 10%) and IVIG preparations with a low osmotic load (glycine instead of sucrose for instance, see Table I) should be preferred; and infusion rates should be slow. Between 70% and 90% of the renal side-effects seen with IVIG have been shown to be associated with the use of sucrose-containing IVIG (105).

Stroke is a rare, but life-threatening, complication of high-dose IVIG therapy. According to a retrospective study (106), the overall incidence of stroke in patients receiving IVIG therapy can be estimated at approximately 0.6%. Risk factors for stroke include a prior history of stroke, carotid artery stenosis, chronic hypertension, and high blood viscosity states.

Deep venous thrombosis, pulmonary embolism and, more rarely, thrombosis of the central retinal vein have been reported to occur in patients treated with IVIG, especially in patients with a history of prior thrombosis, or in the context of immobilization and hyperviscosity states (107, 108).

Myocardial infarction has been reported after a first cycle of IVIG in occasional patients with known cardiac risk factors (hypertension, diabetes, coronary artery disease). Hyperviscosity seems to play a role by favouring

the occlusion of blood vessels that are already narrowed by atherosclerotic plaques.

Exceptionally an anaphylactic reaction can occur, especially in patients with low IgA levels (also see the section devoted to "monitoring"), and some cases of haemolytic anaemia with positive Coombs tests as well as transient neutropaenia occurring in general on the fourth or fifth day of successive IVIG infusions have been reported (100). Significant decreases in lymphocyte counts, in particular CD4 lymphocytes, have been noted after high-dose IVIG therapy, but usually normalize by the next cycle (77).

Lastly, as with all products derived from human plasma, there is a risk of infection. Today it is, however, very low, since modern means of production and infection screening, including for prion disease, have greatly improved the quality and safety of IVIG.

In practice, when prescribing IVIG therapy, and because the patients being treated are more frequently older and often have a series of co-morbidities that are potential risk factors, it is important to match patient risk factors with the attributes or deficiencies of a given type of IVIG (Table VI). For example, it is clear that sugar content in an IVIG preparation should be of concern in patients with renal dysfunction; that very old or very young patients are at risk of fluid overload in a similar manner to patients with cardiac insufficiency or thromboembolic risk; and that IgA content is of concern in patients with IgA deficiency and circulating anti-IgA antibodies. It should be noted, however, that with the current improvement in IVIG quality, the incidence of problems with anti-IgA antibodies is less problematic than previously, and their presence does not preclude the use of such IVIG preparations.

COST OF IVIG AND PHARMACO-ECONOMIC CONSIDERATIONS

IVIG products are expensive and their prices vary between manufacturers/suppliers. Moreover, the cost may vary depending on contracts between manufacturers/suppliers and the medical institution that administers the treatment. At an approximate cost of 50 Euros per

Table VI. Matching patient and intravenous immunoglobulin (IVIG) risk factors

Patient risk factors	IVIG risk factors				
	Volume load	Osmolality	Sodium content	Sugar content	pH IgA
Cardiac insufficiency	•	•	•		
Renal insufficiency	•	•	•	•	
Anti-IgA antibodies					•
Thromboembolic risk	•	•	•		
(Pre-) Diabetic				•	
Elderly patients	•	•	•	•	
Neonates/paediatrics	•	•	•		•

gram, the cost-benefit ratio should thus be considered carefully for each patient before prescription, as the pharmaco-economic impact of IVIG is not unimportant. Accepting that the average cost of a gram of IVIG is 50 Euros, the cost of treating a 70 kg pemphigus patient with 2 g/kg IVIG amounts to approximately 7000 Euros per cycle. The same would be true for the treatment of a patient with toxic epidermal necrolysis, but in this case only one cycle is required, whereas in autoimmune bullous diseases and most other dermatological indications, several cycles of therapy are usually needed. In each of these indications the benefit must be kept constantly in perspective, notably the quality of life; potential for a life-saving effect; and the profile of side-effects with IVIG compared with the use of alternative therapies, such as corticosteroids or cytotoxic drugs.

Daoud et al. (32) have recently evaluated the cost-effectiveness of IVIG therapy compared with conventional immunosuppressive therapy in patients with autoimmune mucocutaneous bullous diseases. This study revealed that, in each distinct cohort of patients with a selected autoimmune mucocutaneous bullous disease, conventional immunosuppressive therapy had significant side-effects, many of which were hazardous and required frequent and prolonged hospitalization. Interestingly, the data suggest that the total cost of conventional immunosuppressive therapy (actual cost of drug + cost of management of side-effects) was, on average, statistically significantly more expensive than the total cost of IVIG therapy (actual cost of IVIG + cost of management of side-effects) during the entire course of the disease and on an annual basis. The differences in total cost were close to two-fold, and were largely explained by the high cost of late side-effects that are often overlooked when choosing a drug and calculating its cost at the onset of disease.

CONCLUSION

Over the past several years our knowledge of the properties, clinical management and potential benefits of IVIG has increased greatly. In parallel, the quality of available IVIG products continues to improve, and consequently their safety, tolerability, and perhaps efficacy. Although we still lack evidence-based data supporting the use of IVIG in many indications, often as a consequence of the "orphan" nature of the disease, we should not ignore the interesting benefit-risk profile of IVIG in several severe dermatological diseases. As illustrated throughout this review, not all IVIGs are the same, and not all patients are the same. Optimal use of IVIG for the benefit of patients requires careful matching of the most appropriate IVIG preparation with each patient and his or her risk factors, and consideration of the actual cost-benefit ratio of treatment with IVIG compared with alternative therapeutic options.

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