Consensus Statement on the Use of Intravenous Immunoglobulin Therapy in the Treatment of Autoimmune Mucocutaneous Blistering Diseases

A. Razzaque Ahmed, MD, DSc; Mark V. Dahl, MD; for the Consensus Development Group

Objectives: The purpose of the meeting of the Consensus Development Group was to critically evaluate the current published data on the use of intravenous immunoglobulin (IVIg) therapy in the treatment of autoimmune mucocutaneous blistering diseases (AMBDs) and to discuss the industrial preparation and safety features of this biologic agent.

Participants: The participants were physicians who frequently treat patients with these diseases and included dermatologists, oral medicine specialists, ophthalmologists, and immunologists. The members of the group provided input and discussion in their areas of expertise. The participants were invited attendees.

Evidence: Data samples included only published information in the English-language literature. The expert opinions and experience of the members of the Consensus Development Group were vital to the discussion.

Consensus Process: A consensus was achieved by an open discussion and cumulative agreement on all issues relevant to the use of IVIg therapy in the treatment of AMBDs. Special emphasis was placed on indications for its use, determination of outcome parameters, and development of a protocol for its therapeutic use. We also focused on its safety and on prevention of adverse effects.

Conclusion: This consensus statement outlines the scope of IVIg treatment; provides guidelines for its use, including indications, prescreening, premedications, dose, frequency, and monitoring; and defines the end point of therapy.

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From the Department of Dermatology and Oral Medicine, Harvard Medical School and Harvard School of Dental Medicine, Boston, Mass (Dr Ahmed); and Department of Dermatology, Mayo Clinic, Scottsdale, Ariz (Dr Dahl). A complete list of the members of the Consensus Development Group appears on page 1057. The authors have no relevant financial interest in this article.

AUTOIMMUNE mucocutaneous blistering diseases (AMBDs) are a group of uncommon diseases that have at least 3 common features[1-6]: (1)they involve the skin and frequently one or more mucous membranes derived from stratified squamous epithelium; (2) the weight of the evidence suggests that they have an autoimmune cause or pathogenesis; and (3) they can cause serious sequelae that diminish quality of life and sometimes cause death.

During the last several decades, the conventional therapy for AMBDs has been high-dose, long-term systemic corticosteroids and immunosuppressive agents (ISAs).[1-11] Recently, this paradigm has shifted.[12] Some patients who are nonresponsive to high-dose systemic corticosteroids and ISAs have been successfully treated with intravenous immunoglobulin (IVIg).[12-47] A group of physicians with interests in the treatment of these diseases gathered to discuss the potential role of IVIg treatment in the management of these diseases. Those unable to attend interacted via mail. The cumulative discussions of this group have resulted in the development of this consensus statement.

In this consensus statement, we focus our discussion on 5 clinical entities: pemphigus vulgaris (PV); pemphigus foliaceus (PF); bullous pemphigoid (BP); mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid; and epidermolysis bullosa acquisita (EBA). We recognize that reports indicate that IVIg treatment may be effective in other AMBDs as well, such as linear IgA bullous disease and pemphigoid (herpes) gestationis, among others, but these will not be discussed herein.

CONVENTIONAL THERAPY

Treatment of AMBDs remains controversial. Only a few double-blind or randomized studies have been done.[48,49] There is currently no declared standard of care, nor are there drugs specifically approved by the US Food and Drug Administration for the treatment of AMBDs. Multicenter trials on any of the currently used drugs have never

been conducted. Conventional therapy has continuously evolved during the last 50 years, since the introduction of corticosteroids as the major anti-inflammatory agents.[1-3,6-10] However, serious adverse effects have been observed with the use of these agents.[50-55] As ISAs became available, they have been used for their corticosteroid-sparing effects. Many of these ISAs affect B cells, T cells, or both, which results in the decreased levels of autoantibodies. Hence, in most patients, the use of high-dose oral corticosteroids together with an ISA has become the prevailing approach to treat AMBDs.[1-6,53]

Pemphigus

Systemic corticosteroids are often considered the mainstay of therapy.[2,3,7] A dose of 1 mg/kg per day of prednisone is often used. In the past, most physicians doubled the dose every 8 to 10 days, reaching doses as high as 240 to 360 mg daily until control was achieved. Once initiated, systemic corticosteroids are often used for months or years. Sometimes doses can be lowered or given on alternate days to minimize adverse effects.

Other agents with possible anti-inflammatory effects that have been used to treat pemphigus include dapsone, minocycline, or tetracycline, in combination with nicotinamide. Immunosuppressive agents used to treat pemphigus include azathioprine, methotrexate, cyclophosphamide, cyclosporine, gold, chlorambucil, and mycophenolate mofetil.[56-64] These agents are typically added to prednisone regimens because of their presumed corticosteroid-sparing effect. In patients with severe disease in whom systemic oral corticosteroids and ISAs have not controlled the disease, intravenous corticosteroids, plasmapheresis, extracorporeal photophoresis, and intravenous cyclophosphamide have been used.[65-69]

Bullous Pemphigoid

The use of systemic therapy in BP is determined by the degree of involvement and progression of disease.[9,53,70] The dose of systemic corticosteroids initiated in patients with BP is similar to that used in patients with PV.[2,8] However, a recent systematic review has demonstrated that high doses of corticosteroids are associated with increased morbidity and mortality.[9] Other agents with anti-inflammatory properties that have been used are dapsone, minocycline, and/or tetracycline with nicotinamide.[9,70-73] Immunosuppressive agents that have been frequently used include azathioprine, methotrexate, chlorambucil, cyclosporine, cyclophosphamide, and mycophenolate mofetil.[8,9,55,58,60,61,70,74-76] When these agents alone or in combination have not been effective, treatment with intravenous corticosteroids, intravenous cyclophosphamide, or plasmapheresis has been instituted.[77-80]

Mucous Membrane Pemphigoid

There has been a recent systematic review of the treatment of MMP.[10] The systemic treatment of MMP or cicatricial pemphigoid is based on the extent, severity, and areas of involvement.[10,81] Patients are frequently treated with dapsone alone or in combination with prednisone (1 mg/kg per day).[82] For nonresponsive disease, cyclophosphamide (1-1.5 mg/kg per day) is added.[81] Azathioprine, mycophenolate mofetil, sulfapyridine, tetracycline, minocycline, nicotinamide, and tacrolimus have also been used.[81,83] In some patients, subconjunctival injection of mitomycin C or intravenous prednisone combined with cyclophosphamide has been successful.[10,81]

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita may be the most difficult of the AMBDs to treat.[10,11] Most patients are corticosteroid resistant. A few patients temporarily respond to dapsone or colchicine.[10,11] Some respond to cyclosporine or extracorporeal photopheresis and plasmapheresis.[10,11] Treatment is often disappointing in that remissions are uncommon.[10,11]

PROBLEMS ASSOCIATED WITH CONVENTIONAL THERAPY

There are numerous dose-related adverse effects, immediate and late, temporary and irreversible, that may occur in patients with AMBDs treated with long-term corticosteroid therapy.[8-10,22,23,29,54] These include immune suppression, severe infection, diabetes mellitus, osteoporosis, bone fractures, steroid-induced myopathy, electrolyte imbalance, cataracts, glaucoma, hypertension, psychological changes, peptic ulcer disease, and others.

Similarly, each ISA has common and serious adverse effects. Bone marrow suppression causes anemia, leukopenia, and thrombocytopenia. Bacterial sepsis and other infections may develop and be life-threatening.[9] Cyclosporine causes hypertension, renal failure, hyperlipidemia, and electrolyte imbalance.[7-9,60,61] Men and women may become sterile after treatment with cyclophosphamide. Other serious adverse effects include hemorrhagic cystitis, fibrosis of the urinary bladder, and bladder cancer.[8,59] Immunosuppressed patients are at an increased risk of developing malignancies such as lymphomas and squamous cell carcinomas of the skin.[8,50]

Autoimmune mucocutaneous blistering diseases are generally chronic diseases necessitating months and even years of treatment with potent and potentially dangerous drugs. While conventional therapies may be effective in controlling the disease in many patients, prolonged immunosuppression may account for high rates of morbidity, disability, and possible mortality.

PROGNOSIS WITH CONVENTIONAL THERAPIES AND THE SCOPE OF THE ISSUE

The mortality rate in PV is between 5% and 10%.[84] The cause of death in these patients is usually opportunistic infection secondary to prolonged immune suppression or directly resulting from high-dose long-term immunosuppressive therapy.[85,86] Most patients require ongoing long-term systemic treatments with prednisone or prednisolone and immunosuppressive agents. Only about 30% of patients enter a sustained medication-free remission.[86] Several patients with PF have been de-

scribed who do not respond to conventional immunosuppressive therapies.

Deaths have been reported in patients with PF, usually due to prolonged immune suppression complicated by opportunistic infections and malignancy.[87] In patients with BP, a 1-year mortality rate of 19% and a 3-year mortality rate of 28% to 30% have been reported.[88,89] The cause of death is usually due to prolonged immunosuppression.[9] In contrast to pemphigus, many patients eventually enter a sustained treatment-free remission.[1,2,9] Thus, in PV, PF, and BP, it would appear that the mortality rate may be an indicator of the probable number of patients with severe disease who required high-dose long-term therapy.

Data on mortality rates in MMP are not available. It is apparent that in spite of aggressive systemic immunosuppressive therapy, as many as 25% of patients with ocular involvement become blind.[90] Others may develop laryngeal, esophageal, urethral, anal, or vaginal stenosis.[81] In a recent review of available therapies for EBA, none showed promise in producing either clinical response or long-term remission.[10,11]

REPORTED EXPERIENCE WITH IVIg TREATMENT IN AMBDs

Pemphigus Vulgaris

In a review of PV case studies and a small series including a total of 21 patients with severe disease, 81% showed improvement and ability to reduce systemic corticosteroid therapy. Some of the nonresponders were patients treated with inadequate doses of IVIg used for brief periods.[13-21]

In a study of 21 patients with severe cutaneous and mucosal disease that was not responsive to conventional immunosuppressive treatments, use of 2 g/kg per cycle produced prolonged clinical remission that was sustained after IVIg therapy was discontinued. Previous systemic therapies were discontinued, and IVIg was used as monotherapy.[22]

In another study of 15 patients who were unresponsive to high-dose systemic corticosteroids and for whom the use of ISAs was contraindicated, the use of 1 to 2 g/kg per cycle of IVIg produced prolonged clinical remissions. Treatment with systemic corticosteroids was discontinued and IVIg was used as monotherapy.[23]

Recently, Bystryn et al[91] used IVIg to treat 6 patients with severe PV who were simultaneously treated with cyclophosphamide and high-dose prednisone or prednisolone. The use of IVIg in combination with these agents produced dramatic clinical response, facilitated a 30% reduction in systemic corticosteroid dose, and reduced pathogenic autoantibody levels.[91] In summary, 53 patients with PV obtained significant clinical benefit from IVIg.

Pemphigus Foliaceus

In the literature, there are 27 patients with PF resistant to conventional therapies who were successfully treated with IVIg.[24-27] In a study of 11 patients with PF and in a second study, 8 patients with widespread PF recalcitrant to high-dose corticosteroids and multiple ISAs were treated with IVIg and experienced prolonged clinical remission that was sustained after IVIg therapy was discontinued. In another series of 7 patients with PF nonresponsive to high-dose systemic corticosteroids and for whom ISAs were contraindicated, IVIg therapy produced prolonged and sustained clinical remission. Thus there are at least a total of 27 patients with PF for whom IVIg has been shown to be effective and beneficial when other therapies had failed.

Bullous Pemphigoid

A review of the English-language literature revealed that 12 (70%) of 17 patients with BP treated with different protocols benefited from IVIg therapy when it was administered for at least 3 months at doses of 2 g/kg per cycle.[12,16,20,28] Patients who did not respond had received lower doses of IVIg and only as a single dose. In a series of 15 patients with recurrent BP that could not be controlled with high-dose systemic corticosteroids and multiple ISAs, use of 2 g/kg per cycle of IVIg produced prolonged clinical remission, which was sustained after IVIg therapy was discontinued.[29] The IVIg was used as monotherapy. Thus, in 27 of 32 cases of BP reported in the literature as nonresponsive to conventional therapy, IVIg was of significant benefit and produced lasting clinical benefit with minimal adverse effects.

Mucous Membrane (Cicatricial) Pemphigoid

In the first published study, IVIg treatment was used in 10 patients who had progressive ocular involvement.[30] These patients were blind in one eye and the vision in the other eye was deteriorating. They did not respond to several ISAs and high-dose corticosteroids and experienced numerous adverse effects from these treatments. The use of 2 g/kg per cycle of IVIg initially given at a frequency of every 2 to 3 weeks arrested the progression of eye disease and maintained vision. Vision was maintained after IVIg was discontinued.

In a series of 15 patients with severe MMP involving multiple mucosal surfaces who were nonresponsive to conventional immunosuppressive therapy and who experienced multiple adverse reactions to these treatments, IVIg therapy at 2 g/kg per cycle was effective in producing a long-term remission.[33] This remission persisted after IVIg therapy was discontinued. The IVIg was used as monotherapy.

In a series of 20 patients with oral pemphigoid who could not be treated with dapsone, a comparison was made between IVIg therapy and treatment with conventional ISAs.[32] Eight patients who received only IVIg had early remission and no disease progression. The disease was poorly controlled in the 12 patients treated with conventional immunosuppressive therapy, who experienced continued involvement in other mucosae and developed several adverse effects. Recently, 7 patients with severe oral pemphigoid that was not responsive to dapsone and for whom systemic corticosteroids and ISAs were contraindicated experienced a prolonged clinical remis-

sion under IVIg treatment without extension of disease to other mucosae, and the remission was sustained after the IVIg therapy was discontinued.[35]

Thus, at least in 40 patients reported in the literature with MMP, IVIg treatment was of significant benefit. It produced clinical remission, which was sustained after discontinuation of treatment, and prevented disease progression, specifically blindness.

Epidermolysis Bullosa Acquisita

Treatment with IVIg has been used in 9 patients with EBA that was resistant and nonresponsive to other therapies. When used for several months, IVIg produced a significant improvement of skin and mucosal disease without adverse effects.[36-43]

GUIDELINES FOR THE USE OF IVIg IN AMBDs

Protocol and Indications for IVIg Treatment

This aspect of IVIg therapy for AMBDs is an evolving process and area of study. Based on the evidence in the available literature, the following indications are currently recommended. The diagnostic criteria for the purpose of using IVIg treatment have been recently described.[2] If biopsy specimens are not available because of the anatomic location or the possibility of a flare, serological confirmatory testing may be considered adequate.

1. **Failure of Conventional Therapy.** Failure of the disease to respond to a maximum dose of 60 mg/d or higher of prednisone (or 1 mg/kg per day of prednisone) for 6 weeks, with a concurrently administered ISA for 10 to 12 weeks at reasonable and acceptable doses.

2. **Significant Adverse Effects of Conventional Therapy.** Patients who experience serious adverse effects may be taking these drugs to maintain control of their disease. Significant adverse effects are defined as adverse reactions that are potentially life-threatening, cause significant morbidity or inability to cope with activities of daily living, and require the intervention of a physician or drug therapy. These may be observed in at least 2 distinct circumstances when patients present without active disease: (1) in patients who require high-dose long-term therapy to control their disease and develop significant adverse effects consequent to it;(2) in some patients who develop drug dependency, especially to systemic corticosteroids, and cannot be weaned from them because of disease recurrence. Such patients can also develop significant adverse effects from prolonged systemic therapy.

3. **Contraindications.** These include absolute and relative contraindications to the use of high-dose long-term systemic corticosteroids or ISAs.

4. **Progressive Disease.** In patients whose diseases are progressive in spite of appropriate maximum yet safe conventional systemic therapy, such progression may be a threat to the life of the patient or seriously impair activities of daily living.

5. **Uncontrolled Rapid Debilitating Progressive Disease.** Some disease cannot be controlled with conventional therapy.

6. **Rapid Progressive EBA With Generalized Cutaneous Diseases.** This applies with or without multiple mucosal involvement.

7. **Age of the Patient and Pregnancy.** These factors are not a contraindication to the use of IVIg therapy.[47,92,93]

Dose

The cumulative published experience would suggest that a dose of 2 g/kg per cycle is most likely to produce desired or expected results.[12-47,94] Some patients, especially those whose disease is not very active clinically but who are experiencing serious or catastrophic adverse effects of conventional therapies, may respond to 1 to 1.5 g/kg per cycle. A cycle consists of the total dose divided into 3 equal doses, each given on 3 consecutive days. Some investigators prefer to use 400 mg/kg per day, given over a course of 5 days, to constitute 1 cycle. The infusion is given slowly over 4 to 4½ hours. During the infusion, vital signs should be monitored.

Frequency

The initial frequency is generally 1 cycle every 3 to 4 weeks.[12,22] In patients with aggressive ocular cicatricial pemphigoid, the infusions are given every 2 weeks.[30] In patients with stable disease, when IVIg is used primarily because of adverse effects of conventional therapy, monthly intervals are effective. This initial frequency is continued until there is effective control of the disease. Effective control of disease is defined as the lack of new lesions for a minimum of 3 weeks and resolution and healing of previous lesions. Thereafter, a slow reduction in the frequency or dose of treatments may be tried to determine if the control can be sustained.

A suggested approach to taper treatment with IVIg maintains the same dose but increases the time intervals between infusions. For example, the interval between infusion cycles can be gradually increased to 6, 8, 10, 12, 14, and 16 weeks.[12,22] The proposed end point is 2 infusions each given 16 weeks apart. The cessation of all systemic therapy, including IVIg, in the absence of clinical disease, is defined as the beginning of the remission period.

Prescreening

Before IVIg therapy is begun, serum levels of immunoglobulins, especially IgA, should be determined.[92,93] Patients with low or absent levels of IgA have been reported to develop anaphylaxis. A complete blood cell count, hepatic and renal function tests, and screening for rheumatoid factor and cryoglobulin are recommended. Patients with cryoglobulin have a higher risk to develop acute renal failure. Therapy with IVIg should be used cau-

tiously in patients with renal insufficiency or impaired cardiac function because fluid overload may occur. It is advisable to screen patients for hepatitis B and C and for human immunodeficiency virus.

Premedications

To avoid infusion-related headaches, rigors, and other adverse events, pretreatment with analgesics, nonsteroidal anti-inflammatory agents (NSAIDS), antihistamines, or low-dose intravenous corticosteroids may be beneficial.

MECHANISM OF ACTION

The exact mechanism of action of IVIg treatment in AMBDs is not completely known.[95] In general, IVIg treatment is considered to produce its clinically beneficial effects via one or more of the following pathways: (1) interactions with Fc receptors; (2) reduction in titers of pathogenic antibody; (3) induction or suppression of production of cytokines; (4) effects of apoptosis; (5) neutralization of toxins; and/or (6) alteration in sensitivity to corticosteroids.[95]

In AMBDs, it is possible that IVIg may work as an anti-inflammatory or as an immunomodulatory agent. The evidence for such proposed mechanisms is preliminary. Patients with PV and MMP have high serum levels of interleukin (IL) 1 (IL-1α and IL-1β) and low levels of IL-1 receptor antagonist (IL-1RA) before beginning IVIg treatment.[96,97] After IVIg therapy, this ratio is reversed, and serum levels of IL-1 decrease, while those of IL-1RA increase. Similarly, peripheral blood leukocytes from these patients before IVIg therapy produce high levels of IL-1 and low levels of IL-1RA. When IVIg is added to cultures of peripheral blood leukocytes from these patients, the levels of IL-1 are decreased, and those of IL-1RA are increased in the culture supernatants. An increase in serum IL-10 levels has been observed during IVIg therapy in patients with dermatomyositis.[98] There is also evidence that IVIg may down-regulate the expression of Fas and Fas-ligand on keratinocytes and thus prevent apoptosis.[99]

When serum levels of pathogenic autoantibodies are observed at monthly intervals over an 18- to 24-month period, preliminary studies suggest that a gradual slow decline in levels begins after 4 to 6 months of therapy and reaches undetectable levels within 8 to 10 months. Thereafter, autoantibodies remain undetectable.[100-103] This has been demonstrated for autoantibodies to desmoglein 1 and desmoglein 3 in PV, desmoglein 1 in PF, BP antigen 2 (a 180-kDa protein) in BP, and antihuman β4 integrin and anti–alpha 6 autoantibody in MMP.[35,100-103]

ADVERSE EFFECTS

Adverse reactions associated with the use of IVIg are usually mild and self-limiting.[92,93] The incidence of adverse effects of IVIg in patients treated for autoimmune diseases is usually lower than 1%.[93] Few, if any, patients require discontinuation of therapy. Most adverse reactions will disappear if the infusion is temporarily discontinued or if the infusion rate is slowed.

Reactions such as headache, back pain, chills, flushing, fever, hypertension, myalgia, nausea, and vomiting appear to be related to infusion rate rather than the dose. Erythema, pain, phlebitis, and eczematous dermatitis may occur at the infusion site.[92,93]

Aseptic meningitis has been reported in patients receiving IVIg.[92-94] Symptoms include severe headache, photophobia, and sometimes fever. These symptoms may last for several days. Patients with a personal or family history of migraine have a greater frequency of developing severe headaches and should be forewarned. Cerebrovascular accidents have occurred. The US Food and Drug Administration, which is currently investigating the association between IVIg and thrombosis, has identified high infusion rates and high doses as potential risk factors for thrombotic events in at-risk patients.[104] Additional risk factors may include older age and a history of stroke, myocardial infarction, hypertension, thrombosis, hypercoagulability, or limited mobility.[105] To decrease the risk of thrombotic events in such patients, some authors have suggested slower rates and lower doses of IVIg administration.[106] Hematologic events such as hemolysis and neutropenia have been reported.[93]

Anaphylactic reactions can occur in IgA-deficient individuals.[92,93] Up to 40% of IgA-deficient individuals have anti-IgA antibodies. Most commercial preparations of IVIg contain small amounts of IgA, administration of which can result in the formation of immune complexes.

Patients with cardiac diseases need careful and constant monitoring because increased blood pressure and congestive heart failure can occur.[93] These presumably result from rapid fluid overload or electrolyte imbalance.

Use of IVIg has been associated with acute renal failure.[92,93] Histologic studies of kidneys from such patients suggest osmotic injury to the proximal renal tubules manifested as renal tubular necrosis and osmotic nephrosis. Patients receiving IVIg reconstituted from powder products or IVIg preparations containing sucrose are at a greater risk for renal failure. To reduce this risk, patients with renal disease need an evaluation for diabetes mellitus, developing dehydration, hypovolemia, sepsis, paraproteinemia, or cryoglobulinemia. If they are undergoing concomitant nephrotoxic drug therapy, this factor must be considered as well. Caution must be exercised in treating elderly patients.

Since IVIg is isolated from pooled human plasma, IVIg therapy carries the potential risk of transferring infectious agents.[92,93] All batches of IVIg are screened for human immunodeficiency virus, syphilis, and hepatitis and are treated to eliminate the transmission of known enveloped viruses.

Sites for Infusion Therapy

Treatment with IVIg is probably best administered in hospitals to patients at high risk for adverse events. Patients with a low risk for such events can be treated in infusion units in an ambulatory environment. Patients can be monitored by a physician in a specialized infusion suite. Clinical progress can be monitored more readily in such a setting, and changes in systemic therapy can be made. Adverse effects of IVIg can be prevented and treated promptly when they occur. This therapy is new to AMBDs

Comparison of the Various Intravenous Immunoglobulin Preparations Available in the United States

	Veno-S (5%)	Veno-S (10%)	Gammagard S/D	Iveegam EN	Polygam S/D	Gamimmune N S/D (10%)	Gammar PIV	Immune Globulin Intravenous (Human)
Commercial preparations	Alpha Therapeutic Corp		Baxter Corp/Hyland Immune Division	Immuno-US	Baxter Corp/Hyland Immune Division, distributed by American Red Cross	Bayer	Aventis Behring	ZLB Bioplasma
Method of preparation (including viral inactivation)	Cold alcohol/fractionation, polyethylene glycol/ bentonite fractionation, ion-exchange, chromatography, solvent detergent treatment		Cohn-Oncley, ultrafiltration, ion-exchange, chromatography, solvent detergent treatment	Cold ethanol, polyethylene glycol, trypsin	Cohn-Oncley, ultrafiltration, ion-exchange, chromatography, solvent detergent treatment	Cohn-Oncley, pH 4.25, solvent detergent treatment	Cohn-Oncley pasteurization, ultrafiltration	Kistler-Nitschmann, pH 4.0 + trace pepsin
Form	Liquid		Lyophilized	Lyophilized	Lyophilized	Liquid	Lyophilized	Lyophilized
Shelf-life, mo	24		27	24	27	36	24	24
Reconstitution time	Liquid solution		<5 min at room temperature; >20 min if cold	≤10 min at room temperature	<5 min at room temperature; >20 min if cold	Liquid solution	<20 min	Several minutes
Recommended concentration, %	5	10	5	5	5	10	5	3
Recommended infusion rate, mL/kg/h	3	3	4	2*	4	4.8	3.6	1.28
Time to infuse 70 g, 1 g/kg/h	6.7	3.4	5	11.6	5	2.1	5.6	27.8
Composition								
Sugar content	5% D-sorbitol	5% D-sorbitol	2% glucose	5% glucose	2% glucose	Sugar free	5% sucrose	5% sucrose
Sodium content	1.3 mEq/L	<1 mEq/L	0.85% at 5% concentration	0.3%	0.85% at 5% concentration	Trace	0.5%	Up to 0.9%, depending on diluent
Osmolality, mOsm/L	300	300	5%, 636; 10%, 1250	≥240	5%, 636; 10% 1250	274	5%, 309; 10%, 600	In sterile water: 3%, 192; 6%, 384; 12%, 768 In normal saline: 3%, 498; 6%, 690; 12%, 1074
pH	5.2-5.8	5.2-5.8	6.8	6.4-7.2	6.8	4.25	6.8	6.6
IgA content, µg/mL	15.1	20-50	<1.2	<10	<1.2	120	<25	720

*Milliliters per minute.

and should be preferably delivered by a physician with experience in the management of AMBDs.

Need for a Multicenter Trial

It is our consensus that IVIg therapy constitutes a potentially valuable agent in the overall management of AMBDs. We encourage the undertaking of a multicenter trial to provide further objective data on a larger cohort of patients related to the efficacy, scope, and influence of IVIg therapy on the clinical course of AMBDs.

CRITICAL ISSUES IN SELECTING AN IVIg PREPARATION

The World Health Organization has provided general guidelines for specific contents including antibodies.[107] There are 7 licensed IVIg preparations available in the United States. Although there are no comparison studies of efficacy and safety among the various preparations, these preparations have many differences. Some of these differences may affect outcome. The differences between these preparations include the manufacturing process, formulations and concentration, composition of the final solution, and approach to viral safety.[108-117]

In the manufacturing process, the number of processing steps and processing times differs. IgG molecules are relatively stable under a wide range of conditions.[108-117] However, shorter processing times, fewer numbers of precipitation steps, and avoidance of proteolytic enzyme treatments allow a preparation to contain a larger number of biologically active IgG molecules.[108,109]

Preparations of IVIg are available in both liquid and lyophilized preparations (**Table**). Liquid preparations offer the advantage of ready-to-use convenience. Lyophilized products require reconstitution.

Members of Consensus Development Group

Grant J. Anhalt MD, *Department of Dermatology, Johns Hopkins University, Baltimore, Md*; Jeffrey P. Callen, MD, *Department of Dermatology, University of Kentucky, Louisville*; Luis A. Diaz MD, *Department of Dermatology, University of North Carolina, Chapel Hill*; Craig Elmets, MD, *Department of Dermatology, University of Alabama, Birmingham*; David P. Fivenson MD, *Department of Dermatology, Henry Ford Hospital, Detroit, Mich*; C. Stephen Foster, MD, *Department of Ophthalmology, Massachusetts Eye & Ear Infirmary, Harvard Medical School, Boston*; Walter R. Gammon, MD, *Eastern Dermatology, Greenville, NC*; Ervin Gelfand, MD, *Department of Pediatrics, National Jewish Medical and Research Center, Denver, Colo*; Vincent C. Ho, MD, *Department of Dermatology, University of British Columbia, Vancouver*; Marcel F. Jonkman, MD, PhD, *Department of Dermatology, Groningen University Hospital, Groningen, the Netherlands*; Robert E. Jordon, MD, *Department of Dermatology, University of Texas Medical School, Houston*; Joseph Jorizzo, MD, *Department of Dermatology, Wake Forest University, Winston-Salem, NC*; A. Paul Kelly, MD, *Department of Dermatology, Martin Luther King Hospital, Los Angeles, Calif*; Neil J. Korman, MD, *Department of Dermatology, Case Western Reserve University, Cleveland, Ohio*; Mark Lebwohl, MD, *Department of Dermatology, Mt Sinai School of Medicine, New York, NY*; Torello Lotti, MD, *Department of Dermatology, University of Florence, Montecatini Terme, Italy*; Thomas Luger, MD, *Department of Dermatology, University of Muenster, Muenster, Germany*; Bartley Mondino, MD, *Jules Stein Eye Institute, UCLA, Los Angeles, Calif*; Samuel L. Moschella, MD, *Department of Dermatology, Harvard Medical School, Boston*; P. Regine Mydlarski, MD, *Department of Dermatology and Clinical Sciences, University of Toronto, Toronto, Ontario*; David A. Norris, MD, *Department of Dermatology, University of Colorado Health Sciences Center, Denver*; Lee T. Nesbitt, MD, *Department of Dermatology, Louisiana State University Health Sciences Center, New Orleans*; Amit G. Pandaya, MD, *Department of Dermatology, University of Texas-Southwestern, Dallas*; Roy S. Rogers III, MD, *Department of Dermatology and Oral Medicine, Mayo Clinic, Rochester, Minn*; Naveed Sami, MD, *Department of Oral Medicine, Infection, and Immunity, Harvard School of Dental Medicine, Boston, Mass*; Robert A. Schwartz, MD, *Department of Dermatology, University of Medicine and Dentistry of New Jersey Medical School, Newark*; Neil Shear, MD, *Department of Dermatology, Sunnybrook Medical Center, Toronto*; Richard D. Sontheimer, MD, *Department of Dermatology, University of Iowa, Iowa City*; Bruce Thiers, MD, *Department of Dermatology, Medical University of South Carolina, Charleston*; Victoria Werth, MD, *Department of Dermatology, University of Pennsylvania, Philadelphia*; Fenella Wojnarowska, MD, *Department of Dermatology, Churchill Hospital, Oxford University, Oxford, England*; Kim Yancey, MD, *Department of Dermatology, Medical College of Wisconsin, Milwaukee*; Joseph J. Zone, MD, *Department of Dermatology, University of Utah, Salt Lake City*.

Since high doses (1-2 g/kg) of IVIg are recommended in the treatment of autoimmune diseases, large volumes of fluid are usually administered with every infusion. The higher the concentration of the solution, the less volume is required for a given dose. For example, a 70-kg individual receiving 1 g/kg of body weight requires only 700 mL of fluid with a 10% solution compared with 1400 mL of fluid with a 5% solution. This may be a critical issue for patients sensitive to fluid overload.

The final composition of the individual products may also vary (Table). Some of these important variables include sugar and sodium content and osmolarity.[116] Sugars are added as stabilizers. These variables may significantly influence the incidence of adverse events. Sugar content, in particular sucrose, has been associated with significant renal adverse events. Reconstitution of lyophilized preparations to higher concentrations than those generally recommended results in solutions with high sodium content and hyperosmolarity. These factors should be taken into account when prescribing IVIg for high-risk patients such as those with compromised renal or cardiac functions.

The process of viral inactivation and removal varies and can include treatment with solvent and/or detergent or polyethylene glycol, pasteurization (heat treatment), or maintaining the IVIg preparation at a low pH[113-115] (Table). It is important that the methods used in an IVIg pathogen safety program be complementary, work by independent mechanisms, and not affect the integrity or bioactivity of the IgG molecule.

In summary, it is possible that the preparation process and the formulation and composition of the final product may have some impact on the efficacy, safety, and tolerability of the different preparations of IVIg. The ideal IVIg preparation would be sugar free with a low sodium content and a physiologic osmolarity. Preparations of IVIg should be purified in the shortest amount of time, should show robust biological activity and efficacy against known and unknown potential pathogens, and should be consistent from one batch to the next. Such a product would provide safety, reliability, consistency, the highest tolerability for patients, and the best outcome or efficacy for patients.

CONCLUSIONS

Treatment with IVIg is an important addition to the therapeutic options available to a physician treating AMBDs. In patients with AMBDs who cannot tolerate and/or are not benefitted by conventional therapy, IVIg therapy has the potential to produce a good clinical outcome. The initial course of therapy should be tailored for duration and frequency to produce clinical control of the disease. Thereafter, a slow tapering may be advisable to prevent recurrences and sustain the obtained clinical benefit. Therapy needs to be tailored to the extent, severity, and duration of the disease, response to previous therapies, associated medical problems, and overall health of the patient. Currently, it is preferable that IVIg for patients with AMBDs be provided directly by physicians with experience and interest in AMBDs.

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Corresponding author and reprints: A. Razzaque Ahmed, MD, DSc, Harvard School of Dental Medicine, Department of Oral Medicine and Diagnostic Sciences, 188 Longwood Ave, Boston, MA 02115 (e-mail: razzaque_ahmed @hms.harvard.edu).

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