

Immunoglobulin Replacement Therapy: A Twenty-Year Review and Current Update

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Key Words

Immunodeficiency · Immunodeficiency diseases · Primary immunodeficiency · Immunoglobulins

Abstract

Objective: The expansion of immunoglobulin replacement to multiple disease entities marks a decade-long advancement in immune therapy. Parallel to its extension, the characteristics and composition of immunoglobulin products have diversified. The aim of this study was to summarize a 20-year comprehensive literature review of currently commercially available immunoglobulin products, particularly examining individual product properties in a comparative format. **Data Sources/Study Selections:** The literature review was performed using PubMed and Ovid, screening a time span of 2 decades. Both authors reviewed the obtained articles for acceptable quality, and the selection was narrowed down based on criteria for randomized clinical and therapeutic trials. **Results:** Product-specific characteristics in terms of purification strategy, stabilizers, composition, and viral inactivation were found among the immunoglobulin products investigated. Such differing characteristics manifest in their variable clinical safety and efficacy as assessed by the comparative product analysis. In subgroups of pa-

tients, subcutaneous immunoglobulin therapy may be an alternative to intravenous immunoglobulin (IVIG) therapy with an equal efficacy and a lower number of systemic adverse events. **Conclusion:** Only few comprehensive clinical synopses are available to clearly demonstrate the differences in IVIG products despite the widespread clinical use of the therapy. This review defines significant characteristics of individual immunoglobulin products, noting important differences in product development and application and allowing informed clinical decisions to match a product with patients' risk factors and comorbidity. This balanced approach to gammaglobulin replacement therapy is imperative to produce the highest clinical efficacy and lowest number of adverse events.

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Introduction

The evolution of serum immunoglobulin replacement therapy since its inception in 1940 encompasses an improvement in the extraction, preparation, and administration of intravenous immunoglobulin (IVIG) [1]. Its use in the treatment of primary immunodeficiency (PID), first reported by Bruton [2] in 1952, has been expanded

to treat a gamut of rheumatological, gastrointestinal, and autoimmune diseases. Currently, IVIG is used most widely, with subcutaneous IgG replacement gaining popularity [3, 4].

Presently, at least 10 licensed IVIG products are used in the USA. Each has unique characteristics and features affecting tolerability, efficacy, biologic activity, and yield [5]. They share the feature that they have been prepared from 3,000–10,000 or more healthy blood donors [6]. The individual IVIG products are distinguished by various steps in their preparation. These steps include the purification strategy, stabilization, and viral inactivation. Consequently, effectively matching patient-specific risk profiles with product-specific characteristics results in overall clinical efficacy.

While the adverse event profiles for the different IVIG products are often patient specific, the brand, concentration, and rate of product infusion have an effect on patient tolerability [6, 7]. Reducing the rate of infusion can diminish the most common side effects such as headache, low-grade fever, nausea, malaise, arthralgia, chest pain and tightness, rashes, hypotension, and myalgia [8]. Pre-infusion medication such as acetaminophen, diphenhydramine, nonsteroidal anti-inflammatory drugs, and/or corticosteroids can also be used if patients experience any side effects. If repeated adverse reactions to a product occur, options include switching to a different product, using an alternative route of administration, or discontinuing treatment.

The standard dosing regimens for IgG replacement differ between IV and subcutaneous routes of administration (subcutaneous immunoglobulin, SCIG). The common dosing regimen for IVIG in PID is 0.3–0.8 g/kg every 2–4 weeks with a 5–12% IgG concentration infused. In comparison, the common dosing regimen for SCIG is 0.05–0.2 g/kg every 0.5–2 weeks with a 10–16.5% IgG concentration infused [9]. Higher doses are recommended for anti-inflammatory/immunomodulatory effects, generally 2 g/kg body weight over 2–5 days on a monthly basis [6].

Current diseases with United States Food and Drug Administration (FDA)-approved usage for treatment with IVIG are PID, idiopathic/immune-mediated thrombocytopenia, pediatric human immunodeficiency virus (HIV) infection, hematopoietic stem cell transplantation, Kawasaki disease, chronic inflammatory demyelinating polyneuropathy (CIDP), and chronic lymphocytic leukemia [10]. The dosing regimens differ for each of these indications (table 1). The clinical utility of IVIG expands beyond these diagnoses to include Guillain-Barré syn-

drome, severe sepsis, and others [11]. As disease indications increase, comparative analyses of various IVIG products are scarce.

Comprehensive reviews on IVIG products and their therapeutic use are lacking. This review aims to provide clinically relevant, product-specific characteristics of available IVIG products in regard to the method of production, product ingredients, and other clinically relevant, pharmacologic characteristics.

Methods

Literature Search

PubMed, Embase and the Cochrane Neuromuscular Disease Group Trials Specialized Register were searched for published articles from January 1990 to December 2013 inclusive on ‘intravenous gammaglobulin’ and ‘treatment’. Medical subject heading (MeSH) search terms were used to search PubMed, and a key word search was used if required. The key word search terms used were; ‘intravenous gammaglobulin’ combined with ‘drug therapy’ or ‘treatment’ or ‘therapy’ or ‘randomized control trial’ or ‘clinical trial’. Included in this study were primarily brand-specific controlled trials. All current and emerging treatments involving IVIG were included in the study.

Study Selection and Participants

When journal articles did not present the necessary data for the analyses, attempts were made to contact the authors. No restrictions were set on suitable settings for inclusion in this review.

Assessment of Methodological Quality

The studies used in the systematic review were assessed for levels of concealment of allocation at randomization and internal validity to determine whether any bias was present. The quality of the evidence for each study was graded from very low to high by both reviewers. Each paper was assessed for risk of bias, inconsistency, indirectness, imprecision, publication bias, and large effect; plausible confounding would change the effect and dose-response gradient. Both reviewers were required to be in agreement to include the study in the review.

Mechanisms of Action

In the treatment of primary and secondary immunodeficiency disorders, IVIG acts by delivering adequate concentrations of affinity-matured antibodies against a broad range of pathogens [12]. They bind antigen, and their effector functions include complement activation, complement binding, and binding to various Fc receptors.

In contrast, the anti-inflammatory and immunomodulatory mechanisms of action by IVIG are incompletely understood. Physiologic or natural autoantibodies, con-

Table 1. Specific considerations of IVIG dosage and administration

	Maximum infusion rate	Maximum recommended dose	Infusion rate in renal disease
Gammagard S/D	0.066 ml/kg/min (5% concentration; 4 ml/kg/h) 0.133 ml/kg/min (10% concentration; 8 ml/kg/h)	PID: 300–600 mg/kg every 3–4 weeks ITP: 1,000 mg/kg, maximum 3 doses on alternative days CLL: 400 mg/kg every 3–4 weeks KS: single 1,000 mg/kg or 400 mg/kg for 4 consecutive days	<4 ml/kg/h (5% concentration) <2 ml/kg/h (10% concentration)
Gamunex 10%	0.08 ml/kg/min (4.8 ml/kg/h)	PID: 300–600 mg/kg every 3–4 weeks ITP: 2,000 mg/kg divided into 2 doses of 1,000 mg/kg on 2 consecutive days or into 5 doses of 400 mg/kg given on 5 consecutive days CIDP: loading dose 2,000 mg/kg; maintenance dose 1,000 mg/kg	<4.8 ml/kg/h
Carimune NF	See calculations in prescribing information	PID: 400 mg/kg ITP: 400 mg/kg on 2–5 consecutive days	<2 ml/kg/h
Flebogamma 5%	0.10 ml/kg/min (5% concentration; 6.0 ml/kg/h) 0.08 ml/kg/min (10% concentration; 4.8 ml/kg/h)	PID: 300–600 mg/kg ITP: not indicated	<3.6 ml/kg/h
Octagam	0.07 ml/kg/min (4.2 ml/kg/h)	PID: 300–600 mg/kg every 3–4 weeks ITP: not indicated	<4.2 ml/kg/h
Gammagard Liquid 10%	0.083 ml/kg/min (5.0 ml/kg/h)	PID: 300–600 mg/kg every 3–4 weeks ITP: not indicated	<2 ml/kg/h
Privigen	PID: 0.08 ml/kg/min (4.8 ml/kg/h) ITP: 0.04 ml/kg/min (2.4 ml/kg/h)	PID: 200–800 mg/kg every 3–4 weeks ITP: 1,000 g/kg IV daily for 2 consecutive days for total of 2,000 mg/kg	<1.2 ml/kg/h
Gammaplex 5%	0.08 ml/kg/min (4.8 ml/kg/h)	PID: 300–800 mg/kg every 3–4 weeks ITP: 1,000 mg/kg for 2 consecutive days	<4.8 ml/kg/h
Gammaked 10%	0.08 ml/kg/min (4.8 ml/kg/h)	PID: 300–600 mg/kg ITP: 2,000 mg/kg CIDP: loading dose 2,000 mg/kg; maintenance dose 1,000 mg/kg	<4.8 ml/kg/h
Bivigam 10%	0.06 ml/kg/min (3.6 ml/kg/h)	300–800 mg/kg every 3–4 weeks	<3.6 ml/kg/h

CLL = Chronic lymphocytic leukemia; KS = Kawasaki syndrome.

tained in pooled IVIG, are thought to contribute to the anti-inflammatory effects of IVIG [12–14]. Further, autoantibodies act as a first line of defense and control physiologic autoreactivity. The presence of anti-idiotypic antibodies against idiotypes on circulating autoantibodies accounts for their ability to neutralize these autoantibodies in autoimmune disease. They may also shield epitopes and prevent the immune reactivity against self-antigens stemming from damaged or aged cells [12].

Standardized Gammaglobulin Preparation

IVIG is purified from human plasma in steps by which potential product differences occur. Each step may affect the integrity and activity of the final protein as it modifies

the original product. All IVIGs are purified from the plasma of thousands of blood donors [15]. IgG concentration and virus inactivation are secondary to cold ethanol fractionation [15]. This process results in product purity with trace amounts of highly active contaminants such as prekallikrein activator, prekallikrein, activated coagulation factors, and complement proteins. These contaminants have the potential to cause clinically significant adverse events through their capability to activate the complement and through their opsonizing properties [5, 16]. Therefore, many IVIG products undergo further purification via anion exchange diethylaminoethanol (DEAE)-sepharose chromatography, leading to a separation of IgG from fibrinogen, prekallikrein, IgM, and IgA [16]. The following section provides detailed information on each IVIG product, with a summary provided in table 2.

Table 2. Comparison of different IVIG product properties

	Gammagard S/D	Gamunex 10%	Carimune NF	Flebogamma 5%	Octagam	Gammagard Liquid 10%	Privigen	Gammaplex 5%	Gammaked 10%	Bivigam 10%
Manu- facturer	Baxter Healthcare	Grifols Therapeutics Inc.	CSL Behring	Grifols Therapeutics Inc.	Octapharma USA Inc.	Baxter Healthcare	CSL Behring	Bio Products Laboratory	Grifols Therapeutics Inc.	Biotech Pharmaceuticals
Form	Lyophilized	Liquid, 10%	Lyophilized, 3, 6, and 12%	Liquid, 5%	Liquid, 5%	Liquid, 10%	Liquid, 10%	Liquid, 5%	Liquid, 10%	Liquid, 10%
Preparation time	Unknown, must be dissolved	Ready to use	Up to 20 min	Ready to use	Ready to use	Ready to use	Ready to use	Ready to use	Ready to use	Ready to use
Indications	PID, ITP, CLL, Kawasaki syndrome	PID, ITP, CIDP	PID, ITP	PID	PID	PID	PID, ITP	PID, ITP	PID, ITP, CIDP	PID
Purification method	S/D, ultrafiltration	Caprylate chromatog- raphy, final low-pH incubation	pH 4/pepsin, 50-nm nanofiltration, depth filtration	S/D, double nanofiltration (35-nm, 20-nm filters), pasteurization, PEG precipitation	S/D, pH 4 incubation, ultrafiltration	S/D, 35-nm nanofiltration, low-pH incubation at elevated temperature	pH 4 incubation, nanofiltration, depth and virus filtration	S/D, nanofiltration, final low-pH incubation TSE removal	Caprylate chromatography, low-pH incubation, TSE removal	S/D, 35-nm nanofiltration
Sugar content	20 mg/ml glucose in a 5% solution	0	1.67 g sucrose per gram protein	50 mg/ml D-sorbitol in 100 ml water for injection	100 mg/ml maltose	0	0	50 mg/ml D-sorbitol	0	0
Sodium content	8.5 mg/ml (5%)	Trace amounts	<20 mg sodium chloride per gram protein	<3.2 mEq/l (<0.02%)	≤30 mmol/l	No added sodium	Trace amounts	2.3 mg/ml	Trace amounts	0.100–0.140 mol/l
Stabilizer	Glucose	Glycine	Sucrose	D-sorbitol	Maltose	Glycine	L-proline	Sorbitol, glycine, and polysorbate 80	Glycine	Glycine
Potential for TSE/prion removal	No	Yes	Yes	Yes	No	No	No	No	Yes	No
pH when liquid (goal 4.0–5.0)	6.4–7.2	4.0–4.5	6.4–6.8	5.0–6.0	5.1–6.0	4.6–5.1	4.6–5.0	4.8–5.1	4.0–4.5	4.0–4.6
Osmolality/ osmolarity (goal 280–300 mosm/l)	636 mosm/l (5%) 1,250 mosm/l (10%)	258 mosm/kg	192–1,074 mosm/kg depending on diluent type, concentration, and volume	240–350 mosm/l	310–380 mosm/kg	240–300 mosm/kg	240–440 mosm/kg	420–500 mosm/kg, but not <240 mosm/kg	264±4 mosm/kg	<510 mosm/kg
Albumin	<300 µg/ml	<20 µg/ml	0	2 µg/ml	Not available	0	Trace amounts	0	<2 µg/ml	0
IgA content	<1.0 µg/ml	46 µg/ml	720 µg/ml	<50 µg/ml	<200 µg/ml	37 µg/ml	<25 µg/ml	<10 µg/ml	46 µg/ml	≤200 µg/ml
IgG	>90%	>98%	>96%	>99%	>96%	>98%	98%	>95%	>98%	>96%
Latex content in packaging	Yes	No	No	No	No	No	No	No	No	No

Table 2 (continued)

	Gammagard S/D	Gamunex 10%	Carimune NF	Flebogamma 5%	Octagam	Gammagard Liquid 10%	Privigen	Gammaplex 5%	Gammaked 10%	Bivigam 10%
Adverse effects	Headache (31%), nausea (22%), chills (7%), diarrhea (3%)	Headache (8%), nausea (5%), pharyngitis (5%), urticaria (5%)	Headache, dizziness, weakness, chills	Headache (21%), pyrexia (20%), diarrhea (9%), urticaria (7%)	Headache (15%), nausea (7%), back pain (4%), chest pain (4%), rigors (4%)	Headache (44%), fever (21%), nausea (13%), urticaria (7%), dizziness (8%), migraine (7%)	Headache (43%), nausea (12%), pyrexia (7%), cough (6%), diarrhea (6%)	Headache (36%), pyrexia (16%), sinusitis (16%), fatigue (12%), nausea (12%), hypertension (6%)	Headache (8%), nausea (5%), pharyngitis (5%), urticaria (5%)	Headache (51%), sinusitis (38%), fatigue (29%), upper respiratory tract infection (25%), diarrhea (21%), cough (22%), bronchitis (19%), pyrexia (19%), nausea (14%)
Shelf life/storage requirements	24 months at room temperature, not to exceed 25°C; do not freeze	36 months at refrigerated temperature 2–8°C; up to 6 months at 25°C until expiration date; do not freeze	24 months at room temperature, not to exceed 30°C until expiration date; do not freeze	24 months at 2–25°C until expiration date; do not freeze	24 months at 2–25°C until expiration date; do not freeze	36 months at refrigerated temperature 2–8°C; up to 12 months at 25°C within 24 months of the date of manufacture; do not freeze	24 months at room temperature, not to exceed 25°C; do not freeze, protect from light	24 months at 2–25°C until expiration date; do not freeze	36 months at refrigerated temperature 2–8°C; do not freeze; 6 months at room temperature, not to exceed 25°C anytime during the 36-month shelf life	Until expiration date on vial (under refrigeration at 2–8°C)

CLL = Chronic lymphocytic leukemia; PEG = polyethylene glycol; TSE = transmissible spongiform encephalopathy.

Specific IVIG Products

Gammagard S/D

Gammagard is an IVIG first licensed in the USA in 1986, developed by the Hyland Immune Division of Baxter Healthcare Corporation. In 1993, a significant number of patients receiving Gammagard infusions developed hepatitis C. Some of these episodes were associated with immunoglobulin preparations made without the cold ethanol fractionation step. Other episodes were associated with DEAE-Sephadex chromatography performed after cold ethanol fractionation, a process that was not sufficient to fractionate the hepatitis C viruses into waste fractions. It was then understood that additional viral inactivation steps such as solvent/detergent (S/D) treatment or incubation at pH 4.0 is required for IVIG preparation using chromatographic procedures [17, 18]. As such, the FDA implemented guidelines and standards for virus elimination [18]. Gammagard was reintroduced to the market as Gammagard S/D in 1994 in purified form treated with S/D for virus sterilization.

Method of Production (Including Viral Inactivation/Removal)

Purification is achieved by cold ethanol fractionation (Cohn-Onclay) and ion exchange chromatography. S/D is used for the inactivation of lipid-enveloped viruses such as HIV, hepatitis B virus, and hepatitis C virus [19]. S/D requires removal from the IVIG after viral inactivation. While newer agents have been produced to efficiently remove S/D with as little an effect on IVIG recovery as possible, 5–10% of the initial IgG content is lost. S/D treatment lengthens the manufacturing time [20–22]. The final virus extraction for Gammagard S/D is via ultrafiltration.

Ingredients/Properties

Gammagard S/D is a lyophilized preparation. Dry powder preparations offer less convenience with the requirement of a preinfusion preparation [23]. Reconstitution with various diluents has led to an increase in adverse events [6]. These osmolality-associated adverse events stem from reconstitution at a higher than recommended concentration. At a pH of 6.8 ± 0.4 , Gammagard S/D uses 20 mg/ml glucose in a 5% solution and 3 mg/ml albumin. The sodium content of 0.85% is comparatively higher than in other IVIG products. The content of IgA is $\leq 2.2 \mu\text{g/ml}$, which is among the lowest found in IVIGs [6, 8].

Adverse Effects

The adverse event profile for this product had been studied for several years before its conversion to Gammagard S/D. In a study of patients with B-cell chronic lymphocytic leukemia, 84 patients were randomized to receive either Gammagard or placebo. The incidence of minor adverse events was 1.3 versus 0.6% with placebo [24]. Gammagard has been shown to be safe in neonates. Homan et al. [25] administered Gammagard 5% as a treatment to 10 control neonates. No adverse events were noted in either group.

The safety of Gammagard S/D was evaluated more recently in young children. Manlhiot et al. [26] compared the incidence of adverse events with juvenile dermatomyositis. Among the 38 patients at a median age of 10 years, Gammagard S/D was associated with the lowest frequency of adverse events compared with 3 other products. The most common reactions included fever, headache, nausea/vomiting, and lethargy. No life-threatening reactions occurred [26].

Comparative Studies

A multicenter double-blind study by Schiff et al. [27] compared the safety and clinical efficacy of 4 different IVIG preparations (Gammagard, Intraglobin-F, Gamimune-N, and Sandoglobulin) and found no adverse reactions in 24 infusions of Gammagard S/D. The 2008 observational study by Manlhiot et al. [26] compared 4 different IVIG products (Iveegam, Gammagard S/D, Gamimune 5%, and Gamimune 10%) in juvenile dermatomyositis patients, assessing differences in tolerance. In the 38 patients with a median age of 10 years, Gammagard S/D was associated with the lowest frequency of adverse events likely due to having the lowest IgA concentration. In this study, the osmolality, sodium content, and preparation concentration did not affect tolerance.

Gamunex 10%

Gamunex 10%, manufactured by Grifols Therapeutics Inc., became available in 2003 and is manufactured through caprylate/chromatography. FDA-approved indications are PID and idiopathic thrombocytopenic purpura (ITP).

Method of Production

Caprylate, the salt form of caprylic acid, is the enveloped virus-inactivating agent [28]. When the lipophilic nonionized form of caprylate partitions into the viral lipid membrane, enveloped virus inactivation occurs. The rapid inactivation kinetics leads to a decreased processing time. In contrast to S/D, which requires the removal of

the mixture before the finalization of the IVIG product, caprylate processing requires no such step. Thus, caprylate yields 10% more product [29–31]. Korneyeva et al. [29] illustrated an efficacy of caprylate inactivation similar to that in IVIG processed via S/D [30, 32]. The secondary purification steps involve tandem anion exchange chromatography. Ultrafiltration with pH and temperature modification follows. Incubation at a low pH serves as a second viral inactivation step [31].

Ingredients/Properties

Gamunex is a 10% liquid ready-to-use IVIG preparation with no sugar content and trace sodium. It contains glycine [6, 33] and has an osmolality of 258 mosm/kg. Its pH range is comparatively low at 4.0–4.5, thus preventing IgG aggregation [6, 8, 23]. It contains over 98% IgG, 46 µg/ml IgA, and <20 µg/ml albumin.

Adverse Effects

The adverse effect profile reported with Gamunex has been consistent with that of other IVIGs [30, 32]. In 2003, a double-blind multicenter trial randomized 172 subjects to receive Gamunex or Gamimune. The incidence of adverse events for Gamunex was 5.7% in comparison with 5.5% with Gamimune. The majority of events were mild and controlled by infusion rate reduction [32]. Headaches were the most common adverse event. Hughes et al. [34] found similar results in the treatment of CIDP. Among the 59 patients treated with Gamunex, the incidence of serious adverse events per infusion was 0.8% as compared with 1.9% with placebo.

Comparative Studies

Numerous studies proved the equality in efficacy, pharmacokinetics, and safety of caprylate-processed Gamunex to Gamimune. Lebing et al. [31] demonstrated several molecular advantages in the newer product. With 70% less processing time and 50% more IgG, Gamunex was shown to be more purified with lower IgA, IgM, and albumin levels.

A randomized double-blind multicenter study over 9 months compared the efficacy, safety, and toxicity of Gamunex with those of Gamimune [32]. With 172 patients enrolled, the Gamunex arm showed significantly less acute sinusitis, pneumonia, and chronic sinusitis than the Gamimune arm. No serious infections were reported with either product. The frequency and severity of drug-related adverse events were equal. A pharmacokinetic study demonstrated equal postinfusion IgG concentrations [30]. Gammaglobulin subclass stability was

found to be higher in Gamunex, and it had higher mean postinfusion levels of IgG₂ and IgG₄.

Disease-specific benefits have also been studied with Gamunex. A 2004 randomized double-blind multicenter trial compared Gamunex and Gamimune in the treatment of ITP [35]. Gamunex was as efficacious as Gamimune in increasing and maintaining the platelet count. Ninety percent of the patients treated with Gamunex and 83% of the patients treated with Gamimune had their platelet counts increased to the goal level. In addition, fewer patients treated with Gamunex required corticosteroids for symptom management beyond day 7. The incidence of adverse events was equivalent between the two products.

Carimune NF

Carimune NF (nanofiltered), also known as Sandoglobulin NF and Redimune NF, is a lyophilized preparation with available concentrations of 3, 6, and 12%. The 12% concentration is higher than any other IV preparation in the USA. The liquid preparation is not available in the USA. It is manufactured by CSL Behring and received FDA approval in 2003.

Method of Production

The clearance of enveloped/nonenveloped viruses involves six manufacturing steps: cold ethanol fractionation, depth filtration, nanofiltration, pH 4/pepsin incubation, batch absorption to DEAE-Sephadex, and aluminum hydroxide [36, 37]. Nanofiltration also removes transmissible spongiform encephalopathy agents [38].

Ingredients/Properties

After the viral elimination steps are completed, sucrose is added to reduce IgG aggregate formation. IVIG products containing sucrose as a stabilizer have been noted by the CDC to account for a disproportionate share, 90%, of total reports [20, 23, 39]. The preparation contains at least 96% of IgG and, after reconstitution with a neutral unbuffered diluent, has a pH of 6.6. It contains an IgA concentration of 720 µg/ml, the highest of all the IVIGs. Final container lyophilized units are prepared so as to contain 3, 6, or 12 g protein with 1.67 g sucrose and less than 20 mg NaCl per gram of protein. The lyophilized preparation contains no preservative and may be reconstituted with sterile water, 5% dextrose, or 0.9% saline. The osmolarity of the 12% solution reconstituted in normal saline is 1,074 mosm/l, whereas it is 690 mosm/l for the 6% solution and 498 mosm/l for the 3% solution. The osmolarities are lower if reconstituted in dextrose and lowest if reconstituted in sterile water [40].

Adverse Effects

The tolerability and pharmacokinetics of Sandoglobulin, Sandoglobulin NF, and Sandoglobulin liquid were examined by Andresen et al. [41] in a randomized double-blind parallel-group study in 30 subjects. Over a 6-week period, approximately half of the subjects in the Sandoglobulin and Sandoglobulin liquid cohorts reported 1 or more adverse events, as compared with only 1 subject who received Sandoglobulin NF. Half (16/29 or 55%) of these events were mild-to-moderate headache, with the remainder being dizziness, sweating, weakness, and chills. All three products generally demonstrated good tolerability with no evidence of immunogenicity or viral transmission.

Comparative Studies

Lamari et al. [42] compared different IgG subclass and specific antibody levels in patients treated with Sandoglobulin NF and Gamimune using an ELISA assay. All the 10 male patients enrolled received Sandoglobulin and Gamimune in alternate months. Immunoglobulin classes and IgG subclasses were analyzed in the patients 30 days after IVIG administration. While the IgG level was comparable between both preparations, the IgG subclass levels differed. Sandoglobulin had significantly higher levels of IgG₂ and IgG₄, whereas Gamimune had higher levels of IgG₁. The most notable difference was that IgG₄ levels were significantly lower in patients who received Gamimune than in patients who received Sandoglobulin. The protective antibody against specific bacteria was determined as well. Sandoglobulin treatment results in higher antibody levels to *Escherichia coli* isolates and *Staphylococcus epidermidis* in patients than Gamimune treatment. Gamimune is noted to have higher amounts of *Enterococci* species-specific antibodies. Both IVIG preparations had comparable specific antibody levels to *Klebsiella pneumoniae* and *S. aureus*. During the study period, both IVIGs were well tolerated, and no adverse reactions were observed.

Flebogamma 5%

Flebogamma 5%, a liquid IVIG, has been marketed by Grifols Therapeutics Inc. for more than 15 years in more than 30 countries and gained FDA approval in the USA in 2003.

Method of Production (Including Viral Inactivation/Removal)

Pasteurization at 60°C for 10 h is used for viral inactivation, effectively inactivating both enveloped and non-enveloped viruses [43]. An additional polyethylene glycol precipitation step is used for further impurity elimina-

tion. Another formulation, Flebogamma 5% DIF, was recently approved by the FDA and shares identical biochemical and stability profiles with Flebogamma 5% with additional viral elimination steps. This formulation will not be incorporated in this review.

Ingredients/Properties

Flebogamma 5% contains >99% IgG and only trace amounts of IgA. Stabilizers are <3 mg/ml polyethylene glycol and 50 mg/ml of D-sorbitol. There are no preservatives, and it is free from sucrose and maltose. It contains <3.2 mEq/l of sodium chloride and 2 µg/ml of albumin. Its osmolality is in the physiologic range.

Adverse Effects

The safety, efficacy, and pharmacokinetics of Flebogamma 5% were investigated by Berger et al. [43] in patients with PID. The 51 patients enrolled in the study received a total of 702 infusions of Flebogamma over 12 months; 96% of the patients experienced adverse events throughout the 12 months, with the most adverse events being mild to moderate. The most common adverse events related to Flebogamma were pyrexia (18%), headache (16%), rigors (8%), and injection site reaction (8%). There were 2 serious infection episodes that were thought to be related to Flebogamma.

In 2005, Sarmiento et al. [44] investigated the use of IVIG in heart-transplanted patients with secondary hypogammaglobulinemia from immunosuppressive therapy and CMV disease. In addition to antiviral therapy, Flebogamma 5% was administered every 21 days to 5 heart-transplanted patients with relapsing CMV gastrointestinal disease. In addition to a favorable clinical response, there were no immediate or delayed adverse events observed during the therapy with Flebogamma 5%.

Comparative Studies

To date, there have been no comparative human studies using Flebogamma 5%.

Octagam

Octagam is a liquid ready-to-use S/D-treated IVIG that was first approved for use in patients with PID in Europe in 1995 and received FDA approval in 2004. It is manufactured by Octapharma USA Inc. Its FDA-approved indication is for PID as well.

Method of Production

Octagam is manufactured by the Cohn-Oncley cold alcohol fractionation process, S/D viral inactivation, and

incubation at a low pH of 4.0 for 24 h for further viral inactivation. The purification process has two ultrafiltration steps.

Ingredients/Properties

In the USA, Octagam is available as 5 and 10% liquid human immunoglobulin preparations. When liquid, it has an osmolality of 310–380 mosm/kg. It contains >96% IgG, <200 µg/ml IgA, and <100 µg/ml IgM. It also contains 100 mg/ml of maltose and <30 mmol/l of sodium.

Adverse Effects

In August 2010, Octapharma initiated a voluntary market withdrawal of selected lots of Octagam 5% due to an increased number of reported thromboembolic events. A total of 31 lots were voluntarily withdrawn at that time [45].

Octagam was studied for minimal efficacy requirements in PID subjects [46]. Forty-six subjects with PID received a total of 654 infusions. Headache was the most common adverse event. No serious adverse events were noted. Its clinical efficacy has been further validated [47]. During a 24-month period, Octagam infusion was followed in 54 leukemia, myeloma, ITP, and antiphospholipid syndrome patients. IgG levels were stable in patients with multiple myeloma and chronic lymphocytic leukemia. HIV as well as hepatitis B and C viral safety assays were all negative.

To date, one of the largest prospective studies on IVIG evaluated the tolerability and safety of Octagam [48]. Commencing in 1995, data were collected over 10 years in 310 study sites. A total of 6,357 patients were enrolled in the study. Patients with various PIDs, secondary immunodeficiencies, and autoimmune diseases were included. Adverse events were recorded in 4.2% of the cases. The majority of the events were mild (55.9%) or moderate (34.3%). Rigors were the most common adverse event (0.12% of all infusions), followed by fever, headache, nausea, and flushing symptoms. Three serious cases of aseptic meningitis were observed. The patients tolerated preceding or subsequent infusions with Octagam without problems. One case of cerebrovascular hemiplegia in a 71-year-old man with ITP was noted. Two multiple sclerosis patients suffered eczema with palmar papulous eruptions.

Comparative Studies

Limited comparative human studies exist on Octagam. Pichyangkul et al. [49] studied IVIG preparations including Octagam specifically against strains of influenza A and avian flu viruses. All three IVIGs were effica-

cious in reducing measures indicative of virus replication. In 2006, Zhang et al. [50] used an immune neuropathy experimental model to investigate the efficacy of different IVIGs. Octagam was compared with 7 other IVIG brands in terms of its protective efficacy in autoimmune nerve injury. The study found a similar protective efficacy among all the 8 IVIGs studied.

Gammagard Liquid 10%

Gammagard Liquid 10% became FDA approved in 2005 for PID. It is developed by Baxter Healthcare Corporation. This sugar-free glycine-stabilized formulation is a ready-to-use IVIG [51].

Method of Production

Three dedicated virus inactivation/removal steps are incorporated into the manufacturing process. S/D treatment inactivates lipid-enveloped viruses to below the limits of detection. The 35-nm nanofiltration removes all viruses >35 nm, including parvovirus B19 and hepatitis A virus. The low-pH treatment (4.0–5.0) at elevated temperature provides further virus inactivation via lipid-enveloped and nonenveloped inactivation [51, 52].

Ingredients/Properties

Gammagard Liquid 10% contains no sugar, sodium, or preservatives [8, 51]. Its near-physiologic osmolality ranges from 240 to 300 mosm/kg. Glycine stabilizes the solution. The IgA content is 37 µg/ml with a 98% IgG concentration. Generally, 10% IVIGs such as Gammagard Liquid demonstrate concentration-based benefits at a low pH, including a decreased IgG dimerization during storage. Due to this, sodium is not added and carbohydrate stabilizers are not required; 10% IVIGs maintain higher concentrations, allowing increased infusion rates (maximum of 8 ml/kg/h) with lower volumes [5, 53].

Adverse Effects

Initial studies conducted on murine anaphylactoid models by Teschner et al. [52] demonstrated a high safety margin. Bjorkander et al. [51] portrayed similar safety and efficacy results in human clinical studies. While receiving Gammagard Liquid 10%, the rate of mild infection episodes per subject ranged from 0 to 1.42 per month. No severe adverse events occurred. Urticaria (in 1 of 22 subjects), headache, and fever/pyrexia were reported adverse events.

A phase III multicenter study evaluated the efficacy, pharmacokinetics, and safety of Gammagard Liquid in PID patients [54]. Sixty-one subjects were enrolled, and they received in 826 infusions over 12 months. Nearly 1% reported headache followed by fatigue, pyrexia, rigors, and migraine. No serious viral transmission from administration was detected. Aseptic meningitis documented twice in the same subject remained the most significant adverse event.

Comparative Studies

Teschner et al. [52] compared the efficacy and safety of Gammagard Liquid 10% with those of Gammagard S/D in animal models. Three murine intervention arms included treatment with Gammagard Liquid 10%, Gammagard S/D, or human albumin as a negative control. The mice were then challenged with dilutions of *K. pneumoniae* or *Streptococcus pneumoniae*. The survival rates of both products were similar. The opsonic activity of Gammagard Liquid 10% against *E. coli* or *S. agalactiae* was also found to be similar.

Gammagard Liquid 10% had efficacy and safety profiles similar to those of Gammagard S/D [51]. One study showed 22 subjects with PID receiving both types of product, Gammagard S/D initially for 3 weeks, to standardize their therapy to the same IV product, and then Gammagard Liquid 10% 3 weeks later. The efficacy of Gammagard Liquid was shown to be no less than that of Gammagard S/D with a similar postinfusion infection rate. No product-related serious adverse events were noted.

One head-to-head study revealed differences between a 10% IVIG ready-to-use solution and a 6% IVIG lyophilized product [53]. The solution had a 44% faster infusion rate and 51% decreased infusion time than the lyophilized product. Drug-related adverse events also varied between the products. Three patients in either IVIG arm suffered 7 and 20 minor adverse events with the solution and the lyophilized product, respectively.

Privigen

Privigen is manufactured by CSL Behring and received FDA approval in 2007. It is a ready-to-use 10% liquid immunoglobulin.

Method of Production

Privigen is purified by a combination of cold ethanol fractionation which isolates crude immunoglobulin fractions. Octanoic acid precipitation purifies the immunoglobulins, and anion exchange chromatography removes the non-IgG immunoglobulins and polishes the IgG fraction

[55, 56]. These steps eventually lead to 99% IgG purity. Two viral clearance steps include pH 4 incubation and nanofiltration. Virus inactivation, virus filtration, and partitioning (depth filtration with filter aids) are three different mechanisms of virus clearance used. Even the potential for prion elimination and the capacity for virus reduction by virus filtration and partitioning steps have been studied [57]. Several different detection methods demonstrated the efficient prion elimination. Virus validation studies showed a significant reduction of enveloped and nonenveloped viruses.

Ingredients/Properties

Privigen is the first, and currently the only, immunoglobulin stabilized with natural amphiphilic amino acid L-proline (250 mmol/l) [55, 56]. The formulation minimizes the formation of IgG degradation, aggregation, and denaturation. Its unique feature is its enhanced long-term stability at room temperature up to 36 months [55, 56, 58]. The minimization of IgG dimer formation is important, given the improved clinical tolerance observed with a reduced IgG dimer formation [56, 58]. It has an IgG content of 99.2% with trace IgA concentrations (<25 µg/ml). It contains no preservative, trace albumin, and trace sodium content (<1 mmol/l), and it has an osmolality of 320 ± 9 mosm/kg [58].

Adverse Effects

In 2009, Stein et al. [56] evaluated Privigen in 72 adults and children with PID. All patients received Privigen at 3- or 4-week intervals over a 12-month period, totaling 1,038 infusions. The primary endpoint was acute serious bacterial infectious episodes. The annual rate of acute serious bacterial infections was 0.08%. Headache, fatigue, and nausea were the most commonly reported temporally associated adverse events in 43.8, 16.3, and 12.5% of the patients, respectively. While the majority of adverse events observed were mild, 16 patients (20%) experienced 38 serious adverse events. The serious adverse events included pneumonia, septic arthritis, and hypersensitivity reaction. This study's reported annual rate of any infection was consistent with annual infection rates found in other published reports [32, 46, 54].

An open-label multicenter study by Robak et al. [58] evaluated the efficacy and safety of Privigen in 57 adolescent and adult patients with chronic ITP. The majority of the adverse events were mild or moderate, with 52 of the 57 patients (91.2%) having experienced at least 1 adverse event. The most common adverse event was headache (67%), while others included epistaxis (19%), contusion (18%), petechiae (12%), anemia (11%), skin hemorrhage (11%), and vomiting (11%). There were 3 serious adverse

events: vascular dizziness, acute hearing loss, and aseptic meningitis. However, only the case of aseptic meningitis was considered to be drug related.

Comparative Studies

The comparative complement-inhibitory capacities of different IVIG products were investigated via in vitro assay by Spycher et al. [59]. Privigen was one of 7 IVIG products studied. Complement inhibition or 'scavenging' was measured by reduced C3 binding and fluid-phase C3-IgG complex formation. Compared with the other IVIG preparations, Privigen demonstrated a significantly higher complement system inhibition.

A study by Kahwaji et al. [60] in 2009 evaluated the incidence of IVIG-induced hemolytic anemia in end-stage renal disease patients receiving Privigen, Gamunex, or Gammagard Liquid and 2 other lyophilized IVIG preparations for desensitization or treatment of antibody-mediated rejection. All the 18 cases of IVIG-induced hemolytic anemia observed were in patients who had received a liquid nonlyophilized product. The authors postulated the products with the highest titers of isohemagglutinin were implicated.

Gammaplex 5%

Gammaplex 5% is a ready-to-use liquid IVIG preparation that obtained FDA approval in 2009. It is manufactured by Bio Products Laboratory [61].

Method of Production (Including Viral Inactivation/Removal)

Cold ethanol fractionation is used to isolate the IgG-rich fraction II precipitate, and this precipitate is then purified to approximately 100% IgG, using ion exchange chromatography to remove impurities. The three virus inactivation steps used are S/D, 20-nm virus filtration, and terminal low-pH incubation [61].

Ingredients/Properties

Gammaplex contains 5 g human normal immunoglobulin and 5 g D-sorbitol in 100 ml buffer solution containing 0.6 g glycine, 0.2 g sodium acetate, 0.3 g sodium chloride, and approximately 5 mg polysorbate 80. The pH is slightly acidic (4.8–5.1) for improved stability and to provide additional virus inactivation during incubation. It has an osmolality of 420–500 mosm/kg and has an IgG purity of 95%, with the distribution of the four IgG subclasses being approximately 64% IgG₁, 30% IgG₂, 5% IgG₃, and 1% IgG₄. The content of IgA is <10 µg/ml. It contains no reducing carbohydrate stabilizers and no preservative [61, 62].

Adverse Effects

Moy et al. [62] conducted a phase III multicenter open-label study of Gammalex on 50 subjects with PID to evaluate its safety profile and efficacy. Twenty-two subjects were treated with Gammalex for 12 months at a 21-day dosing interval, and 28 subjects were treated for 12 months at a 28-day dosing interval. The subjects' mean age was 44 years. The most common adverse reaction was headache (36.0%), followed by fatigue (12.0%), nausea (12.0%), pyrexia (12.0%), hypertension (6.0%), myalgia (6.0%), pain (6.0%), and vomiting (6.0%). One subject with antiphospholipid syndrome was hospitalized because of thrombosis and chest pain possibly related to Gammalex.

Comparative Studies

No comparative studies have been published to date.

Gammaked 10%

Gammaked 10% is a ready-to-use liquid immunoglobulin preparation manufactured by Grifols Therapeutics Inc. that was FDA approved for IV and subcutaneous (PID only) administration in 2011.

Method of Production (Including Viral Inactivation/Removal)

Gammaked is manufactured by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion exchange chromatography. It is incubated at a low pH of 4.0–4.3 for further viral inactivation. Caprylate, the salt form of caprylic acid, is the enveloped virus-inactivating agent [63].

Ingredients/Properties

Gammaked is a 10% liquid ready-to-use IVIG with no sugar content. Isotonicity is achieved by the addition of glycine. It consists of 9–11% protein in 0.16–0.24 mol/l of glycine. It has an IgG purity of >98% with a sub-class distribution of IgG₁, IgG₂, IgG₃, and IgG₄ of approximately 62.8, 29.7, 4.8, and 2.7%, respectively. It contains trace levels of IgA (an average of 0.046 mg/ml). The osmolality is 258 mosm/kg solvent, which is close to the physiologic osmolality (285–295 mosm/kg), and it has a pH of 4.0–4.5 [63].

Adverse Effects

The most common adverse reactions observed in subjects treated for PID were infusion site reactions, headache, fatigue, arthralgia, and pyrexia. In subjects treated for ITP, the most common adverse reactions were headache, vomiting, fever, nausea, back pain, and rash, and in

those treated for CIDP, the most common adverse reactions were headache, fever, chills, hypertension, rash, nausea, and asthenia [63].

Out of 157 subjects treated with Gammaked in four different clinical trials, 4 subjects discontinued due to Coombs-negative hypochromic anemia, autoimmune pure red cell aplasia, arthralgia, hyperhidrosis, fatigue, myalgia, nausea, and migraine [63].

Comparative Studies

No comparative studies have been published to date.

Bivigam 10%

Bivigam is a sugar-free glycine-stabilized IVIG that was approved by the FDA in December 2012. It is manufactured by Biotest Pharmaceuticals.

Method of Production (Including Viral Inactivation/Removal)

Bivigam is produced by Cohn-Oncley fractionation followed by ion exchange chromatography. Cold ethanol fractionation, S/D inactivation, and nanofiltration are incorporated into the manufacturing process [64].

Ingredients/Properties

Bivigam contains 0.100–0.140 mol/l of sodium chloride, 0.20–0.29 mol/l of glycine, and 0.15–0.25% polysorbate 80 at a low pH of 4.0–4.6. The IgG monomer plus dimer content is >95%, and it contains ≤200 µg/ml of IgA [64].

Adverse Effects

An open-label phase III safety, efficacy, and pharmacokinetic study of 63 patients with PID found the most frequent (>20%) reported adverse event to be headache (50.8%). This was followed by sinusitis (38.1%), fatigue (28.6%), upper respiratory tract infection (25.4%), cough (22.2%), pharyngolaryngeal pain, and diarrhea (both 20.6%) [64].

Comparative Studies

No comparative studies have been published to date.

SCIG Therapy

In the late 1970s, SCIG administration had failed in Europe primarily due to prolonged infusion rates [4, 65]. In the past 2 decades, this subcutaneous route of immunoglobulin therapy has become increasingly popular,

since rapid SCIG infusion was developed in 1991 and shown to be safe [3, 66, 67].

Some of the demonstrated benefits of SCIG are the low risk of adverse systemic reactions and the improved quality of life [66, 68, 69]. Several studies have shown SCIG and IVIG to be equally efficacious in preventing infections in patients with PID [70, 71]. The efficacy and safety of SCIG therapy was compared with that of IVIG therapy in a randomized cross-over study, and no significant differences in efficacy or adverse reactions were found [65]. In addition, SCIG and IVIG therapy achieved comparably high serum IgG trough levels. In one of the largest studies of SCIG including 51 patients over 12 months, Ochs et al. [70] reported 0.04 serious infections and 4.4 nonserious infections per patient per year. These results are comparable to the overall mean of 0.068 serious and 3.02 nonserious infections per year in the licensing trials of all IVIG preparations in the USA [71]. A statistically significant difference between the efficacy of SCIG and that of IVIG was shown in a 2009. A small pilot study evaluated the efficacy and tolerability of Gamunex given at the same dosage subcutaneously and intravenously [72]. While both the subcutaneous and the IV preparations demonstrated an acceptable efficacy, SCIG was associated with 26 infection episodes as compared with 18 with IVIG.

While IVIG is usually administered every 3–4 weeks, SCIG is most often given weekly [9, 71]. One recent study on SCIG pharmacokinetics potentially demonstrated the administration every other week to be safe and effective in achieving high serum IgG trough levels [71, 73]. The systemic absorption of IgG is slower by the subcutaneous route than by IV injection. IV injection raises the serum IgG level rapidly, with the peak decreasing by 48 h. In contrast, more steady-state levels of IgG are seen with SCIG [71]. This difference may explain the significant decrease in systemic adverse events in patients switching from IV to subcutaneous IgG treatment [74, 75]. Systemic adverse events have been less commonly reported with SCIG than with IVIG, and their rate ranges from 0 to 3.3% [75]. Chapel et al. [65] reported a 3.3% systemic adverse event rate with SCIG as compared with 5% with IVIG in a randomized study in 40 subjects. Most SCIG patients experience a local reaction ranging from swelling, redness, and itching to a burning sensation at the site of injection [71]. However, most studies report a decreasing incidence over several months with continued SCIG therapy [70, 72]. SCIG has also demonstrated better tolerance in IgA-deficient patients with antibodies against IgA. No cases of anaphylaxis due to SCIG injection have been reported [71, 76].

Table 3. Important IVIG characteristics corresponding to patient risk factors

	Sodium content	Volume load	Sugar content	Osmolality	pH	IgA
Neonates/children	x	x		x		x
Elderly (>60 years)	x	x	x	x		
Cardiac impairment	x	x		x		
Renal dysfunction	x	x	x	x		
Diabetes			x			
Vascular disease	x	x		x		
Thromboembolic risk	x	x		x		
Anti-IgA antibodies						x

Cardiac impairment: history of myocardial infarction, congestive heart failure, or decreased ejection fraction. Renal dysfunction: creatinine ≥ 1.5 mg/dl. Thromboembolic risk: history of thromboembolic disease, myocardial infarction, or stroke. Diabetes: type 1 or 2 or prediabetic. Vascular disease: prior history of stroke, myocardial infarction, or peripheral vascular disease.

Health-related quality-of-life analyses have compared SCIG and IVIG. Most SCIG studies demonstrate a significant improvement in health-related quality of life in patients who had previously been on IVIG [68, 69, 77]. In 2004, Gardulf et al. [68] demonstrated an increase in treatment satisfaction and an improvement in ‘mental health’ and ‘social functioning’ in patients receiving SCIG infusions at home who had previously been on IVIG. Of note, although SCIG may be preferred by a number of patients, it is not the best choice for every patient [71].

In 2006, the first FDA-approved SCIG, Vivaglobin, was introduced to the US market, and in 2011, it was discontinued in the USA [75]. Currently, there are 4 approved SCIG products: Gamunex-C 10%, Gammagard Liquid 10%, Hizentra 20%, and Gammaked 10% [78]. Gamunex-C 10%, Gammagard Liquid 10%, and Gammaked 10% were initially approved for IV use and subsequently obtained approval for subcutaneous use in PID patients. Gamunex-C 10% was approved for subcutaneous administration in 2010 and Gammagard Liquid 10% in 2011; Gammaked 10% was approved for IV and subcutaneous administration in 2011. For their specific properties, refer to each specific product as listed in the section entitled Specific IVIG Products.

Hizentra 20% is the only 20% ready-to-use immunoglobulin preparation approved for subcutaneous administration [79]. It received FDA approval for the treatment of PID in 2010. It has >98% IgG purity, <50 μ g/ml of IgA, and a pH of 4.6–5.2. It contains 250 mmol/l of L-proline

Table 4. Comparison of characteristics of specific IVIG products

	IgG yield	Infusion rate	IgG dimerization	Sodium content	Room temperature stability	IgA content
Gammagard S/D	++	++	++++	+++	+++	+
Gamunex 10%	+++	+++	+	+	++	++
Carimune NF	++	+	++++	++	+++	++++
Flebogamma 5%	++++	++++	++	++	+++	+
Octagam	++	++	++	++	+++	+++
Gammagard Liquid 10%	+++	++++	++	0	++	++
Privigen	++++	++	+	+	+++	++
Gammaplex 5%	+++	+++	+	++	+++	+
Gammaked 10%	++++	+++	+	+	+++	++
Bivigam 10%	++++	+	+	+++	+++	+++

0 = None; + = low; ++ = medium; +++ = high; ++++ = highest.

as a stabilizer, as compared with glycine, which is used as a stabilizer in the other immunoglobulin products approved for subcutaneous administration. It also contains 10–30 mg/l of polysorbate 80 and trace amounts of sodium. It does not contain carbohydrate stabilizers or preservatives.

A three-step virus inactivation method is used: pH 4 incubation is used to inactivate enveloped viruses, virus filtration is used to remove (by size exclusion) both enveloped and nonenveloped viruses, and a depth filtration step further contributes to the virus reduction. To date, no journal articles have been found comparing the different subcutaneous immunoglobulin products.

Clinical Considerations for the Clinician when Using IVIG Products

The differences in composition and concentration between the IVIG products affect patient tolerability and should be considered when selecting an IVIG preparation. These characteristics include volume load, sodium content, sugar content, osmolality, pH, and IgA content (table 3 [33], 4).

Volume Load

In patients who are unable to tolerate large fluid volumes or long infusion times – such as those with compromised cardiac or renal function, the elderly, or neonates – the total volume load is a clinical consideration. For such patients, the possibility of delivering higher

amounts of IgG in lower volumes is essential. Clinical consideration should be given to avoiding increases in solution osmolality due to reduced volume, as there are associated adverse events [23, 39].

Osmolality

Hyperosmolar solutions can lead to significant adverse events when administered intravenously, as they may cause fluid shifts leading to hemodynamic changes, thromboembolic incidents, or renal complications [23]. The major contributors to osmolality in IVIG solutions include sodium, sugars, and other solutes or proteins such as albumin that may be present. While the physiologic osmolality is 280–296 mosm/kg of water, among the available IVIG products, the osmolality varies widely, ranging from the physiologic osmolality to >1,000 mosm [39]. In general, sugar-stabilized products tend to have higher osmolalities than sugar-free (glycine) preparations.

Sugar Content

To prevent or reduce IgG aggregate formation, sugars such as sorbitol, glucose, and sucrose are added to some IVIG preparations. IVIG preparations which are not stabilized with sugar are stabilized with glycine [20]. The concentration of sugar affects the osmolality of the solution. Sugar content is associated with increased significant adverse events. The most commonly associated adverse events are acute renal failure, renal insufficiency, and osmotic nephrosis [39]. IVIG products containing sucrose as a stabilizer have been

noted by the CDC to account for a disproportionate share (90%) of the total reports, while 8% of the reports were associated with glucose/maltose-containing preparations [20, 23, 39]. In patients predisposed to renal failure, lower osmolar concentrations or a sugar-free IVIG product, such as Gamunex, may be preferred [20].

Sodium Content

In addition to sugar content, another significant osmolar agent of IVIG solutions is sodium content. The sodium content of available IVIG products varies from trace amounts to 0.9%. When lyophilized preparations are reconstituted to higher concentrations in order to reduce the volume load, it may likely increase the sodium concentrations and osmolarity to risky levels. This is particularly challenging in patients with hypertension, renal impairment, and heart failure [20].

pH

The stability of an IVIG preparation is profoundly affected by its pH. Most available IVIG products have a final pH close to neutral (6.0–7.5) in order to reduce local injection site reactions [39]. However, the optimal pH is 4.0–4.5 to prevent IgG aggregation and maintain the IgG monomer content. Therefore, IVIG formulations at the physiologic pH require the addition of stabilizing agents to maintain IgG stability, and the addition of these stabilizers has been linked to significant adverse events [39]. IVIG preparations stabilized with a low pH during production do not require stabilizers and have maximized monomer content. It has also been

shown that the acid load of the low-pH products are rapidly neutralized after infusion by the bicarbonate/protein buffer system in the blood and therefore tolerated by neonates and patients with renal dysfunction [39].

IgA Content

All IVIG preparations contain a small amount of IgA. Therefore, most IVIG products are contraindicated in patients with IgA deficiency who have antibodies against IgA, which may lead to anaphylactic shock after administration. Since reactions to IgA are rare, the NIH consensus conference on IVIG did not recommend screening patients who receive IVIG for anti-IgA antibodies. There are no clear thresholds for safety with respect to IgA as the maximum tolerable amount is not known [33].

Conclusion

This review aimed to provide a clear description to the clinician of how different IVIG products are manufactured. In particular, the focus was placed on molecular and clinical studies which determined the efficacy of different products. Product selection is becoming more imperative as immunoglobulin processing and composition have diversified and therefore have the potential to affect clinical outcomes such as tolerability, safety, and efficacy. Clinical guidelines should consider the medical history of patients when using particular IVIG products, especially in regard to their hemodynamics as well as renal and cardiovascular status.

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