ELSEVIER

International Immunopharmacology 3 (2003) 1325–1333

International Immunopharmacology

www.elsevier.com/locate/intimp

Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency☆ A randomized double-blind trial

Chaim M. Roifman[a,*], Harry Schroeder[b], Melvin Berger[c], Ricardo Sorensen[d], Mark Ballow[e], Rebecca H. Buckley[f], Anita Gewurz[g], Phillip Korenblat[h], Gordon Sussman[i], Georg Lemm[j] and the IGIV-C in PID Study Group[1]

[a] *Division of Immunology/Allergy, Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada M5G 1X8*
[b] *University of Alabama, Birmingham, AL, USA*
[c] *University Hospitals of Cleveland, Cleveland, OH, USA*
[d] *LSU Health Sciences Center, New Orleans, LA, USA*
[e] *Children's Hospital of Buffalo, Buffalo, NY, USA*
[f] *Duke University Medical Center, Durham, NC, USA*
[g] *Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, USA*
[h] *The Clinical Research Center, LLC, St. Louis, MO, USA*
[i] *The Wellesley Central Hospital, Toronto, ON, Canada*
[j] *Bayer Healthcare, Biological Products Division, Research Triangle Park, NC, USA*

Received 5 May 2003; received in revised form 12 May 2003; accepted 20 May 2003

Abstract

A novel method of large-scale chromatography has been developed to improve recovery and purity of immunoglobulin G (IgG) from pooled plasma. The current study compares safety, toxicity and efficacy of two intravenous immunoglobulin products: a novel formulation, IGIV caprylate/chromatography (IGIV-C; Gamunex™, 10%) and a licensed solvent/detergent-treated product, Gamimune®N, 10% (IGIV-SD). The study, a randomized, double-blind, parallel group, therapeutic equivalence

☆ This study (Identifier 100175) was funded by Bayer Healthcare, Biological Products Division, Research Triangle Park, NC, as part of the clinical development of Gamunex™, 10%.

* Corresponding author. Tel.: +1-416-813-8623; fax: +1-416-813-8624.
E-mail address: croifman@sickkids.on.ca (C.M. Roifman).

[1] The IGIV-C in PID Study Group includes Mark Stein, MD, Allergy Associates of the Palm Beaches, North Palm Beach, FL; Donald Stark, MD, Vancouver, BC; Maria Louisa Ermitano, LSU Health Sciences Center, New Orleans, LA; Anne Desroches, MD, Hopital Ste. Justine, Montreal, Quebec; Bruce Mazer, MD, Montreal Children's Hospital, Quebec; Joseph Church, MD, Children's Hospital of Los Angeles, CA; Zuhair Ballas, MD, University of Iowa Hospitals and Clinics, Iowa City, IA; Alexandra Filipovich, MD, Children's Hospital Medical Center, Cincinnati, OH; Gilbert Friday, MD, Children's Hospital of Pittsburgh, PA; Donatella Graffino, MD, Asthma, Allergy and Sinus Center of New Jersey, Morristown, NJ; Melvin Haysman, MD, Allergy Research of Savannah, GA; Alan Knutsen, MD, St. Louis University Health Sciences Center, St. Louis, MO; Wendel Richmond, MD, Oakbrook, IL; Arye Rubinstein, MD, Albert Einstein College of Medicine, Bronx, NY; Frederick Marquinez, MD, Mogadore, OH; Don McNeil, MD, Columbus, OH; Suzanne Skoda-Smith, MD, University of Florida, Gainesville, FL.

1567-5769/03/$ - see front matter
doi:10.1016/S1567-5769(03)00134-6

trial, was conducted at 25 treatment centers in Canada and the United States. Patients ($n=172$) having confirmed chronic primary immunodeficiency (PID), aged 1–75 years, and receiving IGIV therapy were enrolled. For 9 months, patients were treated with IGIV-C or IGIV-SD in accordance with the patient's individualized treatment regimen utilized before study entry. The primary endpoint was the proportion of patients with ≥ 1 validated acute sinopulmonary infection during the treatment period. Secondary endpoints included the proportion of patients with all infections, time to first infection, annual infection rates, lung function parameters, infusion-related safety and viral safety. The annual validated infection rate in the IGIV-C group was 0.18 compared to 0.43 in the IGIV-SD group ($p=0.023$). Nine patients receiving IGIV-C experienced validated infections, compared to 17 patients in IGIV-SD group ($p=0.06$). Acute sinusitis (validated plus clinically defined) was less frequent in the IGIV-C group ($p=0.012$). Presence of bronchiectasis did not affect efficacy. Adverse reactions were similar in frequency and severity in both groups. No evidence of viral transmission was observed. IGIV-C appears to be superior to IGIV-SD in preventing validated sinopulmonary infections, especially acute sinusitis, in patients with PID.

Keywords: IgG; IGIV; Immunoglobulin; Immunotherapy; IVIG; Primary immunodeficiency; Sinopulmonary infection; Sinusitis; Viral safety

1. Introduction

Immunoglobulin G (IgG) has been traditionally manufactured from pooled plasma for replacement therapy in patients with primary immunodeficiency (PID). Advances in preparation of IgG suitable for intravenous infusions (IGIV) permitted delivery of larger doses, which resulted in improved protection from infection [1]. A novel method of large-scale chromatography, which uses caprylate for purification and viral inactivation, has recently been developed to improve the recovery and purity of IgG from pooled plasma [2–4]. The intravenous immunoglobulin product resulting from this novel preparation has been named IGIV-C (Gamunex™, 10%).

Although IGIV has been manufactured using different methods, it is widely assumed that all IGIV preparations are similar. However, the efficacy and toxicity of different IGIV preparations have previously never been compared directly. This prospective, randomized, double-blind, controlled and statistically powered study compares for the first time the safety, toxicity and efficacy of two intravenous immune globulin products: the novel formulation (IGIV-C) and a licensed solvent/detergent-treated product (IGIV-SD; Gamimune®N, 10%).

2. Methods

2.1. Subjects

Twenty-five centers in the USA and Canada enrolled 172 patients, aged 1–75 years, who were receiving stable IGIV replacement therapy and had a confirmed chronic primary humoral immune deficiency as defined by the World Health Organization [5]. All study sites had Institutional Review Board approval. Patients had medical records available for retrospective review for at least 3 months prior to study entry and at least one documented IgG trough level of >390 mg/dl during the previous 6 months while on their usual dosing regimen.

Exclusion criteria included severe infection the day of first infusion, history or suspicion of significant allergic reactions to IGIV or other blood products, documented history of selective IgA deficiency and known antibodies to IgA, isolated IgG subclass deficiency with a normal total serum IgG level, or any condition which was likely to interfere with evaluation of the trial drug or satisfactory conduct of the trial. Subjects provided informed consent, and parental consent was obtained for minors.

2.2. Study design

This was a randomized, double-blind, parallel group, multicenter, therapeutic equivalence trial. Investigators screened charts of patients potentially eligible to participate and enrolled eligible patients. Patients were stratified based on the presence of bronchiectasis as documented by chest X-ray or CT diagnosis at screening. Randomization was achieved by a list of unique block random codes supplied by the study sponsor to each pharmacist, revealing the trial preparation allocated to that random number. The pharmacist dispensed the required dosage of the

appropriate trial preparation, IGIV-C or IGIV-SD, into an infusion bottle/bag labelled "Intravenous Immune Globulin (Human), 10%." The investigator, patient, infusionist and trial nurse were blinded to the preparation administered during any given drug infusion. Patients were treated for 9 months with one study drug. Premedication with steroids to alleviate infusion-related adverse events was not permitted. Dosage and frequency of dosing for each patient was in accordance with the individualized treatment regimen utilized in his/her immune globulin therapy prior to study entry and remained constant throughout the trial. Protocol-specified doses ranged 100–600 mg IGIV/kg body weight, given as a single daily dose by intravenous (IV) infusion every 3–4 weeks.

2.3. IGIV preparations

2.3.1. IGIV-SD (Gamimune®N, 10%)

The currently licensed product, IGIV-SD, was prepared as a 10% solution from Fraction II/III concentrate of pooled plasma from screened donors using the Cohn-Oncley process. Solvent (tri-*n*-butyl phosphate; TNBP) and detergent (sodium cholate) were utilized for viral inactivation.

2.3.2. IGIV-C (Gamunex™, 10%)

The novel preparation was manufactured as a 10% solution from the same sources of Fraction II/III. Following re-suspension, primary purification was accomplished by caprylate precipitation and filtration. Caprylate incubation and further filtration were combined for integrated ongoing viral inactivation [2]. Secondary purification steps employed tandem anion exchange chromatography where the filtrate was passed through two successive anion-exchange chromatography columns (Q Sepharose FF followed by ANX Sepharose FF) at pH 5.2 [3]. The product then underwent ultrafiltration, and the final formulation, a sterile 9–11% solution of human protein in 0.16–0.24 M glycine containing no preservative, was incubated at pH 4.25 at room temperature for 21 days serving as a second viral-inactivation step [3]. IGIV-C contains less IgA (40 vs. 98 μg/ml), IgM (<2 vs. 47 μg/ml), and albumin (<20 vs. 160 μg/ml) than IGIV-SD, but more IgG_4 than IGIV-SD (2.6% vs. 1.1%) [3]. Furthermore, IGIV-C has slightly higher isoantibody levels to blood group type A and B antigens than IGIV-SD (1:20 and 1:9, respectively, vs. 1:17 and 1:4). These levels are below release specifications set by the European Pharmacopoeia (1:64) [6]. The increased isoantibody reactivity of IGIV-C resides predominantly in the IgG_4 subclass, and the IGIV-C preparation more closely resembles the normal subclass distribution in plasma than does IGIV-SD (Bayer, Research Triangle Park, NC, data on file). In a powered pharmacokinetic cross-over trial with 18 PID patients, total IgG serum levels after IGIV-C infusions were demonstrated to be bioequivalent to levels after IGIV-SD exposure [7].

2.4. Outcome measures

The primary objective was to demonstrate that the new product, IGIV-C, is at least as effective as the current product, IGIV-SD. Any diagnosis of acute sinusitis, acute exacerbation of chronic sinusitis, or pneumonia was to be validated and documented. The primary endpoint was the proportion of patients with at least one validated acute sinopulmonary infection during a 9-month treatment period with either experimental or control IGIV. Acute sinusitis or acute exacerbation of chronic sinusitis was considered validated if they met the following criteria.

Symptoms lasted ≥5 consecutive days but <28 consecutive days or patient had documented fever (>38 °C or >100.4 °F) plus 2 of the following symptoms: nasal congestion, facial pressure, pain, tightness (toothache, frontal headache, pain behind the eyes), headache, bad breath, taste disturbances, plus sero- or mucopurulent nasal drainage; plus documentation by one of the following: CT-scan (air fluid level, sinus opacification) or lateral X-ray (Waters; air fluid level, sinus opacification) or ultrasound of maxillary sinus in different angles (sinus opacification). Diagnostic imaging must have been conducted ≤48 h after initiation of antibiotic therapy and evaluated by a radiologist or ENT specialist.

A diagnosis of pneumonia in children (age <6 years) required two of the following symptoms: cough, or production of purulent sputum or consolidation signs on auscultation/percussion: rales, bronchial breath sound, dullness; or tachypnea, dyspnea, hypoxemia; plus fever (>38 °C or >100.4 °F) or WBC count >10,000 or <4500 cells/mm^3, or >15% immature bands. In children (age ≥6 years), adolescents

and adults, diagnosis of pneumonia required all of the above plus positive X-ray (conducted ≤ 48 h after initiation of antibiotic therapy).

The secondary objectives were to compare the proportion of patients with all infections (both validated and clinically defined), time to first infection, annual infection rates, lung function parameters, infusion related safety and viral safety.

2.5. Evaluation of safety

Safety was evaluated by the number and character of clinical and laboratory adverse events on study. Vital signs were closely monitored during infusion. Evaluation of viral safety was conducted by comparing the number of patients to develop positive viral serologic and/or PCR markers at 8 and 16 weeks after the first and fifth or sixth infusion. Patients were monitored for HIV antigen (p24), Hepatitis B virus (HbsAg), Hepatitis C (HCV-PCR), and Parvovirus B19 (Parvo B19-PCR).

2.6. Statistical analysis

The hypothesis tested was that the test product, IGIV-C, is not inferior to the reference/control product, IGIV-SD. The sample size was estimated using the method of Rodary based on the assumption that both IGIV products have a rate of validated infection of 28% (based on survey data), 80% power, 5% alpha (one-sided), equivalence delta of 20%, and a 10% invalidity rate [8]. Using these data, 76 patients per treatment arm were needed to obtain a total of 136 patients (68 per treatment group) valid for analysis. Non-inferiority between the two products was established if the upper bound of the Mantel Haenszel weighted two-sided 90% confidence interval (CI) for the difference between groups in percentage of patients with at least one validated infection was less than 20%, and the lower bound of the two-sided 90% CI was not greater than 0%. Efficacy outcomes regarding secondary infection rates amongst treatment and reference groups were analyzed using appropriate statistical methods for each type of variable, specifically survival analysis, analysis of variance and categorical methods of comparison. Independent statistical analyses were performed by the study sponsor (Bayer, West Haven, CT) and the Statistical Department of the Hospital for Sick Children, Toronto. Results were comparable.

3. Results

3.1. Patient enrollment and compliance

A total 172 patients were randomly assigned to receive IGIV-C ($n=87$) or IGIV-SD ($n=85$). The study period, first patient's first visit to last patient's last visit, spanned from March 1999 to June 2000. Common variable immunodeficiency was the most common PID (Table 1). In each group, 73 patients were valid for per-protocol efficacy analysis.

Demographic data were comparable for both groups (Table 2). Mean IGIV dosages prior to the study were similar and most patients were on a 4-week schedule. Of the 26 patients not used for the per-protocol efficacy analysis, 24 (13, IGIV-C; 11, IGIV-SD) were excluded because of protocol violations. Twenty-two protocol violations were the result of patients receiving fewer than 36 weeks of study drug. Two protocol violations resulted from patients with IGIV doses fluctuating prior to study entry. Two patients were not valid because they were non-compliant.

3.2. Efficacy of IGIV-C and IGIV-SD preparations

Seventy-three patients were valid for per-protocol assessment of efficacy in each arm of the study. They

Table 1
Patient population by disease type

	IGIV-C, *N* (%)	IGIV-SD, *N* (%)	Total
Common variable immune deficiency (CVID)	46 (53)	44 (52)	90
Hypogammaglobulinemia, unspecified	31 (36)	24 (28)	55
Congenital hypogammaglobulinemia	8 (9)	11 (13)	19
Combined immune deficiency	1 (1)	5 (6)	6
Immunodeficiency with increased IgM	0	1 (1)	1
Other immunoglobulin deficiency	1 (1)	0	1
Total	87	85	172

Table 2
Demographics and disease characteristics population: all patients valid for per-protocol efficacy analysis

		IGIV-C, 10% ($N=73$)	IGIV-SD, 10% ($N=73$)
Gender	Male	51 (70%)	43 (59%)
Race	Caucasian	63 (86%)	64 (88%)
Age, mean	Years	35.1	29.5
Weight, mean	Kg	65.8	62.9
Pre-existing bronchiectasis	Yes	15 (21%)	16 (22%)
3-week dosing schedule of IGIV		9 (12%)	14 (19%)
Previous IGIV dose	mg/kg	434	452

received a mean 10.2 ± 1.3 and 10.7 ± 1.6 infusions in the IGIV-C and IGIV-SD groups, respectively, over a period of 9 months. The doses per infusion were similar, with a mean of 443.4 ± 133.9 and 454.1 ± 114.9 mg/kg being administered in the IGIV-C and IGIV-SD groups, respectively.

An impressive observation was the occurrence in the frequency of validated infections between the two arms of the study (Fig. 1A). Only 9 patients receiving IGIV-C had validated infections as compared with 17 such patients registered in IGIV-SD group ($p=0.06$). The rate of validated infections was significantly lower in those patients treated with IGIV-C versus those treated with IGIV-SD (Fig. 1B). This difference was primarily accounted for by more patients with acute sinusitis in the IGIV-SD (10) than in the IGIV-C (4) group. Pooling the incidence of patients with both validated and clinically defined acute sinusitis shows significantly fewer IGIV-C treated patients had acute sinusitis than those receiving IGIV-S/D (11/73 vs. 24/73; $p=0.012$; Fig. 2). Six acute exacerbations of chronic sinusitis and two episodes of pneumonia were observed in the IGIV-SD group as compared to 5 and 0, respectively, in the IGIV-C group (Table 3). Uneven distribution of patients with Combined Immune Deficiency (CID) between the treatment groups did not explain observed differences between the preparations, as exclusion of these patients from the analysis results in similar findings; among the six CID patients, at least one infection was observed in one IGIV-C patient (100%) and in only 60% (3/5) of IGIV-SD patients.

Clinically defined, non-validated infections occurred in comparable frequency in each group (Fig. 2). No remarkable differences were observed with regard to non-respiratory infections. Notably, no serious infections were reported with either product (Table 4). Pulmonary function tests were carefully monitored on study. No changes in any parameters including FVC and FEV_1 were noted.

3.3. Relation of infection frequency and replacement dose and IgG trough levels

Validated infections occurred in 10.5% (4/38) of patients receiving IGIV-C at a >400 mg/kg dose versus 14.3% (5/35) with a <400 mg/kg dose. In the IGIV-SD group, the rate was 22.6% at the lower dose and 23.8% at the higher dose. For IGIV-C and IGIV-SD groups, respectively, validated infection rates were 13.6% and 28.6% for an IgG trough level <7 g/l, 15.2% and 23.1% for trough levels between >7 and 9 g/l and 5.6% and 19.2% for trough levels >9 g/l.

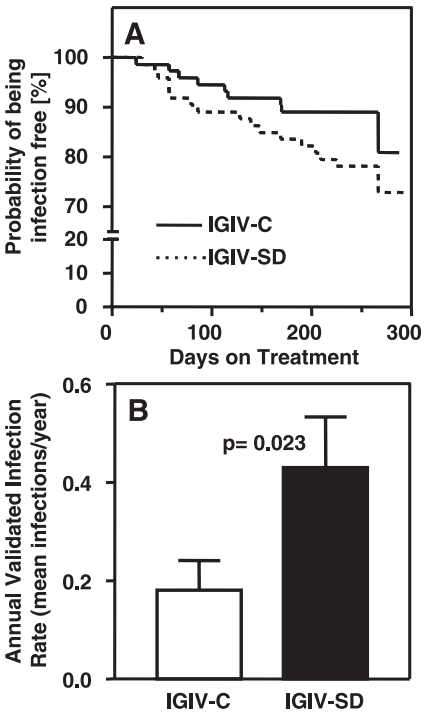

Fig. 1. (A) Kaplan Meier analysis for validated infections. Data show the probability of being infection free during the study period. (B) Rate of validated infections. Data show the mean rate of validated infections for each treatment group (IGIV-C, $n=73$; IGIV-SD, $n=73$). Error bars depict standard error of the mean.

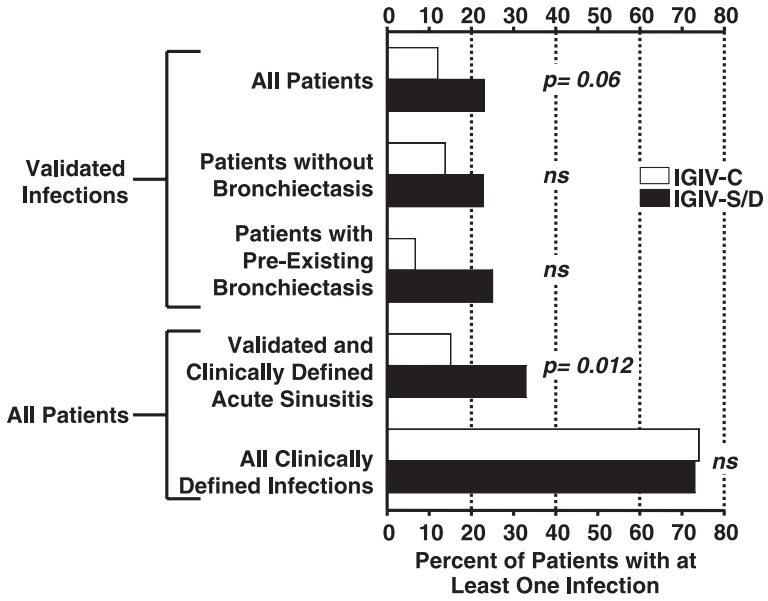

Fig. 2. Proportion of patients with at least one infection. Data for validated infections for patients treated with IGIV-C and IGIV-SD were compared for all patients, patients without bronchiectasis, and patients with pre-existing bronchiectasis. For all patients, those having validated and clinically defined acute sinusitis, as well as clinically defined infections, are compared by treatment group. ns indicates $p>0.1$.

3.4. Adverse events

Adverse events were recorded and analyzed for all enrolled patients. Eighty patients with at least one adverse event were equally registered in each treatment group. By far, the most common adverse event for both IGIV preparations was headache. Headaches were reported with an incidence per infusion of 6.9% for IGIV-C and 8.0% for IGIV-SD and were considered drug-related in 0.8% and 1.3% of cases, respectively. To determine which adverse events are actually related to infusions, adverse events within 2 days of infusion were analyzed and events such as accidental injury, obvious acute infections, or symptoms of underlying disease were excluded from this analysis. The incidence of adverse events, irrespective of relationship to product, in relation to infusions was 18.8% for IGIV-SD and 17.1% for IGIV-C. The incidence of drug-related adverse events was 5.5% and 5.7%, respectively. These included abdominal pains, asthma, chest pain, chills, diarrhea, dizziness, dyspnea, fever, flu-like syndrome, headache, hypertension, nausea, neck rigidity, facial and peripheral edema, pruritus, rash, urticaria, hypotension and vomiting. Overall,

Table 3
Patients with validated infections (category)

	IGIV-C, $N=73$	IGIV-SD, $N=73$	p
Validated infections	9 (12%)	17 (23%)	0.060
Acute sinusitis	4 (5%)	10 (14%)	0.092
Acute exacerbation of chronic sinusitis	5 (7%)	6 (8%)	ns*
Pneumonia	0	2 (3%)	ns*

*ns indicates $p>0.1$.

Table 4
Patients with clinically defined infections (category)

	IGIV-C, $N=73$	IGIV-SD, $N=73$	p
All infections	56 (77%)	56 (77%)	ns*
Acute URI	20 (27%)	13 (18%)	ns*
Acute sinusitis	7 (10%)	16 (22%)	0.041
Acute exacerbation of chronic sinusitis	11 (15%)	6 (8%)	ns*
Otitis media	9 (12%)	12 (16%)	ns*
Bronchitis	5 (7%)	8 (11%)	ns*
Acute pharyngitis	4 (5%)	6 (8%)	ns*
Conjunctivitis	5 (7%)	5 (7%)	ns*
Pneumonia	3 (4%)	5 (7%)	ns*

*ns indicates $p>0.1$.

adverse events most likely to be related to infusion were associated with both preparations with similar frequency.

3.5. Relevant laboratory parameters

HIVp24 Ag, Parvovirus B19 DNA and Hepatitis B antigen were not detected in either group. Hepatitis C RNA was positive prior to initiation of the study in two patients who were assigned to the IGIV-SD group.

The direct Coombs' test (DAT) was transiently positive after infusion in 29 patients (37%) in the IGIV-C group as compared with 16 patients (20%) in the IGIV-SD treated patients. One episode of significant anemia was recorded in the IGIV-C group; however, this patient's DAT was negative. No evidence of hemolysis was observed and the investigator believed this episode of anemia was not related to IGIV treatment.

4. Discussion

Immunoglobulin preparations pooled from human blood were first used in the early 1950s to treat primary immunodeficiency conditions. Early preparations required intramuscular injections, which delivered limited amounts of antibodies. Consequently, serum concentrations of IgG remained unchanged and infection control was suboptimal [9]. The introduction of immunoglobulin preparations suitable for intravenous administration permitted replacement to normal serum IgG levels resulting in a dramatic reduction in the frequency of sinopulmonary infections [9,10]. However, after decades of using IGIV, many fundamental questions remain unanswered. The optimal dose and serum IgG trough level has never been established. Surprisingly, various IGIV products, which are manufactured differently, have not been thoroughly compared for efficiency and adverse events. Currently, according to regulatory guidelines, IGIV products are tested for sterility, purity, pyrogenicity and safety. However, no strict requirements exist for desired concentrations of specific antibodies. Similarly, no strict guidelines, which distinguish the nature and frequency of acceptable from unacceptable adverse events, are available.

One way to begin this process is to compare various preparations, which are manufactured by different methods. In the present study, we have compared efficiency and tolerability of two products. The licensed product was prepared using solvent detergent (IGIV-SD) and the investigational product was manufactured using a new caprylate/chromatographic method [3]. Seventy-three patients valid for assessment of per-protocol efficacy in each treatment group received comparable numbers of infusions and dosing regimens over a period of 9 months.

In patients treated with IGIV-C, acute sinusitis occurred significantly less frequently ($p = 0.012$), and validated infections, which includes acute sinusitis, acute exacerbation of chronic sinusitis, and pneumonia, were less common ($p = 0.06$). This finding is especially striking given that clinically defined exacerbations of chronic sinusitis occurred more frequently in the IGIV-C group (15% vs. 8%). Upper respiratory infections such as the common cold may have lead to false positive diagnoses of sinusitis, as some radiographic abnormalities of sinuses occur in the majority of patients with common colds [11]. However, IGIV-C may possibly offer superior protection against bacterial infection. In support of this consideration, patients treated with IGIV-C tended to have fewer episodes of validated or non-validated pneumonia (4% vs. 10%; $p = 0.19$), fewer days of fever (0.8% vs. 1.6%; $p = 0.16$), and fewer days of prophylactic antibiotic therapy (14% vs. 20%; $p = 0.29$) compared to those treated with IGIV-SD. Differences in the manufacturing processes for IGIV-C and IGIV-SD, resulting in differences in the content, integrity, or biologic activity of some specific antibodies, may be responsible for this decreased infection rate with IGIV-C.

The gammaglobulin subclasses IgG_2 and IgG_4 contain anti-polysaccharide antibodies, which are important in protecting against sinopulmonary infections, particularly bacterial sinusitis. Clinical confirmation is found in the frequency of such sinopulmonary infections in patients with IgG_2 and combined IgG_2 and IgG_4 subclass deficiencies [12]. In a previous pharmacokinetic study comparing IGIV-C and IGIV-SD, 18 pre- and post-infusion measurements of gammaglobulin subclasses were obtained [7]. For the IGIV-C group, the mean post-infusion IgG_2 increased by 3.34 g/l compared to 2.93 g/l for IGIV-SD-treated patients.

More strikingly, post-infusion IgG_4 increased by 0.23 g/l in the IGIV-C group in contrast to 0.09 g/l in the IGIV-SD group [7] (Bayer, RTP, NC, data on file). It is unclear at present whether the decreased frequency of sinopulmonary infections in patients treated with IGIV-C is related to these differences in IgG subclass levels.

A relationship between IGIV dose and therapeutic response has been long suspected [13–16]. A recent multicenter, double-blind, randomized crossover study in the Netherlands demonstrated that a high dose, 600 mg/kg for adults and 800 mg/kg for children, significantly reduced the number and duration of infections in patients with primary hypogammaglobulinemia [17]. Similarly, the current study shows fewer patients treated with higher (>400 mg/kg) doses developed any infection. Since any such relationship would be presumed to be related to the plasma trough IgG levels obtained with different IGIV doses, we evaluated the relationship of validated infections to trough IgG levels. Combining the two treatment groups revealed that validated infections occurred in 20.9% (9/43) of patients with trough levels <7 g/l, 18.6% (11/59) of those with trough levels of 7–9 g/l and 13.6% (6/44) of those with trough levels >9 g/l. Clearly, higher monthly doses resulting in higher trough levels might better protect patients from recurrent infections.

IGIV is a safe modality of therapy. No evidence of viral transmission was seen with either product. Adverse reactions, which occur during or within several days of infusion, are usually mild and can be controlled by reducing the infusion rate. The most severe adverse events such as aseptic meningitis and vasculitis are extremely rare, and did not occur in this study [1,9,10]. Overall, the type and frequency of adverse reactions in both study groups were in keeping with previous reports [1,9,10]. Further, no significant difference in the frequency and severity of adverse reactions was detected among the two groups.

The most notable difference between the groups was the increased frequency of a positive DAT in the IGIV-C group. These isoantibodies reside in the IgG_4 subclass, which do not activate the classical complement pathway and are unlikely to cause hemolysis [18]. No clinical or laboratory evidence of hemolysis was ever detected in the DAT-positive patients.

This study directly compares for the first time, in a controlled randomized fashion, two IGIV products which are prepared by different methods. Although designed as a study of non-inferiority of IGIV-C to IGIV-SD, the findings provide support for the conclusion that IGIV-C appears to be superior to IGIV-SD, especially in preventing sinopulmonary infections. This study implies that not all IGIV preparations are equal and highlights the need for larger comparative studies to identify the standards for optimal treatment of patients with primary humoral immune deficiency, and other conditions, which are currently treated with immunoglobulins.

Acknowledgements

The authors thank Dr. Joe Kiss, Institute for Transfusion Medicine, Pittsburgh, PA, for in-depth analysis of Coombs' reactivity, Dr. Derek Stephens, Hospital for Sick Children, Toronto, ON, and Drs. Keith Bangerter and Lawrence Schwartz for statistical analysis.

References

[1] Buckley RH, Schiff RI. The use of intravenous immune globulin in immunodeficiency diseases. N Engl J Med 1991; 325(2):110–7.
[2] Korneyeva M, Hotta J, Lebing W, Rosenthal RS, Franks L, Petteway Jr SR. Enveloped virus inactivation by caprylate: a robust alternative to solvent–detergent treatment in plasma derived intermediates. Biologicals 2002;30(2):153–62.
[3] Lebing W, Remington K, Schreiner C, Paul H-I. Properties of a new intravenous immunoglobulin (IVIG-C, 10%) produced by caprylate virus inactivation and column chromatography. Vox Sang 2003;84:193–201.
[4] Trejo SR, Hotta J, Lebing W, Stenland C, Evans Storms R, et al. Evaluation of virus and prion reduction in a new intravenous immunoglobulin manufacturing process. Vox Sang 2003;84:176–87.
[5] Primary immunodeficiency diseases. Report of a WHO scientific group. Clin Exp Immunol 1997;109(Suppl 1):1–28.
[6] Human normal immunoglobulin for intravenous administration. European pharmacopoeia. 3rd ed. Strasbourg: Council of Europe; 1997. p. 963–5.
[7] Ballow M, Berger M, Bonilla FA, Buckley R, Cunningham-Rundles CH, et al. Pharmacokinetics and tolerability of a new intravenous immunoglobulin preparation, IGIV-C, 10% (Gamunex™, 10%). Vox Sang 2003;84:202–10.
[8] Rodary C, Com-Nougue C, Tournade MF. How to establish

equivalence between treatments: a one-sided clinical trial in paediatric oncology. Stat Med 1989;8(5):593–8.
[9] Ammann AJ, Ashman RF, Buckley RH, Hardie WR, Krantmann HJ, et al. Use of intravenous gamma-globulin in antibody immunodeficiency: results of a multicenter controlled trial. Clin Immunol Immunopathol 1982;22(1):60–7.
[10] Stiehm ER, Ashida E, Kim KS, Winston DJ, Haas A, Gale RP. Intravenous immunoglobulins as therapeutic agents. Ann Intern Med 1987;107(3):367–82.
[11] Gwaltney Jr JM, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. N Engl J Med 1994;330(1):25–30.
[12] Schur PH. IgG subclasses—a review. Ann Allergy 1987;58(2): 89–96, 99.
[13] Cunningham-Rundles C, Siegal FP, Smithwick EM, Lion-Boule A, Cunningham-Rundles S, et al. Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. Ann Intern Med 1984;101(4):435–9.
[14] Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. Lancet 1987;1(8541):1075–7.
[15] Roifman CM. Gs chronic sinopulmonary disease in patients with hypogammaglobulinemia. Pediatr Infect Dis J 1988;7(5 Suppl):S92–6.
[16] Gelfand EW, Reid B, Roifman CM. Intravenous immune serum globulin replacement in hypogammaglobulinemia. A comparison of high- versus low-dose therapy. Monogr Allergy 1988;23:177–86.
[17] Eijkhout HW, van Der Meer JW, Kallenberg CG, Weening RS, van Dissel JT, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. Ann Intern Med 2001;135(3):165–74.
[18] van der Zee JS, van Swieten P, Aalberse RC. Inhibition of complement activation by IgG4 antibodies. Clin Exp Immunol 1986;64(2):415–22.