IGIV-C, a novel intravenous immunoglobulin: evaluation of safety, efficacy, mechanisms of action, and impact on quality of life

James B. Bussel[1], Amiram Eldor†[2], John G. Kelton[3], David Varon[4], Benjamin Brenner[5], Shmuel Gillis†[4], Anne Angiolillo[6], Roshni Kulkarni[7], Thomas C. Abshire[8], Jack Kelleher[9] and the IGIV-C in ITP Study Group

[1]New York Presbyterian Hospital, New York, New York, USA, [2]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]McMaster University Medical Centre, Hamilton, Ontario, Canada, [4]Hadassah Hebrew University Medical Center, Jerusalem, Israel
[5]Rambam Medical Center, Haifa, Israel, [6]Children's National Medical Center, Washington, District of Columbia, USA
[7]Michigan State University, East Lansing, Missouri, USA, [8]Emory University, Atlanta, Georgia, USA
[9]Bayer Corporation, West Haven, Connecticut, USA

Summary

The general safety and efficacy of intravenous immunoglobulin (IGIV) as treatment for idiopathic thrombocytopenic purpura (ITP) has been well-studied. The current study compares the safety and efficacy of a novel IGIV (IGIV-C; Gamunex®, 10%) with a licensed solvent/detergent-treated product (IGIV-S/D; Gamimune®N, 10%) in treatment of ITP. Ninety-seven pediatric and adult patients with acute and chronic ITP were treated in a multi-center, prospective, randomized, double-blind parallel group, non-inferiority trial at 26 international sites. Baseline data (age, duration of ITP, platelet counts, previous treatment) were comparable between groups. Patients were treated with 1 g/kg/day of IGIV-C or IGIV-S/D for 2 days. The primary endpoint, proportion of patients whose platelet counts increased from $\leq 20 \times 10^9$/L to $\geq 50 \times 10^9$/L within 7 days after dosing, was achieved by 35/39 (90%) and 35/42 (83%) of patients treated with IGIV-C and IGIV-S/D, respectively. A secondary endpoint, maintaining platelet counts $\geq 50 \times 10^9$/L for ≥7 days, was achieved by 29/39 (74%) of IGIV-C and 25/42 (60%) IGIV-S/D treated patients. Compared with IGIV-S/D, fewer patients treated with IGIV-C received corticosteroids beyond day 7 ($p = 0.02$). Efficacy was independent of the presence of isoantibodies or blood type, supporting mechanisms of effect different from anti-D treatments. Adverse events were generally mild and occurred with similar frequency in each group. Viral safety monitoring for HIV, HCV, HBV and Parvovirus B19 showed no seroconversions on study. In conclusion, IGIV-C is as safe and efficacious as IGIV-S/D in treatment of ITP.

Keywords

IVIG, immunoglobulin, immunotherapy, viral safety

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Correspondence to:
James B. Bussel, M.D.
New York Presbyterian Hospital
Payson 695, 525 East 68th Street
New York, New York 10021-4885
USA
Tel.: +1 212-746-3474, Fax: +1 212-746-5121
E-mail: jbussel@med.cornell.edu

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Introduction

Idiopathic (immune) thrombocytopenic purpura (ITP), an autoimmune disorder affecting both children and adults, is characterized by a low platelet count, a normal bone marrow examination, and the absence of specific causes of thrombocytopenia such as leukemia, aplastic anemia or disseminated intravascular coagulation (1). Childhood ITP is typically of acute onset; more than 70% of children will have a spontaneous and permanent remission within one year of onset (2). In contrast, the majority of adults have persistent ITP, although the natural history is less defined than for ITP in children (3) and certain patients improve with time (4). Rarely, life-threatening bleeding occurs with intracranial hemorrhage being the principle cause of death (5, 6). Serious hemorrhage is most likely to occur when the platelet count falls below 10-20 $\times$ 10^9/L (1,5). Therefore, initial treatment options for ITP are intended to rapidly increase the platelet count and include glucocorticoids, immune globulin intra-venous (IGIV) and intravenous anti-D(Rho) globulin in Rh(+) patients (1).

The first report of the efficacy of IGIV in the treatment of ITP appeared in 1981 (7). More than 100 studies have subsequently confirmed the safety and efficacy of IGIV as treatment of ITP in children and adults (8-12). A substantial and rapid platelet increase can be achieved with an IGIV dosage of 1 g/kg/day repeated for two consecutive days as opposed to the initial dosage of 400 mg/kg/day repeated for 5 days (13, 14).

The purpose of the current study was to investigate the safety and efficacy of a novel IGIV product, IGIV-C (Gamunex®) compared with Gamimune®N, 10% (IGIV S/D). Additionally, this study provides the most comprehensive, prospective data reported to date on the efficacy of IGIV treatment of both acute and chronic ITP in both adults and children.

Materials and methods

Patients

Pediatric and adult patients between the ages of 1 and 80 with acute or chronic ITP and a platelet count less than 20 $\times$ 10^9/L were eligible for this trial. Patients were enrolled July 29, 1999 through June 22, 2000, with the last patient visit occurring on November 8, 2000.

ITP was defined as isolated thrombocytopenia in a patient with no other clinically apparent associated condition or factors known to cause thrombocytopenia.

Prospectively defined administration criteria required that patients receiving corticosteroid therapy at the time of enrollment must have completed at least 2 weeks of therapy at a stable dose, with no planned dosage increase during the 7 days after completion of the study drug infusion. Patients treated with cyclophosphamide, azathioprine or attenuated androgens must have received a stable dose for at least 3 months prior to entering the study. Patients previously treated with IGIV for thrombocytopenia must have demonstrated a clinically significant response to therapy. Patients were excluded if they had a history or clinical evidence of medical conditions felt to be the underlying cause of their thrombocytopenia, or had any condition which was likely to interfere with the evaluation of the trial drug and/or the satisfactory conduct of the trial. Pre-medication with corticosteroids to decrease adverse infusion reactions was not allowed.

Methods

The prospectively defined primary objective of this trial was to demonstrate that IGIV-C was at least as effective as IGIV-S/D in raising platelet counts in patients with ITP. This was a randomized, double blind, multicenter, parallel group noninferiority trial. Patients were stratified by age, and whether they had acute versus chronic ITP prior to randomization. A positive response was defined as an increase from a platelet count $\leq$20 $\times$ 10^9/L to $\geq$50 $\times$ 10^9/L by the seventh day after completing the first dose of IGIV, i.e., after 2 consecutive days. The secondary outcome was the percentage of patients who maintained a platelet count $\geq$50 $\times$ 10^9/L for at least 7 days. The 7-day endpoint was anticipated to capture adequately the varied kinetics of platelet response to IGIV therapy observed in previous studies (15-17).

Randomization was achieved by supplying numbers to each participating pharmacist, who was the only person not blinded to the patients' treatment group. He/she then dispensed the required dosage of the appropriate trial preparation into an infusion bottle/bag, which was labeled "Intravenous Immune Globulin, 10%". The investigator, patient, infusionist and trial nurse were all blinded as to whether the IGIV-C or IGIV-S/D preparation was administered during any given drug infusion.

Each patient was treated with IGIV-C or IGIV-S/D at a total dose of 2g/kg body weight divided over two consecutive days (i.e., 1 g/kg on Day 1 and 1 g/kg on Day 2). IGIV was infused at a starting rate of 0.01-0.02 mL/kg/minute for 30 minutes. If well tolerated, the infusion rate was gradually increased to a maximum of 0.08 mL/kg/minute (0.06 mL/kg/minute at Canadian centers). Vital signs (blood pressure, heart rate, temperature, respiratory rate) were routinely monitored and recorded at the beginning of each infusion, 5-10 minutes after the start of infusion, every 30 minutes during infusion while the rate was changing, otherwise at 60 minute intervals, and at completion of the infusion. If the patient was hospitalized, vital signs were again repeated 12 and 24 hours after infusion (if an outpatient, at 24 hours only). If adverse events occurred, vital signs were monitored more frequently.

Platelet counts were determined on Days 1 and 2 pre-infusion and 24 hours following the second infusion. Additional platelet counts were measured daily on Days 4-8 or until the count reached or exceeded 50 $\times$ 10^9/L, then every 3 $\pm$ 1 days

through Day 21. Laboratory analyses included CBC, indirect and Direct Antiglobulin (Coombs') Test (DAT), blood type, serum chemistries, and urine analysis. Viral markers (PCR and/or serologic markers for HIV, HCV, HBV, HAV, and Parvovirus B19 infection) were monitored up to 6 months, but at least for 3 months after infusion.

The need for emergent corticosteroid use or additional IGIV per the discretion of the Investigator was documented. Use of concomitant glucocorticoids and/or cytotoxic agents was allowed at the Investigator's discretion if the patient was not responding with platelet counts > 20×10^9/L by Day 5. Patients who received steroids in this manner were considered "non responders" and followed for safety only. Patients previously receiving a stable corticosteroid dose for at least 10 days could be maintained on a constant or decreasing dose of corticosteroids during the first week after the first IGIV infusion. Patients were also assessed for evidence of minor bleeding episodes, specifically ecchymoses and petechiae.

IGIV-S/D (Gamimune®N, 10%)

IGIV-S/D 10%, was prepared from Fraction II/III concentrate from cold ethanol precipitation of pooled plasma from screened donors. Solvent (tri-n-butyl phosphate; TNBP) and detergent (sodium cholate) were added to the solution, which was then heated to 30°C and maintained at that temperature for at least 6 hours. After this step, precipitation, filtration, diafiltration and ultrafiltration removed the reactants. Viral inactivation and removal of model enveloped and non-enveloped viruses spiked during the manufacturing process has been documented by laboratory studies (18-20) Following further cold ethanol precipitation and centrifugation steps, and low pH storage at room temperature for 21 days for continuous viral inactivation, the product was finally formulated as a protein solution ranging from 9% to 11% gamma globulin.

IGIV-C (Gamunex®, 10%)

This preparation was prepared from the same sources of Fraction II/III as above including cold ethanol precipitation of pooled plasma. Following re-suspension, primary purification of the product was accomplished by caprylate precipitation and filtration. Korneyeva, et al. demonstrated that the fatty acid caprylic acid (caprylate) is a robust enveloped virus inactivating agent for immunoglobulins and albumin (18). Caprylate incubation and further filtration were combined for integrated ongoing viral inactivation. Secondary purification steps employed tandem anion exchange chromatography (19). The product then underwent ultrafiltration, and the final formulation was sterile 9% to 11% solution of human protein in 0.16-0.24 M glycine, containing no preservative and incubated at pH 4.25 at room temperature for 21 days. This incubation at low pH also served as a second viral inactivation step. Each milliliter contained approximately 100 mg of protein, not less than 98% of which had the electrophoretic mobility of gamma globulin. Not less than 96% of the gamma globulin was monomer.

IgA (40 ± 11 vs. 98 ± 26 μg/ml), IgM (<2 vs. 47 ± 26 μg/ml), and albumin (<20 μg/ml vs. 160 ± 93 μg/ml) levels for IGIV-C were all several-fold lower than that contained in IGIV-SD (19). The level of IgG_4 in IGIV-C was 2.6% (IGIV-SD, 1.1%); the IgG subclass distribution of IGIV-C resembles that of normal human serum (19). Viral inactivation and removal of model enveloped and non-enveloped viruses spiked during the manufacturing process has been documented by laboratory studies (18-20). Clinical pharmacokinetic evaluation has shown that IGIV-C and IGIV-S/D are bioequivalent (21).

Statistical analysis

The objective of the statistical analysis was to examine whether the experimental product (IGIV-C) was as at least as effective as the control product (IGIV-S/D) in raising platelet counts in patients with ITP. The two-sided 90% confidence interval for the difference (IGIV-C, 10% minus IGIV-S/D, 10%) in percentage of patients whose platelet count increased to $\geq 50 \times 10^9$/L by the seventh day after completing treatment was set with an upper bound of 0% and a lower bound of -20%. Statistical power was set at 80%, and the alpha level was 0.05. Summary statistics were provided for all four strata (acute adults, acute pediatrics, chronic adults, and chronic pediatrics). For definition of strata, pediatric refers to all patients <18 years old. Additional information for children age <11 years was also reported.

Comparison of the incidence rates of adverse events (AEs) was done in a descriptive manner. Events were tabulated by type and frequency, and were recorded as number of patients who experienced an event, versus number of events. Those events reported included any adverse events that occurred from the time of infusion to 3-6 months post-treatment, as well as those events considered by the investigator to have a possible relationship to drug.

Results

Ninety-seven patients were enrolled and randomized from 26 sites in the U.S., Canada, South Africa, and Israel. Seventy-five percent of the patients were adults and 72% female. Forty-one percent of the patients had a diagnosis of acute ITP at study entry. Forty-eight patients were treated with IGIV-C (experimental) and 49 patients were treated with IGIV-S/D (controls). All enrolled patients were valid for safety analysis. A total of 16 patients (IGIV-C, 9; IGIV-S/D, 7) were excluded from the efficacy analysis. Therefore, 39 patients in the IGIV-C experimental group and 42 patients in the IGIV-S/D control group, 81 of the 97 enrolled, were available for the per protocol efficacy analysis. Both groups were similar with regard to demographics and percent of patients with acute versus chronic ITP. Patient

Table 1: Demographic* and infusion data

		IGIV-C	IGIV-S/D
Total patients valid per protocol analysis		39	42
Sex	Male	10(26%)	13(31%)
	Female	29(74%)	29(69%)
Race	Caucasian	30(77%)	37(88%)
	Black	3 (8%)	0 (0%)
	Asian	3 (8%)	3 (7%)
	Other	3 (8%)	2 (4%)
Age (years)	Mean	34.3	36.7
Weight (kg)	Mean	64.4	68.0
Height (cm)	Mean	155.9	157.1
Hemoglobin (g/dL)*	Mean	12.5 ± 1.6	13.4 ± 1.5
Leukocytes ($x10^9$/L)	Mean	7.6 ± 2.9	9.0 ± 3.8
Platelets at baseline ($x10^9$/L ± SD)	Mean	11.2 ± 5.6	9.6 ± 5.4
ITP (pediatric, adult)	Pediatric (<18)	10(26%)	10(24%)
	Adult (≥18)	29(74%)	32(76%)
ITP (Diagnosis at entry)	Acute	15(38%)	15(36%)
	Chronic	24(62%)	27(64%)
Mean dose/infusion (mg/kg)	Both infusions	987.3 ±77.8	968.2 ± 78.5
Infusion duration (h)	Mean	4.7 ± 2.4	4.3 ± 2.0

*No significant differences between treatment groups with regard to patient characteristics at baseline were observed, except for significantly lower mean hemoglobin, hematocrit and RBC in the IGIV-C group.

Table 2: Responder rates in patient subsets (per protocol analysis)

		Responder Rate (platelet count ≥$50x10^9$/L)	
		by Day 7	for ≥7 Days
Treatment	Any IGIV	70/81 (86%)	54/81 (67%)
	IGIV-C, 10%	35/39 (90%)	29/39 (74%)
	IGIV-S/D, 10%	35/42 (83%)	25/42 (60%)
Age	<11 year	11/13 (85%)	9/13 (69%)
	11 to <18 years	4/7 (57%)	3/7 (43%)
	≥18 years	55/61 (90%)	42/61 (69%)
Diagnosis at study entry	Acute ITP	22/30 (73%)	17/30 (57%)
	Chronic ITP	48/51 (94%)	37/51 (73%)
Diagnosis at study end	Acute ITP	9/10 (90%)	7/10 (70%)
	Chronic ITP	58/66 (88%)	45/66 (68%)
	End diagnosis not recorded	3/5 (60%)	2/5 (40%)
Blood type	A	22/26 (85%)	14/26 (54%)
	B	10/12 (83%)	9/12 (75%)
	AB	2/2 (100%)	1/2 (50%)
	O	15/17 (88%)	14/17 (82%)
	Rh(-)	8/9 (89%)	7/9 (78%)
	Rh(+)	41/48 (85%)	31/48 (65%)

groups were likewise similar with regard to baseline mean WBC count and mean hemoglobin (Table 1).

Both groups were similar in achieving the primary efficacy endpoint: percentage of patients achieving an increase in platelet count to $\geq 50 \times 10^9$/L by the seventh day after completing treatment. Ninety percent of patients treated with IGIV-C and 83% of patients treated with IGIV-S/D met this goal. As illustrated in Table 2, these results were not influenced by patient age, duration of ITP (acute or chronic), or blood type.

The secondary outcome (percentage of patients with maintenance of elevated platelet count for at least 7 days) was achieved by seventy-four percent of patients treated with IGIV-C versus 60% of IGIV-S/D-treated patients. The kinetics of the mean platelet count are displayed in Figure 1. Due to the non-synchronized nature of sampling across patients for platelet counts, the sample sizes vary by day, thus direct comparison of the treatment groups must be made with caution. Table 2 shows the overall response rate by day 7 for subsets of patients, strati-

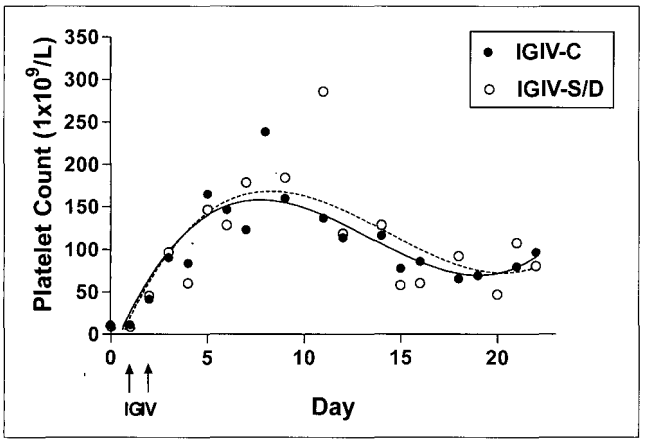

Figure 1: Mean platelet kinetics after IGIV treatment. Patients were treated with IGIV-C or IGIV-S/D at a total dose of 2 g/kg body weight divided over two consecutive days (i.e., 1 g/kg on Day 1 and 1 g/kg on Day 2). Values represent the mean platelet count at indicated time points. Non-linear regression (Curve fit- 3rd order polynomial); solid line: IGIV-C; dashed line: IGIV-S/D.

Table 3: Adverse events within 14 days after infusion whether or not attributed to study drug.

Number of patients with adverse event	IGIV-C (Experimental) N=48	IGIV-S/D (Licensed Control) N=49
Any event	25(52%)	27(55%)
Headache	24(50%)	24(49%)
Fever	5 (10%)	5 (10%)
Back pain	3 (6%)	2 (4%)
Asthenia	2 (4%)	3 (6%)
Neck pain	0 (0%)	2 (4%)
Vomiting	6 (13%)	8(16%)
Nausea	5 (10%)	4 (8%)
Arthralgia	2 (4%)	0 (0%)
Dizziness	1 (2%)	3(6%)
Rash	3 (6%)	0 (0%)

fied by treatment, age, acute or chronic disease, and blood type. No apparent differences exist among these subsets.

Adverse events experienced by patients up to 14 days after treatment include headache, vomiting, fever, nausea, rash, arthralgia, and dizziness (Table 3). These adverse events were recorded irrespective of their relationship to the study products. None of these patients received steroid pre-medication to alleviate infusion-related discomfort. Approximately half the patients in both treatment groups, 44% and 41% respectively, experienced mild-to-moderate headaches during the first 3 days after infusion. Headaches were reported as severe adverse events for 7 patients (IGIV-C, 1; IGIV-S/D, 6) within the first few days of treatment; these headaches were documented as "probably" related to treatment with study drug and none were considered to be "serious." Eight to 16% of patients in both treatment groups had episodes of nausea and vomiting associated with treatment.

This was the first internationally conducted trial to monitor viral safety (HAV, HCV, HBV, HIV, Parvovirus B19) according to the guidelines suggested by The European Association for the Evaluation of Medicinal Products (EMEA). Serum was collect-

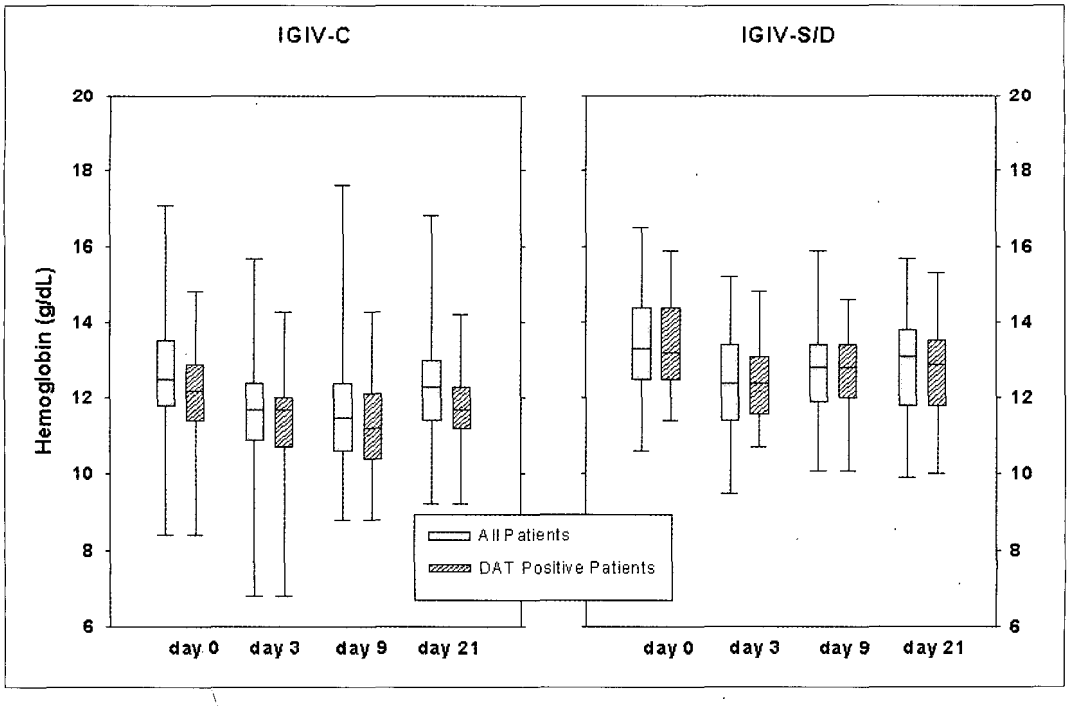

Figure 2: Mean hemoglobin change with IGIV treatment. The Y-axis depicts patient hemoglobin levels (g/dL) and the X-axis shows day of treatment. Boxes extend from the 25th percentile to the 75th percentile. The horizontal line within each box depicts the median (50th percentile) value. Whiskers represent minimum and maximum values.

Percentage of patients with:	IGIV-C	IGIV-S/D	P value*
Ecchymosis	40%	47%	NS
Petechiae	21%	31%	NS
Use of corticosteroids beyond Day 7	25%	47%	0.02
Use of additional IGIV doses beyond Day 21	6%	6%	NS
Splenectomy beyond Day 7	6%	12%	NS

*Analyses were conducted using a chi-square test for all comparisons, except in use of additional IGIV beyond Day 21 and splenectomy beyond Day 7 where a Fisher's Exact Test was used.

Table 4: Minor bleeding episodes and need for additional treatment*.

ed for measurements of viral antigens, antibodies to viral antigens, and viral nucleic acid (as appropriate) for 3 to 6 months after IVIG infusion. No evidence of any transmission of these 5 viruses was observed.

A mild and transient decrease in hemoglobin was observed in both treatment groups (Fig. 2). The mean changes from baseline for hemoglobin, hematocrit and RBC concentration were not different between IGIV-C and IGIV-S/D treatment groups, and the magnitude of these changes were small and not considered to be clinically significant. Importantly, at baseline, mean hemoglobin, hematocrit, and RBC levels were statistically significantly lower in the IGIV-C treated patients versus baseline levels of these same parameters in the IGIV-S/D group. As such, at study entry the IGIV-C patients may have had a pre-disposition to having abnormally lower values post baseline. Thirty-seven percent of IGIV-C and 30% of IGIV-S/D patients exhibited a transient positive DAT, although the indirect antiglobulin tests were all negative. None of these patients had any evidence of clinically significant hemolysis. As shown in Figure 2, a positive DAT had no impact on the hemoglobin decrease in either the IGIV-C or IGIV-S/D groups.

Clinically significant bleeding, such as percent of patients with ecchymoses and petechiae, and outcomes such as the need for corticosteroids, subsequent IGIV therapy, and performance of splenectomy beyond day 7 and throughout the viral safety monitoring period, were examined (Table 4). The administration of additional doses of IGIV occurred with similar frequency in the treatment groups. However, fewer patients initially treated with IGIV-C than IGIV-SD received corticosteroids beyond day 7 ($p = 0.02$). Bruising and ecchymoses during the 23-day study period were no more frequent in patients treated with IGIV-C than in those treated with IGIV-SD. Likewise, patients treated with IGIV-C were not more likely to have a splenectomy than were those treated with IGIV-SD.

Discussion

The three best known previously reported prospective, randomized, controlled studies of IGIV treatment in ITP were all restricted to children (15, 22, 23). The randomized controlled trial reported here is the largest study to date including substantial numbers of both adults (n = 61) and children (n = 20), and confirms the efficacy of IGIV for treating both acute (n = 30) and chronic (n = 51) ITP in these populations (9). In the current evaluation, 86% of all patients achieved the primary endpoint which was to increase their platelet count to $\geq 50 \times 10^9$/L by the seventh day of study, 67% achieved the secondary endpoint which was a sustained platelet increase to $\geq 50 \times 10^9$/L for at least 7 days. These excellent results may be at least partially explained by the study criteria, which excluded patients known to be refractory to IGIV or corticosteroids.

The new formulation, IGIV-C, is at least as efficacious, as the licensed product, IGIV-S/D, in increasing and maintaining the platelet count in patients with ITP. The results of the study show clearly that IGIV-C, like IGIV-S/D, is an effective method for rapidly increasing platelet counts to $\geq 50 \times 10^9$/L in patients with severe thrombocytopenia. Ninety percent of patients treated with IGIV-C, and 83% receiving IGIV-S/D, showed an increase in their platelet counts to $\geq 50 \times 10^9$/L by the seventh study day. This response was maintained for at least a week in 74% of the IGIV-C group and 60% of the IGIV-S/D treated patients ($p = 0.115$). By the end of the 23-day assessment period, during which additional corticosteroids were permitted by protocol after day seven if deemed necessary by the investigator, 94% of all patients had achieved a platelet count of $\geq 50 \times 10^9$/L.

Adverse events observed in this study are consistent with those previously reported (15), and were essentially identical for IGIV-C and IGIV-S/D. The most common treatment side effects were mild or moderate headache, vomiting, fever, and nausea. Corticosteroid pre-medication was prohibited in the study to allow optimal toxicity assessment. The omission of corticosteroids probably increased the rates of headache, nausea and vomiting; they were seen equally in the licensed IGIV-S/D and the experimental IGIV-C. Many published studies of treatment for acute and chronic ITP do not report specific adverse event rates. Hence, the current study describes the real incidence of side effects experienced during IGIV therapy. It encourages the performance of a study to demonstrate the efficacy of steroid pre-medication.

A slight decrease in mean hemoglobin levels was observed in both treatment groups, as seen previously in other studies (15, 24). This decrease in hemoglobin levels was minimal (Fig. 2) and not associated with clinical consequences. Likewise, the

hemoglobin decrease was not related to either the platelet response or development of a positive DAT.

The observation that patients in both IGIV treatment groups experienced a transient positive DAT in approximately one-third of cases was examined closely. The efficacy of intravenous anti-D (Rho) globulin in Rh (+) ITP patients has suggested the possibility that IGIV may confer a part of its efficacy by sensitization of RBC (25). In this study 36% and 31% (IGIV-C and IGIV-S/D, respectively) of patients experienced transient positive DAT. No correlation of a positive DAT with platelet response was observed, as 88% of DAT negative and 85% of DAT positive patients had an increase in platelet count to $\geq 50 \times 10^9$/L by day 7. Furthermore, DAT status showed no correlation with the previously described decrease in hemoglobin.

The present study was unique in that the effect of patient blood group type on platelet response was examined. ABO or Rhesus blood group types appeared to be unrelated to response as shown in Table 3. All patients in this study with a positive DAT had blood group types A or B. The similar response of patients with these blood types compared to patients with blood type O reinforces the conclusions above that the IgG_4 isoantibodies contained in IGIV, which may cause a positive DAT, play no role in the therapeutic response.

Evaluation of bleeding symptoms and the need for additional treatment showed a significant reduction in corticosteroid use beyond Day 7 and a general tendency towards reduced splenectomy, ecchymoses, and petechiae in patients receiving IGIV-C as compared to those treated with IGIV-S/D. This difference may be associated with the slightly lower number of IGIV-S/D-treated patients who achieved a successful platelet rebound. For individual patients, such outcomes may prove to be important quality of life parameters.

In conclusion, IGIV remains the gold standard for rapid and substantial platelet increase in children and adults with acute and chronic ITP (9, 17, 26, 27). This study demonstrated that IGIV-C is a safe and effective treatment for acute and chronic ITP in both adults and children. Specifically, it is at least as efficacious and at least as safe as the licensed IGIV-S/D preparation to which it was compared.

The study also confirmed that a mild and transient decrease in hemoglobin is a frequent consequence of IGIV therapy. However, this hemoglobin decrease is rarely clinically significant and may be dilutional since DAT status and blood type had no association with the response of ITP to IGIV or the hemoglobin decrease. Treatment with IGIV-C was associated with a trend toward more rapid symptom resolution and less frequent need for additional corticosteroid treatment compared with IGIV-SD treatment. Further studies examining the effects of IGIV infusion on quality of life and cost reduction are warranted and would include the impact of steroid medication on IGIV-related adverse events.

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The IGIV-C in ITP Study Group includes Koon-hung Luke, Childrens Hospital of Eastern Ontario, Ottawa, Ontario, Canada; Pierre Whitlock, Dr. Leon Richard, Oncology Centre, Moncton, N.B. Canada; Bruce Ritchie, University of Alberta, Edmonton, Alberta, Canada; Jonathan Wilson, Humber River Regional Hospital, Toronto, Ontario, Canada; Indira Warrier, Children's Hospital of Michigan, Detroit, MI, USA; Irene Cherrick, University Hospital-SUNY, Syracuse, NY, USA; Kerry Blanchard, LSU Health Sciences Center, Shreveport, LA, USA; Scott Hall, Stanford University Hospital, Stanford, CA, USA; Louis M. Aledort, Mount Sinai Medical Center, New York, NY, USA; Craig M. Kessler, Georgetown University Medical Center, Washington, DC, USA; Herbert Cooper, University of North Carolina, Chapel Hill, NC, USA; M. Francisco Gonzalez, University of South Carolina, Columbia, SC, USA; William Owen, Children's Hospital of the King's Daughters, Norfolk, VA, USA; Douglas W. Blayney, Wilshire Oncology Medical Group, Pomona, CA, USA; David Bodensteiner, University of Kansas Medical Center, Kansas City, KS, USA; C Karabus, Red Cross Childrens Hospital, Cape Town, Western Cape, South Africa; M Vaithilingum, Addington Hospital, Durban, Kwazulu Natal, South Africa.

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