Title:

A CLINICAL INVESTIGATION TO ASSESS THE SAFETY AND PHARMACOKINETICS OF IMMUNE GLOBULIN INTRAVENOUS (HUMAN) SOLVENT/DETERGENT-TREATED IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASE

FINAL REPORT

JULY 1, 1992

TABLE OF CONTENTS

APPENDICES

FINAL REPORT SUMMARY

Patients with primary immunodeficiencies require regular infusions of intravenous immunoglobulin (IGIV) as part of their routine care. As a result of isolated reports of the transmission of non-A, non-B hepatitis by various IGIV preparations, Baxter Healthcare Corporation, Hyland Division has chosen to increase the margin of safety of its IGIV product through the inclusion of a viral inactivation step in the manufacturing procedure. A single-center study was undertaken to evaluate the safety and pharmacokinetics of a 400 mg/kg dose of this solvent/detergent-treated IGIV (IGIV S/D), as compared with that of the existing commercial formulation (IGIV).

Fifteen primary immunodeficient patients, ten with previous exposure to IGIV and/or Immune Serum Globulin (previously treated) and five with no previous exposure (previously untreated) received a total of 38 infusions over a four month period. The previously treated patients each were to receive a total of three infusions. The first infusion was randomized in a double-blinded fashion to either IGIV or IGIV S/D, with a cross-over to the alternate agent for infusion two. Infusion three for all patients was carried out with IGIV S/D. Nine of the ten previously treated patients received all three infusions. One patient was removed from the study after the first infusion due to a complication of his underlying disease. All five previously untreated patients received two infusions of IGIV S/D. Safety was measured in terms of the incidence of adverse reactions reported and any abnormal changes in vital signs.

Four of the ten previously treated patients experienced five adverse reactions in association with their twenty-eight infusions (17.9%). All five reactions consisted of systemic symptoms. Three were classified as mild, and two were classified as moderate. These adverse reactions were associated with three of ten (30%) of the commercial (licensed) product (IGIV) infusions, and with two of eighteen (11.1%) of the IGIV S/D infusions. These rates were not significantly different.

Four of the five previously untreated patients experienced five adverse reactions in association with their ten infusions (50%). All five reactions consisted of systemic symptoms. Two were classified as moderate, and three were classified as mild.

Pharmacokinetics did not differ between the IGIV and IGIV S/D formulations administered to the previously treated patients. The pharmacokinetics of the IGIV S/D formulation in the previously untreated patients were similar to the results obtained in the previously treated patients.

Data from this study support the safety and equivalent pharmacokinetics of a 400 mg/kg dose of IGIV S/D in both previously treated and previously untreated patients with primary immunodeficiencies.

GRO-C

Edward D. Gomperts, M.D.
Vice President
Medical and Clinical Affairs

1. INTRODUCTION

Intravenous immunoglobulin (IGIV) has been an established therapy in the United States since its introduction in 1981. The products manufactured by Baxter Healthcare Corporation, sold under the trade names Gammagard® and Polygam®, have been commercially available since 1986. IGIV has become a mainstay for treatment of primary immunodeficiency[1] diseases, idiopathic thrombocytopenic purpura[2], and B-cell chronic lymphocytic leukemia[3]. In addition, studies have documented utility in CMV pneumonitis in post-bone marrow transplant patients[4], neonatal sepsis prophylaxis[5,6], surgical sepsis prophylaxis[7,8], and many other therapeutic areas. Thus, IGIV has found widespread utility in a wide variety of patients, many of whom would not otherwise receive blood or blood products.

Over the course of time, there have been several reported instances[9,10,11,12,13,14] in which non-A, non-B hepatitis (now largely attributed to hepatitis C) was apparently transmitted by various IGIV preparations. As a result of these scattered events, and despite a documented lack of transmission of hepatitis C in a study of viral safety[15], recent concerns over the long term sequelae of hepatitis C virus infection prompted Baxter Healthcare Corporation, Hyland Division to increase the margin of safety of its IGIV product through the inclusion of a viral inactivation step in the manufacturing procedure. The method chosen, addition of organic solvent tri(n-butyl) phosphate (0.3%) and detergent octoxynol 9 (1.0%) (Triton X-100), has been utilized worldwide in the treatment of factor VIII products. To date, no episode of transmission of lipid enveloped viruses [(e.g. hepatitis B or C or human immunodeficiency virus (HIV)] has been attributed to products undergoing this viral inactivation step[16]. Baxter Healthcare's direct experience with its own studies conducted in its factor VIII product in more than 40 patients has contributed to this overall record of safety.[17]

Baxter Healthcare Corporation, Hyland Division has undertaken a clinical study to evaluate the safety and pharmacokinetics of IGIV that has been treated with organic solvent and detergent (IGIV S/D). The following report documents the results of this trial.

2. METHODS

2.1 Study Objective

The study had two objectives: (a) to evaluate the acute safety of solvent/detergent-treated immune globulin intravenous (human) (IGIV S/D) in patients with primary immunodeficiency disease; and (b) to establish the half-life of IGIV S/D and compare it to the half-life of commercially available immune globulin intravenous (human) (IGIV).

2.2 Study Design

This was a single center study, conducted by Raif F. Geha, M.D., at the Children's Hospital in Boston, Massachusetts. Pharmacokinetics and acute safety of IGIV S/D were evaluated in two populations of immunodeficiency patients. Ten previously treated patients

underwent a randomized, double-blind, cross-over study. These patients were randomized to receive either IGIV S/D or commercially available IGIV in the first phase of the study. A pharmacokinetics study was performed in conjunction with these first infusions. Each patient's IgG levels were allowed to return to their baseline IgG plus or minus 20% (trough). The patients were then crossed over to receive the alternate IGIV preparation, and a second pharmacokinetics study was performed in association with this infusion. Upon return to baseline IgG level plus or minus 20%, all such patients received a third infusion consisting of IGIV S/D and were followed for 21 to 28 additional days.

Five previously untreated patients received infusions of IGIV S/D, open label, for half-life determination. Approximately twenty-eight days after their first infusion, all patients received an additional dose of IGIV S/D.

All patients in both groups underwent laboratory testing as described in Observations (below) before each infusion and approximately twenty-one to twenty-eight days after their last infusion.

In addition, after completing the acute safety and pharmacokinetic study, the 5 previously untreated patients were given the option to continue with a 9 month viral safety follow-up study. This protocol amendment was submitted on March 26, 1992; reference BB IND 4261-002.

2.3 Entry Criteria

Patients meeting the following criteria were enrolled and treated:

2.3.1 Inclusion Criteria:

1) Patients must have been diagnosed with primary immunodeficiency as defined by WHO criteria[18].

2) Patients must have been more than twenty-four (24) months old.

3) Patients could be male or female.

4) Patients or their parent/legal guardian must have given written informed consent.

2.3.2 Exclusion Criteria:

1) Patients could not have positive viral markers for Hepatitis B Surface Antigen, Hepatitis B Core Antibody, Hepatitis B Surface Antibody, Hepatitis A Antibody, Hepatitis C Antibody, or antibodies to the Human Immunodeficiency Virus (HIV-1), Epstein-Barr virus or cytomegalovirus.

2) Female patients of child bearing age could not be pregnant, as demonstrated by serum human chorionic gonadotropin levels monitored prior to study entry. Any patient who became pregnant while on the study would have to be removed from the study immediately.

In addition, previously treated patients could not have received any blood or blood products other than an IGIV and/or immune serum globulin preparation, and previously untreated patients could not have received any blood or blood product including an IGIV and/or immune serum globulin preparation.

2.4 Dosage and Administration

Patients were to receive intravenous infusions of IGIV or IGIV S/D at a dose of 400 mg/kg for all infusions. The initial infusion rate was to be 1.0 mL/kg/hr, but the rate could be increased by doubling every half hour to a maximum of 8.0 mL/kg/hr, provided there were no adverse reactions.

In the event of a minor adverse reaction, the investigator was instructed to slow the rate of administration until symptoms ceased, or to stop the infusion completely if necessary. For more serious symptoms suggesting an allergic reaction, the investigator was instructed to stop the infusion completely. The maximum infusion rate for each infusion was recorded.

The IGIV and IGIV S/D used in this study were manufactured by Baxter Healthcare Corporation, Hyland Division, Glendale, California. IGIV S/D was supplied as a 5% (50 mg of protein/mL) lyophilized powder in 5.0 gram single use bottles. Sterile water for injection (U.S.P.), 96 mL fill size, a transfer device to aid in reconstitution, and an administration set with a 15 micron filter were also supplied. All reconstituted vials were pooled into an appropriate container for administration. Rate was controlled through the use of an intravenous infusion pump.

2.5 Observations

All patients provided a complete medical history and underwent a thorough physical examination prior to the first infusion. Physical examinations were also performed before each subsequent infusion and at the last study visit. Vital signs were monitored during all infusions, and the values were recorded at the beginning, middle, and end of each infusion.

All adverse reactions occurring during the infusions were recorded and described in detail. Each reaction was evaluated as to symptomatology, severity, and relationship to the IGIV or IGIV S/D infusion. The vital signs and any treatment administered during the adverse reaction were also recorded. Forty-eight (48) hours after the conclusion of each infusion, all patients were interviewed by telephone regarding possible adverse events. Any reactions occurring during this time were also recorded in detail.

The following laboratory assays were performed on each patient before each infusion and twenty-one to twenty-eight days after their last infusion:

Complete blood count with differential
Platelet count
Alanine aminotransferase
Aspartate aminotransferase
Lactate dehydrogenase
Blood urea nitrogen
Creatinine

Virology assays consisting of the following were performed prior to the first infusion and twenty-one to twenty-eight days following the last infusion:

Human Immunodeficiency Virus-1 Antibody
Hepatitis A Antibody
Hepatitis B Surface Antibody
Hepatitis B Surface Antigen
Hepatitis B Core Antibody
Hepatitis C Antibody
Epstein-Barr Virus Antibody
Cytomegalovirus Antibody

An additional aliquot of serum was frozen in the event later studies became necessary. The assays specific to the pharmacokinetics study were performed according to the following table:

	TIMEPOINT								
ASSAY	Pre Infusion (Baseline)	15 min. post	Day 1	Day 4	Day 7	Day 10	Day 14	Day 21	Day 28
Total Serum IgG	X	X	X	X	X	X	X	X	X
IgG Subclasses IgG 1 IgG 2 IgG 3 IgG 4	X	X	X	X	X	X	X	X	X
Antigen Specific Antibodies	X	X	X	X	X	X	X	X	X

Antigen specific antibodies referred to in the table included tetanus, cytomegalovirus, and pneumococcus. Furthermore, those patients who returned to baseline IgG before day twenty-eight did not require a twenty-eight day sample collection.

2.6 Criteria for Determining Safety and Pharmacokinetics

The primary criterion for determining safety was the percentage of patients who experienced treatment related adverse reactions. Any clinically significant changes in vital signs during the infusion were assessed, as were clinically significant changes in measured laboratory values.

The pharmacokinetic variables determined for both IGIV and IGIV S/D included total serum IgG levels versus time and half-life. These variables were compared for the two preparations.

2.7 Data Analysis

The adverse reaction rate in the IGIV and IGIV S/D preparations were compared using the Mainland-Gart χ^2-test with an adjustment for small sample size[19].

The vital signs measured during the infusions were compared qualitatively for clinically significant changes. All other quantitative data were summarized descriptively using means and standard deviations.

Total IgG half-life for all infusions were calculated using the method of Lee, Poon, and Kingdon[20]. The pharmacokinetics of the two products were compared using the analysis of variance allowing for the possibility of a period effect[21].

3. RESULTS

3.1 Patient Characteristics

Fifteen primary immunodeficient patients participated in this study between January 16, 1992 and May 26, 1992 at one center located at Children's Hospital in Boston, Massachusetts. A total of thirty-eight infusions were administered.

Nine previously treated primary immunodeficient patients were treated with three infusions of IGIV: one infusion of the commercially available IGIV preparation, and two infusions of the IGIV S/D preparation. Four of these nine patients received the commercial formulation as their first infusion, while the remaining five patients received the solvent/detergent treated formulation first. One patient, #SDP008, was taken off study by the study investigator after developing cellulitis requiring a larger dose of IGIV several weeks after the first infusion, consisting of the commercial formulation of IGIV. Among those patients receiving the complete series of three infusions, the maximum infusion rates ranged from 0.31 mL/kg/hr to 4.10 mL/kg/hr.

Five previously untreated primary immunodeficient patients each received two infusions of IGIV S/D. Among these five patients, maximum infusion rates ranged from 1.17 mL/kg/hr to 4.24 mL/kg/hr.

A summary of patient demographics for all patients is provided in Table 1.

Five of the ten previously treated patients reported a history of various allergies including: one patient to penicillin, the second to sulfa drugs, cats, horses, trees, dust mites, and mold; the third with eczema; the fourth patient to trimethoprim/sulfamethoxazole, penicillin, use of ciprofloxacin, clindamycin phosphate, and tetracycline; and the fifth patient to mold and trees. Two of the five previously untreated patients reported environmental allergies or aeroallergies.

3.2 Adverse Reactions

3.2.1 Previously Treated Patients

A total of five of twenty-eight infusions (17.9%) in previously treated patients were associated with adverse reactions. All five of these reported reactions were described as systemic symptoms, e.g., flushing, chills, nausea, or abdominal pain. No previously treated patients reported local pain or irritation at the intravenous (IV) needle site. The reported reactions among the previously treated patients included:

Adverse Reaction	Episodes Reported
Chills	3
Nausea	3
Elevated temperature	2
Flushing	1
Anxiety	1
Emesis	1
Abdominal pain	1

Of the five infusions associated with adverse reactions in previously treated patients, three were classified as mild, and two were classified as moderate. Of these reported reactions, four required systemic therapy, with acetaminophen used in two, ibuprofen in one, aspirin in one, and diphenhydramine in one. Two reactions were treated by reduction in the infusion rate, one infusion was stopped, then restarted, and one infusion was discontinued. Classification of the severity of these adverse reactions was performed at the discretion of the investigator according to his standard ratings. The investigator deemed the relationship of the adverse reactions to the infusion as probable in four reactions and remote in one reaction.

Among the previously treated patients, four of the five adverse reactions were related to the first infusion, while one adverse reaction was related to the second infusion. Three of the

adverse reactions in this group were associated with the administration of the commercial IGIV product, while two of the adverse reactions were associated with the administration of IGIV S/D. The three adverse reactions associated with the commercial formulation occurred at infusion rates of 0.77, 3.00, and 3.18 mL/kg/hr, and the two adverse reactions in the IGIV S/D formulation occurred at infusion rates of 0.31 and 3.08 mL/kg/hr. In summary, adverse reactions in previously treated patients occurred in three of ten (30%) of the commercial IGIV product infusions, while adverse reactions occurred in two of eighteen (11.1%) of the IGIV S/D infusions. These rates are not significantly different.

Six previously treated patients completed the study with no adverse reactions reported or documented during the infusion or within forty-eight hours post-infusion. Three patients experienced an adverse reaction with only one infusion during their time on study, one patient experienced an adverse reaction associated with two of the three infusions (one with commercial product, one with IGIV S/D), and one patient experienced an adverse reaction associated with his only infusion on study (commercial IGIV). Refer to Table 2 for a summary of individual patient adverse reactions.

3.2.2 Previously Untreated Patients

A total of five of ten infusions (50.0%) in the previously untreated patients were associated with adverse reactions. All five of these reported reactions were described as systemic symptoms, e.g., chills, nausea, elevated temperature, or flu-like symptoms. No adverse events were reported as local pain or irritation at the intravenous (IV) needle site. The reported reactions among the previously untreated patients included:

Adverse Reaction	Episodes Reported
Chills	4
Elevated temperature	2
Nausea	1
Flu-like symptoms	1
Hypertension	1
Flushing	1

Of the five infusions associated with adverse reactions in previously untreated patients, two were classified as moderate, and three were classified as mild. Of these reported reactions, three required systemic therapy, with acetaminophen used in three and diphenhydramine used in one. One reaction was treated by stopping, then restarting, the infusion. Classification of the severity of these adverse reactions was performed at the discretion of the investigator according to his standard ratings. The investigator deemed the relationship of the adverse reaction to the infusion as probable in two reactions and possible in three reactions.

Among the five infusions which were associated with adverse reactions in the previously untreated patients, three occurred in association with the first infusion, and two occurred in association with the second infusion. The rates of infusion associated with these adverse reactions ranged from 2.91 to 4.24 mL/kg/hr. All of these adverse reactions were associated with the use of IGIV S/D, the only formulation administered to this group of patients.

One previously untreated patient completed the study with no adverse reactions reported or documented during the infusion or within forty-eight hours post-infusion. Three patients experienced an adverse reaction associated with only one infusion during their time on study (two with the first infusion, one with the second infusion). One patient experienced adverse reactions associated with both infusions during the study. Refer to Table 3 for a summary of individual previously untreated patient adverse reactions.

3.3 Vital Signs

3.3.1 Previously Treated Patients

The summary statistics for each treatment (IGIV S/D and IGIV) and time point (beginning, middle and end infusion) are given in Table 4. The vital signs were compared over time and between the two treatments using a two-way analysis of variance model with repeated measures[22]. The findings are given in Table 5. Although there were slight differences in treatments for respiratory rates and small differences over time for temperature and diastolic blood pressure, it is clear from the summary statistics that these differences were not clinically meaningful.

3.3.2 Previously Untreated Patients

The results for vital signs in previously untreated patients are shown in Table 6. A one-way ANOVA[22] was used to compare the timepoints. There were no significant differences.

3.4 Physical Examinations

There were no clinically meaningful differences in physical examinations during the study among either the previously treated patients or the previously untreated patients.

3.5 Laboratory Evaluation

3.5.1 Previously Treated Patients

Laboratory data were analyzed using the one-way analysis of variance (ANOVA) repeated measures model. The summary statistics for the previously treated patients are given in Table 7. Note that in some instances, a logarithmic transformation was required in order to

achieve normality and, thus, use the ANOVA model properly. The p-values given in Table 7 refer to the comparisons of the mean values across time. There were no significant findings, except for the slight decline in hemoglobin levels (the post-infusion 3 mean is lower), a change in blood urea nitrogen (the pre-infusion 3 mean is slightly elevated) and a slight increase in mean basophil level. In no case were these changes clinically significant.

3.5.2 Previously Untreated Patients

For the previously untreated patients, the results are given in Table 8. Again, there were small changes in two variables: red blood cells (the pre-infusion 1 mean is higher) and hematocrit (the pre-infusion 1 is higher than the post-infusion 2 results).

Patient #U001 who has Down's Syndrome and recurrent pneumonias secondary to IgG_2 subclass deficiency, showed elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at baseline (prior to first infusion) and at pre-infusion 2. His red blood cell indices showed a fall post-infusion with the pre-infusion #2 hemoglobin level being 2.7 g/dl lower than baseline.

Timepoint	Date	ALT (IU/L)	AST (IU/L)
Pre-infusion 1	1/16/92	134	109
Pre-infusion 2	2/13/92	250	137
21-28 days post-infusion 2	3/13/92	43	44

Figure 3.5.2-1: Patient #U001 ALT and AST Levels

This patient was hospitalized between January 11, 1992 and January 19, 1992 with an admitting diagnosis of right middle lobe pneumonia. The patient received a full seven day course of ampicillin sodium/sulbactam sodium which has been associated with reports of elevated ALT, AST, lactate dehydrogenase and alkaline phosphatase levels. The patient's blood culture from the time of admission grew H. influenzae. A repeat blood culture after approximately two days of antibiotic treatment was negative.

Upon discharge the patient remained on amoxicillin/clavulanate potassium, 125 mg by mouth every 8 hours. This antibiotic is also associated with moderate rises in ALT, and/or AST levels. The observed red blood cell changes are considered secondary to the pneumonic process as there were no further changes after the second infusion of the trial.

At no time did patient #U001 show any clinical signs of hepatic dysfunction. The post-infusion #2 sample showed much improved ALT levels, although this was still marginally

abnormal. (Refer to Table 9 for a complete summary of liver function assay results for all patients on study.)

Due to the fact that the previously untreated patients were to continue with the 9-month follow-up study, viral safety was also considered during this portion of the trial. Hepatitis A and Hepatitis C antibody was positive at the 21-28 days post last infusion timepoint for patients #U002, #U003, #U004, and #U005. Hepatitis B core antibody was positive for patients #U002 and #U005 at this same timepoint. Also, Hepatitis B surface antibody was positive for patient #U005 at 21-28 days post last infusion. Patient #U001 demonstrated positive results for Hepatitis A antibody, Hepatitis B core antibody, and Hepatitis C antibody at the 21-28 post last infusion timepoint. These findings are not unexpected being the result of passive antibody transmission.

3.6 Pharmacokinetics

3.6.1 Previously Treated Patients

The pharmacokinetics were analyzed by the method of Lee, Poon, and Kingdon[20]. Since this was a cross-over study the pair-wise results (IGIV and IGIV S/D) were compared using the Wilcoxon signed-rank test[23].

The individual half-lives for each of the parameters analyzed are given in Table 10. Total IgG, IgG1, IgG2, IgG3, IgG4, and pneumococcal antibody levels were considered. Tetanus and cytomegalovirus antibody levels were too low to attempt a reasonable pharmacokinetics analysis. In addition, in Table 10 a value indicated as "not valid" represents a result over 100 days, which is typically caused by a flat β-phase (data points late in the collection point period that are close together).

The summary statistics are given in Table 11. There is no evidence of any difference between the two treatments with regards to any of the parameters considered.

3.6.2 Previously Untreated Patients

The individual pharmacokinetics results with summary statistics are given in Table 12. (The numbers for IgG4, tetanus, and cytomegalovirus were too small to warrant analysis.)

4. DISCUSSION

The primary endpoint for assessing the safety of the solvent/detergent-treated IGIV was the percentage of patients who experienced treatment-related adverse reactions. In the previously treated patient group, there was no difference in the rate of adverse reactions occurring during infusions of IGIV and IGIV S/D. Whereas these rates were higher than the rates reported in studies of IGIV in such populations[24], they do not differ from those experienced in a recent study of varying rates and concentrations of IGIV[2]. Furthermore, the

type and character of the adverse reactions reported were similar for the test and control agents and to those reported previously. In addition, they were self-limited and did not result in the administration of less than the 400 mg/kg dose except in the single patient, #P008, as previously discussed.

In the previously untreated patient group, five of ten infusions, 50%, were associated with adverse reactions. Three of the five reactions occurred during the patients' first exposure to IGIV. It is important to note that the majority of adverse reactions, should they occur, do so most often in association with a previously untreated patient's first exposure to intravenous immune globulin.[25] The causes of these reactions are unknown. Also, these five patients are continuing with a nine month viral safety follow-up study in which adverse reaction rate will be evaluated. As more data is collected on these patients, it is expected that the adverse reaction rate will normalize to that experienced in the previously treated patient group. None of the reactions were serious and none resulted in the administration of less than the 400 mg/kg dose required by the protocol.

Overall, patient tolerance of the infusions was excellent. There were no significant differences in vital signs recorded during the infusions, and no significant laboratory abnormalities occurred.

The pharmacokinetics of the two products did not differ in the previously treated patients, and the IGIV S/D displayed similar pharmacokinetics in the previously untreated patients.

All of the raw data related to this clinical trial are available both on written case report forms as well as in a Paradox® (Borland) database archived in the Clinical Development Department of Baxter Hyland Division.

5. CONCLUSION

In summary, IGIV S/D was infused safely in both previously treated and previously untreated primary immunodeficient patients. Adverse reactions were associated with 30% of commercial IGIV infusions and 11.1% of IGIV S/D infusions in previously treated patients, and with 50% of IGIV S/D infusions in previously untreated patients. All of the adverse reactions associated with infusions of IGIV S/D were similar to that experienced by the control commercial IGIV and none were serious, unexpected or life-threatening. All but one patient (#P008, removed for a complication of his underlying immunodeficiency) completed the protocol.

The pharmacokinetics of the commercial IGIV and the IGIV S/D did not differ.

We believe that the additional protection afforded in relation to viral safety by the addition of a step to treat IGIV with a solvent/detergent mixture, support its use in primary immunodeficiency patients, whether previously treated or previously untreated. In addition,

this study shows approximate equivalence between the commercial IGIV and the IGIV S/D concerning pharmacokinetics and adverse reactions.

REFERENCES

1. Ochs HD, Lee ML, Fischer SH, et al. Efficacy of a new Intravenous Immunoglobulin preparation in Primary Immunodeficiency Patients. Clin Ther 9(5) pp512-522 1987.

2. Data on file.

3. Bunch C, Gale R, Chapel H, et al. Intravenous Immunoglobulin for the Prevention of Infection in Chronic Lymphocytic Leukemia: A Randomized, Controlled Clinical Trial. NEJM 319 (14) pp902-907, 1988.

4. Emanuel D, Cunningham I, Elyser K-J, et al. Cytomegalovirus Pneumonia after Bone Marrow Transplantation Successfully Treated with the Combination of Ganciclovir and High Dose Intravenous Immune Globulin Ann Int Med 109(10) pp777-782, 1988.

5. Baker CJ: Multicenter Trial of Intravenous Immunoglobulin (IGIV) to Prevent Late-Onset Infection in Preterm Infants: Preliminary Results. Abstract 1633, Society for Pediatric Research, May 1988.

6. Baker CJ, Melish ME, Hall RT, et al. Intravenous Immune Globulin for the Prevention of Nosocomial Infection in Low Birth Weight Neonates. New Engl J Med to appear July 24, 1992.

7. Cometta A, Baumgartner JD, Lee M, et al. Prophylaxis of High Risk Surgical Patients with Standard Intravenous Immunoglobulin G or with Antibody to Core Glycolipid. Abstract 476, ICAAC 1990.

8. Cometta A, Baumgartner JD, Lee ML et al. Prophylactic Study of Standard Intravenous Immunoglobulin and Core Lipopolysaccharide Immunoglobulin in High Risk Post-Surgical Patients. New Engl J Med. To appear July 24, 1992.

9. Ochs HD, Fischer SH, Virant FS, et al. Non-A Non-B Hepatitis and Intravenous Immunoglobulin Lancet: 404-405, 1985.

10. Ochs HD, Fischer SH, Virant FS, et al. Non-A Non-B Hepatitis after Intravenous Immunoglobulin Lancet: p323, 1986.

11. Lane RS, Non-A Non-B Hepatitis from Intravenous Immunoglobulin Lancet ii, p974-975, 1983.

12. Lever AML, Webster ADB, Brown D, et al. Non-A Non-B Hepatitis occurring in the agammaglobulinemia patients after intravenous immunoglobulin Lancet ii, 1062-1064, 1984.

13. Bjorkander J, Cunningham-Rundles C, Lunden P, et al. Intravenous Immunoglobulin Prophylaxis causing liver damage in 17 of 144 patients with hypogammaglobulinemia or IgG subclass deficiency. Abstract 27 Second Meeting, European Group for Immunodeficiencies, 1986.

14. Williams PG, Yap PL, Gillon J, et al. Transmission of Non-A Non-B Hepatitis by pH4-Treated Intravenous Immunoglobulin Vox Sang 157, pp15-18, 1989.

15. Lee ML, Courter SG, Tait D, et al. Long Term Evaluation of Intravenous Immune Globulin Preparation with regard to Non-A Non-B Hepatitis Safety Viral Hep and Liver Dis p596-599, 1988.

16. New York Blood Center, data on file.

17. Addiego, et al. Treatment of Hemophilia A with a Highly Purified Factor VIII concentrate prepared by anti-FVIII, immunoaffinity chromatography. Thrombosis and Hemostasis. January 1992.

18. World Health Organization Report: Immunodeficiency, Report of a WHO Scientific Group. Clin Immunol Immunopath. 13:296-359, 1979.

19. Jones B, Kenward MG: Design and Analysis of Cross-Over Trials. London: Chapman and Hall, 1989.

20. Lee ML, Poon WY, Kingdon HS: A Two-Phase Linear Regression Model for Biologic Half-Life Data. Journal Lab and Clin Med, Vol 115, No. 6, pp745-748, June 1990.

21. Crowder MD, Hund DJ: Analysis of Repeated Measures. London: Chapman and Hall, 1990.

22. Glantz SA, Slinker BK. Primer of Applied Regression and Analysis of Variance. New York: McGraw-Hill, Inc., 1990.

23. Conover WJ. Practical nonparametric Statistics. New York: John Wiley & Sons, 1971.

24. Direction Insert - "Immune Globulin Intravenous (Human) Gammagard®"; Baxter Healthcare Corporation, Hyland Division, Glendale, California, Dec., 1990.

25. Cunningham-Rundles, C. Intravenous Immunoglobulin: Development as a Therapy and Unresolved Issues. NIH Consensus Development Conference on Intravenous Immunoglobulin: Prevention and Treatment of Disease, May 21-23, 1990. Program and Abstracts, pp 25-29.

TABLE 1
PATIENT DEMOGRAPHICS

	Previously Treated Patients	Previously Untreated Patients	Total
Total Patients Treated			
Male	4	3	7
Female	6	2	8
Age at Study Entry (years)			
Mean	15.71	16.60	
Range	2.53 - 41.00	2.96 - 30.71	
Weight at Study Entry (kg)			
Mean	42.38	53.56	
Range	15.9 - 82.0	13.0 - 103.0	
Diagnosis			
IgA Deficiency		1 female	1
Common Variable Immunodeficiency	3 females	2 males	5
X-linked Agammaglobulinaemia	2 males		2
IgG2 Subclass Deficiency	1 male 3 females	1 male	5
IgG3 Subclass Deficiency		1 female	1
IgG2 Subclass and IgA Deficiency	1 male		1
Age at Disease Diagnosis (years)			
Mean	9.18	16.03	
Range	0 - 36.58	1.75 - 30.75	
Pre-existing Allergies	5[1]	2[2]	

[1] penicillin; sulfa drugs, cats, horses, trees, dust mites, mold; eczema; trimethoprim/sulfamethoxazole, penicillin, ciprofloxacin, generic clindamycin, tetracycline; mold, trees

[2] environment allergies; aeroallergies

TABLE 2
ADVERSE REACTION SUMMARY - PREVIOUSLY TREATED PATIENTS

Patient ID	Study Drug	Infusion Number	Patient Weight (kg)	Volume Infused	Max. Rate mL/hr/kg	Overall Severity	Symptoms	Relationship to Infusion	Actions Taken
P001	IGIV	1	57	468	3.18	mild	mild flushing	remote	slowed infusion, gave 625 mg Tylenol
P007	IGIV	2	65	518	0.77	mild	mild chills, mild nausea	probable	gave ibuprofen, 400 mg
P008	IGIV	1	35	200	3.00	moderate	moderate chills, mild anxiety, moderate elevated temperature	probable	stopped infusion, gave Benadryl 1 mg/k and Tylenol 15 mg/k
P007	IGIV S/D	1	65	508	0.31	moderate	mild chills, mild nausea, moderate emesis, mild elevated temperature	probable	stopped and restarted infusion, gave aspirin 650 mg
P010	IGIV S/D	1	39	312	3.08	mild	mild nausea, mild abdominal pain	probable	Slowed infusion, gave Tylenol 325 mg

TABLE 3
ADVERSE REACTION SUMMARY - PREVIOUSLY UNTREATED PATIENTS

Patient ID	Study Drug	Infusion Number	Patient Weight (kg)	Volume Infused	Max. Rate mL/hr/kg	Overall Severity	Symptoms	Relationship to Infusion	Actions Taken
U002	IGIV S/D	1	103	824	2.91	moderate	mild chills, moderate elevated temperature	probable	none
U003	IGIV S/D	2	59	460	4.24	mild	mild chills, mild flu-like symptoms	possible	none
U004	IGIV S/D	1	17	138	3.04	mild	mild elevated temperature, mild flushing	possible	gave Tylenol 240 mg
U005	IGIV S/D	1	75	600	3.99	moderate	moderate chills, mild nausea, mild hypertension	probable	stopped and restarted infusion gave Benadryl 60 mg IV, Tylenol 975 mg
U005	IGIV S/D	2	75	600	3.99	mild	mild chills	possible	gave Tylenol 650 mg

TABLE 4
PREVIOUSLY TREATED PATIENTS
VITAL SIGNS - SUMMARY STATISTICS

IGIV S/D (mean±S.D.)			
Parameter	**Pre-infusion**	**Mid-infusion**	**End-infusion**
Temperature (°C)	36.7±0.4	36.7±0.5	36.8±0.6
Pulse (min)	92±9.5	90±9.4	90±6.4
Respiratory Rate (min)	21±1.7	21±1.5	21±2.1
SBP (mm/Hg)	104±11.2	105±9.8	104±11.3
DBP (mm/Hg)	66±7.4	70±5.4	66±5.4
IGIV (mean±S.D.)			
Temperature (°C)	36.5±0.4	36.9±0.7	37.1±0.9
Pulse (min)	94±11.9	97±18.9	96±9.9
Respiratory (min)	21±2.2	23±3.6	23±2.6
SBP (mm/Hg)	102±14.0	102±11.0	102±10.6
DBP (mm/Hg)	64±10.6	69±7.8	65±9.3

TABLE 5
PREVIOUSLY TREATED PATIENTS
VITAL SIGNS
P-VALUES FOR 2-WAY REPEATED MEASURES ANOVA

Parameter	Treatment Differences	Time Differences
Temperature (°C)	p=0.42	p=0.02
Pulse (min)	p=0.12	p=0.57
Respiratory Rate (min)	p=0.04	p=0.21
SBP (mm/Hg)	p=0.40	p=0.996
DBP (mm/Hg)	p=0.49	p=0.03

TABLE 6
PREVIOUSLY UNTREATED PATIENTS
VITAL SIGNS - SUMMARY STATISTICS

Parameter	Pre-infusion	Mid-infusion	End-infusion	P (comparing time points)
Temperature(°C)	36.4±0.6	36.7±0.5	37.0±0.9	0.17
Pulse (min)	100±14	101±11.9	98±16.0	0.92
Respiratory Rate (min)	21±2.7	21±2.1	21±1.6	0.99
SBP (mm/Hg)	112±15.3	109±15.6	112±11.9	0.90
DBP (mm/Hg)	61±15.9	67±14.1	70±11.9	0.38

TABLE 7
LABORATORY RESULTS - PREVIOUSLY TREATED PATIENTS
SUMMARY STATISTICS

Parameter	Pre-infusion 1	Pre-infusion 2	Pre-infusion 3	Post-infusion 3 (28 days)	p*
White Blood Cell ($x10^3/mm^3$)	6.23 ± 2.45**	5.58 ± 1.40	5.75 ± 1.89	5.45 ± 2.04	0.8776
Red Blood Cell ($x10^6/mm^3$)	4.45 ± 0.43	4.40 ± 0.44	4.40 ± 0.44	4.46 ± 0.42	0.6145
Hemoglobin*** (gm/dL)	12.69 ± 1.15	12.60 ± 1.18	12.45 ± 1.02	12.60 ± 1.25	0.0479
Hematocrit*** (%)	37.01 ± 3.40	36.20 ± 3.76	36.64 ± 3.39	36.94 ± 3.49	0.3886
Segments (%)	56.72 ± 14.76	53.66 ± 16.74	52.24 ± 17.00	54.40 ± 12.52	0.9920
Lymphocytes (%)	29.69 ± 12.48	33.44 ± 14.20	33.95 ± 11.08	32.66 ± 8.68	0.7546
Monocytes*** (%)	5.70 ± 1.50	6.30 ± 2.16	5.11 ± 0.91	6.08 ± 1.38	0.1918
Eosinophils*** (%)	3.12 ± 2.75	3.16 ± 2.11	3.98 ± 3.89	3.66 ± 2.21	0.9616
Basophils (%)	0.47 ± 0.11	0.71 ± 0.40	0.64 ± 0.29	1.08 ± 0.71	0.0481
Platelets*** ($x10^3/mm^3$)	246.22 ± 58.38	244.67 ± 70.21	276.00 ± 73.32	276.40 ± 64.44	0.2665
Alanine*** Aminotransferase (IU/L)	25.20 ± 7.22	24.33 ± 3.43	26.00 ± 4.17	24.00 ± 3.16	0.1809
Aspartate*** Aminotransferase (IU/L)	22.80 ± 6.70	22.44 ± 5.29	22.12 ± 4.88	21.83 ± 4.71	0.7343
Lactate*** Dehydrogenase (mu/ml)	108.70 ± 38.48	119.00 ± 38.83	98.75 ± 20.37	113.33 ± 41.05	0.2809
Blood Urea Nitrogen (mg/dL)	11.90 ± 3.87	11.11 ± 3.62	15.25 ± 5.39	12.67 ± 1.51	0.0293
Creatinine (mg/dL)	0.66 ± 0.17	0.68 ± 0.16	0.69 ± 0.16	0.70 ± 0.15	0.6648

* By one-way ANOVA - repeated measures
** mean ± standard deviation
*** log-transformed to achieve normality

TABLE 8
LABORATORY RESULTS - PREVIOUSLY UNTREATED PATIENTS
SUMMARY STATISTICS

Parameter	Pre-infusion 1	Pre-infusion 2	Post-infusion 2 (28 days)	p*
White Blood Count*** ($x10^3/mm^3$)	8.56 ± 5.74**	7.89 ± 3.22	6.43 ± 2.33	0.6426
Red Blood Count ($x10^6/mm^3$)	5.02 ± 0.39	4.63 ± 0.44	4.67 ± 0.50	0.0366
Hemoglobin (gm/dL)	13.80 ± 1.08	12.82 ± 1.87	12.90 ± 1.84	0.0771
Hematocrit (%)	41.76 ± 3.01	38.32 ± 3.85	38.50 ± 4.25	0.0475
Segments*** (%)	52.84 ± 6.14	56.68 ± 16.02	50.56 ± 15.82	0.4222
Lymphocytes (%)	29.66 ± 5.45	31.16 ± 14.78	35.18 ± 14.66	0.4841
Monocytes (%)	5.78 ± 2.07	5.08 ± 1.00	5.64 ± 1.69	0.2893
Eosinophils*** (%)	4.15 ± 3.36	2.42 ± 1.91	2.24 ± 1.87	0.5011
Basophils*** (%)	0.85 ± 0.49	0.68 ± 0.18	1.10 ± 0.54	0.2909
Platelets ($x10^3/mm^3$)	260.20 ± 59.60	270.20 ± 114.42	267.40 ± 112.78	0.9402
Alanine*** Aminotransferase (IU/L)	46.80 ± 48.84	71.40 ± 99.96	27.60 ± 9.37	0.2714
Aspartate*** Aminotransferase (IU/L)	44.60 ± 36.45	49.00 ± 49.36	34.40 ± 10.41	0.8167
Lactate Dehydrogenase (mu/ml)	152.40 ± 57.27	141.60 ± 52.60	160.00 ± 73.66	0.7774
Blood Urea*** Nitrogen (mg/dL)	13.80 ± 4.87	13.40 ± 5.68	18.00 ± 8.40	0.6444
Creatinine (mg/dL)	0.82 ± 0.47	0.86 ± 0.48	0.84 ± 0.48	0.7588

* By one-way ANOVA - repeated measures
** mean ± standard deviation
*** log-transformed to achieve normality

TABLE 9
LABORATORY RESULTS - LIVER FUNCTION ASSAYS
PREVIOUSLY TREATED AND UNTREATED PATIENTS

	Alanine Aminotransferase (IU/L)	Aspartate Aminotransferase (IU/L)	Lactate Dehydrogenase (mu/mL)	Blood Urea Nitrogen (mg/dL)	Creatinin (mg/dL)
PREVIOUSLY UNTREATED PATIENTS					
Patient SDU001					
pre-infusion 1	134	109	208	19	0.30
pre-infusion 2	250	137	211	20	0.40
post-infusion 2	43	44	212	24	0.50
Patient SDU002					
pre-infusion 1	28	31	181	15	1.20
pre-infusion 2	32	30	185	13	1.30
post-infusion 2	27	31	122	24	1.20
Patient SDU003					
pre-infusion 1	26	19	66	6	0.70
pre-infusion 2	19	20	95	5	0.80
post-infusion 2	27	19	63	5	0.60
ıtient SDU004					
pre-infusion 1	20	34	183	13	0.50
pre-infusion 2	26	29	110	12	0.40
post-infusion 2	18	44	250	14	0.40
Patient SDU005					
pre-infusion 1	26	30	124	16	1.40
pre-infusion 2	30	29	107	17	1.40
post-infusion 2	23	34	153	23	1.50

	Alanine Aminotransferase (IU/L)	Aspartate Aminotransferase (IU/L)	Lactate Dehydrogenase (mu/mL)	Blood Urea Nitrogen (mg/dL)	Creatinin (mg/dL)
PREVIOUSLY TREATED PATIENTS					
Patient SDP001					
pre-infusion 1	20	14	99	14	0.9
pre-infusion 2	25	16	98	9	0.8
pre-infusion 3	26	18	89	19	0.8
post-infusion 3	18	30	179	11	0.7
Patient SDP002					
pre-infusion 1	31	30	114	16	0.4
pre-infusion 2	29	29	123	16	0.4
pre-infusion 3	27	31	122	24	0.4
post-infusion 3	24	23	122	15	0.4
Patient SDP003					
pre-infusion 1	26	14	62	7	0.8
pre-infusion 2	28	14	70	7	0.9
pre-infusion 3	29	18	106	8	0.9
post-infusion 3	26	16	88	14	0.8
Patient SDP004					
pre-infusion 1	15	32	194	6	0.6
pre-infusion 2	21	30	189	5	0.5
pre-infusion 3	19	25	133	8	0.6
post-infusion 3	not done	not done	not done	not done	not done
Patient SDP005					
pre-infusion 1	25	23	105	16	0.6
pre-infusion 2	23	23	134	12	0.7
pre-infusion 3	24	22	86	18	0.7
post-infusion 3	not done	not done	not done	not done	not done

	Alanine Aminotransferase (IU/L)	Aspartate Aminotransferase (IU/L)	Lactate Dehydrogenase (mu/mL)	Blood Urea Nitrogen (mg/dL)	Creatinin (mg/dL)
Patient SDP006					
pre-infusion 1	22	25	97	13	0.4
pre-infusion 2	23	24	113	14	0.6
pre-infusion 3	23	26	93	15	0.6
post-infusion 3	not done	not done	not done	not done	not done
Patient SDP007					
pre-infusion 1	25	24	128	17	0.80
pre-infusion 2	23	20	106	10	0.80
pre-infusion 3	33	20	90	15	0.80
post-infusion 3	27	22	132	12	0.80
Patient SDP008					
pre-infusion 1	42	30	137	10	0.60
pre-infusion 2	-- OFF STUDY --				
pre-infusion 3	-- OFF STUDY --				
post-infusion 3	-- OFF STUDY --				
Patient SDP009					
pre-infusion 1	22	16	86	10	0.80
pre-infusion 2	19	24	163	14	0.70
pre-infusion 3	not done	not done	not done	not done	not don
post-infusion 3	24	19	99	12	0.70
Patient SDP010					
pre-infusion 1	24	20	65	10	0.70
pre-infusion 2	28	22	75	13	0.70
pre-infusion 3	27	17	71	15	0.70
post-infusion 3	25	21	60	12	0.80

TABLE 10

PREVIOUSLY-TREATED PATIENTS-HALF-LIFE
(in days)

	IGIV						IGIV S/D					
Pt ID	Total IgG (mg/dL)	IgG1 (mg/dL)	IgG2 (mg/dL)	IgG3 (mg/dL)	IgG4 (mg/dL)	Pneumo-coccus (AU)	Total IgG (mg/dL)	IgG1 (mg/dL)	IgG2 (mg/dL)	IgG3 (mg/dL)	IgG 4 (mg/dL)	Pneumo-coccus (AU)
SDP001	47.7	49.6	32.0	not valid	44.3	43.0	40.1	45.5	84.3	85.5	22.0	not valid
SDP002	62.2	87.0	90.2	20.4	5.3	not valid	27.5	not valid	9.9	19.4	29.2	24.4
SDP003	40.4	40.7	40.6	18.3	26.8	30.6	30.9	79.6	not valid	10.0	not valid	15.6
SDP004	not valid	35.4	not valid	not valid	not valid	61.4	not valid	not valid	not valid	not valid	47.5	91.9
SDP005	not valid	19.5	41.4	43.1	not valid	not valid	not valid	21.2	26.7	29.5	10.6	53.4
SDP006	26.4	25.8	28.0	5.6	22.2	20.4	47.4	48.3	22.8	not valid	not valid	59.6
SDP007*	20.4	18.2	31.8	9.1	12.0	25.4	22.5	19.6	28.7	6.2	33.1	17.8
SDP008**	14.9	28.6	25.5	2.7	76.9	9.2	not done - patient off study					
SDP009	24.3	11.2	13.5	10.6	30.9	2.9	66.0	10.6	14.3	25.0	27.6	11.4
SDP010	36.4	74.4	70.2	34.6	72.2	not valid	29.8	71.2	31.7	not valid	26.6	57.2

*IGIV: Three data points
**IGIV: Five data points
(all others have 6-8 data points)

TABLE 11
PREVIOUSLY TREATED PATIENTS
SUMMARY STATISTICS-HALF-LIFE
(in days)

Parameter	IGIV (mean ± S.D. range)	n	IGIV S/D (mean ± S.D. range)	n	P*
Total IgG (mg/dL)	34.1±15.7 (14.9-62.2)	8	37.7±15.0 (22.5-66)	7	0.87
IgG1 (mg/dL)	39.0±24.8 (11.2-87.0)	10	42.3±26.6 (10.6-79.6)	7	0.50
IgG2 (mg/dL)	41.5±24.0 (13.5-90.2)	9	31.2±24.7 (9.9-84.3)	7	0.24
IgG3 (mg/dL)	18.0±14.3 (2.7-43.1)	9	29.3±28.9 (6.2-85.5)	6	0.50
IgG4 (mg/dL)	36.3±26.4 (5.3-76.9)	8	28.1±11.2 (10.6-47.5)	7	0.69
Pneumococcus (AU)	27.6±20.0 (2.9-61.4)	7	41.4±28.5 (11.4-91.9)	8	0.35

*-value (2-tailed) for comparison of the two treatment groups by Wilcoxon signed-ranks test

TABLE 12
PREVIOUSLY UNTREATED PATIENTS
HALF-LIFE WITH SUMMARY STATISTICS
(IgIV S/D)
(in days)

PT ID	TOTAL IgG (mg/dL)	IgG1 (mg/dL)	IgG2 (mg/dL)	IgG3 (mg/dL)	Pneumococcus (AU)
SDU001	not valid	not valid	18.9	not valid	57.3
SDU002	41.5	35.3	not valid	82.4	66.4
SDU003	not valid	56.5	39.3	27.4	63.6
SDU004	49.1	not valid	38.7	52.2	77.5
SDU005	67.8	37.6	not valid	29.8	5.5
Mean±S.D. (range)	52.8±13.5 (41.5-67.8)	43.1±11.6 (35.3-56.5)	32.3±11.6 (18.9-39.3)	48.0±25.5 (27.4-82.4)	54.1±28.1 (5.5-77.5)