

Efficacy and Safety of Privigen in Children and Adolescents With Primary Immunodeficiency

Joseph A. Church, MD,¹ Michael Borte, MD, PhD,² Hassan Taki, MD,³ Robert P. Nelson Jr, MD,⁴
John W. Sleasman, MD,⁵ Alan P. Knutsen, MD,⁶ Edouard Le Gall, MD,⁷
Marianne Debre, MD,⁸ and Peter Kiessling, MD⁹

The objective of this prospective, open-label, single-arm, Phase III study was to assess the efficacy and safety of Privigen®, the first 10% liquid intravenous immunoglobulin stabilized with L-proline, in patients with primary immunodeficiency. As part of a larger study, 19 children (3–11 years) and 12 adolescents (12–15 years) received Privigen 200–741 mg/kg intravenously for 12 months at a maximum infusion rate of 8 mg/kg/min. Thirteen patients received infusions at up to 12 mg/kg/min as part of an extension study. The primary endpoint was the annual rate of acute serious bacterial infections (aSBIs) per patient. Privigen was effective, as indicated by the annual rate of aSBI of 0.12 per patient (upper 1-sided 99% CI 0.499) in 3- to 11-year-olds and 0.10 (CI 0.642) in 12- to 15-year-olds. Three patients experienced 1 aSBI each, but did not discontinue treatment. The annual rate of all infections (including aSBIs) per patient was 4.63 in children and 2.42 in adolescents. The annual rate of days missed from school/day care was 11.5 days in children and 4.8 days in adolescents, consistent with the low annual rate of hospitalization (0.53 days and 0 days, respectively). Privigen administration was well-tolerated even at high infusion rates. The proportion of infusions with temporally associated AEs for the entire pediatric population was 0.18 (upper 1-sided 95% CI 0.221). One patient experienced serious AEs considered related to study drug and was withdrawn. Privigen was effective in sustaining a low incidence of infections, including aSBIs, and showed a good tolerability profile, with adverse events typical of disease and treatment.

Introduction

RECURRENT INFECTIONS IN CHILDREN with primary immunodeficiencies (PIDs) can cause extensive morbidity and even mortality. The intervention considered a standard and life-saving treatment in these patients is the infusion of purified human gammaglobulin antibodies. Privigen® is a new, high-purity intravenous immunoglobulin (IVIG) preparation formulated with L-proline for optimal tolerability. A relatively high number of children (31/80) were included in a Phase III study of Privigen, presenting an opportunity to selectively describe the use of this new agent in a pediatric population.

Primary immunodeficiencies are a large group of genetically heterogeneous disorders affecting the development and maturation of cells of the immune system.¹ Genetic defects affecting B- or T-cell receptors, cytokine receptors, or signaling molecules can cause a similar phenotype, that is, antibody deficiency.² More than 140 distinct inherited PIDs have been identified to date.³ The true incidence of these deficiencies is not known; however, some estimates are ~1 of every 10,000 live births.^{2,3} It is likely that many more individuals with PID remain undiagnosed and thus untreated. Recently, Boyle and Buckley conducted a phone survey of 10,005 US households and reported a PID prevalence of

¹Childrens Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, California.

²Municipal Hospital "St. Georg" Leipzig, Academic Teaching Hospital of the University of Leipzig, Germany.

³Fort Wayne Medical Institute, Fort Wayne, Indiana.

⁴Indiana University School of Medicine and the Indiana University Simon Cancer Center, Indianapolis, Indiana.

⁵Department of Pediatrics, University of South Florida, St. Petersburg, Florida.

⁶St. Louis University Health Sciences Center, St. Louis, Missouri.

⁷Department of Pediatrics, CHU Hôpital Sud, Rennes, France.

⁸Hôpital Necker-Enfants Malades, Paris, France.

⁹CSL Behring GmbH, Marburg, Germany.

1:1,200, comprised predominantly of B-cell immunodeficiencies.⁴ Common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA) are antibody deficiency disorders that predispose patients to otitis and recurrent infections of the upper and lower respiratory tracts, and the potential to progress to severe chronic lung disease. The onset of recurrent infections in patients with XLA often begins in the first year of life, whereas patients with CVID may have a congenital onset in 1–5 years of age or acquired onset in 16–20 years of age.^{5,6} Patients with CVID are also susceptible to autoimmune disorders and lymphoreticular malignancies.⁷

Immunoglobulin replacement by the intravenous (IVIG) or subcutaneous (SCIG) routes is considered a standard and life-saving therapy in patients with diseases characterized by impaired antibody production.⁸ Appropriate IgG antibody replacement reduces the rate of infections and infectious complications and improves patients' and parents' quality of life.^{8,9} Treatment of antibody deficiency has been studied in numerous clinical trials with different IVIG products.^{10–13} It has been proposed that IVIG replacement therapy should be adjusted for each individual patient.¹⁴ Published guidelines call for serum IgG trough levels of at least 5 g/L to preserve pulmonary function, but higher doses may be preferable in patients with established chronic lung and/or sinus disease.^{12,15–18}

Privigen is a 10% liquid preparation of polyvalent human IgG formulated for intravenous administration. Stabilization with L-proline at pH 4.8 is unique in that it fully preserves IgG functional activity without a requirement for refrigeration for up to 36 months,¹⁹ and minimizes the formation of IgG dimers during storage.^{20,21}

We report herein the results of the pediatric subpopulation of an open-label Phase III study utilizing Privigen for the treatment of patients with PID.

Patients and Methods

Patients

The patient population was comprised of 31 pediatric patients who were part of a larger efficacy and safety study performed in 80 patients (3–69 years) with primary immunodeficiency diagnosed as CVID or XLA.^{22,23} This subpopulation was further divided into children (3–11 years; $n = 19$) and adolescents (12–15 years; $n = 12$). Patients received stable IVIG therapy at 3- or 4-week intervals for at least 6 months prior to receiving Privigen and at least 1 documented IgG trough serum level of ≥ 4 g/L during the previous 6 months.

Exclusion criteria included a history of allergic reactions to immunoglobulins or other blood products, selective IgA deficiency or antibodies to IgA, recent history of migraine, hyperprolinemia, and lymphoid malignancy. Administration of glucocorticosteroids above 0.15 mg of prednisone equivalent/kg/day and of other immunosuppressive drugs as concomitant medication was also an exclusion criterion.

Written informed consent was obtained from the parents and, when appropriate, assent was also obtained from the child, as per local Institutional Review Board policies. This study complied with the Good Clinical Practice guidelines and the Declaration of Helsinki.

Study design

This study was a prospective, open-label, multicenter, single-arm, Phase III study (pivotal study). The primary endpoint was the annual rate of acute serious bacterial infections (aSBI) per patient. Acute SBIs included pneumonia, bacteremia, and septicemia, osteomyelitis/septic arthritis, bacterial meningitis or visceral abscess; diagnostic criteria according to FDA guidelines²⁴ were set in the study protocol. Secondary endpoints were annual rate of any infections per patient, number of days missed from school/day care or when unable to perform normal daily activities (abbreviated further as “days missed from school/day care”), number of days of hospitalization, use of antibiotics, and overall feeling of well-being.

This manuscript describes the subset of pediatric and adolescent patients enrolled into the study.

Study treatment. Patients were to receive 200–800 mg Privigen/kg body weight intravenously at a 3- or 4-week interval for 12 months, consistent with the dose and interval of their prestudy treatment. The infusion regimen remained unchanged on a milligram per kilogram body weight basis throughout the study period. The 3-week schedule included 17 infusions and the 4-week schedule included 13 infusions per patient over the course of 1 year.

Privigen infusions were begun at an infusion rate of 0.5 mg/kg/min, increasing to 1 mg/kg/min after 30 min if well-tolerated, and then to a maximum of 4 mg/kg/min for the first 3 infusions. From the fourth infusion on, if well-tolerated, the infusion rate could be increased to a maximum of 8 mg/kg/min.

Premedication. Preinfusion medication was not routinely administered. If the patient experienced an infusion-related adverse event (AE) during or after 2 consecutive infusions, premedication was permitted for future infusions, including 1 or more of the following: acetaminophen, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), or antiemetics. Preinfusion medication with glucocorticosteroids was prohibited.

Efficacy and safety assessments

For the assessment of the primary efficacy endpoint, aSBIs were clearly defined.²⁴ Information on days missed from school/day care, days of hospitalization, use of antibiotics, and overall feeling of well-being was collected via a Patient Diary, which was distributed to the patients at the Screening Visit and reviewed at each subsequent study visit. All AEs with the system organ class “infections and infestations” in Medical Dictionary for Regulatory Activities [MedDRA] and AEs with the preferred term “conjunctivitis” and “enterocolitis” were classified as infections. The overall feeling of well-being was summarized by the patient on a five-point scale: 1 = very well, 2 = well, 3 = fair, 4 = poor, 5 = very poor. IgG trough levels were determined on blood samples collected before each Privigen infusion.

Adverse events were considered temporally associated with the study drug infusion if they occurred during or within 72 h of the end of an infusion. Routine laboratory tests were performed at screening, 10–30 min before and 5–20 min after the first 2 Privigen infusions, 10–30 min before the fifth infusion of the 3-week treatment schedule or before the fourth infusion of the 4-week treatment schedule

and at the final visit. Laboratory analyses included blood chemistry (total bilirubin, creatinine, urea, total protein, lactate dehydrogenase, creatine kinase, blood urea nitrogen, alanine aminotransferase, and aspartate aminotransferase), hematology (hemoglobin, hematocrit, platelets, red blood cells, white blood cells, and differential counts), and urinalysis (pregnancy test, protein, glucose, blood, bilirubin, urobilinogen, and pH by dipstick). Trough IgG serum concentrations were measured before each infusion in all subjects. Serum concentrations of L-proline were determined 10–30 min before and 5–20 min after the first and second infusion and before the fourth/fifth Privigen infusions. Direct antiglobulin (Coombs') tests were performed as a measure for passively transmitted antibodies to erythrocyte antigens; blood samples were taken before and 5–20 min after the first 2 infusions, prior to the Week 12 infusion and at the completion visit.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) were evaluated at screening, before, during, and after each Privigen infusion and at the completion visit.

Statistical methodology

The analysis of the primary endpoint, the annual rate of aSBIs per patient, was estimated along with its upper 1-sided 97.5% and 99% confidence interval (CI) based on chi-square distribution. Descriptive statistical analysis was performed for the evaluation of primary and secondary efficacy endpoints as well as for IgG trough levels. The proportion of infusions with at least 1 temporally associated AE was evaluated with an upper 1-sided 95% CI by using normal approximation. As an ad-hoc analysis, the rate of aSBI and the rates of all secondary efficacy endpoints were analyzed for the patients who completed the study.

Extension study

A Phase III, open-label, single-arm, prospective, multicenter extension study of Privigen in patients with PID was performed in US study centers. The study assessed tolerability of high infusion rates. Patients could be enrolled at the discretion of the local investigator if they had completed the pivotal Privigen study at the US sites and provided additional consent/assent. In the extension study, Privigen was administered at maximum infusion rates of 8 mg/kg/min (low infusion rate group) or 12 mg/kg/min (high infusion rate group) at the discretion of the local investigator and depending on that patient's tolerance of Privigen in the pivotal study. Depending on patient response, infusion rates could be increased or decreased to provide maximum comfort for the patients. Treatment duration in the extension study varied for each patient and continued up to 785 days at investigator's discretion. Infusions were started at a low rate. If the infusion was well-tolerated in the first 30 min, the rate could be increased at the discretion of the investigator up to a maximum of 12 mg/kg/min. AEs occurring during and/or within 72 h of completing infusions (temporally associated) were evaluated as in the pivotal study. The proportion of infusions with temporally associated AEs was statistically evaluated using negative binomial regression.

Results

Patients

Thirty-one patients with CVID (18) or XLA (13) were treated in 11 centers in the USA, France, and Germany. Of the 31 patients, 19 were children (3–11 years) and 12 were adolescents (12–15 years) (Table 1). The vast majority of patients (27 patients, 87%) completed the 1-year study. Four patients discontinued the study due to AEs ($n = 3$) or withdrawal of consent ($n = 1$).

Nineteen patients participated in the extension study (13 children, 6 adolescents).

Treatment

Most patients (81% of all pediatric patients enrolled) received Privigen infusions every 4 weeks. Two patients, 1 in each age group, received additional infusions due to imminent surgery (14 instead of 13 infusions) or to variations in the treatment schedule (17 instead of 13 infusions, performed often at shorter intervals and considered minor protocol deviations). For 1 patient of the 3-week schedule, a deviation from the treatment schedule of >14 days was documented for 1 infusion (major protocol deviation). The median Privigen dose was 488 mg/kg in children and 466 mg/kg in adolescents, with minimal changes in dose between the first and subsequent infusions. A total of 392 infusions were administered to pediatric patients in the pivotal study. The maximum approved rate of 8 mg/kg/min was used in all but 1 patient after the third infusion. Infusion rates were decreased temporarily during only 10 (2.6%) infusions because of AEs.

IgG trough serum levels

Median IgG trough levels achieved with Privigen treatment were 8.11 g/L (5.68–14.51 g/L) in children and 9.79 g/L (8.2–13.9 g/L) in adolescents. No substantial changes in IgG trough levels were observed during the course of the study with either the 4-week infusion schedule (Fig. 1) or the 3-week schedule (not shown due to the low number of patients). Stable IgG trough levels above 5 g/L were consistently observed in all patients except 1, who experienced fluctuation of trough levels around 5 g/L (4–6 g/L), consistent with variability in that patient's prestudy levels (5–6 g/L).

Efficacy

Annual rate of aSBI. Treatment with Privigen was effective in sustaining a low rate of aSBI in pediatric patients. The annual rate of aSBI per patient was 0.12 in children (upper 1-sided 99% CI of 0.499) and 0.10 in adolescents (upper 1-sided 99% CI of 0.642) (Table 2).

As 4 patients discontinued the study after their second or third infusions, the annual rates of aSBI and the secondary efficacy parameters were also calculated for the 27 patients who completed the study and were thus at risk for occurrence of any infection throughout the entire study period. The annual rate of aSBI for completing patients was 0.12 per patient (upper 99% CI 0.509) in children and 0.10 per patient (upper 99% CI 0.690) in adolescents and thus still below the FDA target of 1.

TABLE 1. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF PATIENTS AND TREATMENT SCHEDULE

Baseline characteristics	3–11 years (n = 19)	12–15 years (n = 12)	Total (n = 31)
Male gender, n (%)	12 (63)	7 (58)	19 (61)
Age, years			
Mean	7	14	9
Median	7	14	9
Ethnic group, n (%)			
Caucasian	13 (68)	5 (42)	18 (58)
African American	2 (11)	2 (17)	4 (13)
Hispanic	4 (21)	5 (42)	9 (29)
Weight, kg (mean)	27.0	53.1	37.1
BMI, kg/m ² (mean)	17.6	21.1	18.9
Diagnosis, n (%)			
CVID	9 (47)	9 (75)	18 (58)
XLA	10 (53)	3 (25)	13 (42)
Disease duration, years (median [range])			
CVID	5.3 (0.8–11.0)	8.8 (1.5–11.8)	6.9 (0.8–11.8)
XLA	3.9 (1.2–10.2)	11.4 (5.1–15.0)	4.9 (1.2–15.0)
IVIG replacement schedule, n (%)			
3-week	5 (26)	1 (8)	6 (19)
4-week	14 (74)	11 (92)	25 (81)
Privigen dose, mg/kg (median [range])			
Overall	487.8 (200.0–740.7)	465.8 (319.0–720.0)	477.1 (200.0–740.7)
3-week	521.1 (306.1–740.7)	416.7 (400.0–438.8)	500.0 (306.1–740.7)
4-week	482.6 (200.0–710.2)	471.7 (319.0–720.0)	476.7 (200.0–720.0)

Abbreviations: BMI, body mass index; CVID, common variable immunodeficiency; IVIG, intravenous immunoglobulin; XLA, X-linked agammaglobulinemia.

Three patients (10%) experienced 1 aSBI each: 2 patients had an episode of pneumonia, 1 in each age group; and 1 adolescent developed an episode of septic arthritis. The three aSBIs were considered unrelated to study treatment. A 9-year-old girl with CVID experienced pyrexia, neutropenia, and pneumonia, which was classified as an aSBI. No cultures were performed. The patient recovered and completed the study as planned. A 15-year-old male with XLA presented with headache, muscle aches, and cough; examination led to the diagnosis of pneumonia secondary to

influenza infection. Influenza virus Type A was detected in the sputum. The patient recovered uneventfully and completed the study. A 7-year-old male patient with XLA had an episode of severe septic arthritis, which was classified as an aSBI. In retrospect, this subject's viral, blood, and synovial fluid cultures as well as Gram stain were negative and the arthritis was a manifestation of HLA-B27-positive spondyloarthropathy. That patient also recovered and completed the study.

Secondary endpoints. Twenty-eight patients (90%) experienced at least 1 episode of infection. The most frequent infection was sinusitis (Table 3). The annual rates of infections were 4.63 and 2.42 episodes per patient for children and adolescents, respectively (Table 2). The annual rates of infections calculated for patients completing the study were similar (4.60 for children and 2.18 for adolescents).

Corresponding to the low rate of infections, the annual rate of days missed from school/day care was 11.5 per patient in children: 16 patients (84%) missed 194 days (Table 2). In adolescents, the annual rate of days missed from school/day care was 4.8 per patient, with 7 patients missing 50 days. The corresponding rates for patients completing the study were similar (11.6 in children and 5.1 in adolescents). While five of the 3- to 11-year-old children were hospitalized for a total of 9 days (annual rate 0.53 per patient; for patients completing the study, 0.54), adolescent patients were not hospitalized at all during the entire study period. Thus, the total rate of days of hospitalization was 0.1% of all study days. Antibiotics were commonly used in both groups in a total of 25 patients (81%), with annual rates of 47.9 and 56.6 per

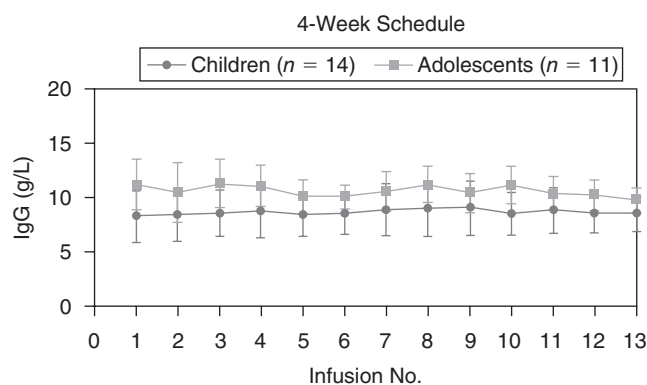


FIG. 1. IgG trough serum levels by infusion. Blood samples were collected from all subjects prior to each Privigen infusion. The value measured before the first infusion was used as the baseline value. Values are shown as mean $\pm$ SD.

TABLE 2. ANNUAL RATES OF EFFICACY PARAMETERS (EXTENSION STUDY NOT INCLUDED)

	3–11 years (n = 19)	12–15 years (n = 12)	Total (n = 31)
Total number of study days	6,152	3,776	9,928
Annual rate of aSBI per patient (upper 97.5%/99% CI)	0.12 (0.429/0.499)	0.10 (0.539/0.642)	0.11 (0.322/0.369)
Number of patients with aSBI	2	1	3
Number of aSBI	2	1	3
Annual rate of all infections per patient (upper 97.5%/99% CI)	4.63 (5.776/6.000)	2.42 (3.567/3.800)	3.79 (4.593/4.749)
Number of patients with infections	17	11	28
Number of episodes of infections	78	25	103
Annual rate of days missed from school/day care per patient	11.51	4.83	8.97
Number of patients who missed days	16	7	23
Number of days missed	194	50	244
Annual rate of days hospitalized per patient	0.53	0	0.33
Number of patients who were hospitalized	5	0	5
Number of days hospitalized	9	0	9
Annual rate of days with antibiotics per patient	47.88	56.64	51.21
Number of patients who used antibiotics	16	9	25
Number of days with antibiotics	807	586	1,393

Abbreviation: aSBI, acute serious bacterial infection.

patient for the children and adolescents, respectively. The corresponding rates for patients completing the study were 48.9 and 60.9, respectively.

Patients' own assessment of their well-being was "well" for both age groups and treatment schedules, evaluated with a scale ranging from "very well" to "very poor." The median overall feeling of well-being in children was "well": 2.0 (range 1–4.9) for the 3-week schedule and 1.7 (1–3.5) for the 4-week schedule. Adolescent patients estimated their feeling of well-being as 1.9 (1.5–2.5) and 2.0 (1–3.7), respectively.

Safety

Temporally associated adverse events. Privigen administration was generally well-tolerated and AEs were as expected for an IVIG treatment. AEs considered "temporally associated" with infusions (occurring during or within 72 h of the end of an infusion) were experienced on at least 1 occasion

by 14 children (74%) and 7 adolescents (58%). The most frequent temporally associated AEs were headache, fatigue, chills, and vomiting (Table 4). Twenty-three temporally associated headaches were reported for the 392 infusions. Seven headaches started during infusions and 16 within 72 h after the end of an infusion. The frequency of temporally associated AEs per infusion was 0.36 in children and 0.28 in adolescents. The proportion of infusions with temporally associated AEs for the entire pediatric population was 0.18 (upper 1-sided 95% CI 0.221). The corresponding proportions in children and adolescents were 0.21 (95% CI 0.262) and 0.13 (95% CI 0.196), respectively. Approximately half of the temporally associated AEs were considered at least possibly related to the study treatment. The proportion of infusions with related temporally associated AEs was 0.06 (95% CI 0.089) in the entire pediatric population, 0.07 (upper one-sided 95% CI 0.107) in children, and 0.05 (upper 1-sided 95% CI 0.093) in adolescents.

TABLE 3. INCIDENCE OF INFECTIONS OCCURRING IN $\geq 10\%$ OF ALL PATIENTS

	3–11 years (n = 19)	12–15 years (n = 12)	Total (n = 31)
Infection ^a	No. of patients (%)	No. of patients (%)	No. of patients (%)
Total	17 (89)	11 (92)	28 (90)
Sinusitis	6 (32)	3 (25)	9 (29)
Nasopharyngitis	1 (5)	2 (17)	3 (10)
Upper respiratory tract infections	8 (42)	2 (17)	10 (32)
Bronchitis	6 (32)	0 (0)	6 (19)
Rhinitis	4 (21)	2 (17)	6 (19)
Influenza	2 (11)	2 (17)	4 (13)
Gastroenteritis	4 (21)	1 (8)	5 (16)
Ear infection	2 (11)	1 (8)	3 (10)

^aAll adverse events with the system/organ/class "infections and infestations" and the adverse events with the preferred term "conjunctivitis" and "enterocolitis" were classified as infections.

TABLE 4. MOST FREQUENT^a TEMPORALLY ASSOCIATED ADVERSE EVENTS^b

	3–11 years (n = 19)	12–15 years (n = 12)	Total (n = 31)
Adverse event (preferred term)	No. of patients (%)	No. of patients (%)	No. of patients (%)
Headache	8 (42.1)	5 (41.7)	13 (41.9)
Fatigue	4 (21.1)	1 (8.3)	5 (16.1)
Chills	2 (10.5)	3 (25.0)	5 (16.1)
Vomiting	4 (21.1)	1 (8.3)	5 (16.1)
Back pain	2 (10.5)	1 (8.3)	3 (9.7)
Pyrexia	2 (10.5)	1 (8.3)	3 (9.7)
Sinusitis	3 (15.8)	0	3 (9.7)
Stomach discomfort	1 (5.3)	2 (16.7)	3 (9.7)
Upper respiratory tract infections	3 (15.8)	0	3 (9.7)
Diarrhea	1 (5.3)	1 (8.3)	2 (6.5)
Nausea	0	1 (8.3)	1 (3.2)

^aExperienced by ≥ 3 patients (10% of all); ^bTemporally associated adverse events were defined as adverse events occurring during infusion or within 72 h of the end of an infusion.

The proportion of infusions with temporally associated AEs decreased over time (Fig. 2). Two children and 2 adolescents received antihistamines or antiemetic agents prior to most infusions for alleviation of temporally associated AEs, such as viral or upper respiratory tract infection, sinusitis, back pain, headache, and stomach discomfort. Two other patients had their Privigen administration interrupted on 1 and 3 occasions due to AEs including headache, chills, or decreased blood pressure: a 7-year-old girl suffered headache during the first infusion; a 12-year-old girl suffered chills and headache during the first infusion, and decreased blood pressure during the fourth infusion.

Overall adverse events. Overall, 30 patients (97%) experienced AEs, including the temporally associated AEs described earlier. Half of the infusions were associated with AEs (50% in children and 49% in adolescents), regardless of causality and time of occurrence with respect to infusions. Most of the AEs were mild or moderate. The most frequent AEs related to Privigen infusion were headache, vomiting, fatigue, chills, nausea, and back pain (Table 5). Seven children and 3 adolescents experienced AEs that were

considered at least possibly related to Privigen administration. AEs graded as severe were experienced by 3 children and 4 adolescents.

Serious adverse events. Seven patients experienced 15 serious AEs: 6 (32%) children (14 serious AEs) and 1 (8%) adolescent (1 serious AE). Unrelated serious AEs in children were pyrexia, neutropenia, pneumonia (an aSBI), joint swelling, arthralgia, arthritis, septic arthritis (an aSBI), paronychia, testicular torsion.

Five of the 14 serious AEs in children occurred in a single patient and were considered related to study drug. This patient, an 11-year-old girl with CVID experienced hypersensitivity, chills, fatigue, dizziness, and increased body temperature during the second infusion and discontinued the study. All these symptoms were manifestations of an allergic reaction; however, according to current regulations, they were reported as separate serious AEs. During the first infusion, the patient felt cold and tired and became very pale, but the infusion was completed according to study protocol. Five days later, the patient was diagnosed with viral infection of the upper respiratory tract, from which she recovered within 6 days. During the second infusion, the patient experienced the same symptoms and started to shake uncontrollably. She could not be stabilized by reduction in the infusion rate or by infusion of saline and thus the infusion was interrupted. The patient was not considered infected at the time the serious AEs occurred and had never suffered from similar events during previous IGIV treatment. Selective IgA deficiency was ruled out.

Two of the 3 aSBIs were also classified as serious AEs (pneumonia in a 9-year-old girl and septic arthritis in a 7-year-old boy). No deaths occurred in the pediatric population during this study.

Adverse events leading to withdrawals. Three patients from 1 study center were withdrawn early in the study because of AEs. An 11-year-old girl discontinued after the second infusion because of hypersensitivity reactions (see *Serious adverse events*). She had responded occasionally to previous IVIG treatments (Sandoglobulin®) with mild to moderate reactions, such as malaise, fatigue, and mild headache. A 14-year-old girl discontinued after the second infusion due to chills and headache (the first infusion was uneventful),

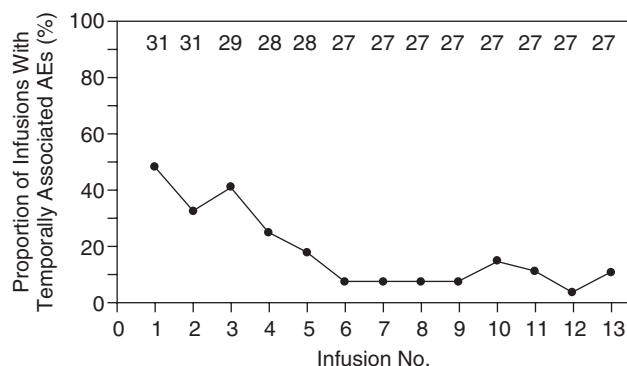


FIG. 2. Proportion of patients with temporally associated adverse events (AEs) (72 h) over time. The proportion of pediatric patients experiencing temporally associated AEs between infusion start and 72 h after infusion end is shown. Numbers of patients from which data were available are given.

TABLE 5. MOST FREQUENT ADVERSE EVENTS (AEs) RELATED TO TREATMENT^a

	3–11 years (<i>n</i> = 19) (total 250 infusions)		12–15 years (<i>n</i> = 12) (total 142 infusions)	
	Not related, no. (rate per total no. of infusions)	At least possibly related, no. (rate)	Not related, no. (rate)	At least possibly related, no. (rate)
Total AEs	248 (0.992)	41 (0.164)	131 (0.923)	19 (0.134)
Headache	41 (0.164)	6 (0.024)	16 (0.113)	4 (0.028)
Vomiting	9 (0.036)	4 (0.016)	4 (0.028)	2 (0.014)
Fatigue	2 (0.008)	7 (0.028)	0 (0.000)	2 (0.014)
Chills	1 (0.004)	6 (0.024)	0 (0.000)	3 (0.021)
Nausea	0 (0.000)	0 (0.000)	1 (0.007)	4 (0.028)
Back pain	1 (0.004)	5 (0.020)	1 (0.007)	0 (0.000)

^aAEs related to study medication regardless of the time of their occurrence.

and a 3-year-old boy discontinued after the third infusion because of vomiting (the first and second infusions were uneventful). The latter 2 patients had experienced no reactions to previous IVIG treatment (Sandoglobulin).

Laboratory tests. Changes in direct Coombs' tests from negative at baseline to transiently positive were noted in 14 (45%) patients, mainly in samples taken immediately (5–20 min) after infusions. No signs or symptoms of hemolysis or anemia were observed in any patient. Routine laboratory values (chemistry, hematology) were mostly within normal limits, with occasional single measurements out of range but not considered to be of clinical significance.

High infusion rates in the extension study. In the extension study, 13 of 19 pediatric patients (68.4%) received infusions at a maximum rate of 12 mg/kg/min. Of all infusions in pediatric patients in the extension study (277), 54.5% were administered at the maximum rate of 12 mg/kg/min. Only 30 (10.8%) infusions in the extension study were accompanied by temporally associated AEs. Moreover, fewer infusions in the group receiving Privigen at rates as high as 12 mg/kg/min were associated with AEs compared to the group receiving Privigen at lower rates, which did not exceed 8 mg/kg/min (Fig. 3). The proportion of infusions with temporally associated AEs in the high infusion rate group was lower in both the pivotal study (statistically significant; $P = 0.0368$) and the extension study (not significant; $P = 0.2914$) compared to the low infusion rate group, suggesting that selected patients who generally tolerated Privigen infusions well could tolerate infusion rates up to 12 mg/kg/min without an increase in the AE incidence.

Discussion

This study demonstrated that Privigen was effective in maintaining a low incidence of aSBI and of infections in general in children and adolescents with PID. The use of Privigen in the study population was well-tolerated.

The Privigen doses used in this study were similar to the average IVIG dose reported in an Immune Deficiency Foundation survey (445 mg/kg for CVID and 423 mg/kg for agammaglobulinemia)²⁵ and to the average Privigen dose administered to the entire study population (444.4 mg/kg).²³ With these doses, stable IgG trough levels above the therapeutic minimum were achieved in all patients. It should be

noted that for many drugs the recommended per kilogram dosing is higher in young children than in adults. For example, zidovudine dosing in children weighing 4–9 kg is 12 mg/kg, 9 mg/kg in children 9–30 kg, and 4.3 mg/kg for an “average” 70-kg adult.²⁶ Further studies in pediatric patients are required to establish the applicability of higher doses of IVIG compared to adults.

The annual rates of aSBI per patient were similarly low in both age groups, and the upper bound of the 99% CI was well below the FDA guideline of 1.0 in both age groups.²⁴ Comparison of the primary endpoint data obtained in children and adolescents to those obtained in the general patient population (3–69 years) in the larger Privigen study revealed no striking difference.²³ The annual rate of aSBI for the pediatric patients was slightly higher than that seen in the 3- to 69-year olds (0.11 vs. 0.08, upper 1-sided 97.5% CI of 0.182).²³

Untreated patients with PID are estimated to experience up to 4 aSBIs per year.²⁴ In contrast, the frequency of aSBI

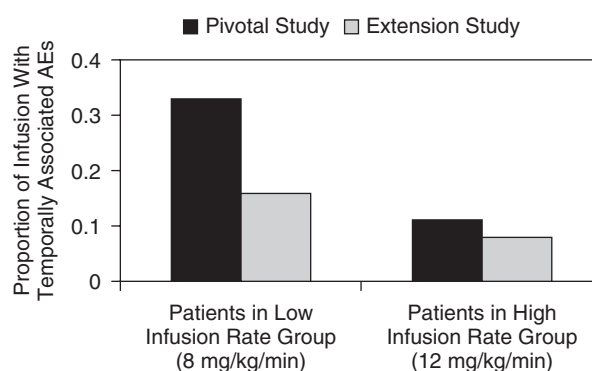


FIG. 3. Proportion of infusions with temporally associated adverse events (AEs) (72 h) in the pediatric patients participating in the pivotal and extension studies. The same patients were infused at a maximum infusion rate of 8 mg/kg/min in the pivotal study and at a maximum infusion rate of 8 or 12 mg/kg/min in the extension study (low infusion rate group or high infusion rate group, respectively). Temporally associated AEs are defined as AEs occurring between infusion start and 72 h post-infusion end.

under regular administration of IVIG has been reported to be 0.5 per patient per year.²⁴ The efficacy of Privigen as shown in this study (annual rate of aSBI of 0.11 per patient; 99% CI 0.369) was comparable to that of other liquid IVIG preparations tested recently in mixed pediatric and adult patient populations with PID.^{18,27–29} Prior studies reporting efficacy and safety of IVIG products have not reported specific rates of aSBI in pediatric patients, nor have declared the proportion of pediatric patients in the study populations. In a study of Flebogamma® 5% performed in 51 patients aged 14–74 years, the rate of aSBI was 0.061 per patient per year (upper 1-sided 99% CIs of 0.183).²⁸ A rate of 0.1 aSBI per patient per year (upper 1-sided 98% CIs of 0.279) was reported for Octagam® 5% in 46 patients aged 6–74 years.²⁹ In 61 adults and children (6–72 years) treated with GAMMAGARD LIQUID 10%, no aSBIs occurred during the 12-month period of the study (upper 1-sided 95% CIs of 0.060 per patient per year).²⁷ In a trial comparing efficacy of Gamunex® 10% and Gamimmune® N, 9 of 73 (12%) patients treated with Gamunex 10% for 9 months experienced aSBIs resulting in a rate of <0.2 per year.¹⁸ This study documents for the first time efficacy and safety of an IVIG product in pediatric patients with PID. Studies reporting efficacy of IVIG exclusively in pediatric patients are rare, as most studies in children have used subcutaneous administration. In a retrospective study in 31 infants and children with XLA, Quartier et al. showed that the incidence of acute bacterial infections decreased significantly from 0.40 per patient per year before commencement of therapy to 0.06 per patient per year during IVIG therapy ($P < 0.001$).¹²

The primary efficacy result was further substantiated by the secondary endpoint results. The annual rate of days missed from school/day care (8.97 days per patient) was comparable to the rate obtained previously with the general patient population with the same product (7.9 days per patient).²³ However, the annual rates of hospitalization for children and adolescents (0.53 and 0, respectively) were lower than the rate for the entire population, which was 2.3. Moreover, patients in the entire population used antibiotics for twice as long compared to children: the annual rate of days with antibiotics for 3- to 69-year olds was 87.4 days compared to 47.9 days and 56.6 days for children and adolescents, respectively. These results may reflect long-term respiratory tract deterioration in adult patients with chronic disease. Similar results have been published for other IVIG preparations in mixed pediatric and adult study populations. The number of days missed from school/work was reported to be 6.2 days per patient per year with Flebogamma 5%²⁸ and 5 days per patient per year with Octagam 5%,²⁹ while days spent in hospital were 0.8 and 0.3 per patient per year, respectively.

The safety of Privigen treatment was comparable to that published for other IVIG preparations, the administration of which may frequently be accompanied by headache, chills, and/or fatigue.^{30,31} The low content of IgG dimers in Privigen (typically 4%–8%) may contribute to its good tolerability. The proportion of infusions with temporally associated AEs for the entire pediatric population was 0.18 (upper 1-sided 95% CI 0.221). During the pivotal study, the proportion of infusions with temporally associated AEs declined with infusion number, consistent with previous observations that first time use of a given IVIG preparation is associated with a higher incidence of AEs.³² Furthermore, as the later infusions in the pivotal study were carried out at higher infusion rates

(maximum rate of 8 mg/kg/min was allowed only after the third infusion), the decline in AE rate is particularly impressive. A similar pattern of decrease in AE rate was observed in the entire population.²³ Transiently positive direct Coombs' tests were observed in 14 patients (45%), similarly to the results obtained with another liquid IVIG product,¹⁸ but no clinically significant hemolysis occurred.

Three patients were withdrawn from the study by their parents after experiencing AEs. The patients were previously treated with Sandoglobulin, with occasional mild or moderate reactions observed only in the 11-year-old girl. Presumably, the AEs experienced by these patients in the Privigen study were due to the change of the product, a phenomenon that has been well-established.³³ Upon withdrawal from this study, Sandoglobulin treatment was continued for a while before switching to subcutaneous administration of Vivaglobin, which all patients tolerated well.

Privigen was generally well-tolerated at high infusion rates, as evidenced by the fact that most of the infusions were carried out at maximum rate allowed by protocol. Pediatric patients were infused at the same rate as adults without major complications. In the extension study, children and adolescents tolerated infusion rates up to 12 mg/kg/min without an increase in the occurrence of temporally associated AEs. Together with the advantages conferred by room temperature storage of the proline-stabilized liquid 10% product, more rapid administration of Privigen in both pediatric and adult patients has obvious advantages for the patients and their parents and families, and may result in a reduction in treatment costs. The results of this study demonstrate that this has been achieved with no loss in efficacy.

Timely and appropriate IVIG therapy could extend the life expectancy of children with immunodeficiencies. Treatment aims to provide life-long safety and improve the quality of life of patients and their families, whereby good tolerability to the product administered is mandatory for success.

Acknowledgments

The study was supported by CSL Behring, King of Prussia, PA. We would like to acknowledge the collaboration and commitment of all patients, investigators, and their staff. The support provided by Corinna Miede and Cordula Massion (Accovion GmbH, Germany) on statistical analyses is gratefully appreciated.

Author Disclosure Statement

J.A.C. reports clinical trial support from CSL Behring and Nabi Biopharmaceuticals for IVIG and from Gilead Sciences and Tibotec Pharmaceuticals for HIV studies; H.T., clinical trial support from CSL Behring; R.P.N., clinical trial support from CSL Behring; J.W.S., consulting fees and clinical trial support from CSL Behring; A.P.K., lecture fees from CSL Behring, Genentech, Novartis, clinical trial support from CSL Behring, Genentech, Novartis, grant support from Genentech, Novartis. No other potential conflict of interest to this article was reported.

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Address correspondence to:
 Dr. Joseph A. Church
 Childrens Hospital Los Angeles
 4650 Sunset Blvd.
 MS #75
 Los Angeles, CA 90027
 E-mail: jchurch@chla.usc.edu

Received for publication February 20, 2009; accepted after revision May 18, 2009.

