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BRIEF REPORT

Subcutaneous Immunoglobulin Twenty Percent Every Two Weeks in Pediatric Patients with Primary Immunodeficiencies: Subcohort Analysis of the IBIS Study

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Background: Subcutaneous immunoglobulin G (SCIG) may be a better option than intravenous immunoglobulin G (IVIG) for patients with primary immunodeficiencies (PID) due to reduced systemic and serious adverse reactions and easier administration. The Infusione Bimensile di Immunoglobuline Sottocute (IBIS) study investigated the effects of Hizentra®, a 20%-concentrated SCIG, administered biweekly in patients with PID. This subanalysis aimed to evaluate clinical and laboratory outcomes in the IBIS pediatric subcohort.
Methods: Thirteen children with PID were observed for 12 months retrospectively (with previous IVIG/SCIG) and prospectively with biweekly Hizentra.
Results: Mean ± standard deviation serum IG levels during the retrospective (833.8 ± 175.7 mg/dL) and the prospective (842.0 ± 188.0 mg/dL) phases were comparable; there were also no differences in the number of infections.
Conclusions: Biweekly Hizentra is a noninferior option with respect to previous IVIG/SCIG-based treatment.

Keywords: children, immunoglobulin, pediatric, primary immunodeficiencies, subcutaneous

Introduction

Primary immunodeficiencies (PID) are a heterogeneous group of ~330 rare, serious, and chronic disorders of the immune system.[1–3] Many patients with primary antibody deficiency (PAD) that requires replacement therapy have switched from the traditional intravenous immunoglobulin G (IVIG) therapy to subcutaneous immunoglobulin G (SCIG)[4–6] due to systemic and serious adverse reactions[7–9] with the former, and ease of administration and patient compliance with the latter. Hizentra® (CSL Behring, King of Prussia, PA) is a 20%-concentrated, L-proline-stabilized human SCIG approved by the U.S. Food and Drug Administration (FDA) and the European Medical Agency for the treatment of PAD in adults and children.[10,11] The ''Infusione Bimensile di Immunoglobuline Sottocute'' (IBIS), translated to biweekly infusion of SCIG, study was a prospective clinical study that aimed to investigate the clinical and laboratory parameters of patients with PID receiving biweekly (ie, once every 2 weeks) Hizentra, at double the weekly dose. Results in the overall population (2–56 years of age) demonstrated that serum levels of immunoglobulin G (IgG)

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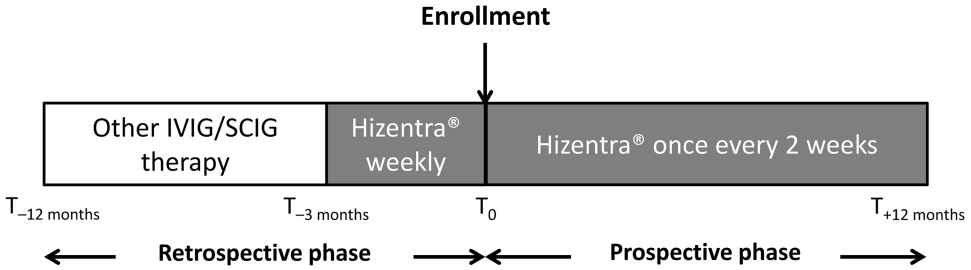

FIG. 1. Design of the IBIS study. IBIS, Infusione Bimensile di Immunoglobuline Sottocute; IVIG, intravenous immunoglobulin G; SCIG, subcutaneous immunoglobulin; T, time.

achieved during the prospective phase of the study with SCIG administered biweekly were similar to those determined during the retrospective phase with once-weekly SCIG, despite a slight reduction in the monthly dose.[12] In this subanalysis, clinical and laboratory outcomes of the pediatric population of the IBIS study were evaluated.

Methods

Study design

The full methods of the multicenter, observational IBIS study have been published previously.[12] In brief, clinical data were collected for each patient over a 24-month period, which included 12 months each of retrospective and prospective observations (Fig. 1). The current subanalysis of IBIS examined outcomes in the subcohort of pediatric patients enrolled in the study.

The study was approved by the Comitato Etico Area Vasta Centro, Azienda Ospedaliera Universitaria Careggi, Firenze and the Ethics Committees of each study center and was conducted in accordance with the Declaration of Helsinki and the current regulations for observational studies. All patients provided written informed consent before any evaluations or procedures were conducted.

Patients

Patients were included in the study if they were 1–70 years of age with PID, who required IgG replacement therapy at a dose that the investigator considered stable and protective against most infections, undergoing treatment with IgG (IVIG or SCIG) for ≥12 months, with a switch to 20% SCIG ≥3 months before enrollment. Patients who changed to administration of SCIG once every 2 weeks upon enrollment could also be included.

Minimum retrospective data for the 12 months preceding enrollment included one or more measurement of minimum plasma IgG concentration representative of the mean value during the period, details of previous IVIG/SCIG therapy (monthly doses, frequency of infusions, number of infusion sites for each session, infusion speed, and number of pumps used for SCIG), number and type of serious bacterial infections (SBI), such as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, meningitis, visceral abscess, other infections, and number of hospitalizations for PID-related illness.

Main exclusion criteria were treatment with IVIG within 3 months before the enrollment visit, protein-losing illnesses (eg, lymphangiectasia, nephrosis, protein-losing enteropathy) or solid tumors/hematological neoplasms at enrollment or during the retrospective phase of the study, ongoing treatment with systemic corticosteroids, immunosuppressive drugs, plasma, or other blood derivatives; positivity for HIV-1, HIV-2, hepatitis C, or hepatitis B markers; pregnancy, or participation in clinical trials of investigational agents; or receiving any other medicinal product that could interfere with the IgG replacement therapy.

Concomitant or prior therapies for comorbidities related to PID or other pathologies were allowed during the study period.

Treatment

The decision to treat patients with 20% SCIG was based on the judgment of patients' treating physician in accordance with normal clinical practice.

During the prospective phase of the study, all patients received biweekly (every 14 ± 2 days) Hizentra 20% SCIG. Patients or caregivers received training on drug administration from their nurses or treating physician in the hospital. SCIG therapy was administered at home using pumps for subcutaneous drug infusion (Crono S-PID, Canè S.r.l., Italy).

Endpoints

A database extraction was performed, before database lock, allowing exploratory preliminary analyses of the primary objectives in 13 pediatric patients (ages 2–16). In this subcohort of patients, age, sex, type of PID, serum IgG trough levels, number of SBI and of other infections, and number of days with antibiotic therapy were examined.

Table 1. Patient Demographics and Clinical Characteristics

	N = *13*
Sex, *n* (%)	
Males	10 (76.9)
Females	3 (23.1)
Age at enrollment, years	
Median (IQR)	13 (9–14)
Range	2–16
Age at diagnosis, years	
Median (IQR)	3 (2–6)
Range	1–13
Primary immunodeficiency diagnosis, *n* (%)	
CVID	8 (61.5)
XLA	3 (23.1)
IgGSCD	1 (7.7)
DGS	1 (7.7)

CVID, common variable immunodeficiency; DGS, DiGeorge syndrome; IgG, immunoglobulin G; IgGSCD, IgG subclass deficiency; IQR, interquartile range; *n*, number; XLA, X-linked agammaglobulinemia.

Table 2. List of Demographics and Clinical Characteristics for Each Patient

Patient ID	*PID type*	*Sex*	*Age at enrollment, years*	*Age at diagnosis, years*
02-01	CVID	M	8	5
02-02	XLA	M	13	1
02-03	XLA	M	2	1
05-02	CVID	M	16	13
06-01	CVID	F	15	1
06-02	CVID	M	14	6
06-03	DGS	M	15	2
06-04	IgGSCD	M	14	12
06-06	CVID	M	7	4
06-08	CVID	F	14	8
07-01	XLA	M	13	3
07-02	CVID	F	10	2
08-01	CVID	M	9	3

PID, primary immunodeficiency.

During the prospective phase, patients were followed up at 3, 6, and 12 months, and data were collected using electronic case report forms.

Statistical analyses

Evaluable patients were those receiving IgG and with data available for both the retrospective and prospective periods. Parameters of interest were summarized, in the entire subcohort and for each study phase, using descriptive statistics [mean, standard deviation (SD), 25th and 75th percentiles, median, minimum, and maximum].

Results

Patients

A total of 13 pediatric patients were enrolled from 5 centers in Italy. Patient demographics and clinical characteristics at enrollment are shown in Table 1; the same data, separated by each patient, are listed in Table 2. The majority of patients were male ($N=10$, 76.9%) and the most frequent PID diagnosis was common variable immunodeficiency ($N=8$, 61.5%). In this subcohort, median [interquartile range (IQR)] age at enrollment was 13 (9–14) years, whereas the median (IQR) age at diagnosis was 3 (2–6) years. All patients were previously on substitution therapy with SCIG and only 3 patients received IVIG previously and only for a short time.

Serum IgG levels

The mean serum IgG trough levels remained stable with SCIG administered biweekly (Fig. 2). During the retrospective and prospective phases of the study, mean ± SD serum IgG levels were similar, at 833.8 ± 175.7 and 842.0 ± 188.0 mg/dL, respectively (Fig. 3A).

In the prospective analysis, all serum IgG trough levels collected during the 12-month-long follow-up were included, and not only those referred to the 3-, 6-, and 12-month scheduled follow-up visits.

Number of serious and other infections

No significant differences were observed between the 2 study phases either in the number of SBI or in the number of other infections. Two episodes of SBI were reported (pneumonia during the retrospective period and visceral abscess in the prospective period), with a mean ± SD annualized rate of 0.08 ± 0.28 in both periods.

During the retrospective period, 29 episodes of nonserious infections (Fig. 3B) were recorded, with a mean annualized rate of 2.23 ± 2.62 (Fig. 3C). Of the 13 patients, 10 (77%) experienced one or more infections. The most frequent type of infection was bronchitis ($N=9$, 31.0%). During the prospective phase, there were 35 cases of nonserious infections (Fig. 3B), with a mean annualized rate of 2.69 ± 3.64 (Fig. 3C). Nine out of the total 13 patients (69%) experienced one or more infections. Pharyngitis was the most common type of infection ($N=9$, 25.7%).

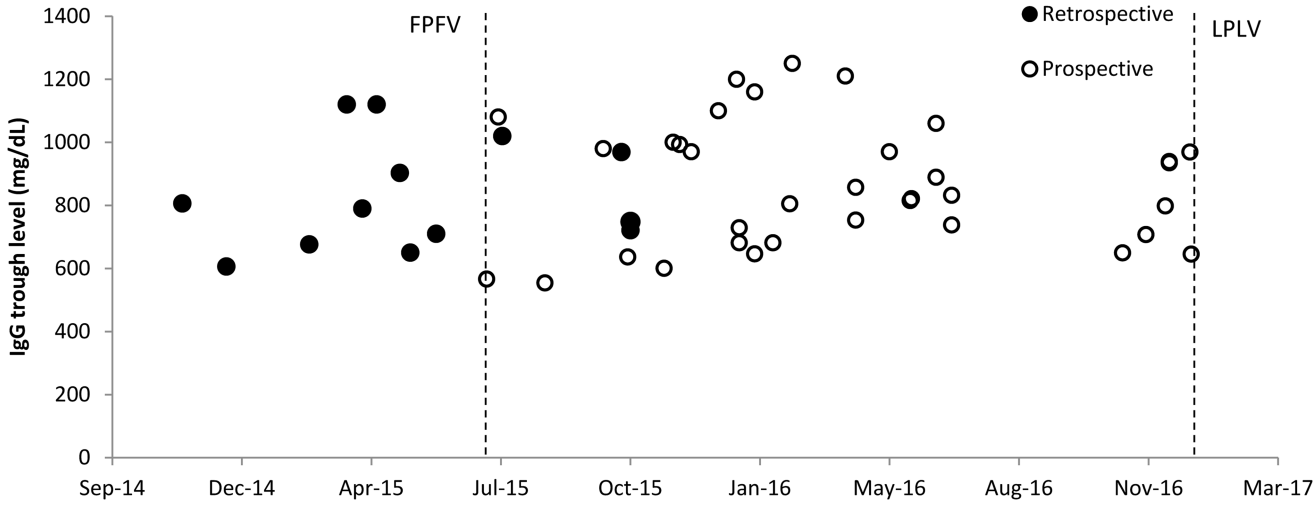

FIG. 2. Serum IgG trough levels during the retrospective and prospective phases when patients received subcutaneous immunoglobulins. FPFV, first patient first visit; IgG, immunoglobulin G; LPLV, last patient last visit.

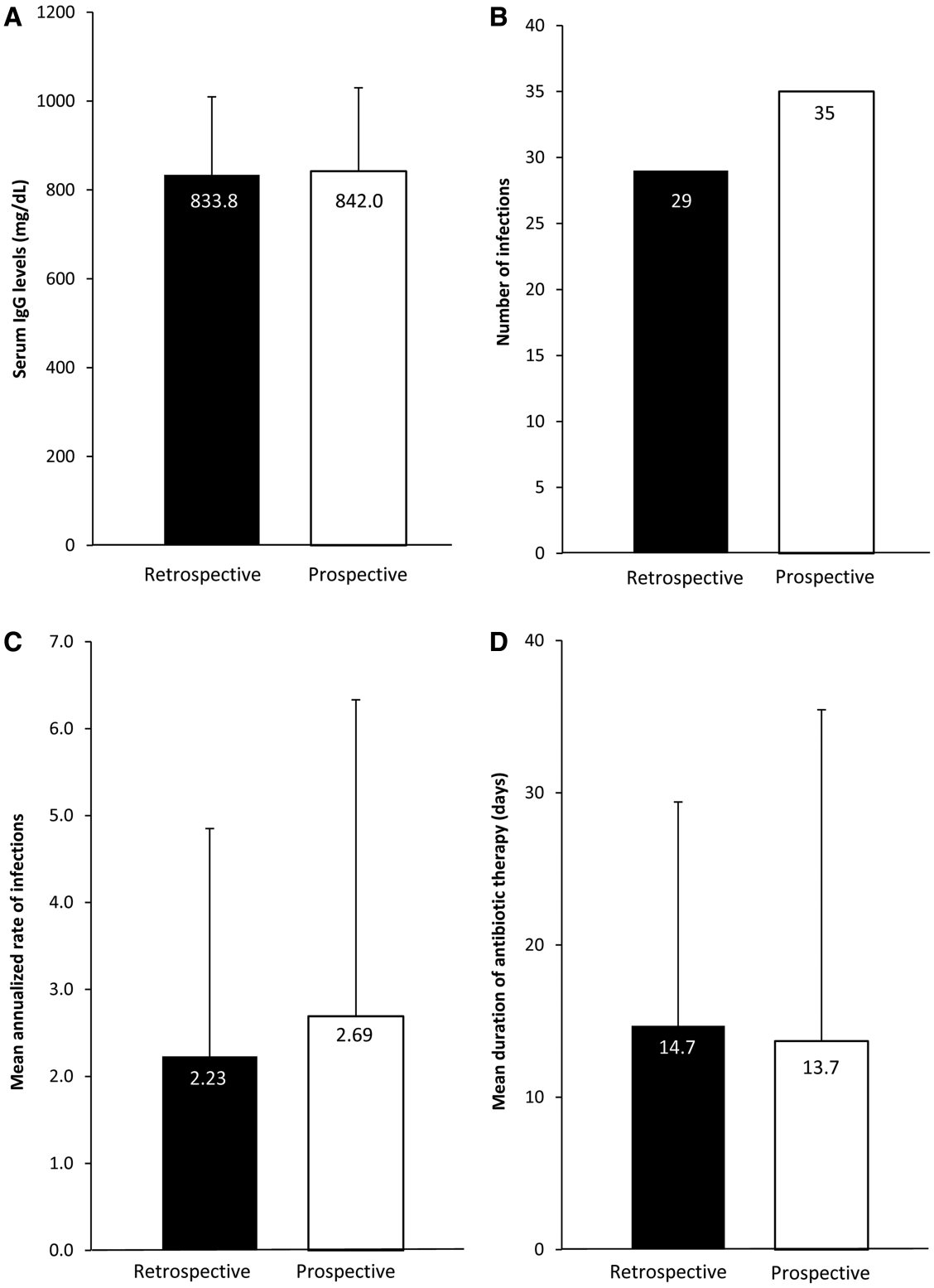

FIG. 3. Comparison of **(A)** IgG levels, **(B)** number of infections, **(C)** rate of infections, **(D)** antibiotic therapy.

Duration of antibiotic therapy

There was no significant difference between the 2 study phases in the duration of antibiotic therapy. The mean ± SD duration of antibiotic therapy was 14.7 ± 15.7 and 13.7 ± 21.8 days per patient during the retrospective and prospective phases, respectively (Fig. 3D).

Discussion

This subanalysis of the IBIS study investigated the effect of biweekly SCIG on serum IgG levels and its clinical efficacy in pediatric patients with PID. Compared with the previous weekly SCIG regimen, 20% SCIG administered biweekly at double the weekly dose maintained similar

serum IgG levels and similar rates of serious bacterial and nonserious infections in pediatric patients with PID.

Biweekly administration of 20% SCIG maintained pre-infusion trough levels of IgG above the recommended level of 500 mg/dL[13] throughout the prospective study period. These results are consistent with published literature and data generated by pharmacometric modeling and simulations. As there are no specific studies of biweekly SCIG published specifically in children, it is difficult to perform direct comparisons. Nevertheless, the serum IgG levels observed in this study were similar to those reported in a study of weekly SCIG in 23 pediatric patients with PID.[14] In another study, 12 adults with PID had constantly high serum IgG levels without major variations over 24 weeks of treatment with 16% SCIG infusions every other week.[15]

There was no increase in the number of days of antibiotic therapy for infections during the prospective phase of the study compared with the retrospective phase of the study. The mean annualized rate for SBI was 0.08 in both periods and was comparable to a previously published study with Hizentra treatment[16]; this rate is significantly less than the threshold of 1 SBI, as recommended by the U.S. FDA required to show IgG therapy efficacy.[17] Accordingly, the proportion of patients with at least 1 infection was 77% during the retrospective period and 69% in the prospective period, which was consistent with the published literature (78.3%).[16] Since the pediatric cohort was observed for 12 consecutive months, bias related to the seasonality of infections is mitigated.

The IBIS study did not compare the rate of adverse drug reactions (ADRs) between IVIG and SCIG. However, in our experience, systemic ADR—such as fever, headache, and flu-like symptoms—are less common during biweekly administration of Hizentra compared with IVIG treatment. As expected, transient and mild, local infusion site reactions were observed.

In our opinion, a further advantage of biweekly SCIG therapy is on the psychological aspect of the patient related to the treatment of these chronic diseases. In fact, biweekly administration at home reduces the number of infusion sessions per month so that less time is dedicated to therapy allowing more time for other playful activities that are so fundamental in childhood without the need for periodic hospitalization required by IVIG.

The main limitation of this subanalysis was the retrospective design, in which missing or incomplete data, as well as recall bias, could have affected the primary analysis. To limit this potential source of distortion, a minimum retrospective set of required data was defined. Furthermore, the limited sample size affected the statistical power of study endpoints and rare adverse events may have been undetected. This may be addressed in future studies on a larger population of patients with PID.

Conclusions

This subanalysis of the IBIS study provided real world evidence that switching from Hizentra with weekly administered to a biweekly regimen, in pediatric patients, did not compromise serum IgG levels or the rate and severity of infections and was noninferior with respect to previous IVIG/SCIG-based treatment. Therefore, biweekly 20% SCIG Hizentra was an effective option in pediatric patients with PID.

Availability of Data and Materials

The data that support the findings of this study are available from CSL Behring Italy (study sponsor), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of CSL Behring.

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Author Disclosure Statement

G.M.B. is an employee of CSL Behring. C.C., V.G., C.P., A.T., S.G., B.M., V.M., V.P., A.M., A.P., G.S., A.V., and C.A. declare no conflicts of interest.

Author Contributions

All authors, but G.M.B., participated in the IBIS study. C.C., V.G., C.P., A.T., S.G., B.M., V.M., V.P., and C.A. enrolled pediatric patients in the IBIS study. AV reviewed the statistical analysis report. C.C. contributed to writing of the article. All authors reviewed and approved the article. All authors had full access to the data, reviewed, and approved the final article before submission.

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