

Shift from intravenous or 16% subcutaneous replacement therapy to 20% subcutaneous immunoglobulin in patients with primary antibody deficiencies

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Abstract

In patients with primary antibody deficiencies, subcutaneous administration of IgG (SCIG) replacement is effective, safe, well-tolerated, and can be self-administered at home. A new SCIG replacement at 20% concentration (Hizentra[®]) has been developed and has replaced Vivaglobin[®] (SCIG 16%).

An observational prospective multi-centric open-label study, with retrospective comparison was conducted in 15 Italian centers, in order to investigate whether and to what extent switching to Hizentra[®] would affect frequency of

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infusions, number of infusion sites, patients' satisfaction, and tolerability in patients previously treated with Vivaglobin® or intravenous immunoglobulins (IVIg).

Any variations of dosage, frequency and duration of the infusions, and of number of infusion sites induced by Hizentra® with respect to the former treatment were recorded. Practical advantages and disadvantages of Hizentra®, with respect to the medicinal product formerly used, and the variations in patients' therapy-related satisfaction were monitored by means of the TSQM (Treatment Satisfaction Questionnaire for Medication); number, frequency, and duration of infectious events and adverse effects were recorded.

Eighty-two patients switched to Hizentra®: 19 (23.2%) from IVIg and 63 (76.8%) from Vivaglobin®. The mean interval between infusions was not affected by the shift (7.0 ± 2.0 days with previous treatment versus 7.1 ± 1.2 during Hizentra®). A decrease in the number of infusion sites with Hizentra® was recorded in 12 out of 56 patients for whom these data were available. At 6 months, 89.7% of patients were satisfied with Hizentra®; no difference in terms of effectiveness, side effects, convenience, and global satisfaction was observed. No difference in the incidence of adverse events was reported.

Keywords

immunoglobulin replacement, intravenous immunoglobulins, primary immunodeficiency, subcutaneous immunoglobulins, therapy satisfaction

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Introduction

In adults and children with primary immunodeficiencies (PID), replacement therapy with immunoglobulins is required in order to reduce risk of infections.¹ Lifelong immunoglobulin (IgG) replacement therapy represents the only effective treatment for these patients, and is thus the gold standard therapy in the management of PID. It also prolongs survival, reduces morbidity, and exerts a positive effect on patients' quality of life.^{2,3} Although intravenous administration of IgG (IVIg) has been the therapy of choice and it has been widely used for many years, subcutaneous administration of IgG (SCIG) has recently gained considerable attention among patients and physicians.⁴ SCIG infusions were shown to be efficacious, and they can also be self-administered at home.^{5,6} Few systemic adverse reactions have been reported, indicating a favorable safety profile compared with IVIGs.^{5,7,8} The average serum levels of Ig are comparable to those obtained during IVIg therapy, but with reduced oscillations between consecutive infusions.^{6,9,10} With recent technical advances in IgG formulation, pure and highly concentrated SCIG preparations that have relatively low viscosity, and can therefore be infused more rapidly, have been developed and are increasingly used worldwide.^{11–13} The potential improvement in quality of life in patients switching from inpatient-based IVIg therapy to home-based SCIG therapy is another important aspect of this

treatment. The aim of this prospective, observational study—conducted in a field-practice scenario—was to monitor frequency and number of infusions variations, the tolerability, and the degree of patient satisfaction following the use of Hizentra® (IgPro20, CSL Behring GmbH, Berne, Switzerland), a new immunoglobulin preparation for subcutaneous administration at 20% concentration, in patients suffering from PID.

Methods

Design

This was an observational, prospective multi-centric open-label study, with retrospective comparison. The study was conducted in 15 Italian centers (see Appendix).

All centers followed pediatric and/or adult patients with PID. The prospective observation lasted 6 months: every patient was monitored starting from the signing of the informed consent form. Data were collected from 1 August 2012 to 9 January 2014. Local Institutional Review Board/Ethics Committee approval was obtained by all participating centers. Informed consent was obtained from all patients as appropriate.

Patients

The study included patients of any age and gender suffering from PID (according to European Society

for Immunodeficiencies criteria¹⁴ in regular replacement treatment with immunoglobulins. In more details, patients treated with Vivaglobin® (CSL Behring, Berne, Switzerland), which has been replaced on the market by Hizentra® since November 2011, who were about to switch or had already switched to Hizentra®, and patients formerly treated with IVIG who have been switched to Hizentra® for at least 3 months could be included. In patients enrolled from previous IVIG treatment, only the latter criteria had to be met; they were analyzed in a separated subgroup.

Exclusion criteria were as follows: patients participating in other experimental studies; those who had been included in other clinical studies and who received the last dose of experimental drug <2 months before enrolment (or before a longer period if a longer effect of the experimental drug is expected); participants carrying HIV, HBV, or HCV infection; patients with non-collaborative attitude or unable to perform auto-injection of Ig (related only to adult patients); pregnant women; and patients who cannot complete the planned 6-month follow-up.

Treatment

In line with the field-practice nature of the study, in patients who were about to switch from Vivaglobin® to Hizentra®, the scheduling of switch was decided by the treating physician. In addition, drug dosage, interval between infusions, and duration of each infusion was also decided by the treating physician. Treatment adjustment in frequency of administrations, sites of injections, and infusion length were recorded.

SCIG was infused using an SC needle under the skin via infusion pump. The SCIG product was allowed to reach room temperature prior to infusion. The skin sites were cleansed prior to needle insertion with an antiseptic (e.g. alcohol). The needle was placed at a 90° angle to the skin and inserted through the dermal layer. After insertion patients and/or their caregiver were advised to gently pull back on the syringe plunger and examine the tubing for any blood return. If the needle placement was correct, the same procedure was repeated for the other sites and the infusion pump was turned on.¹⁵

Evaluations and outcomes

Over the 6-month study period, three evaluations were performed: visit 1 at enrolment (V1), then

after 3 months (V3), and at the end of the observation period (V6).

The research hypothesis was based on the data gathered from phase III studies^{16,17} conducted on this indication, as well as on the clinical experience of the Members of the Scientific Board. The following represented the primary objective of the analysis: variations in frequency of Ig infusions and number of infusion sites associated with the use of Hizentra® compared to those from the same monthly interval of the previous year with the former treatment.

Secondary objectives were as follows:

- (1) evaluation of advantages and disadvantages of Hizentra®, as reported by patients compared with the previously used Ig formulation (using a TSQM questionnaire;¹⁸ in detail, patients expressed about 11 items and four main areas were evaluated: drug effectiveness; side effects; convenience; and global satisfaction. These data were also assembled in four points to obtain a 0–100 score: effectiveness [items 1 and 2]; side effects [items 4–6]; convenience [items 7–9]; and global satisfaction [items 10 and 11]);
- (2) evaluation of number, frequency, and length of single infectious episodes;
- (3) the comparison of tolerability of Hizentra® in this field-practice scenario with results obtained in phase III studies (SBI <1; other infections <5.18%/year/patient; local reaction <50% of patients).^{16,17}

The following variables were analyzed at every visit:

- Comparison of trough serum IgG levels
- Variations of the TSQM results
- Change in the health conditions reported in patient's diary or observed in the clinical and/or laboratory parameters during the monitoring visits
- Incidence of systemic adverse reactions and their classification by severity during the treatment with Hizentra®
- Incidence and trend of local adverse reactions at the infusion site during Hizentra®
- Other treatment-related signs and symptoms
- Laboratory investigations and diagnostic tests significant for the primary endpoint and commonly performed in the normal diagnostic

and therapeutic practice (e.g. total level of serum IgG)

- Number of days on antibiotic therapy

Statistical analysis

Data obtained from case report forms were analyzed by descriptive statistics. χ^2 or Fisher's exact probabilities tests were used to assess group differences in categorical variables. Odd ratios (OR) and 95% confidence limits (CL), when possible as all values were different from zero, were calculated. For continuous variables, the t-test was used with logarithmic transformation of non-normal distributed variables. Two tailed *P* values were used and *P* values <0.05 were considered statistically significant. Data were processed with the SPSSX (SPSS 11.0) statistical package (SPSS Inc., Chicago, IL, USA).

Results

Study populations and treatment

In total, 82 patients were enrolled. For 76/82 patients, gender, age, and ethnicity were known. All patients were Caucasian, 34/76 (44.7%) were female and 42/76 (53.3%) were male. Fifteen patients were of pediatric age (median age, 13 years; interquartile [IQ] range, 11–15 years); the median age in the remaining 61 patients was 40 years (age range, 19–71 years).

Data regarding replacement Ig therapy were known for all the 82 patients included. Nineteen patients (23.2%) had been using IVIG, while the remaining 63 (76.8%) had been using SCIG (Vivaglobin®).

Underlying PID was known for 76/82 patients: it was a common variable immunodeficiency in 53/76 (69.7%), X-linked agammaglobulinemia in 8/76 (10.5%), autosomal recessive agammaglobulinemia in 2/76 (2.6%); the remaining 13 patients (17.1%) were affected by other types of PID, including severe combined immunodeficiency. Disease duration was known in 74/82 patients; median disease duration was 8.5 years (range, 1–41 years; IQ range, 4–16 years). Of the 92 patients, eight patients (9.8%) dropped out of the study. Reasons for drop-outs were transfer of the patient to other center or abroad in some cases, unspecified personal reasons in other cases.

Dose adjustments: Difference between the pre-study and the study period

Information regarding dosage of infused Ig was available for 70/82 patients. In 11/70 patients, the same monthly dosage was maintained after treatment switch, with no difference between the pre-study and the study period. In those patients, the mean level of serum IgG was not different in V6 when compared to V1 (V1: 894 ± 186 mg/dl; V6: 865 ± 184 mg/dl). In 22 patients, the dosage was decreased during the study compared with the pre-switching period. The mean reduction was -2.97 ± 3.24 g/month (median, -1.6 g/month; range, 0.8–14 g/month). In those patients, the mean level of serum IgG did not differ between V1 and V6 (850 ± 164 mg/dl versus 853 ± 134 mg/dl). In 39 patients, the dosage was increased during the study, with a mean increase of 5.18 ± 4.68 g/month (median, 4 g/month; range, 0.8–19 g/month). Also in those patients, no differences in the mean level of serum IgG between V1 and V6 were disclosed (817 ± 153 mg/dl versus 825 ± 176 mg/dl).

In order to evaluate whether the choice to increase or decrease the dosage of infused Ig was dependent by the serum IgG levels in the pre-study period, mean serum IgG level at V1 was evaluated in patients who received an increased dosage during the study (869.3 ± 164.1 mg/dl) and in patients who received a decreased dosage during the study (814.6 ± 151.6 mg/dl). No differences in IgG levels at V1 between the two groups were found.

Interval between infusions in the pre-study and study period

With the aim to verify whether the difference in IgG concentration in Hizentra® compared with Vivaglobin® could result in modification in intervals between infusions or in the number of infusion sites, we evaluated the subgroup of patients (*n* = 63) who were already on SCIG in the pre-study period. Data regarding interval between infusions and number of infusion sites per session were available for 56/63 patients.

The mean interval between infusions in the pre-study period was 7 ± 2 days, while during the study it was 7 ± 1 days. This interval was increased in 8/56, decreased in 6/56, and unchanged in 42/56 patients. Forty-one out of 56 participants

had an interval between infusion of 7 days in the pre-study period; the number of participants which had such interval increased to 43/56 in the study period. Among those 43 patients, 36/43 had continued with the same interval used in the pre-study period, five of them had prolonged the interval (2 patients from 3 to 7, 1 patient from 5 to 7, 2 patients from 6 to 7) and two patients had reduced the interval between infusion (from 15 and from 8 days, respectively). In the pre-switch period, 9/56 patients received infusions with an interval of time <7 days; during the study period the patients who received infusions with an interval <7 days were 7/56. Among those seven patients, 3/7 had continued with the same interval used in the pre-switch period (4, 5, and 6 days, respectively), one of them had increased the interval from 2 to 6 days, two patients had reduced the interval between infusion from 7 to 5 days and one patient had reduced the interval between infusion from 7 to 4 days. Six patients had reduced the interval between infusions totally. Among those patients, 3/6 also had a reduction in the number of infusion sites (from 4 to 2, from 3 to 2, from 2 to 1, respectively), while in 3/6 the number of sites remain unchanged (1, 1, and 2, respectively). Nevertheless, those patients who reduced both variables did not maintain the same dosage at the shift from Vivaglobin® to Hizentra®. An increase in the number of infusions sites was recorded in two patients, a decrease was recorded in 12 patients and no variation was recorded in 42 patients. Both patients who had an increase (from 1 to 2 sites) showed a longer interval between infusion and did not require any variation of monthly dosage. For that reason, the amount of product per session increased together with the number of infusion. Among 12 patients who had a decrease and maintained the same monthly dosage, one patient reported a decrease in interval between infusions, too. The number of patients who experienced reduction in the number of sites was sixfold than the number of patients with increased number of sites (Figs. 1 and 2).

IgG levels

The levels of serum IgG at V1 was recorded in 51/82 patients. The mean serum level of IgG was 841 ± 157 mg/dl (range, 604–1110 mg/dl). At V3,

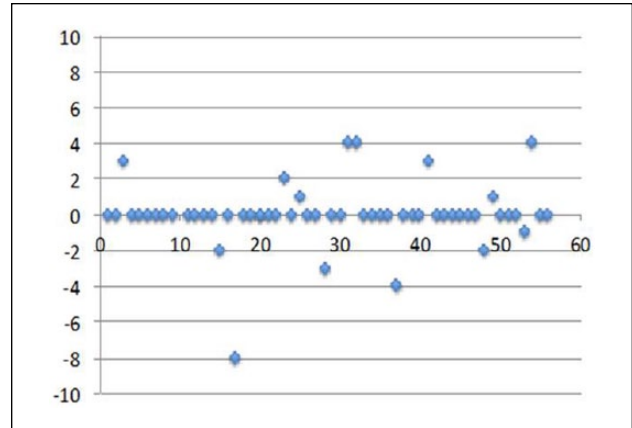


Fig. 1. Differences* in the interval (number of days) between infusion in the pre-study (V1) and study period (V6). *Differences correspond to the number of days between infusions in the pre-study period less the number of days between infusions in the study period. Positive values indicate increased intervals, negative values indicate decreases intervals. Zero indicates no variation.

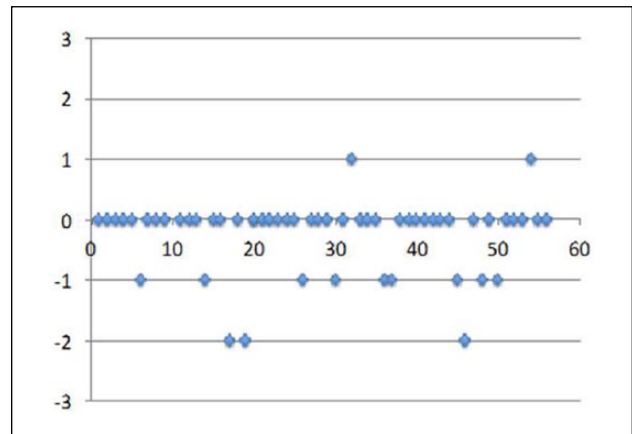


Fig. 2. Differences* in the number of infusion sites in the pre-study (V1) and study period (V6). *Differences correspond to the number of infusion sites in the study period less the number of infusion sites in the pre-study period. Positive values indicate an increase in the number of sites, negative values indicate a decrease in the number of sites. Zero indicates no variation.

IgG levels were evaluated in 47/82 patients; the mean IgG level was 817 ± 151 mg/dl (range, 580–1320 mg/dl). At V6, IgG levels were evaluated in 51/82 patients; the mean IgG level was 840 ± 166 mg/dl (range, 631–1280 mg/dl).

In 35/82 patients, IgG levels have been measured at all visits (V1, V3, and V6). No differences between IgG levels between V3 and V6 were disclosed (Table 1).

Table 1. IgG levels at different timepoints.

	Patients (n)	Serum IgG levels (mg/dl)		
		Mean	SD	Range
Enrollment (V1)	51	841	157	604–1110
III month (V3)	47	817	151	580–1320
VI month (V6)	51	840	166	631–1280

Advantages and disadvantages of Hizentra®:

Results from the TSQM questionnaire

The questionnaire was presented to all 82 patients: a mean of 86.4% answered questions at V1, except for items number 4, 5, and 6, that were filled only from 38.7% of patients meanly. At V2, a mean of 62.9% completed the questionnaire, but the mean was lower for the items 4, 5, and 6 (39.7%). The number of answered questions decreased at V6, when 46.1% of patients completed the form meanly, and the percentage was even less for items 4, 5, and 6 (19%).

At V1, 87.3% were satisfied about therapy and 63.4% were very satisfied. At V3 and V6, 84.6% and 89.7% were satisfied, respectively, and after 6 months the number of unsatisfied patients was even lower.

Most patients were satisfied with symptoms palliation at V1 (85.9%) and this percentage increased at V6 (94.5%).

Regarding the influence of side effects on physical state, at V1 40% of patients were unsatisfied. This percentage slightly increased at V3 (42.9%) and even more at V6 (56.1%). Similar results were reported about the influence of side effects on mental state: the number of unsatisfied patients increased during the study period, from 21.5% to 38.5%. On the other hand, the number of patients unsatisfied from influence of SCIG therapy on emotional sphere remained almost unchanged and lower than 50% all over the study period.

The number of patients that were satisfied from how the product is easy to use was around 70% with negligible variations over the 6-month follow-up. Moreover, the percentage of very satisfied patients increased from 14.3% to 21% during the observation period. Regarding the scheduling of SCIG, most patients were satisfied at V1 (81.4%) and the percentage was even higher at V6 (86.8%). Similar findings were obtained for the frequency of infusions, with an increase of satisfied patients from 65.7% to 71.1%. The rate of satisfaction

about the balance between advantages and disadvantages did not change during the study period, remaining >90%.

Global satisfaction about therapy was 90% at V1 and slightly higher at V6 (94.5%) (Tables 2 and 3).

Safety considerations

Infections were reported in the clinical history of seven patients at V1, in 22 participants at V3, and in 24 patients at V6. Autoimmune diseases were reported in the clinical history of four patients at V1, three patients at V3, and no patients at V6.

Data on tolerability in the pre-switch period were available for 76 patients. Among them 69/76 (90.8%) reported a good tolerability; 6/76 (7.9%) reported rare minor systemic adverse events, and 1/76 (1.3%) reported frequent minor systemic adverse events. As for the local adverse events, 16/76 (21%) reported swelling, 7/76 (9.2%) experienced pain, 36/76 (47.4%) reported redness, and 11/76 (14.4%) had itching. Overall, side effects were reported by 11.3% of patients at V1, by 17.3% at V3, and by 13.5% at V6.

During the study period, pain was never reported by 66/76 patients (86.4%). Overall, pain was reported in 65/246 infusions in the 10 patients experiencing pain (26.4%). Taking all infusions and all patients, pain was reported in <5% of infusions.

Swelling was never reported by 49/76 patients during the study period (64.4%) and it was reported by 27/76 patients with a range of 1/26 (4.8%) infusions and 26/26 (100%) infusions. Among the 63 patients who were already on SCIG before switching, five lacked safety data prior to study inclusion. The analysis of local adverse events was therefore performed on 58 patients. In the pre-study period, 15/58 patients had reported swelling: among them 7/15 also had swelling in the study period. Of these seven patients who reported swelling with Hizentra®, the symptom was not reported at all infusions, but with its occurrence range of 7.7–100% of infusions. Three out of these seven patients reported swelling at all infusions. Among the 43 patients who had not reported swelling with Vivaglobin®, 31/43 had no swelling using Hizentra®; in the 12 patients who did not report swelling with Vivaglobin® but reported swelling with Hizentra®, the symptom was not present at all infusions, but with a range of 3.8–100%. Eight out of these 12

Table 2. TSQM questionnaire, effectiveness, and side effects: number of respondents and score (mean, median, SD, range).

	Effectiveness			Side effects			
	V1	V3	V6	V1	V3	V6	
Respondents (n)	71	52	38	32	33	14	
Score	Mean*	72.5	68.2	73.9	87.8	85.7	78.0
	Median	83.3	66.6	75.0	100.0	95.8	85.4
	SD	23.7	24.6	18.8	16.7	25.2	27.4
	Range	0–100	0–100	8.3–100	41.7–100		8.3–100

* No differences in the mean score attributed to “effectiveness” or “side effects” between V1 and V6 were found.

Table 3. TSQM questionnaire, convenience, and global satisfaction: number of respondents and score (mean, median, SD, range).

	Convenience			Global satisfaction			
	V1	V3	V6	V1	V3	V6	
Respondents (n)	70	51	38	70	51	37	
Score	Mean*	68.6	70.2	69.3	77.3	73.4	75.7
	Median	72.2	72.2	72.2	83.3	75.0	75.0
	SD	19.8	19.4	21.1	19.4	23.0	17.1
	Range	16.67–100	0–100	5.56–100	0–100	0–100	16.67–100

* No statistically significant differences in the mean score attributed to “convenience” or “global satisfaction” in V1 and V6 were found.

patients reported swelling at all infusions. Overall 236/307 (77.4%) infusions in the 12 patients were associated with swelling. The difference between swelling incidence in the pre-study and study period was not statistically different.

Overall, 7/58 (12.1%) patients reported pain in the pre-study period: among them, 2/7 reported pain in the study period in at least one infusion. Pain was not present at all infusions, but in 1/26 infusion in one patient and in 13/26 infusions in the other. Among the 51 patients who had not reported pain with Vivaglobin®, 44/51 (86.3%) had no pain either using Hizentra® while 7/51 (13.7%) reported pain in at least one infusion. The symptom was not present at all infusions, but with a range of 7.4–96.2% of infusions. Overall 75/222 (33.8%) infusions in the seven patients were associated with pain. The difference between pain incidence in the pre-study and study period was not statistically different.

In total, 32/58 patients had reported redness in the pre-study period. Among them, 12/32 had redness also during the study period. This symptom was not reported at all infusions, but with a range of 4.0–100% of infusions (overall: 145/310, 46.8%). Only 1/12 patient reported redness at all infusions. Among the 26 patients who had not reported redness with Vivaglobin®, 22 did not

experience redness on Hizentra® treatment; in the remaining four patients, redness was not present at all infusions, but with a range of 4.3–96.2%. Overall, 51/87 (58.6%) infusions in the four patients were associated with redness. The difference between redness incidence in the pre-study and study period did not reach statistical significance.

With respect to itching, 11/58 patients reported this symptom with Vivaglobin®; among them, 2/11 experienced itching also with Hizentra®. Itching was not present at all infusions but in 5/26 (19.2%) infusions in one patient and in 7/24 (29.2%) in the other patient. Among the 47 patients who did not reported itching with Vivaglobin®, 41/47 had no itching either using Hizentra; when reported, itching was not present at all infusion but with a range between 1/27 (3.7%) and 13/26 (50.0%). In the six patients who reported itching, this symptom was present in 28 out 142 infusions (19.7%). No differences in the incidence of itching incidence between the pre-study and study period were disclosed.

In total, 19/58 patients had reported other unspecified symptoms with Vivaglobin®: among them, none reported other unspecified symptoms with Hizentra®. Among the 39 patients who had not reported unspecified symptoms with Vivaglobin®, 37 had no unspecified symptoms also

using Hizentra®; in the two patients who reported symptoms with Hizentra®, the symptoms were not present at all infusions, but at 1/26 (4.3%) in one patient and at 4/26 (96.2%) in the other. The difference between the two treatments was not significant.

Data regarding school or work days lost due to PID at each visit was available for 73/82 patients. Mean days lost at V1 was 4 ± 12 days, 1 ± 2 days at V3, and 1 ± 3 days at V6. The difference between V3/6 versus V1 was significant ($P = 0.0158$ and $P = 0.0318$, respectively). Since data in V1 were referred to the previous 12 months while data in V3 and V6 were referred to a 3-month interval, the comparison was recalculated using for V1 a projection of the data to a trimester. Using that estimate, no difference was found between the baseline and the two following visits ($P = 0.2347$ for V3 versus V1 and $P = 0.7723$ for V6 versus V1, respectively).

Discussion

Unlike the expectations, this study suggests that in clinical practice Hizentra® has been introduced in substitution of other products without variations in the interval between infusions; and among patients in whom intervals were modified, more patients had an increase rather than a decrease. The choice to maintain patients on an interval between infusions of about 7 days suggests that physicians consider this time span as the best interval to guarantee a stable level of serum IgG over time.

Although the small number of patients did not allow to reach statistical significance, an increased number of sites was reported only in two patients, while 12 participants did not experience changes in this parameter. Together, data show that reduction in the number of sites is preferred over shorter intervals between infusions. Differing from interval between infusions, the number of sites does not interfere with drug effectiveness, but can influence only logistic issues. Moreover, it may result in fewer side effects in the absence of any effect on drug effectiveness. Data from the TSQM questionnaire showed no difference in effectiveness, side effects, convenience, and global satisfaction for the study period compared with the pre-study period. When patients who were in IVIG therapy in the pre-study period were separately analyzed, the

results did not change as well. IgG preparation for subcutaneous administration is confirmed to be safe, easy to use, and well-tolerated by patients. Overall, about half of the patients were not satisfied with at least one item; in particular, influence of therapy on daily life. Nevertheless, only one-third of those unsatisfied patients clearly experienced some side effects. Dissatisfaction seemed to correlate more with occurrence of infective episodes despite therapy, with loss of school or work days. However, none of the unsatisfied patients was hospitalized. Nevertheless, and despite the number of answers decreasing over time, the majority of patients, both those already using SCIG and those using IVIG in the pre-study, have reported satisfaction for IgG therapy with a global satisfaction score over 75%. The shift from previous therapy to Hizentra® was not associated with changes in serum IgG, independent of the previously used treatment (IVIG or SCIG). Such data confirm that the more concentrated product retains the same efficacy as the previous one. Finally, side effects have been evaluated, overall showing no difference between Hizentra® and previous IgG used. The obtained data are comparable with the results of the study of Niebur et al.¹⁹ about transition from Vivaglobin to Hizentra. Different from ours, the authors made a direct comparison of the pharmacokinetics and efficacy of the two products, showing that these are similar. Although it was a monocentric study involving a smaller cohort of participants with primary antibody deficiency, results on safety and treatment satisfaction are comparable. In fact, they showed that Hizentra was considered more favorably than Vivaglobin in the domain of side effects but that, overall, the two products are similar.

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Appendix

List of centers participating in the study and clinical research coordinators (indicated in parentheses)

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- Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy (A. Plebani)
- Clinica Pediatrica II AOU Meyer, Florence, Italy (C. Azzari)
- Dipartimento di Medicina Interna CISI Azienda Ospedaliera Universitaria “Federico II” Napoli, Naples, Italy (G. Spadaro)
- Unità Operativa di Oncoematologia Pediatrica Ospedale CIVICO, Palermo, Italy (A. Trizzino)
- Centro di Riferimento Immunodeficienze Primitive Azienda Policlinico Umberto I, Rome, Italy (I. Quinti)
- UOC di Immunoinfettivologia Ospedale Pediatrico Bambino Gesù, Rome, Italy (A. Finocchi)

- Centro Interdisciplinare di Pediatria. Rome, Italy (V. Moschese)
- Struttura Semplice di Immuno-Reumatologia Ospedale Regina Margherita, Turin, Italy (S. Martino)
- Medicina generale Ospedale Torrette, Ancona, Italy (M.G. Danieli)
- Dipartimento di Medicina Interna e Oncologia Clinica Università degli Studi di Bari, Bari, Italy (A. Vacca)
- Dipartimento di Medicina (DIMED), Immunologia Clinica Università di Padova, Padua, Italy (C. Agostini),
- Allergologia ed Immunologia Dipartimento di Medicina Interna (pad.8) Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Udine, Italy (M. De Carli)
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