



Correlations Among Subcutaneous Immunoglobulin Dosage, Immunoglobulin G Serum Pre-infusional Levels and Body Mass Index in Primary Antibody Deficiency Patients: A Pooled Analysis from the SHIFT/IBIS Studies

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Abstract

Background and Objective In recent years, two Italian non-interventional studies evaluated subcutaneous immunoglobulin (SCIG) treatment in patients affected by primary antibody deficiency (PAD). The SHIFT study considered patients who were treated with intravenous immunoglobulin (IVIG) or SCIG 16% (Vivaglobin[®]) and then replaced this therapy with weekly treatments of SCIG 20% (Hizentra[®]). The IBIS study evaluated patients previously taking a weekly SCIG 20% regimen, who instead began therapy with biweekly SCIG 20% to assess the correlation between the dose of immunoglobulin G (IgG) administered and the body mass index (BMI) of patients, determine if there is a need for dosage adjustments on a BMI basis, and identify the predictors of serum IgG trough levels in our cohort.

Methods In this study, we analyzed the pooled data of 109 PAD patients enrolled in the SHIFT and IBIS studies. Only prospective phases were considered.

Results The total monthly SCIG dose showed comparable trends among weight categories, except for underweight patients. When we considered the monthly SCIG dosage per kilogram of body weight, a significant decreasing trend according to BMI was observed. Data on IgG trough levels were available for 88 patients, with a mean IgG serum level of 8.4 ± 1.6 g/L. A stepwise regression model revealed that the mean monthly dosage of SCIG 20% ($p = 0.04248$) and the mean monthly dosage of IgG per kilogram of body weight were the only two independent predictors associated with IgG trough levels. No association was found between BMI and IgG trough levels.

Conclusions These findings support the concept that the cumulative monthly dose of SCIG and the dose of SCIG per kilogram of body weight affect IgG trough levels in PAD patients, irrespective of BMI.

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Key Points

Data for 109 patients from two Italian observational studies (SHIFT and IBIS) who were affected by primary antibody deficiency (PAD) were pooled to investigate the presence of possible correlations among pre-infusion concentration, immunoglobulin G (IgG) dosage, and body mass index (BMI).

BMI did not correlate with trough concentrations, and IgG dosage had comparable trends among weight categories (except for underweight patients).

IgG dose adjustment seems to be unnecessary in overweight and obese patients.

1 Introduction

Primary antibody deficiency (PAD) includes a heterogeneous group of disorders affecting one or more functions of the immune system [1]. With the growing development of genetic equipment, many new genes affected, and their related mutations, have been discovered. PADs encompass a myriad of presentations, ranging from immune deficit-related symptoms (i.e. infections and malignancies) and immune dysregulation-related manifestations (i.e. auto-inflammation phenomena, autoimmunity disorders and allergies) [2]. PADs have been estimated to affect 6 million people worldwide [3]. According to the European Society for Immunodeficiency Database (ESID), more than 50% of the registered cases of PADs are “predominantly antibody disorders” [4].

The gold-standard treatment for patients with PAD is immunoglobulin G (IgG) replacement therapy (IGRT) [5]. Intravenous (IVIG) and subcutaneous (SCIG) infusions are the two routes used to administer IgG. In contrast to IVIG, SCIG allows home-based self-administration and results in more stable IgG serum levels, thus improving the quality of life and clinical efficacy. In addition, the self-administration of IgG improves patient compliance and empowerment [6]. Most national and international guidelines suggest a mean dosage of 0.4–0.6 g/kg/month for both IVIG and SCIG [7]; however, according to the Hizentra[®] Summary of Product Characteristics (SPC), IgG dosage needs to be adjusted on an individual basis, with the aim of reaching IgG trough levels > 5–6 g/L.

Two Italian observational studies, SHIFT [8] (CSL Behring protocol IgPro20_5001) and IBIS [9] (CSL Behring protocol IgPro20_5002), analyzed PAD patients requiring IGRT. In the SHIFT study, patients who were previously receiving therapy with IVIG or weekly SCIG 16% (Vivaglobin[®]; CSL Behring, King of Prussia, PA, USA) were then treated with weekly SCIG 20% (Hizentra[®]; CSL Behring), while the IBIS study evaluated the real-life aspects of patients taking weekly Hizentra[®] who were then administered biweekly (i.e. every other week) treatments with Hizentra[®]. Both studies showed that mean serum IgG trough levels were maintained above the protective threshold of 5 g/L.

This analysis pooled data from the SHIFT and IBIS studies to (1) assess the correlation between the dose of SCIG administered and the body mass index (BMI) of patients; (2) determine if there is a need for dosage adjustments on a BMI basis; and (3) identify the predictors of IgG trough levels in our cohort.

2 Methods

Patient data on the prospective phases from IBIS and SHIFT were pooled and uniformed in a unique database.

2.1 Monthly Dosage: Assumptions

For patients enrolled in the SHIFT study, monthly dosage was retrieved from the screening visit, since all patients were deemed stabilized by their treating physician at enrollment, and the dosages registered in the 3- and 6-month visits were reported as summary statistics without any difference from baseline. Therefore, we assumed that variations in the dosage during the study were negligible.

For patients enrolled in the IBIS study, the monthly dosage was calculated starting from the mean dose per infusion and the infusion frequency (number of days between two consecutive infusions).

2.2 Body Mass Index-Based Categorization of Patients

Adult patients were categorized according to the World Health Organization (WHO) criteria [10] based on BMI calculation (the weight of an individual in kilograms divided by the square of the height of an individual in meters), i.e. underweight: below 18.5 kg/m²; normal weight: in the 18.5–24.9 kg/m² range; overweight or pre-obese: in the 25.0–29.9 kg/m² range; and obese: over 30 kg/m².

In contrast, as reported by the WHO [11], pediatric patients have to be evaluated on the basis of percentile tables, as BMI in patients under 18 years of age is characterized by high variability and is mainly sex- and age-related. Therefore, pediatric patients were categorized as underweight if BMI was less than the 5th percentile, normal weight if BMI was in the 5th–85th percentile range, overweight if BMI was in the 86th–97th percentile range, and obese if BMI was greater than the 97th percentile.

However, we used the BMI-for-age clinical growth charts of Cacciari and colleagues [12], which are similar to those of the WHO and are more representative of the Italian population. As in the latter curves, data regarding the 5th percentile were not available, and we used the 3rd percentile as a proxy.

2.3 Statistical Analyses

The association among categorical variables was measured using the Chi square test. Analysis of variance (ANOVA) was used to evaluate the mean differences among groups. Statistical analyses and the relevant graphics were performed using the statistical software R [13].

To evaluate the influence of all the possible predictors on the serum IgG trough concentration, a linear regression analysis was performed considering all the independent variables available in the database: administration frequency, type of patient (adult or pediatric), age, sex, height, weight, BMI, weight category (underweight, normal weight, overweight, obese), and monthly dosage (total and per kilogram of body weight). The model was analyzed using the stepwise regression technique to determine the best regression model with the lowest number of variables.

3 Results

A pooled database containing 111 patients was obtained from aggregation of the SHIFT (76 patients) and IBIS (35 patients) studies. Two patients from the SHIFT study were excluded as data regarding monthly dosage was not available, leaving 109 patients to be analyzed. Table 1 shows the general characteristics of the pooled database.

The populations of the two databases were comparable in all characteristics except age; IBIS patients were, on average, 8 years younger than SHIFT patients ($p=0.0152$).

Analysis of the pediatric cohort included in the prospective phases of the SHIFT and IBIS studies was performed by Moschese et al. and is under consideration for publication.

In the pooled database analyzed in this study, 60% of patients were normal weight, 35% were overweight or obese, and 5% were underweight. No statistically significant differences among the distribution of weight categories were detected when analyzing adult and pediatric populations separately (Chi square test, $p=0.2022$).

The distribution of weight categories in the adult population is comparable with that observed in the Italian population aged > 18 years [14] (Fig. 1a). In contrast, the distribution of weight categories in the pediatric population is slightly different from the national mean [15], particularly in the overweight category (Fig. 1b).

3.1 Immunoglobulin G Dosage and Pre-infusion Trough Concentration

Total monthly IgG dosage showed comparable trends among weight categories, except for underweight patients (Table 2, Fig. 2a), as highlighted by the ANOVA test ($p=0.02428$).

Table 1 General characteristics of the pooled database, aggregating the SHIFT (74 patients) and IBIS (35 patients) databases

Characteristic	N (%)	Mean (SD)	Median (IQR)	Range	p value
Sex, male	64 (58.7)				0.2191
SHIFT	40 (54.1)				
IBIS	24 (68.6)				
Age, years		31.4 (16.3)	29 (18–43)	2–71	0.0152
SHIFT		33.9 (16.7)	33 (21–47)	2–71	
IBIS		26.1 (14.4)	24 (14–40)	2–56	
Height, cm		163.9 (18.2)	168 (158–175)	87–191	0.3313
SHIFT		165.1 (17.5)	169 (158–177)	87–190	
IBIS		161.5 (19.5)	166 (157–174)	87–191	
Weight, kg		64.8 (19.1)	65 (52–79)	12–100	0.3022
SHIFT		66.2 (18.9)	66 (55–85)	12–100	
IBIS		62.1 (19.4)	65 (50–78)	12–91	
BMI, kg/m ²		23.5 (4.5)	23 (20–26)	14–35	0.5396
SHIFT		23.7 (4.4)	23 (21–27)	14–35	
IBIS		23.1 (4.7)	24 (20–27)	14–34	
Monthly IgG dosage, g		23.0 (9.2)	24 (16–26)	4–50	0.5899
SHIFT		24.0 (9.6)	24 (16–27)	4–50	
IBIS		21.0 (8.1)	22 (16–26)	5–35	
Monthly IgG dosage, mg/kg		365.5 (132.1)	357 (268–414)	152–33	0.9199
SHIFT		374.9 (143.8)	357 (276–405)	194–833	
IBIS		345.5 (102.0)	364 (258–432)	152–521	
Pediatric patients	28 (25.7)				0.0994
SHIFT	15 (20.3)				
IBIS	13 (37.1)				

BMI body mass index, IQR interquartile range, SD standard deviation, IgG immunoglobulin

When underweight patients ($n=5$) were excluded, an homogeneous dosage was obtained among normal weight, overweight, and obese patients ($p=0.1092$). In the monthly IgG dosage per kilogram of body weight, a significant decreasing trend according to BMI was observed (Table 2, Fig. 2b). These differences among groups were significant, independent of the inclusion or exclusion of the underweight category ($p=0.04066$ and $p=0.03673$, respectively).

Data on the pre-infusion trough concentrations were available for 88 patients (Table 2). The mean pre-infusion trough concentration was 8.4 g/L, and for every patient it was > 5 g/L (range 5.5–13.9 g/L). This predictor was comparable in the weight categories ($p=0.5331$) (Fig. 3), even though a non-significant lower mean was detected in the obese group (7.8 g/L).

A stepwise regression was performed to highlight factors predicting serum IgG trough levels (Fig. 4). The

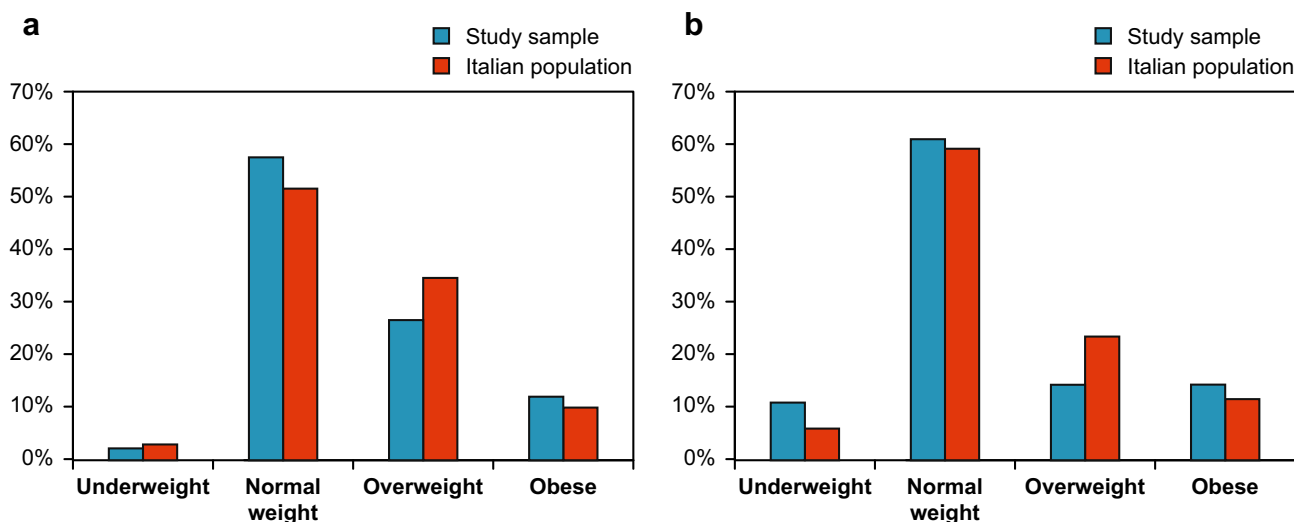


Fig. 1 a Study sample and the Italian adult population are compared in terms of distribution of weight categories, showing similar results. b Study sample and the Italian pediatric population are compared in

terms of the distribution of weight categories, showing slight differences, especially in the overweight category

Table 2 IgG monthly dosage administered (total and per kilogram of body weight) per weight category and pre-infusion trough serum levels (g/L; total and per weight category)

Variable	N (%)	Mean (SD)	Median (IQR)	Range
IgG dosage, g/month	109 (100)	23.0 (9.2)	24 (16–26)	4–50
Underweight	5 (4.6)	14.2 (4.2)	16 (10–16)	10–19
Normal weight	64 (58.7)	22.1 (8.1)	24 (16–24)	4–50
Overweight	26 (23.9)	26.5 (11.1)	22 (17–35)	12–50
Obese	14 (12.8)	23.9 (9.0)	24 (21–30)	6–40
IgG dosage, mg/kg/month	109 (100)	365.5 (132.1)	357 (268–414)	152–833
Underweight	5 (4.6)	437.0 (95.1)	406 (400–457)	334–588
Normal weight	64 (58.7)	385.1 (132.6)	374 (304–422)	166–833
Overweight	26 (23.9)	344.3 (147.6)	285 (231–409)	195–794
Obese	14 (12.8)	289.7 (64.4)	284 (259–330)	152–412
Pre-infusion trough IgG concentration, g/L	88 (80.7)	8.4 (1.6)	8.1 (7.1–9.5)	5.5–13.9
Underweight	5 (5.7)	8.4 (2.5)	8.2 (6.6–10.8)	5.5–11.1
Normal weight	50 (56.8)	8.5 (1.5)	8.3 (7.4–9.7)	6.2–13.9
Overweight	21 (23.9)	8.3 (1.8)	7.8 (7.0–9.4)	6.0–13.0
Obese	12 (13.6)	7.8 (1.5)	7.4 (6.5–8.2)	6.2–11.5

IQR interquartile range, SD standard deviation, IgG immunoglobulin G

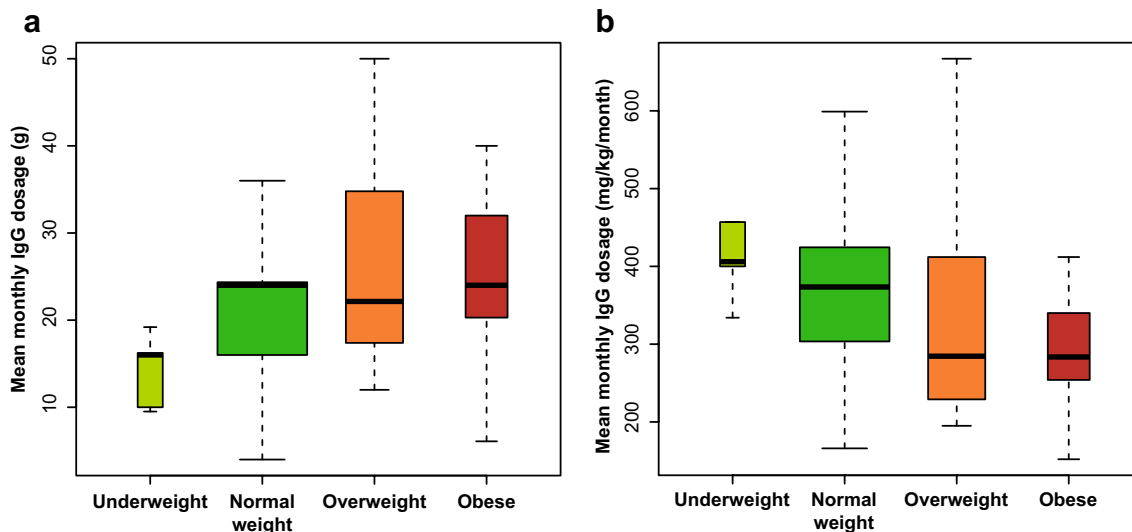


Fig. 2 **a** Total monthly IgG dosage per weight category. **b** Monthly IgG dosage per kilogram according to weight categories. The bold lines represent the median values, the boxes indicate the interquartile

range, and the whiskers represent the minimum and maximum values. *BMI* body mass index, *IgG* immunoglobulin G

mean monthly dosage of SCIG 20% ($p=0.04248$) and the mean monthly dosage of IgG per kilogram of body weight ($p=0.03312$) were the only two independent predictors associated with pre-infusion IgG serum concentrations. These relationships, even if significant, were weakly linear; the model had a very low adjusted R^2 (0.03592 and 0.04068, respectively).

BMI was eliminated in the regression model during the selection of the variables. Figure 4c shows that this variable did not correlate with the pre-infusion trough concentration.

4 Discussion

International guidelines recommend dose immunoglobulin replacement therapy with reference to actual body weight [7]; however, how dosing might be tailored to maximize efficacy while minimizing costs is an open question. From this perspective, pinpointing the factors that mainly affect IgG trough levels in each individual patient is a very important issue. Over the past decades, several studies have investigated the efficacy, safety, tolerability, and pharmacokinetics of various novel IVIG or SCIG preparations [16–19]; however, the main outcomes of these studies were the rates of serious bacterial infections and drug-related adverse events rather than the definition of the most correct doses to achieve a suitable IgG trough level.

In our retrospective analysis of the pooled data derived from the SHIFT and IBIS studies, the mean monthly dosage of SCIG 20% and IgG per kilogram of body weight were the only two independent predictors associated

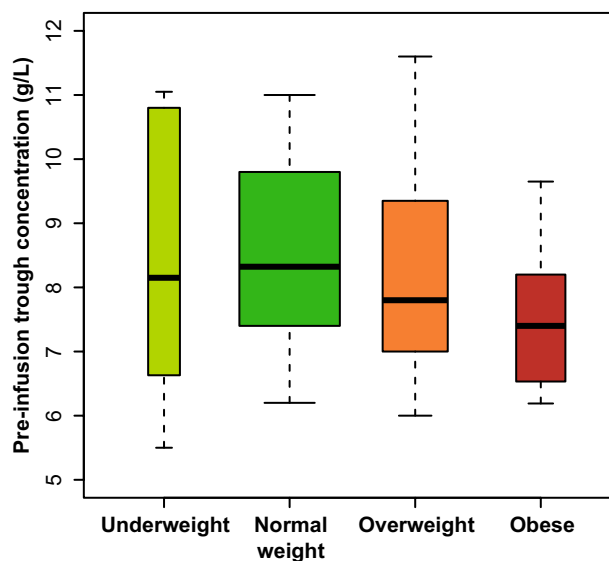


Fig. 3 Pre-infusion trough concentration (g/L) per weight category. The bold lines represent the median values, the boxes indicate the interquartile range, and the whiskers represent the minimum and maximum values

with IgG trough levels in patients treated with IVIG or SCIG 16% immunoglobulin replacement therapy who subsequently replaced that therapy with SCIG 20%. On the other hand, no association was found between BMI and IgG trough levels. These findings are consistent with the results of a previous large cohort study involving 40 obese PAD patients [20]. In particular, similar SCIG dose/serum IgG level ratios were observed between obese and

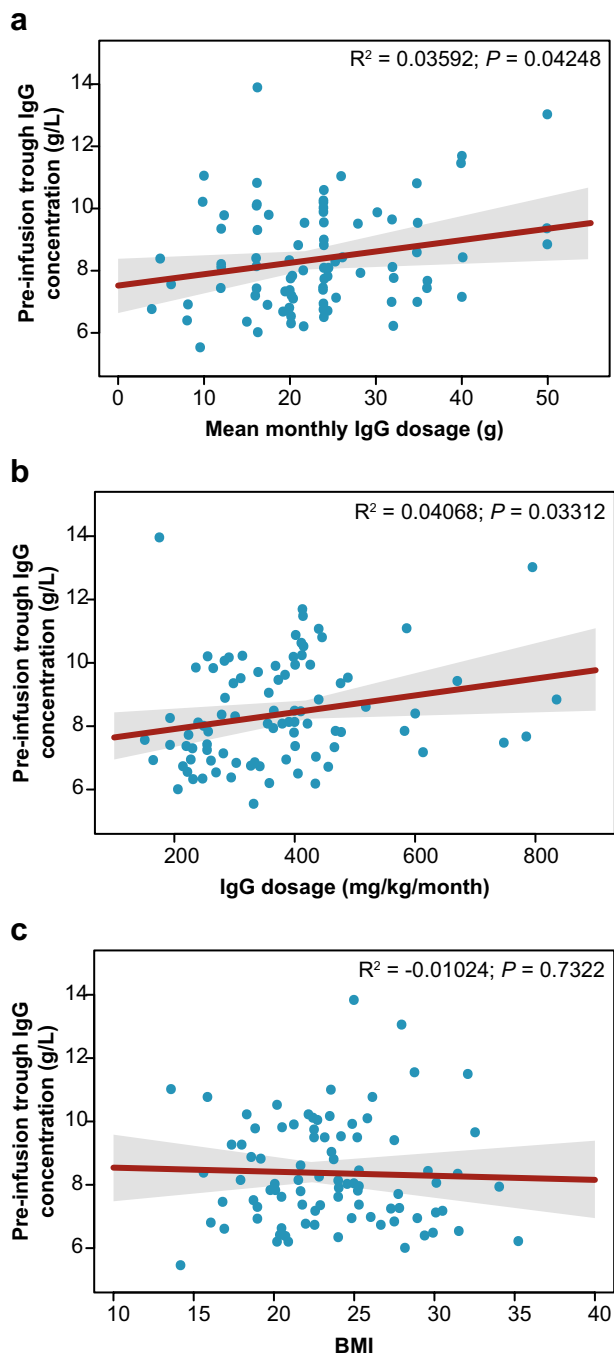


Fig. 4 **a** Linear regression model showing the predictor ‘mean monthly dosage of SCIG 20%’. Blue dots represent data observed. **b** Linear regression model showing the predictor ‘mean monthly dosage of IgG per kilogram of body weight’. **c** Linear regression model showing the predictor ‘BMI’. Red line represents the linear regression line. Light grey stripe: confidence region of the regression line. Blue dots: data observed. *BMI* body mass index, *SCIG* subcutaneous immunoglobulin, *IgG* immunoglobulin G

non-obese patients, suggesting the similar bioavailability of administered immunoglobulin irrespective of BMI.

Additionally, in a cohort of 107 patients with common variable immunodeficiency, Khan and colleagues found no relationship between the annual dose of IgG and trough IgG levels regardless of infusion frequency or adjustment for weight or body mass index [21]. Conversely, a poster presented in 2017 by Checkley et al. [22] suggested that increasing the SCIG dose might improve clinical outcomes in PID patients suffering from frequent infections. On the other hand, we should consider that immunoglobulin does not distribute to adipose tissue and is only present in the intravascular space and extracellular fluids. Indeed, various authors [23, 24] recently suggested the use of adjusted BMI instead of the actual BMI for obese patients because subjects with increased adipose tissue are supposed to have increased extracellular fluid compared with normal-weight subjects.

In our analysis, the mean dosage of IgG per kilogram of body weight per month was 365.5 g. Although this predictor was slightly below the minimum generally recommended by guidelines, the serum levels remained stable. In fact, in all patients included in the pooled database, the mean trough concentration was above the threshold considered protective against most infections.

This finding supports the need for individualization of the posology according to patient clinical conditions and IgG levels. Tailoring the IgG dosage based on the serum IgG levels of the patient has also been suggested by other studies [25]. While deciding the dosing interval, even the preferences of the patient may be taken into account. In fact, by using a pharmacokinetic model and simulation, Landersdorfer et al. [26] have reported that it is possible to administer the same total IgG dose as one biweekly dose (once every 2 weeks, such as in the IBIS cohort) or two weekly doses in SCIG therapy without any changes in the IgG peaks and trough concentrations (only a $\pm 10\%$ variability is observed during the 14-day period).

This study has some limitations. First, the two patient populations were significantly different in terms of age; IBIS patients were almost 8 years younger compared with those analyzed in the SHIFT study. Second, a difference in mean monthly IgG dosage was observed when the pediatric population was stratified according to weight categories, possibly due to the low sample size in the underweight category (five patients). Third, trough-level information was not available for all patients; however, the availability of these data for approximately 80% of patients may represent a reliable overview.

In addition, it should be considered that the trough level observed during IVIG treatment represents the minimum level attained at the end of the interval between two consecutive infusions, whereas the trough level detected during SCIG therapy represents an estimate that should not differ by more than 10% from the mean level during

the therapy and is frequently defined as ‘the steady-state level’. This consideration may modify the interpretation of pre-infusion IgG levels during IVIG or SCIG. Nevertheless, in the European Union, the monthly dose of IVIG is maintained when switching to SCIG, whereas a conversion factor is applied in the United States.

It should also be considered that, by developing a pharmacokinetic model, Bexon and colleagues [27] have found that there is great pharmacokinetic variability among individuals due to several factors, and such variability may affect an individual IgG trough/dose relationship.

5 Conclusions

This analysis showed total monthly IgG dosages had comparable trends among weight categories (except for underweight patients), the mean pre-infusion trough concentration was comparable among the weight categories, and the only two independent predictors associated with pre-infusion IgG trough levels in patients previously treated with IVIG or SCIG 16% and then received SCIG 20% were the mean monthly dosage of SCIG 20% and the mean monthly dosage of IgG per kilogram of body weight. As highlighted by stepwise regression, BMI did not correlate with pre-infusion trough concentrations. All patients treated with SCIG 20% maintained a pre-infusion trough concentration greater than the recommended thresholds. This effect was obtained using a mean monthly dosage of 23 g (interquartile range 16–26), which was not differentiated on a BMI basis. Therefore, dose adjustment may not be necessary in overweight and obese patients.

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Dataset Availability Statement CSL will only consider requests to share individual patient data (IPD) that are received from systematic review groups or bona fide researchers. CSL will not process or act on IPD requests until 12 months after article publication on a public website. An IPD request will not be considered by CSL unless the proposed research question seeks to answer a significant and unknown medical science or patient care question. Applicable country-specific privacy and other laws and regulations will be considered and may prevent sharing of IPD. Requests for use of the IPD will be reviewed by an internal CSL review committee. If the request is approved and the researcher agrees to the applicable terms and conditions in a data sharing agreement, IPD that has been appropriately anonymized will

be made available. Supporting documents, including study protocol and statistical analysis plan, will also be provided. For information on the process and requirements for submitting a voluntary data sharing request for IPD, please contact CSL at clinicaltrials@cs Behring.com.

Compliance with Ethical Standards

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Conflict of interest AP and GS received an unrestricted grant from CSL Behring for their research activity; AV has received honoraria for lectures from CSL Behring; and GMB is an employee of CSL Behring. SR declares he has no conflicts of interest.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study, as specified in the SHIFT and IBIS studies.

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