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Privigen® has similar pharmacokinetic properties in primary and secondary immune deficiency

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ABSTRACT

Purpose: Primary (PID) and secondary immune deficiencies (SID) represent diverse groups of diagnoses, yet both can be effectively treated with intravenous immunoglobulin (IVIG) replacement therapy. Guidelines for the use of IVIG in SID vary due to the paucity of data. The objective was to analyze available IVIG Privigen® (IgPro10, CSL Behring, Bern, Switzerland) data on Efficiency Index (EI) and pharmacokinetic (PK) parameters in patients with PID and SID.

Methods: Three Privigen® studies (NCT00168025, NCT00322556, and the observational study IgPro10_5001) were used to identify patients with PID and SID meeting the qualifying criteria for the PK analysis. PK properties of IVIG were estimated using a population PK model based on a standard two-compartment PK model. Immunoglobulin G (IgG) EI was calculated as the gain in serum IgG level per unit external IgG dose.

Results: A similar IVIG dose-serum IgG concentration relationship was observed in patients with PID (N = 90) and SID (N = 91). IgG EI was inversely proportional to the endogenous IgG concentration and comparable in PID (slope = −1.079) and SID (slope = −2.12).

Conclusions: These findings indicate that the disposition of Privigen® is similar during IgG replacement therapy in PID and SID. The results contribute to the understanding of IVIG treatment of SID and may support an evidence-based approach for the use of IVIG in SID in the future.

1. Introduction

Humoral immune deficiency is defined as a decrease in antibody production or function. In general, immune deficiency can be classified as primary (PID) – caused by genetic defects in one or more components of the immune system, or secondary (SID) – acquired as a result of certain diseases such as multiple myeloma (MM), chronic lymphoid leukemia (CLL) or protein-losing enteropathy, chemical factors including immune-suppressive medications, or physical agents such as ionizing radiation. PID and SID constitute a broad variety of individual diagnoses. PID alone is currently an umbrella term for approximately 300 different diseases, with antibody deficiencies being the most frequent (> 150 different conditions) [1–5].

A major clinical manifestation of primary and secondary antibody

Abbreviations: AIDS, acquired immune deficiency syndrome; AUC, area under the curve; CL, clearance; CLL, chronic lymphoid leukemia; CVID, combined variable immunodeficiency; EI, efficiency index; EMA, European Medicines Agency; FcRn, neonatal Fc receptor; FDA, US Food and Drug Administration; IgG, immunoglobulin G; IgG_{endo}, endogenous serum IgG concentration; IVIG, intravenous immunoglobulin; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NIS, non-interventional studies; NONMEM, non-linear mixed effects modeling; OFV, objective function value; PMDA, Pharmaceuticals and Medical Devices Agency; PID, primary immune deficiency; PK, pharmacokinetic; Q, inter-compartmental clearance; SCIG, subcutaneous immunoglobulin; SD, standard deviation; SID, secondary immune deficiency; TGA, Therapeutic Goods Administration; XLA, x-linked agammaglobulinemia; Vc, central volume of distribution; Vp, peripheral volume of distribution

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deficiencies is the predisposition to recurrent infections [5–7]. Biochemically, antibody deficiencies are identified by low or non-detectable serum immunoglobulin G (IgG) levels (hypogammaglobulinemia or agammaglobulinemia, respectively). Different levels of serum IgG have been proposed as cutoff in defining immune deficiency in PID and SID [8], but in general, levels below 5–6 g/L can be regarded as a moderate-to-severe reduction [9]. The first evidence that serum IgG levels of ≥5 g/L lead to substantial reduction of acute infections in PID patients was published 30 years ago [10]. Since then, a number of publications have confirmed that, while there is no absolute protective level for everybody and IgG replacement therapy should be individualized to target the unique "biological" IgG level of every single PID patient, high serum IgG concentrations of 6, 8 and even 11 g/L are associated with better protection against infections and decrease in incidence or progression of bronchiectasis [11]. Both humoral PID and SID can be effectively treated with replacement IgG therapy using regular intravenous IgG (IVIG) or subcutaneous IgG (SCIG) infusions [7,12–14].

IgG replacement therapy with IVIG and SCIG is well established in PID [15,16]. Although the efficacy of IVIG replacement therapy in SID has been demonstrated in several studies [17–21], a Cochrane analysis showed no benefits regarding mortality, recommending IVIG therapy only when patients present with hypogammaglobulinemia and recurrent infections [22]. Furthermore, a separate meta-analysis stated that IgG replacement therapy does not reduce the rate of infections after hematopoietic stem cell transplantation, and cannot be recommended [23]. The discrepancies in the data available and paucity of trials investigating the use of IgG replacement therapy in SID makes the identification of patients with SID that may benefit from IgG replacement therapy difficult [24]. Thus, the practice of granting regulatory approvals to IgG products for humoral SID differs between agencies. Per US Food and Drug Administration (FDA) guidance, all IVIG products licensed by FDA are approved for use in humoral PID [25]. To date, there is only one IVIG product approved for use in an SID indication of CLL in the US (Gammagard S/D®, Shire Plc, Lexington, USA) [26]. In contrast, the European Medicines Agency (EMA) approves IVIG products for PID syndromes with impaired antibody production and, additionally, for secondary hypogammaglobulinemia with recurrent infections in CLL, MM, after stem cell transplantation and in patients with congenital acquired immune deficiency syndrome (AIDS) [27]. Many other regulatory agencies, such as Health Canada, Swiss Medic, the Pharmaceuticals and Medical Devices Agency (PMDA, Japan), and the Therapeutic Goods Administration (TGA, Australia) provide simultaneous approval for broad use of IVIG in PID and SID. Health Canada uses the following definition of the indications for IgG replacement therapy: "…patients with Primary Immune Deficiency (PID) and Secondary Immune Deficiency (SID) who require immune globulin replacement therapy." [28]. A similar definition is used by the Australian TGA: "…indicated in adults and children for replacement therapy in: i) Primary Immunodeficiency Disease (PID) and ii) Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment." [29].

The lack of a scientific consensus regarding SID is also reflected in the differences between clinical indications listed in current guidelines on IVIG use. According to the Australian National Blood Authority, the qualifying criteria for IVIG therapy are acquired hypogammaglobulinemia secondary to hematological malignancies or stem cell transplantation with recurrent or severe bacterial infection(s) and evidence of hypogammaglobulinemia (excluding paraprotein), or hypogammaglobulinemia with IgG < 4 g/L (excluding paraprotein) [30]. In the United Kingdom, the clinical guidelines consider long-term treatment with IVIG to be appropriate in SID, with no specific cause listed [31]. The Canadian guidelines for use of IVIG in acquired hypogammaglobulinemia secondary to malignancy recommend prophylactic use of IVIG in adults with life-threatening or recurrent infections considered to result from low serum IgG levels [32]. In contrast, routine use of IVIG in children, regardless of the presence of hypogammaglobulinemia, is not recommended, except i) in children with a history of "severe invasive infection or recurrent sinopulmonary infections" or ii) as part of multinational clinical trials in hematological malignancy when the trial protocol recommends routine use of IVIG for secondary hypogammaglobulinemia [32].

Table 1
Patient demographics and analysis populations.

Parameter	Patients with PID (N = 90)	Patients with SID (N = 97)
Male, n (%)	49 (54.4)	58 (59.8)
Age (years), mean (SD)	29.8 (20.3)	69.5 (10.4)
Age range (years)	3–81	21–84
Children (< 12 years), n (%)	17 (18.9)	0
Adolescents (> 12–18 years), n (%)	19 (21.1)	0
Adults (> 18–64 years), n (%)	49 (54.4)	25 (25.8)
Elderly patients (≥65 years), n (%)	5 (5.6)	72 (74.2)
Body weight (kg), mean (SD)	62.6 (26.4)	76.8 (16.1)
Disease, n (%)	XLA: 21 (23) CVID: 69 (77)	CLL: 69 (71) NHL: 25 (26) Other: 3 (3)
Duration of IgG treatment, months		
Mean (SD)	25.1 (10.1)	11.8 (10.9)
Median (range)	23.3 (7.64–47.9)	5.82 (4.50–51.8)
Privigen® dose, mg/kg/month		
Mean (SD)	473 (133)	216 (106)
Median (range)	448 (13.3–959)	172 (90.9–678)
Serum IgG trough level at 28 ± 2 days after dose, g/L		
Number of patients with available data[a]	77	74
Mean (SD)	9.19 (2.46)	6.31 (1.97)
Median (range)	9.17 (3.93–27.2)	6.15 (2.05–17.1)

[a] Only patients who had their serum IgG measured at 28 ± 2 days after dose were included in the serum IgG trough level analysis. CLL, chronic lymphoid leukemia; CVID, common variable immune deficiency; IgG, immunoglobulin G; N, number of patients in population; NHL, non-Hodgkin lymphoma; PID, primary immune deficiency; SD, standard deviation; SID, secondary immune deficiency; XLA, x-linked agammaglobulinemia.

Although some data on serum IgG trough levels during IgG replacement therapy in SID are available [6,33], the pharmacokinetic (PK) characteristics of IVIG products in SID are under-investigated and dosing recommendations for the use of any IgG products, IVIG or SCIG, are based on scarce evidence. Existing guidelines of IgG use in SID are mainly based on research results in PID [8,24]. Dosing recommendations range from 0.2 to 0.4 g/kg body weight every 3–4 weeks, which lies within the dosing range recommended for IgG replacement therapy in PID (0.2–0.8 g/kg body weight/month) [34]. While comparative data on the clinical experience with IgG replacement therapy in PID and SID exist [35], a comparison of the PK properties of the same IgG products in PID and SID patient populations has not been reported. Such information is necessary to better understand similarities and/or differences of IgG disposition in these two groups of indications. It may lead to improvement of the treatment paradigm when administering IgG replacement therapy in SID and possibly to a more substantiated, evidence-based approach to regulatory approvals of IgG products in SID and PID.

We conducted a population PK analysis of available data of 10% IVIG Privigen® (IgPro10, CSL Behring, Bern, Switzerland), to characterize its Efficiency Index (EI) and PK parameters in patients with PID and SID.

2. Materials and methods

2.1. Patients

Demographic, dosing, and serum IgG concentrations, and data in patients with PID were extracted from the datasets of Privigen® studies

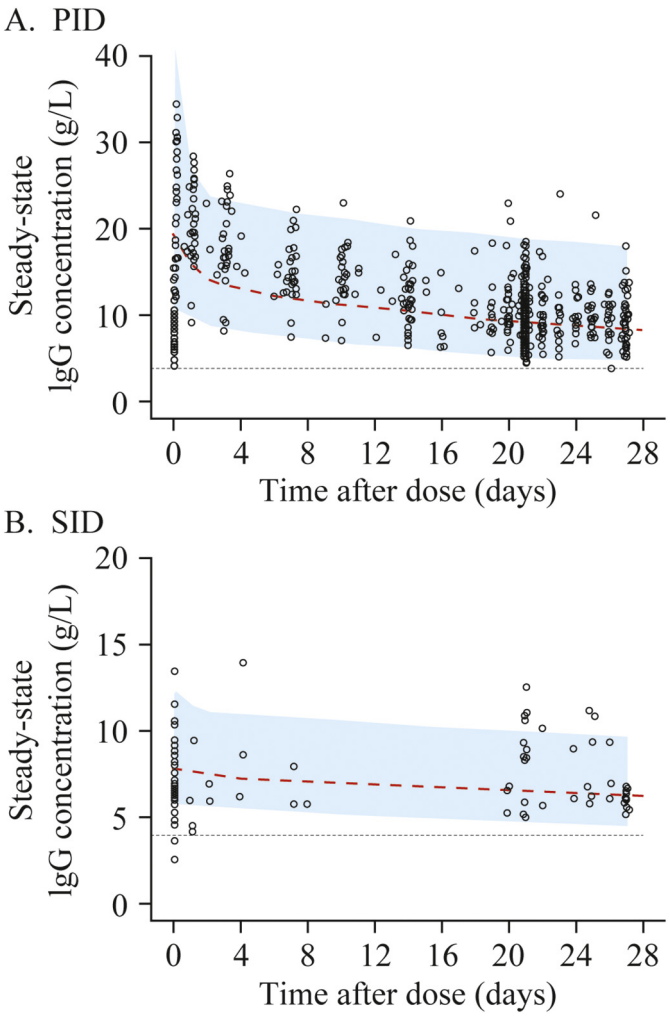

Fig. 1. Comparison of simulated and observed serum IgG concentrations in patients with PID and SID. A. PID population. B. SID population. Observed values (open circles) and median simulated values (dashed lines) with 90% confidence intervals (shaded areas) are shown. IgG_{endo} was set to 4 g/L (dotted lines). Simulations were developed using PID and SID datasets obtained by bootstrapping 1000 subjects for each dataset. PID, primary immune deficiency; SID, secondary immune deficiency.

Table 2
Pharmacokinetic parameters.

Parameter	Estimate (%RSE)	IIV (%CV)	95% CI from bootstrap
CL (L/day)[a]	0.152 (4.5)	53.1[c]	0.14–0.16
Weight on CL	0.796 (12.9)	–	0.59–0.99
Vc (L)[b]		75.4[c]	
Vc in PID (L)	3.08 (12.2)		2.49–3.65
Vc in SID (L)	8.75 (16.9)		3.63–15.33
Weight on Vc	1.1 (33.3)	–	0.52–1.66
Q (L/day)[a]	0.825 (20.5)	–	0.51–1.12
Vp (L)[a]	1.8 (8.9)	–	1.49–2.10
Additive error (g/L)	0.930 (19.5)		
Proportional error (%)	7.1 (32)		

[a] Values for CL, Q, and Vp are the same in PID and SID.
[b] Values in PID and SID are different.
[c] Values are for the combined PID and SID PK model population. CL, clearance; CV, coefficient of variation; IgG, immunoglobulin G; IIV, inter-individual variability; PID, primary immune deficiency; PK, pharmacokinetic; Q, inter-compartmental clearance; RSE, relative standard error; SID, secondary immune deficiency; Vc, central volume of distribution; Vp, peripheral volume of distribution.

ZLB03_002 (NCT00168025) and ZLB05_006 (NCT00322556). In addition, IgG EI data from a previous study [36] were used for comparison with the same outcomes in patients with SID.

Data from 97 patients with SID were captured in the observational study of Privigen® IgPro10_5001 (registered in the German non-interventional studies (NIS) Registry at the Paul Ehrlich Institute, which is the German federal authority for vaccines and biomedicines, NIS-Nr: 182).

2.2. Data collection and PK analysis

Patients with SID fulfilling the following criteria were included in the analysis: SID due to a condition not associated with monoclonal IgG increase; no prior IVIG treatment; observation period ≥120 days; ≥6 Privigen® infusions; infusion intervals 20–60 days. The cut-off date for inclusion of patients with SID was March 8, 2015. For PK analysis, patients with at least one Privigen® dose and one post-baseline serum IgG measurement were included; the same criteria were used for inclusion of patients with PID from the two CSL Behring clinical trials NCT00168025 and NCT00322556.

The population PK model was developed from a total of 2574 serum IgG concentrations from a total of 187 clinical trial patients with PID (90 patients) and SID (97 patients). The modeling was performed based on the guidelines for population PK analysis [25] and a previously developed pharmacometric model for IgG [37,38]. The final dataset was analyzed with non-linear mixed effects modeling software (NONMEM, Icon Development Solutions, Ellicott City, MD, USA) running under Perl-speaks-NONMEM. The model building process involved development of a base model followed by evaluation and testing of covariates to be included in the final model. First order conditional estimation with interaction was used for all model building procedures.

The base model was a standard two-compartment PK model defined by clearance (CL), central volume of distribution (Vc), inter-compartmental clearance (Q), and peripheral volume of distribution (Vp; Fig. S1) [37,38]. Based on the available endogenous serum IgG concentration (IgG_{endo}) data from patients with PID (Cardiff cohort [36]) and SID, IgG_{endo} was close to 4.0 g/L in both populations and, therefore, this value was used in the model. The inter-individual variability for all PK parameters was modeled using an exponential random effect model of the form $\theta_i = \theta * e^{\eta_i}$, where θ_i is the value of the population parameter θ, and η_i is the inter-individual random effect.

The residual variability was modeled using the additive multiplicative error model of the form $Y_{ij} = F_{ij} + \varepsilon_{ij}$, where Y_{ij} denotes the observed concentration for the i^{th} individual at time j, and F denotes the corresponding predicted concentration; ε_{ij} is the intra-individual residual error with a mean of zero and variance σ^2.

The model was evaluated by different criteria including statistical significance, i.e. improvement in the objective function value (OFV) by 7.78 points (i.e. the chi square distribution value associated with a probability of 0.005 and 1 degree of freedom), clinical relevance, goodness-of-fit plots, and plausibility of parameter estimates.

After the base model was validated, covariate testing was performed where the relationships between covariates and inter-individual variability in CL and Vc were explored graphically. Covariates were selected based on prior knowledge and clinical interest and included weight, age, gender, and disease type (PID or SID). Categorical covariates (disease type, gender) were modeled as $Cov\theta = \theta_0 * \theta_x$, where θ_0 denotes the population value of the parameter, and θ_x denotes the fractional change in θ_0 for each subpopulation. Continuous covariates (weight and age) were modeled as

$$Cov\theta = \theta_0 * \left(\frac{x}{x_{median}}\right)^{\theta x} \quad (1)$$

where θ_0 denotes the population value of the parameter when $x = x_{median}$ and θ_x denotes the population values conditional on the

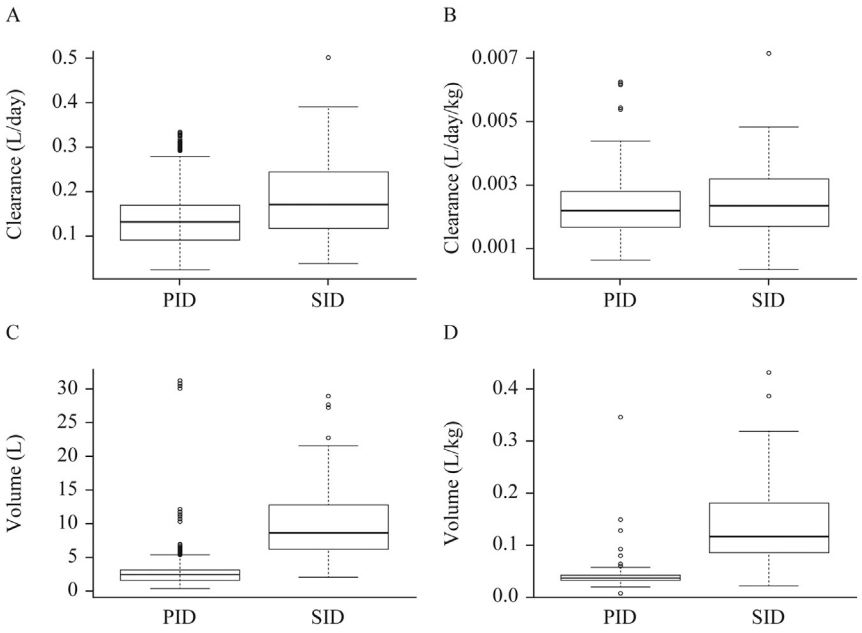

Fig. 2. PK parameters of IgG in patients with PID and SID. A, B. IgG clearance. C, D. Central volume of IgG distribution. Right panels represent parameters after accounting for body weight. To obtain the individual body weight-normalized values, each patient's CL and Vc values were divided by their individual body weight. Thick horizontal lines and whiskers represent median values and ranges, respectively. Boxes show lower and upper quartiles of the data. CL, clearance; PID, primary immune deficiency; SID, secondary immune deficiency; Vc, volume of distribution of central compartment.

value x. The value of x_{median} was set to the median weight of 72 kg of the combined PID and SID population.

For testing of covariates, a stepwise covariate model building approach was used, which involved backward elimination of each covariate from the full model. Two hierarchical models were compared by the chi square test of difference in OFV, with the number of degrees of freedom equal to the difference in number of parameters between the two models.

Simulations with the final model were performed using PID and SID datasets obtained by bootstrapping 1000 subjects for each group from the original datasets in order to preserve the original weight distribution in the two groups. These datasets were used to simulate serum IgG concentrations and calculate the predicted exposure (area under the curve [$AUC_{0–28days}$]) at two normalized IgG doses, the median PID dose (440 mg/kg) and the median SID dose (174 mg/kg), every 28 days.

2.3. Analysis of IgG Efficiency Index

EI is defined as the gain in serum IgG level (trough vs historic pre-treatment IgG_{endo}) per unit external dose of IgG replacement therapy. It is calculated as the ratio of serum IgG trough level (g/L) minus IgG_{endo} (g/L) to the average weekly IgG dose (g/kg/week) [39,40]. Trough levels are used in this analysis to reduce, to the extent possible, the variability of results due to varying serum IgG concentrations during the dosing cycle, especially in patients receiving IVIG. For calculation of EI in SID, at least one Privigen® dose, an IgG_{endo} value, and a serum IgG trough measurement at 28 ± 2 days after dose were required. IgG trough measurements lower than IgG_{endo}, resulting in a negative EI, were removed, as it was assumed that IgG_{endo} levels have decreased further due to progression of immunodeficiency. Clinical efficacy variables were pre-therapy IgG_{endo} levels, and serum IgG trough concentrations measured during Privigen® treatment. IgG_{endo} values were not collected as part of the medical history in the Privigen® studies in PID. Therefore, data for EI calculation in PID are from a cohort of 110 patients from the University Hospital of Wales, Cardiff, UK, treated with IVIG [36].

3. Results

3.1. Patients

Demographic and baseline characteristics of 187 patients included in this analysis are presented in Table 1.

The total number of patients exposed to Privigen® with at least partial PK data was similar in the PID and SID populations. However, their age and body weight were expectedly different: the SID population (mean age 69.5 years, mean weight 76.8 kg) comprised mostly patients with CLL and non-Hodgkin lymphoma, conditions which develop at an older age; the PID population (mean age 29.8 years, mean weight 62.6 kg) had a substantial proportion of pediatric patients (34 patients younger than 16 years; 38%), whose body weight is generally a factor of age.

Monthly Privigen® doses and serum IgG concentrations also differed in the two patient populations (Table 1). On average, patients with SID received less than half the IVIG dose, and had lower mean and median serum IgG levels, compared with patients with PID on IVIG replacement therapy. This reflects current clinical practice of treating these patient populations.

3.2. Population PK analysis

The base model for population PK analysis was developed founded on prior knowledge using the data from 90 patients with PID and 97 patients with SID in a two-compartment model with first-order elimination and was found to fit the data well with good agreement between predicted and observed concentrations at population or individual level (Fig. 1, Fig. S2).

Following development of the base model, the effect of covariates including body weight, age, gender, and disease type (PID vs SID) on CL and Vc was tested. The final model revealed a significant effect of body weight on both CL and Vc, and of patient disease type on Vc (Table 2). With a population estimate of 0.152 L/day for CL and an allometric exponent of weight on CL of 0.796, subjects with baseline body weights of 50 and 100 kg would have a theoretical CL of 0.114 and 0.197 L/day, respectively, based on eq. (1). Likewise, for a population Vc of 3.08 L and an exponent of weight of 1.1, 50- and 100-kg subjects would have a Vc of 2.06 and 4.42, respectively. This effect of body weight is consistent with the theoretical allometric exponents (0.75 on CL and 1.0 on

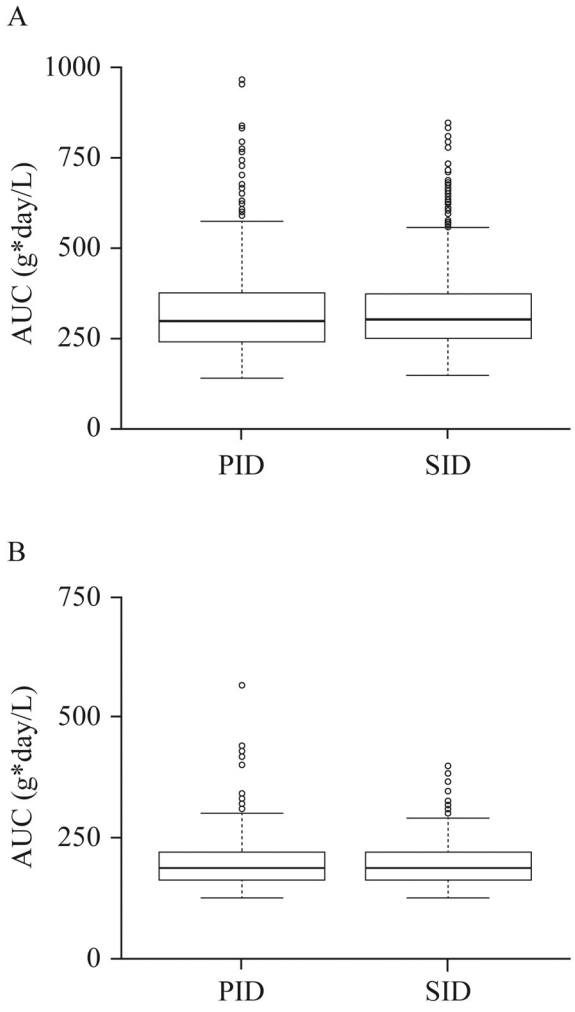

Fig. 3. Steady state AUC plot for PID and SID simulation datasets. A. Treatment with median monthly IgG dose in PID (440 mg/kg) every 28 days. B. Treatment with median monthly IgG dose in SID (174 mg/kg) every 28 days. Thick horizontal lines and whiskers represent median values and ranges, respectively. Boxes show lower and upper quartiles of the data. AUC, area under the curve; PID, primary immune deficiency; SID, secondary immune deficiency.

Vc) [41]. IgG CL was similar in the PID and SID groups (Fig. 2A, B), while median Vc was higher in SID, with greater variation in the lower and upper quartiles (Fig. 2C, D). Sensitivity analyses with different IgG_{endo} values showed no significant effect on PK parameters. The covariates age, gender, and IgG_{endo} had no significant effect on CL and Vc.

Simulation of serum IgG concentrations with the final population PK model showed a similar predicted IgG exposure ($AUC_{0–28days}$) in PID and SID patient populations at both IgG doses tested, 440 mg/kg (typical for PID; Fig. 3A) and 174 mg/kg (typical for SID; Fig. 3B).

3.3. Efficiency Index

Data from 34 patients with SID were available for EI analysis (IgG trough levels determined at 28 ± 2 days after dose and IgG_{endo} values). After excluding 7 patients with IgG trough values at 28 ± 2 days lower than IgG_{endo}, data from 27 patients were used for the EI analysis. The data demonstrated that EI is inversely proportional to IgG_{endo} levels in SID (slope = −2.12; Fig. 4B), i.e., the gain tends to be higher in patients with low IgG_{endo} (Fig. 4B). A similar relationship has previously been found in patients with PID (slope = −1.079; Fig. 4A) [36].

The relationship between dose and serum IgG trough concentration in patients with PID and SID showed a similar trend (Fig. 5).

4. Discussion

This study demonstrated that dose-serum IgG concentration relationship of IVIG treatment and IgG EI are similar in PID and SID. This observation is even more important given the differences between the PID and SID populations used for this study.

Doses in patients with PID were pre-selected and usually adjusted to the severity of their condition (frequency of infections) before they joined the original clinical studies, where standard inclusion criteria required steady-state IgG dosing and a pre-study serum IgG trough level of ≥4 g/L as an indirect evidence of minimally satisfactory IgG replacement therapy. A total of 5 out of 80 PID subjects in ZLB03_002 study had serum IgG trough levels between 4 and 5 g/L at screening. Thus, in a way, IgG doses in patients with PID in mg/kg bw in this analysis reflect their individual PID severity. Further, patients with PID were required to continue on their stable doses for the full duration of the studies, unless there was a medical need to adjust dosing.

Patients with SID did not have the same study requirements; in fact, most of them were assigned IVIG doses rounded to the full vial size of 10 g, 20 g or, rarely, 30 g every 3–4 weeks, with a center effect (results not presented) reflecting local standards of clinical practice. Reasons for dose selection were not reported, but may include economic considerations, in addition to the patients' clinical condition. There was no requirement of receiving steady-state IgG therapy, nor were the patients required to receive doses leading to IgG trough levels of ≥5 g/L. As a result, 26/91 patients with SID had IgG trough levels of < 5 g/L.

A comparison of IgG PK properties showed that body-weight adjusted CL was similar in the PID and SID groups. The only PK parameter that appeared different in these two patient populations was Vc, with a higher population estimate in patients with SID. Both PID and SID cohorts in this analysis had sufficiently large numbers of patients with PK data to allow for meaningful interpretation of results: 90 and 97 patients, respectively. These numbers are larger than the average size of

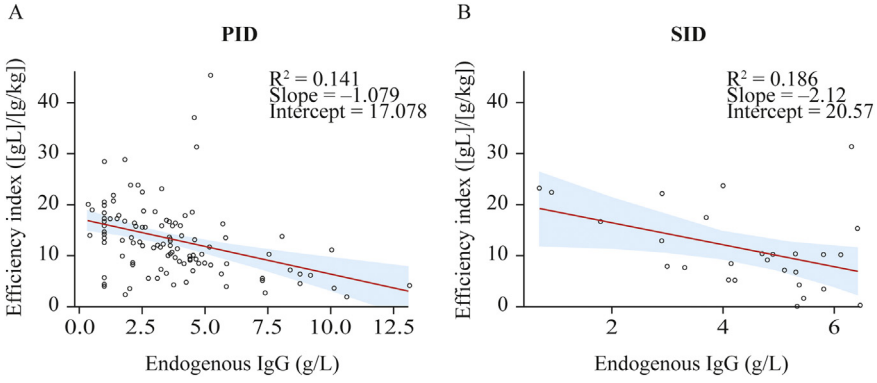

Fig. 4. Efficiency Index of IVIG in patients with PID and SID. **A.** Patients with PID. **B.** Patients with SID. Data for PID are from 110 patients from the University Hospital of Wales, Cardiff, UK, treated with IVIG or SCIG. Data for SID are from 27 patients from the German observational study of Privigen®. Lines represent linear regression trend lines, and shaded areas show the 95% confidence interval thereof. IVIG, intravenous immunoglobulin; PID, primary immune deficiency; SID, secondary immune deficiency; SCIG, subcutaneous immunoglobulin.

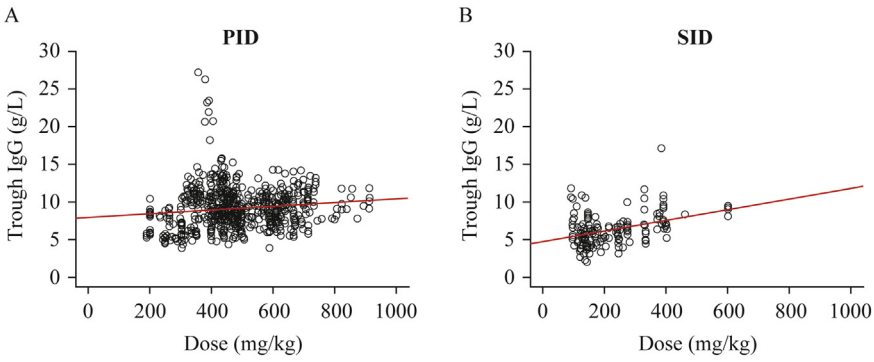

Fig. 5. Correlation between serum IgG trough levels and monthly IVIG dose in patients with PID and SID. A. Patients with PID. B. Patients with SID. Serum IgG trough levels measured at 28 ± 2 days after dose were available for 77 patients with PID and 74 patients with SID. Lines represent linear regression trend lines. IgG, immunoglobulin G; PID, primary immune deficiency; SID, secondary immune deficiency.

Phase III IgG studies in PID (typically 30–70 patients) [42–44]. Demographic characteristics such as age and body weight were unavoidably different due to the nature of the underlying conditions: primary antibody deficiencies are inherited and many of them are diagnosed in childhood, whereas most SID conditions develop in adults. Likewise, the mean IgG doses, and consequently the mean serum IgG trough levels, were different. However, the ranges of these variables overlapped, which allowed more precise pharmacometric modeling of systemic IgG exposure outcomes in the two groups of indications. Serum IgG concentrations are an accepted surrogate efficacy marker in immune deficiency [45,46]. In PID, it has been demonstrated that higher IgG levels at the patient population level are associated with better protection against infections [47,48]. However, there is no universal threshold that would be effective for everyone, and individual serum IgG levels that would keep infections under control can vary significantly depending on the levels of endogenous IgG production, certain comorbidities, and numerous external factors [11].

The intent of the population PK analysis was to determine whether there is an inherent difference in the disposition of IgG between PID and SID populations. The analysis was based on pooled data from patients with PID and SID, and revealed that PK of serum IgG was best described by a two-compartment model with first-order elimination, corroborating previous models [37,38]. Diagnostic plots for the final model showed that the population and individual predictions agreed well with the observed values and the conditional weighted residuals were evenly distributed. A significant effect of body weight on the CL and Vc of IgG was found, consistent with prior analyses [37,38]. After accounting for the effect of body weight on these parameters, the analysis of the disease type (PID or SID) as a covariate showed no significant effect on the CL of IgG in the model; hence, the final model did not include disease type as a covariate of interest. However, disease type appeared to have a significant effect on Vc, with patients with SID having a higher Vc compared with those with PID. The difference in Vc between the two populations had no impact on the overall IgG exposure, as the predicted exposure ($AUC_{0–28days}$) at a normalized dose was similar between the PID and SID populations. The most likely explanation is that higher Vc in patients with SID may reflect a continuing decrease in IgG_{endo} levels as a result of progressing immunodeficiency. The documented relevant comorbidities in the SID population – renal insufficiency, chronic hepatitis, and moderately increased bilirubin levels in one patient each, and moderately elevated creatinine levels in two patients – cannot explain the difference in Vc. The possibility that the difference in Vc is an artefact cannot be excluded.

Accepting that little is known about the variability of IgG_{endo} levels or the functional properties of the circulating IgG molecules in PID and SID, it is reasonable to assume that higher IgG levels in SID confer greater protection against infections, as is the case in PID. In the analysis reported here, the average IVIG dose in SID was half the IVIG dose in PID. Current treatment guidelines for SID recommend starting IgG replacement therapy if recurrent infections occur, and not basing this decision on serum IgG levels alone [27–29]. Even though the general dosing range recommended for use in SID (0.2–0.4 g/kg bw every 3–4 weeks) lies within the range recommended for use in PID (0.2–0.8 g/kg bw every 3–4 weeks), it is at the lower end [34]. Lower dosing of IVIG in SID may be supported by the lack of data on the efficacy of higher doses: the only randomized, double-blind study showed no significant difference in the infection rate in patients with SID treated with 250 mg/kg or 500 mg/kg every 4 weeks [20].

Comparison of EI in the two indication groups, PID and SID, showed a similar general tendency: irrespective of whether immune deficiency is caused by inherited or acquired factors, patients with lower IgG_{endo} values gain higher serum IgG levels for the same external IgG dose used. This suggests that in both patient populations, there is a universal mechanism of increased IgG catabolism at higher serum IgG concentrations [39,40]. IgG catabolism is regulated mainly by the neonatal Fc receptor (FcRn), binding IgG in a pH-dependent, saturable manner [13,39]. High IgG levels increase the rate of IgG catabolism, which can also be seen in the typical IVIG PK concentration versus time curve [39]. Recently, genetic polymorphisms altering the expression of the FcRn receptor have been identified, leading to decreased or increased binding of IgG to FcRn and thus affecting the efficiency of IgG therapy [49,50]. These genetic polymorphisms do not seem to be linked to immunodeficiencies and have been observed in patients with colorectal cancer, as well as in the healthy population [50,51].

However, calculation of EI assumes that the pre-treatment IgG_{endo} values measured at the time of diagnosing PID or SID remain stable during replacement therapy with relatively high IgG doses. There are indications that IgG_{endo} synthesis may change due to disease progression or modifications in the therapy of the underlying condition in patients with SID and in some forms of PID, such as CVID [52]. In the SID population reported in this analysis, IgG_{endo} values were lower than the last measured IgG trough values in 7/34 patients eligible for EI analysis, most likely as a result of progression of immunodeficiency. Determining IgG_{endo} on replacement therapy would require interrupting the therapy for a wash-out period of 4–5 IgG half-lives, i.e. 4–5 months, which is unethical. Therefore, we accept this as a limitation of the analysis.

In conclusion, this study demonstrated the similarity of IgG dose-serum IgG concentration relationships and EI trends with IVIG treatment for PID and SID. Modeling of the PK data allowed comparison of major PK parameters. These findings indicate that IVIG Privigen® is metabolized in a similar manner during IgG replacement therapy of immunodeficient individuals, irrespective of the primary or secondary nature of their immune system defects. Correspondingly, these results support the use of the same approach to dosing in these two groups of conditions. These results contribute to the understanding of IVIG treatment in SID, and may help promote an evidence-based approach for the use of IVIG in SID in the future.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2018.11.008.

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Declaration of conflict of interest

MAT, JPL, JJ, JH, DP, and MAR are employees of CSL Behring. MAT and MAR own CSL Behring shares. During data analysis and development of the manuscript, SP was an employee of CSL Behring. RW reports no potential conflicts of interest.

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