International Immunopharmacology 71 (2019) 404–410

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Population pharmacokinetic modeling and simulation of immunoglobulin exposure with varying dosing intervals of subcutaneous immunoglobulin 20% (Ig20Gly) in patients with primary immunodeficiency diseases

Todd Dumas[a], N. Seth Berry[a], Martin Wolfsegger[b], Stephen Jolles[c], Barbara McCoy[b], Leman Yel[d,e,*]

[a] IQVIA, 6700 W 115th St, Overland Park, KS, 66211, USA
[b] The Takeda group of companies, Vienna DC-Tower 1, Donau-City-Straße 7, 1220 Vienna, Austria
[c] Immunodeficiency Centre for Wales, University Hospital of Wales, Heath Park, Cardiff, CF14 4XW, UK
[d] The Takeda group of companies, 650 E. Kendall St, Cambridge, MA, 02142, USA
[e] University of California, Irvine, CA, USA

ARTICLE INFO

Keywords:
Pharmacokinetic modeling
Ig20Gly
Immunoglobulin
Subcutaneous
Dose adjustment

ABSTRACT

Background: Immunoglobulin (IG) replacement therapy in patients with primary immunodeficiency diseases (PID) can be administered daily to every 2 weeks subcutaneously (SCIG) or every 3 or 4 weeks intravenously (IVIG).

Objectives: Develop a population pharmacokinetic (PK) model simulating IG exposure with Ig20Gly, a 20% SCIG; determine the dose adjustment factor for Ig20Gly relative to IVIG.

Methods: Data from patients with PID treated with Ig20Gly and IVIG 10% were used to characterize IG population PK by nonlinear mixed-effects modeling and validated using data splitting and a visual predictive check. IG profiles were simulated for 1000 patients/interval treated with Ig20Gly (daily, every 2 days, every 3 days, twice weekly, weekly, every 2 weeks). An Ig20Gly adjustment factor of 130% was used to simulate Ig20Gly to IVIG AUC ratios for weekly or every 2 weeks Ig20Gly dosing intervals and a monthly IVIG dosing interval.

Results: A 1-compartment model, using weight as a covariate on clearance, derived from an index modeling dataset (n = 81) demonstrated predictability for a validation dataset (n = 21). The model estimate of bioavailability was 73.9%. Simulations for 6 dosing intervals showed similar mean profiles with overlapping prediction intervals. Mean AUC ratios of Ig20Gly to IVIG with a dose adjustment factor of 1.30:1 were 98.7% for weekly and 97.7% for twice-weekly administration demonstrating comparable exposure.

Conclusion: Ig20Gly exposures from daily to up to every 2 weeks appeared equivalent. A 1.30 conversion factor provided coverage comparable to IVIG when Ig20Gly is administered daily to every 2 weeks.

1. Introduction

Life-long immunoglobulin (IG) replacement therapy is required in patients with primary immunodeficiency diseases (PID) characterized by absent or deficient antibody production that results in recurrent or unusually severe infections [1]. IG replacement therapy can be administered subcutaneously (SCIG) daily to every 2 weeks or intravenously (IVIG) at dosing intervals of 3 to 4 weeks with equivalent efficacy. However, compared with IVIG, SCIG offers the advantages of self-infusion at home, does not require venous access, and is associated with a lower risk of systemic adverse events [2–4]. There are also key pharmacokinetic (PK) differences between SCIG and IVIG administration. IVIG is infused directly into the intravascular space, resulting in an early, high peak of IG concentration followed by a redistribution phase, whereas SCIG must first diffuse through the lymphatic system into the bloodstream, resulting in a more gradual and stable increase in IG concentration over 2 to 3 days without a high IgG serum peak [3,4]. Because bioavailability is lower with SCIG versus IVIG, the US Food and Drug Administration (FDA) requires that the dose of SCIG be increased to achieve equivalent immunoglobulin G (IgG) exposure between SCIG and IVIG as measured by area under the concentration-time curve (AUC) [3,4]. In the United States, current recommendations indicate

* Corresponding author at: The Takeda group of companies, 650 E. Kendall St, Cambridge, MA 02142, USA.
E-mail addresses: Todd.Dumas@quintiles.com (T. Dumas), Seth.Berry@quintiles.com (N.S. Berry), Martin.Wolfsegger@takeda.com (M. Wolfsegger), jollessr@cardiff.ac.uk (S. Jolles), Barbara.McCoy@takeda.com (B. McCoy), Leman.Yel@takeda.com (L. Yel).

https://doi.org/10.1016/j.intimp.2019.03.034
Received 29 August 2018; Received in revised form 14 March 2019; Accepted 19 March 2019

that patients receiving SCIG should use a monthly dose that is 130% or 137% of their previous IVIG monthly dose, depending on the concentration of the SCIG product [5–9].

Ig20Gly (immune globulin subcutaneous [human], 20% solution [Cuvitru™]; Baxalta US Inc., a member of the Takeda group of companies, Lexington, MA, USA) is an SCIG product with an IgG concentration of 20% (w/v) that can be infused at rates up to 60 mL/h/site. Ig20Gly was shown to be efficacious and well tolerated in two phase 2/3 clinical trials in patients with PID conducted in Europe and North America [10,11]. To further explore the bioavailability for Ig20Gly in relation to IVIG, evaluate IgG levels under different Ig20Gly dosing schemes, and determine the most appropriate dose adjustment factor, a population PK model was developed using data from these 2 trials.

2. Methods

The PK data for IG were obtained from 2 prospective, open-label, non-controlled, multicenter phase 2/3 clinical trials evaluating Ig20Gly in patients with PID conducted in North America (NCT01218438) and Europe (NCT01412385) [10,11]. Details of the inclusion and exclusion criteria and study design have been published previously [10,11]. In brief, patients were aged ≥2 years with a documented diagnosis of humoral immunodeficiency for which they had been receiving a stable monthly equivalent dose of IG (SC or IV) at an average minimum dose equivalent of 300 mg/kg body weight every 4 weeks and a maximum dose equivalent to 1000 mg/kg body weight every 4 weeks for ≥3 months before enrollment and had a serum IgG trough level > 500 mg/dL at screening. The European trial consisted of 2 periods. During period 1, patients received IVIG 10% for 13 weeks or SCIG 16% for 12 weeks to attain a stable baseline serum IgG before starting Ig20Gly treatment. In period 2, patients received Ig20Gly for 52 weeks at an equivalent dose [11]. The North American trial had 4 study periods. During period 1, all patients received IVIG 10% for 13 weeks to determine the AUC for IgG after IVIG treatment. During periods 2 to 4, patients received Ig20Gly. In period 2, Ig20Gly was administered in some patients at a dose adjusted to 145% of IVIG dose for approximately 12 to 16 weeks to assess equivalence in exposure, and in period 3, all patients received the same adjusted dose for 12 weeks. All patients received Ig20Gly at individually adapted doses during period 4 for 40 weeks [10].

In both trials, IgG trough levels were assessed in all patients at defined time points throughout the course of each study period, with some additional serial sampling collections for patients aged ≥12 years. Serum IgG concentrations were determined using a validated enzyme-linked immunosorbent assay–based method in an accredited laboratory setting.

Patients were considered for population PK modeling if they had accurate dosing histories and sampling collection information (date and time), along with ≥2 measurable IgG concentrations for a modeled IG product and for Ig20Gly. Data from both studies were pooled and a random data splitting approach was used to create an index data set for model development containing 80% of the total number of evaluable patients from both studies, and a validation data set for model validation consisting of the remaining 20% of patients (only included data from the North American study) [12]. Anticipating the effect of weight on IgG PK, the data splitting was stratified based on age. All modeling was based on simultaneous fits to both Ig20Gly and IVIG data. Given that patients were required to be on stable therapy before the study, steady-state conditions were assumed, with the baseline being a combination of both endogenous and exogenous IgG.

2.1. Pharmacokinetic model development

2.1.1. Base model development

The population PK of total IgG concentration data collected was characterized by nonlinear mixed-effects modeling using NONMEM, version VI, level 1.0. The base model for total IgG was identified by comparing different structural PK models (eg, 1-compartment, 2-compartment) and screening various error models when appropriate. First-order conditional estimation with interaction was used during model development, with model selection based on reduction in objective function value (OFV), Akaike Information Criterion (AIC), goodness-of-fit parameters, and goodness-of-fit plots. Reduction in OFV assessment was based on the likelihood ratio test for nested models and AIC for non-nested models. Inclusion of body weight was tested within the base structural models based on allometric principles.

2.1.2. Covariate model development

The covariates screened were selected a priori and included age, body weight, geographic region, race, and sex. Relationships between continuous and categorical covariates (for categorical covariates, only where the group contained > 10% of the overall specific covariate data), PK parameters, and interindividual variability were examined before covariate development and then tested in a stepwise fashion. The forward stepwise-based approach for the covariate search algorithm used a P value of < 0.01 as the criterion for statistical significance and a more stringent P value of < 0.005 to minimize the risk of false-positives for backward elimination. The covariate model demonstrating the greatest improvement in the population PK model was incorporated into the base population PK model, and remaining candidate covariates were reevaluated incrementally. All methods of this analysis followed the published guidelines suggested by the FDA for the analysis of population PK data [12].

2.2. Model evaluation and quantification

The model was evaluated for stability and predictability. A condition number of < 400 was used to indicate model stability of the parameter estimates in addition to performing a nonparametric bootstrap [13]. Final covariate model predictability was evaluated by visual predictive check. The final model predictability was further assessed by comparing estimates between the index and validation data sets. Performance of the final NONMEM model was based on the evaluation of the individual patient parameters and the mean prediction errors of concentrations [14,15].

2.3. Dosing interval simulations

The model was used to evaluate alternative dosing intervals and conversion factors. Random resampling with replacement from the index set was used to create a 1000-patient population for each simulation, which was used to generate predicted mean and 90% prediction intervals for steady-state IgG concentration-time profiles for 6 alternative dosing intervals (daily, every other day, every third day, twice weekly, weekly, or every 2 weeks). Simulations were divided by study because the North American study had an individualized dosing scheme for Ig20Gly, whereas in the European study, Ig20Gly was administered in monthly doses equivalent to the IVIG dose.

2.4. Conversion factor simulations

Simulations were also conducted to explore Ig20Gly exposure using dosing conversion factors based on the estimated bioavailability by resampling 1000 patients from the index set based on the study start IVIG dosing amounts assumed over 1 month of administration. Investigated dose levels included an adjustment factor for Ig20Gly of 130%, with a target of Ig20Gly ≤137%, which would achieve exposure with weekly administration equivalent to levels after IVIG administration. Individual Ig20Gly to IVIG 10% AUC ratios were calculated from simulated steady-state IgG profiles over a monthly IV dosing interval and weekly or every 2 weeks Ig20Gly dosing intervals.

Table 1
Baseline demographics.

Parameter	All evaluable patients (N = 102)
Sex, n (%)	
Male	57 (55.9)
Female	45 (44.1)
Race, n (%)	
White	95 (93.1)
Black	3 (2.9)
Asian	2 (2.0)
Other	2 (2.0)
Age, y	
Mean (SD)	32.1 (22.9)
Median (min, max)	30.0 (2.0, 83)
< 12 y, n (%)	26 (25.5)
≥12 y, n (%)	76 (74.5)
Weight, kg	
Mean (SD)	62.8 (28.2)
Median (min, max)	63.7 (13.2, 161.8)
Baseline IgG concentration, g/L	
Mean (SD)	10.2 (3.0)
Median (min, max)	9.9 (3.4, 19.9)

IgG = immunoglobulin G; SD = standard deviation.

3. Results

3.1. Model development and evaluation

A total of 2063 IgG concentrations (Ig20Gly, n = 1302; IVIG 10%, n = 761) from 102 evaluable patients (European study, n = 32; North American study, n = 70; Table 1) were identified for inclusion. Subsequently, of the 1657 concentration samples provided by 81 patients (1056 for Ig20Gly, 601 for IVIG) available for index set modeling (~80% of the available data), 7 concentration samples were removed for inaccurate or incomplete information from the index set (2 for Ig20Gly, 5 for IVIG). The remaining ~20% of the data (from 21 patients consisting of 406 samples [Ig20Gly, n = 246; IVIG 10%, n = 160]) comprised the validation set. Fig. 1 depicts observed IgG levels presented by route (SC and IV) and study region (Europe and North America), with a local weighted trend line for graphical illustration of the data used for modeling. It includes all of the observed data collected in both studies across all parts of the trials. Observed IgG levels were higher in the North American study because, as noted in the methods, this study used a dose-adjustment design in which some patients were administered Ig20Gly at a dose adjusted to 145% of the IVIG dose.

The final covariate model was a 1-compartment model with inter-individual variability (IIV) on clearance (CL), central compartment volume (V), and bioavailability (F1), including an off-directional correlation term between CL and V, with a proportional residual error model that adequately described Ig20Gly and IVIG 10% PK. The population parameter estimates for F1, CL, and V were estimated as 73.9%, 0.00384 L/h, and 4.01 L, respectively. The first-order absorption rate constant was fixed at 0.004 L/h and derived from the known time to maximum concentrations after extravascular administration. The off-diagonal correlation was estimated to be 0.507 and proportional error was estimated to be 5.3%.

The effect of bodyweight on CL led to the largest drop in the objective function for forward covariate step 1. Body weight was added as a covariate on CL as shown below:

$$\mathrm{CL}\ (L/h) = 0.00384\ L/h \times \left(\frac{weight\ kg}{70\ kg}\right)^{0.576}$$

The addition of body weight as a covariate on CL resulted in a substantial decrease of IIV of CL from 50.9% to 27.6%, with residual variability unchanged. Given the correlation estimated between CL and V, the IIV estimate for V also decreased substantially from 49.7% to 39.2%. The effects of gender on CL and V and of age on CL were tested in a second step. Possibly due to the known correlations of gender and age with body size, including these variables as covariates did not improve the model fit.

3.1.1. Internal validation

No issues were noted regarding precision or stability with a relative standard error on all structural parameters of < 10%, IIV parameters

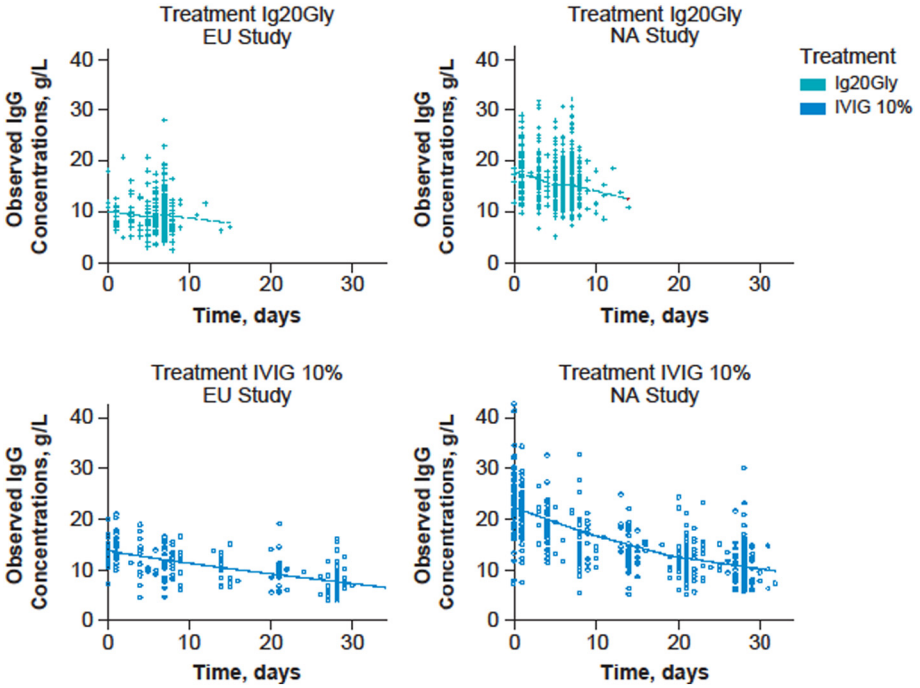

Fig. 1. Observed IgG concentrations over time by study and treatment for all samples overlaid with a loess smooth for varied presentations. EU = European Union; IgG = immunoglobulin G; IVIG = intravenous immunoglobulin; NA = North American.

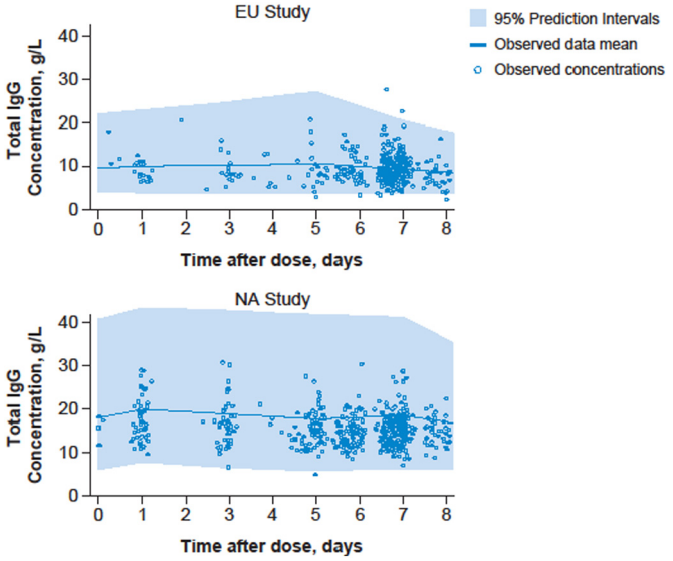

Fig. 2. Ig20Gly visual predictive check of final covariate model. Linear IgG concentrations are shown after the start of the most recent infusion. The majority of the observed concentrations were contained within the 95% prediction CI suggesting that the final model sufficiently predicts the observed data and was robust for trough concentration prediction. EU = European Union; IgG = immunoglobulin G; NA = North American.

of < 48.9%, and a condition number of 23.7. Bioavailability, the key parameter in the current context, was estimated as 74%, 73.4%, and 73.9% from the index data set, the full data set, and the median bootstrap estimate, respectively, demonstrating model stability and indicating agreement across the populations of patients. Model predictability was demonstrated using a visual predictive check showing the bulk of the observed concentrations were contained within the 95% prediction interval, indicating the final model sufficiently predicted the observed data and was robust for trough concentration prediction (Fig. 2).

3.1.2. Validation based on data splitting

The final population PK model derived from the index model development data set successfully predicted the measured total IgG concentrations in the validation data set (ie, mean standardized mean prediction error was not statistically significantly different from zero, $P = 0.3222$ [*t*-test]; using previously described methods [14,15]).

3.2. Simulation of IgG exposure following Ig20Gly administration daily, every 2 days, every 3 days, twice weekly, weekly, or every 2 weeks

Simulations of total IgG concentrations for Ig20Gly administered daily, every 2 days, every 3 days, twice weekly, weekly, and every 2 weeks using the resampled 1000 patients showed similar mean profiles with overlapping prediction intervals (Fig. 3). Compared with weekly administration, administration every 2 weeks of Ig20Gly at double the weekly dose predicted comparable IgG exposure. Ig20Gly infusions given 2 to 7 times per week were predicted to produce IgG exposures comparable to administration every 2 weeks.

Simulations of Ig20Gly exposure based on the estimated bioavailability of 74% using the resampled 1000-patient data (based on the IVIG level) showed the mean monthly equivalent dose (CV%) was 511 mg/kg/mo (31%).

The model-based simulation showed that weekly or every-2-week Ig20Gly administration at 130% of the monthly IVIG dose adequately maintained IgG exposure (median AUC_{0-28} day ratios of 96.0% for weekly and 95.8% for every-2-week dosing compared with IVIG monthly dosing; Table 2). Graphs depicting total IgG concentration-time profiles for weekly and every-2-week dosing of Ig20Gly at 130% of the IVIG dose confirm the comparable exposure achieved with a dose conversion factor of 1.30 with weekly or every-2-week Ig20Gly administration (Fig. 4A and B, respectively).

4. Discussion

The model developed from PK data from two phase 2/3 clinical trials in patients with PID treated with Ig20Gly was a 1-compartment model with IIV on CL, V, and F1, with a proportional residual error model and a correlation between CL and V. This model offered the best fit for the pooled analysis from two clinical trials, even though IG kinetics are often described using 2-compartment structural models. This is likely due to several factors, including design factors (all samples were collected at steady-state) and dose adjustments that were unique to North America. An additional factor for that could account for potential differences from the anticipated PK structural model was the potential limitation of sampling in patients < 12 years of age who could only contribute trough concentrations. This was also a likely contributing factor for imprecision in the estimation of the absorption rate constant (K_a). Consequently, the population K_a was fixed to a value derived based on steady-state time to peak concentration (C_{max}), leading to relatively flat concentration profiles. It is important to note that dose is a study design factor, with differences driven by the practice standards of the country. The model used in this analysis is a function of the dosage and the corresponding IgG level. The model built in this analysis and the published literature is linear. Therefore, dose increases or decreases lead to proportional increases or decreases in IgG levels. The wide range of doses included in the model allow for better characterization of the actual doses being used in clinical practice and for less extrapolation than if one were to try and apply one country's model to another.

The 1-compartment model qualification included multiple steps to demonstrate the predictability and stability of the final covariate model. The data splitting approach confirmed the ability of the model to predict concentrations for patients not included in the modeling. Likewise, the similarity of estimates achieved when the model was fit to all evaluable patients suggests the selected model was useful for reliable extrapolation to the exposure, which would be achieved for varied dosing intervals and different dosing conversion factors.

The model estimate for Ig20Gly bioavailability of 73.9% was supported by bootstrap results. Berger et al. reported a mean bioavailability of 66.7% from 4 different SCIG products (Vivagloblin® [immune globulin subcutaneous [human], 16% liquid; CSL Behring]; Gamunex® [immune globulin injection [human], 10% caprylate/chromatography purified; Grifols Therapeutics]; Gammagard™ [immune globulin infusion [human], 10% solution; Baxalta US Inc.]; and Hizentra® [immune globulin subcutaneous [human], 20% liquid; CSL Behring]) [16]. Similarly observed decreased bioavailabilities among different SCIG products, relative to IVIG, are thought to reflect the subcutaneous route of administration instead of specific product properties or the IgG concentration [16].

In the Ig20Gly study conducted in Europe, a dose conversion for Ig20Gly:IVIG was not used (ie, EMA requires that trough levels are noninferior to those of IVIG and do not recommend an initial dose adjustment) resulting in a bioavailability of Ig20Gly relative to IVIG estimated as part of the clinical trial analysis of 82.07% [11], which was higher than in this combined evaluation of EU and NA studies where the latter contributed the majority of data in this evaluation. In the Ig20Gly pivotal clinical trial conducted in North America, following a 1.45 dose conversion (Ig20Gly:IVIG) and individual dose adjustment (based on IG exposure [AUC] relative to IVIG 10%), Ig20Gly bioavailability determined from the ratio of geometric means of the AUC while on Ig20Gly treatment once per week versus IVIG 10% infusions (standardized to 1 week) was 1.09 [10]. This actual clinical trial result, in conjunction with the model estimated bioavailability, suggested that a

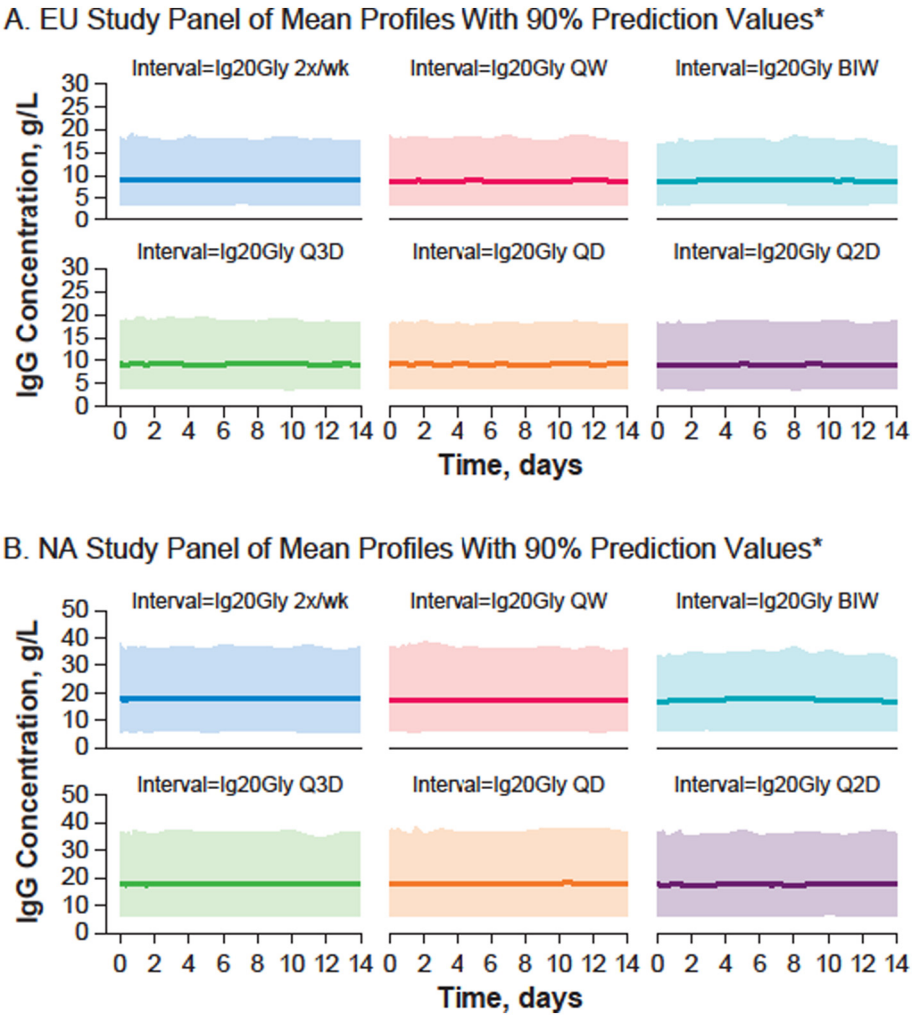

Fig. 3. Simulated mean and 90% prediction intervals for steady-state total IgG concentrations after Ig20Gly administration under varied dosing intervals (daily, every 2 days, every 3 days, twice weekly, weekly, or every 2 weeks) in the (A) European (EU) or (B) North American (NA) populations. 2×/wk. = twice weekly; BIW = every 2 weeks; IgG = immunoglobulin G; Q2D = every 2 days; Q3D = every 3 days; QD = every day; QW = every week. *Lines represent arithmetic mean values, upper and lower bands represent the 95th and 5th percentiles respectively.

Table 2
Exposure parameters comparing weekly or every-2-week dosing of Ig20Gly at 130% of the monthly IVIG dose with once-monthly IVIG 10% (N = 1000).

Parameter	Mean	CV%	Minimum	Median	Maximum
Weekly administration					
Ig20Gly, 20% weekly					
C_{max}, g/L	18.3	48.8	4.78	16.8	79.53
$AUC_{0–672}$, g·h/L	8830	48.3	2433	8010	40,199
C_{trough}, g/L	13.03	50.7	2.71	11.6	41.6
IVIG, 10% monthly					
C_{max}, g/L	23.1	46.2	5.63	21.21	89.14
$AUC_{0–672}$, g·h/L	8974	43.1	2358	8274	29,702
C_{trough}, g/L	9.78	60.0	1.96	8.85	30.1
Biweekly administration					
Ig20Gly, 20% every 2 wk					
C_{max}, g/L	18.3	49.8	3.15	16.6	65.5
$AUC_{0–672}$, g·h/L	8861	50.05	1446	7932	30,046
C_{trough}, g/L	12.8	54.1	1.91	11.2	49.7
IVIG, 10% monthly					
C_{max}, g/L	23.5	48.5	4.40	21.2	75.8
$AUC_{0–672}$, g·h/L	9096	46.1	2182	8280	29,522
C_{trough}, g/L	9.73	53.5	2.03	8.46	40.9

$AUC_{0–672}$ = area under the concentration-time curve from time 0–672 h (672 h = 28 days); C_{max} = maximum concentration; C_{trough} = observation at 672 h; CV% = coefficient of variation; IVIG = intravenous immunoglobulin.

Ig20Gly exposure comparable to IVIG might be achieved using a lower dosing conversion factor than what was initially thought. In parallel with this view, subsequent simulations based on the Ig20Gly population PK model confirmed daily to every-2-week Ig20Gly administration of the same monthly dose (ie, keeping the IG dose over the month constant for the different dosing frequencies) resulted in similar systemic exposure to IgG at steady state where comparable systemic exposures to IV administration can be achieved with a dose-conversion factor of 1.30.

Our data are consistent with the Ig20Gly dose adjustment in the FDA label (dose adjustment factor of 1.30) [6]; the FDA recommends a conversion factor that achieves equivalent systemic IG exposure (AUC) for SCIG and IVIG. PK modeling for another SCIG 20% product, IgPro20, utilized a 2-compartment model to simulate varied dosing regimens. This 2-compartment model estimated 66% population bioavailability and also predicted that the same total weekly dose could be administered at different intervals, from daily to every 2 weeks, providing equivalent systemic IgG exposure as IVIG dosing [17,18]. Simulations with this model estimated equivalent IgG exposure with a dose adjustment factor of 1.53 when switching to every-2-week dosing of IgPro20 from monthly IVIG; however, a dose adjustment ratio of 1:1 with IgPro20 given every 2 weeks reduced systemic IgG exposure (AUC) by 20% and C_{max} by 45% compared with a single IVIG dose every 4 weeks [17]. Additional PK modeling and simulations of IgPro20

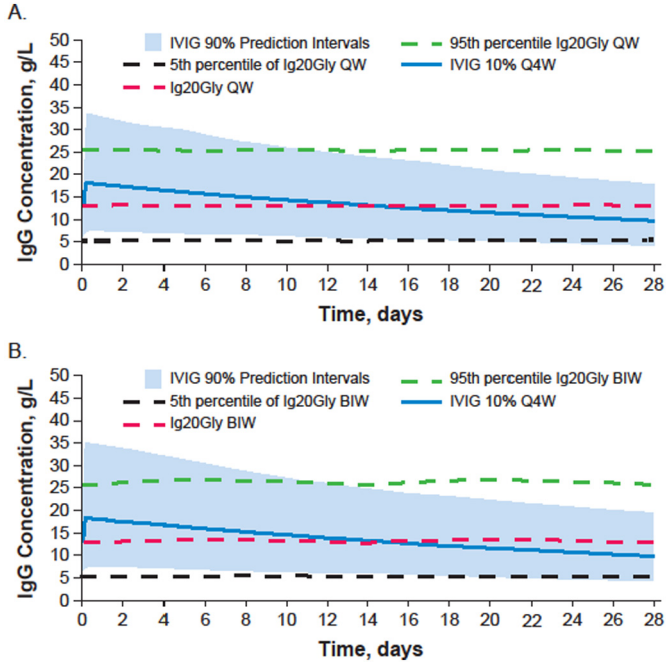

Fig. 4. Simulated mean and 90% prediction intervals for steady-state total IgG concentrations after Ig20Gly (A) weekly or (B) every-2-week dosing at 130% of the IVIG 10% monthly dose. BIW = every 2 weeks; IgG = immunoglobulin G; IVIG = intravenous immunoglobulin; Q4W = every 4 weeks; QW = every week.

dosing have since reduced the dose adjustment factor from 1.53 to 1.37, relative to the prior IVIG dose [5]. Less concentrated IG products (SCIG 10%) also require a dose adjustment factor of 1.37 to achieve bioequivalence when patients switch to weekly SCIG therapy from monthly IVIG administration [19,20].

It should be noted that the clinical relevance of equivalent AUCs has not been proven. However, higher IgG trough levels have been associated with lower rates of infection with IVIG and SCIG administrations [21,22]. The European Medicines Agency requires that trough levels are non-inferior to those of IVIG and does not recommend an initial dose adjustment [3,4]. Although there is utility in estimates for population PK parameters to guide evidence-based decisions, IG replacement therapy must still be individually tailored [23]; there is increasing evidence that the IG dose needed to prevent infection varies with each patient [24,25]. Data suggest a wide range of steady-state serum IgG levels required in patients with PID [26], and individual patients may have their own biological IgG trough level that is essential to prevent infection [25,27]. Thus, each patient's dose should be individualized, taking into consideration the IgG trough levels and the clinical response.

5. Conclusions

In summary, the population PK model based on weekly dosing data from two phase 2/3 clinical trials in patients with PID treated with Ig20Gly showed that the model population estimate for Ig20Gly bioavailability was 73.9%. A conversion factor of 1.30 for Ig20Gly provided comparable exposure to IVIG therapy. Ig20Gly provided equivalent exposure when given daily to every 2 weeks supporting flexible dosing of Ig20Gly, which may translate to greater patient convenience and provide more options for individualized dosing schedules.

Summary disclosure of interest

TD and NSB report grants from Baxalta/Shire, members of the Takeda group of companies, during the conduct of the study. SJ has received personal fees from Shire, CSL Behring, Octapharma, Grifols, LFB, and Biotest, outside the submitted work. MW, BM, and LY are employees of the Takeda group of companies and own stock in Takeda Pharmaceutical Company Limited.

Funding

This work was supported by Baxalta US Inc., a member of the Takeda group of companies. IQVIA provided the PK modeling services which were funded by Baxalta US Inc., a member of the Takeda group of companies.

Role of the funding source

The study was funded by Baxalta US Inc., a member of the Takeda group of companies. Scientific writing support for this manuscript was provided by Charlotte Majerczyk, PhD, and Lisa M. Klumpp Callan, PhD, at C4 MedSolutions, LLC (Yardley, PA), a CHC Group company, and was funded by Baxalta US Inc., a member of the Takeda group of companies. The study design; collection, analysis, and interpretation of the data; writing of the article; and decision to submit the article for publication were fulfilled by the authors, of which Barbara McCoy, Martin Wolfsegger, and Leman Yel are employees of the Takeda group of companies.

Data sharing

The datasets, including redacted study protocol, redacted statistical analysis plan, and individual participant data behind the results reported in this article, will be available 3 months after manuscript publication, to researchers who provide a methodologically sound proposal after de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Data requests should follow the process outlined in the Data Sharing section of the website: http://www.shiretrials.com/en/our-commitment-to-transparency/data-sharing-with-researchers and should be directed to clinicaltrialdata@shire.com.

References

[1] E.E. Perez, J.S. Orange, F. Bonilla, J. Chinen, I.K. Chinn, M. Dorsey, Y. El-Gamal, T.O. Harville, E. Hossny, B. Mazer, R. Nelson, E. Secord, S.C. Jordan, E.R. Stiehm, A.A. Vo, M. Ballow, Update on the use of immunoglobulin in human disease: a review of evidence, J. Allergy Clin. Immunol. 139 (2017) S1–S46, https://doi.org/10.1016/j.jaci.2016.09.023.

[2] H. Shabaninejad, A. Asgharzadeh, N. Rezaei, A. Rezapoor, A comparative study of intravenous immunoglobulin and subcutaneous immunoglobulin in adult patients with primary immunodeficiency diseases: a systematic review and meta-analysis, Expert. Rev. Clin. Immunol. 12 (2016) 595–602, https://doi.org/10.1586/1744666X.2016.1155452.

[3] M. Berger, Choices in IgG replacement therapy for primary immune deficiency diseases: subcutaneous IgG vs. intravenous IgG and selecting an optimal dose, Curr. Opin. Allergy Clin. Immunol. 11 (2011) 532–538, https://doi.org/10.1097/ACI.0b013e32834c22da.

[4] R.L. Wasserman, Progress in gammaglobulin therapy for immunodeficiency: from subcutaneous to intravenous infusions and back again, J. Clin. Immunol. 32 (2012) 1153–1164, https://doi.org/10.1007/s10875-012-9740-x.

[5] Hizentra® (Immune Globulin Subcutaneous [Human], 20% Liquid), Full Prescribing Information, CSL Behring AG, Bern, Switzerland, 2018.

[6] Cuvitru, (Immune Globulin Subcutaneous [Human], 20% Solution), Full Prescribing Information, Baxalta US Inc., Westlake Village, CA, 2016.

[7] Gammagard Liquid™, (Immune Globulin Infusion [Human], 10% Solution), Full Prescribing Information, Baxalta US Inc., Westlake Village, CA, 2017.

[8] Gammaked™, (Immune Globulin Injection [Human] 10% Caprylate/Chromatography Purified), Full Prescribing Information, Grifols Therapeutics Inc., Research Triangle Park, NC, 2013.

[9] Gamunex®-C, (Immune Globulin Injection [Human], 10% Caprylate/Chromatography Purified), Full Prescribing Information, Grifols Therapeutics Inc., Research Triangle Park, NC, 2016.

[10] D. Suez, M. Stein, S. Gupta, I. Hussain, I. Melamed, K. Paris, A. Darter, C. Bourgeois, S. Fritsch, H. Leibl, B. McCoy, D. Gelmont, L. Yel, Efficacy, safety, and pharmacokinetics of a novel human immune globulin subcutaneous, 20% in patients with

primary immunodeficiency diseases in North America, J. Clin. Immunol. 36 (2016) 700–712, https://doi.org/10.1007/s10875-016-0327-9.
[11] M. Borte, G. Krivan, B. Derfalvi, L. Marodi, T. Harrer, S. Jolles, C. Bourgeois, W. Engl, H. Leibl, B. McCoy, D. Gelmont, L. Yel, Efficacy, safety, tolerability and pharmacokinetics of a novel human immune globulin subcutaneous, 20%: a phase 2/3 study in Europe in patients with primary immunodeficiencies, Clin. Exp. Immunol. 187 (2017) 146–159, https://doi.org/10.1111/cei.12866.
[12] Department of Health and Human Services, US Food and Drug Administration, Guidance for industry: population pharmacokinetics, https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf, (1999) , Accessed date: 10 May 2018.
[13] P.L. Bonate, The effect of collinearity on parameter estimates in nonlinear mixed effect models, Pharm. Res. 16 (1999) 709–717.
[14] R. Bruno, N. Vivier, J.C. Vergniol, S.L. De Phillips, G. Montay, L.B. Sheiner, A population pharmacokinetic model for docetaxel (Taxotere): model building and validation, J. Pharmacokinet. Biopharm. 24 (1996) 153–172.
[15] S. Vozeh, P.O. Maitre, D.R. Stanski, Evaluation of population (NONMEM) pharmacokinetic parameter estimates, J. Pharmacokinet. Biopharm. 18 (1990) 161–173.
[16] M. Berger, S. Jolles, J.S. Orange, J.W. Sleasman, Bioavailability of IgG administered by the subcutaneous route, J. Clin. Immunol. 33 (2013) 984–990, https://doi.org/10.1007/s10875-013-9876-3.
[17] C.B. Landersdorfer, M. Bexon, J. Edelman, M. Rojavin, C.M. Kirkpatrick, J. Lu, M. Pfister, J. Sidhu, Pharmacokinetic modeling and simulation of biweekly subcutaneous immunoglobulin dosing in primary immunodeficiency, Postgrad. Med. 125 (2013) 53–61, https://doi.org/10.3810/pgm.2013.11.2712.
[18] J. Sidhu, M. Rojavin, M. Pfister, J. Edelman, Enhancing patient flexibility of subcutaneous immunoglobulin G dosing: pharmacokinetic outcomes of various maintenance and loading regimens in the treatment of primary immunodeficiency, Biol. Ther. 4 (2014) 41–55, https://doi.org/10.1007/s13554-014-0018-0.
[19] R.L. Wasserman, A.M. Irani, J. Tracy, C. Tsoukas, D. Stark, R. Levy, J. Chen, S. Sorrells, R. Roberts, S. Gupta, Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease, Clin. Exp. Immunol. 161 (2010) 518–526.
[20] R.L. Wasserman, I. Melamed, L. Kobrynski, S.D. Strausbaugh, M.R. Stein, M. Sharkhawy, W. Engl, H. Leibl, L. Sobolevsky, D. Gelmont, R.I. Schiff, W.J. Grossman, Efficacy, safety, and pharmacokinetics of a 10% liquid immune globulin preparation (GAMMAGARD LIQUID, 10%) administered subcutaneously in subjects with primary immunodeficiency disease, J. Clin. Immunol. 31 (2011) 323–331, https://doi.org/10.1007/s10875-011-9512-z.
[21] J.S. Orange, B.H. Belohradsky, M. Berger, M. Borte, J. Hagan, S. Jolles, R.L. Wasserman, J.S. Baggish, R. Saunders, B. Grimbacher, Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy, Clin. Exp. Immunol. 169 (2012) 172–181, https://doi.org/10.1111/j.1365-2249.2012.04594.x.
[22] J.S. Orange, W.J. Grossman, R.J. Navickis, M.M. Wilkes, Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies, Clin. Immunol. 137 (2010) 21–30, https://doi.org/10.1016/j.clim.2010.06.012.
[23] S. Jolles, J.S. Orange, A. Gardulf, M.R. Stein, R. Shapiro, M. Borte, M. Berger, Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease, Clin. Exp. Immunol. 179 (2015) 146–160, https://doi.org/10.1111/cei.12485.
[24] R.S. Shapiro, R.L. Wasserman, V. Bonagura, S. Gupta, Emerging paradigm of primary immunodeficiency disease: individualizing immunoglobulin dose and delivery to enhance outcomes, J. Clin. Immunol. 37 (2017) 190–196, https://doi.org/10.1007/s10875-014-9990-x.
[25] V.R. Bonagura, R. Marchlewski, A. Cox, D.W. Rosenthal, Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection, J. Allergy Clin. Immunol. 122 (2008) 210–212, https://doi.org/10.1016/j.jaci.2008.04.044.
[26] S. Misbah, T. Kuijpers, J. van der Heijden, B. Grimbacher, D. Guzman, J. Orange, Bringing immunoglobulin knowledge up to date: how should we treat today? Clin. Exp. Immunol. 166 (2011) 16–25, https://doi.org/10.1111/j.1365-2249.2011.04443.x.
[27] M.A. Rojavin, A. Hubsch, J.P. Lawo, Quantitative evidence of wear-off effect at the end of the intravenous IgG (IVIG) dosing cycle in primary immunodeficiency, J. Clin. Immunol. 36 (2016) 210–219, https://doi.org/10.1007/s10875-016-0243-z.