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ARTICLE

Pharmacometric analysis linking immunoglobulin exposure to clinical efficacy outcomes in chronic inflammatory demyelinating polyneuropathy

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Abstract

The two main objectives of this analysis were to (i) characterize the relationship between immunoglobulin (Ig) exposure and chronic inflammatory demyelinating polyneuropathy (CIDP) disease severity using data from 171 patients with CIDP who received either subcutaneous Ig (IgPro20; Hizentra®) or placebo (PATH study), and to (ii) simulate and compare exposure coverage with various dosing approaches considering weekly dosing to be the reference dose. IgG pharmacokinetic (PK)

parameters, including those from a previous population PK model, were used to predict individual IgG profile and exposure metrics. Treatment-related changes in Inflammatory Neuropathy Cause and Treatment (INCAT) scores were best described by a maximum effect (E_{max}) model as a function of ΔIgG (total serum IgG at INCAT score assessment minus baseline IgG levels before intravenous Ig restabilization). Simulations indicate that flexible dosing from daily to biweekly (every other week) provide an exposure coverage equivalent to that of a weekly Ig dose.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Anecdotal evidence suggests that the level of immunoglobulin (Ig) exposure is linked to the degree of symptom improvement. Therefore, it is important to choose therapeutic regimens that ensure the appropriate level of Ig exposure is maintained between doses.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study addresses how various subcutaneous dosing regimens affect pharmacokinetic (PK) exposure of IgPro20 and how Ig exposure impacts chronic inflammatory demyelinating polyneuropathy (CIDP) disease severity in terms of the Inflammatory Neuropathy Cause and Treatment (INCAT) score.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study suggests that flexible dosing of IgPro20 from daily to biweekly (every other week) provides an exposure coverage equivalent to that of a weekly Ig dose, and that increasing Ig exposure is associated with decreasing severity of CIDP.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This facilitates implementation of personalized medicine in clinical practice allowing patients to choose the dosing regimen that best suits their lifestyle.

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by symmetrical, proximal, and distal bilateral weakness or somatosensory abnormalities in arms and legs that worsens over 8 weeks or longer.[1,2] Due to the probable autoimmune nature of CIDP, immunoglobulin (Ig) products are one of the primary treatments for this disease, with subcutaneous Ig (SCIG) IgPro20 (Hizentra; CSL Behring, King of Prussia, PA, USA) being approved for CIDP maintenance treatment in 2018 in addition to intravenous Ig (IVIG). The mode of action of Ig therapy in CIDP is thought to include direct competition with autoantibodies, neutralization of autoantibodies by anti-idiotypes, inhibition of complement deposition, increased catabolism of pathologic antibodies, and interaction with cell adhesion molecules involved in immune cell motility. The rapid onset of therapeutic effects following IVIG administration suggests a mode of action independent of remyelination.[3] Ig therapy in part blocks the autoimmune pathways responsible for nerve damage and dysfunction that may result in disability. In CIDP, this disability is commonly assessed using the Inflammatory Neuropathy Cause and Treatment (INCAT) validated scale that assesses a patient's level of disability in their arms and legs. The relationship between precise IgG levels and CIDP disease activity in terms of INCAT is unclear. Anecdotal evidence suggests that each patient has a certain minimum threshold IgG concentration level needed to achieve and maintain CIDP disease stability[4–6]; however, this is difficult to measure in a population setting due to large inter-subject variability. Determining the relationship between IgG levels and CIDP disease activity is important for establishing an optimal dosing paradigm for the treatment of CIDP. Furthermore, SCIG is administered at lower, more frequent doses than IVIG and has different concentration-time profiles compared with IVIG. These differences may be important when switching patients from IVIG to SCIG to ensure patients are achieving adequate exposures and target trough concentrations of IgG to maintain treatment efficacy. As SCIG dosing could be undertaken at various frequencies from daily to biweekly (every other week) to fit into patients' lifestyles, it is important to ensure this flexible dosing approach still meets the needed pharmacokinetic (PK) parameters for effective treatment.

In primary immunodeficiency, a two-compartment disposition model has been developed to model IVIG and SCIG

PK parameters.[7] An initial two-compartment disposition IVIG PK model with first-order elimination has also previously been developed for CIDP. Here, using these models as a basis, we present a pharmacometric model used to simulate concentration–time profiles and PK parameters following various SCIG dosing regimens to evaluate flexible dosing schedules in CIDP, which would allow patients to choose the best dosing schedule to optimize therapy. We also detail an exposure–response longitudinal population PK/pharmacodynamic model characterizing the relationship between serum IgG concentrations and disease severity as assessed by change in the INCAT score using data from the PATH study of SCIG IgPro20 in the maintenance treatment of CIDP.[8]

METHODS

PATH study design

Full methods of the PATH study have been previously published.[8,9] Informed consent was obtained for all patients, and all relevant ethics approvals were obtained. Briefly, the PATH study assessed the efficacy and safety of IgPro20 as maintenance therapy for CIDP. Following a 4- to 12-week IgG withdrawal period, subjects identified as IgG dependent were attempted to be restabilized with IVIG IgPro10 (Privigen®; CSL Behring) for 10–13 weeks. Successfully restabilized subjects were randomized to receive weekly placebo, 0.2 g/kg IgPro20, or 0.4 g/kg IgPro20 for 24 weeks. The primary outcome of the PATH study was CIDP relapse, defined as a greater than or equal to (≥) a one-point increase in adjusted INCAT total score from baseline, or withdrawal from the study for any reason.

IgG concentration and INCAT score measurements from PATH were used to build an exposure–response dataset. Baseline INCAT scores were collected before the SCIG treatment period but after IVIG restabilization (week 1). The randomization time point was denoted as week 1. Further INCAT measurements were made at weeks 2, 5, 9, 13, 17, 21, and 25 of the subcutaneous (SC) period. Baseline IgG serum levels were those before restabilization, at the end of the IVIG dependency period, as these levels were nearest to endogenous levels following the 4–12 week washout period. It must be noted that the time point for baseline IgG levels is different from that of the baseline for INCAT scores. Further serum IgG level assessments were performed at weeks 9, 17, and 25 of the SC period (Figure S1).

Pharmacometric population PK analysis

The previous population PK model for IgG in patients with primary immunodeficiency was developed by assessing models with one, two, and three disposition compartments.[7] IVIG was modeled as infusion directly into the central compartment and SCIG absorption from the depot site into the central compartment as a first-order process with an absorption rate constant of 0.493/day. Endogenous plasma IgG was modeled at 4 g/L based on primary immunodeficiency literature.[7] The available IgG concentrations were best described by a two-compartment disposition model with first-order absorption of exogenous IgG from the SC depot compartment into the central compartment and linear IgG elimination. Using this as a basis, prior modeling of IVIG in CIDP also showed a two-compartmental model with first-order absorption and elimination. This pharmacometric model[7] was updated with additional intravenous (IV) data from the single-arm IVIG CIDP PRIMA study[10] and adapted for SCIG administration based on data from the CIDP PATH study, following which, goodness-of-fit of the structural model was assessed by diagnostic plots. In the updated model, baseline IgG was not fixed at 4 g/L as per the previous model, but instead used observed baseline IgG0 values affected by residual error. Outliers were excluded if their absolute conditional weighted residuals were greater than five, the observation in question was atypical in the context of the other samples in the same subject or the data point had a visual influence on diagnostic plots. Additionally, formal covariate analysis was performed; specific covariates of interest included body weight, age, sex, baseline IgG concentration, IgG treatment-naïve versus pretreated, Japanese versus non-Japanese race, and US versus non-US regions. A prediction-corrected visual predictive check (pcVPC) was undertaken to check the model's ability to adequately predict the observed central tendency and variability of the data upon which the model was based. The 95% prediction intervals around the observed median, 5th, and 95th percentiles were assessed.

Using the final pharmacometric model, steady-state IgG concentration–time profiles following different dose regimens (daily to biweekly [every other week] dosing) were simulated (300 simulated trials of 25 patients with CIDP, as the typical size of a PK study). Corresponding exposure metrics were calculated and compared with a weekly dosing regimen. Median, 5th, and 95th percentiles (p5 and p95) of concentrations were calculated for each time point in each of the 300 simulated trials. Of these 300 values for each of the percentiles, a median 95% confidence interval (CI) of the medians, p5, and p95 values was calculated per time point. The calculated percentiles were the basis for determination of maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), time of maximum plasma concentration (T_{max}), and area under the curve (AUC). Regimens were deemed equivalent if exposure metric ratios were between 0.8 and 1.25, as defined by the US Food and Drug Administration (FDA) guidance on bioequivalence. Data exploration and pharmacometric modeling were conducted using R (R Foundation for Statistical Computing 2014, Vienna, Austria) and the nonlinear mixed-effects modelling software NONMEM (version 7.3; ICON, Dublin, Ireland), respectively.

Pharmacometric exposure–response analysis

The intention of the exposure–response analysis was to fit structural models to the data in order to predict specific changes in total INCAT score to answer key pharmacologic questions, such as the maximum IgPro20 drug effect (E_{max}) and the concentration that achieves 50% of the maximum effect (EC_{50}). Exposure–response data obtained during the baseline visit and throughout the SC treatment period from all subjects who had received at least one dose of IgPro20 or placebo were included in this analysis. Data collected prior to the baseline visit (other than demographic or covariate data) were omitted.

Individual IgG PK parameters from the pharmacometric model were used to predict individual PK profiles for the exposure–response model. The relationship between ΔIgG (defined as total serum IgG at INCAT score assessment minus IgG levels at relapse after IVIG withdrawal, before IVIG restabilization) and INCAT scores at various time points was investigated using the model. The INCAT total score is a subjective ordered categorical end point with values that range from 0 to 10 and is composed of the sum of arm (0–5) and leg (0–5) disability scores. Increases in INCAT score represent worsening (relapse), decreases in INCAT score indicate improvement, and no change in INCAT indicates stability.[11] For this analysis, changes in total INCAT score were classified into one of three categories: stable/improved disease (≥0-point decrease in INCAT score), improvement in disease (≥1-point decrease in INCAT score), or worsening of disease (≥1-point increase in INCAT score). The ΔIgG was linked to INCAT effect by a direct effect E_{max} model. A latent variable exposure–response model consisting of baseline and drug effect with inter-individual variability (IIV) was developed to quantify the link between ΔIgG and INCAT score.[12] Placebo data were initially fitted to define the nondrug component of the model. Subsequently, treatment data were incorporated and the drug model component evaluated. The exposure–response model could then predict the expected ΔIgG concentration at the time of INCAT measurement if no Ig concentration was measured at that visit.

The general model form proposed was as:

$$probit\ Pr\left(\text{INCAT} \le m\right) = \mu\left(\eta\right) = f_b\left(t\right) + f_{\text{nd}} + f_d\left(E\left(t\right)\right)$$

where: *probit* = Φ−1 and Φ(•) is the cumulative normal distribution function; m represents the observed INCAT score; $\mu(\eta)$ is the conditional mean on the probit scale (conditioned on η); η is a vector of subject-specific random effects; fb, fnd, and fd, represent the baseline (intercept), nondrug (or placebo), and drug model component, respectively; t is time; and $E(t)$ represents individual predicted exposure or exogenous IgG concentration (baseline-corrected IgG concentration) that can change with time.

The $f_b(m)$ component is the baseline model component. The component is defined as:

$$f_b\left(m\right) = \infty, \quad m = 10$$

$$f_b\left(m\right) = \text{BASE} - \sum_{t=2}^{10} I(10 - i \ge m) \cdot \exp\left(\theta_i\right), \quad m \le 9$$

where BASE is the baseline parameter and the θi ($i \in \{2, \ldots 10\}$) are fixed effects that correspond to the thresholds for the latent variables that map to the observed INCAT scores. BASE = θ1 and may be a function of η as well.

The objective function value (or −2 log-likelihood) was used to assess model development. Additionally, goodness-of-fit plots were used to assess their appropriateness.

The following set of nondrug functions were considered:

$$f_{nd} = \begin{cases} \text{P}_{\max} \cdot 1\left(t > 0\right) & \text{step function} \\ \text{Pslp} \cdot t & \text{linear} \\ \text{P}_{\max} \cdot \left(1 - \exp\left[-\dfrac{\ln 2}{\text{PThalf}} t\right]\right) & \text{exponential plateau} \end{cases}$$

where the slope of a linear placebo effect (Pslp), maximum placebo effect (P_{max}), and half-life of placebo effect onset (PThalf) are functions of θ and possibly η.

The drug model component was evaluated last, after incorporation of the data from the IgPro20 arms of study 3003. Possible forms included direct effects of IgG concentration or indirect model (IDRM):

$$f_d = \begin{cases} \dfrac{\text{E}_{\max} \cdot E\left(t\right)}{\text{EC}_{50} + E\left(t\right)} & E\left(t\right) = C\left(t\right) \\ \dfrac{\text{E}_{\max} \cdot E\left(t\right)^{HC}}{\text{EC}_{50}{}^{\text{HC}} + E\left(t\right)^{HC}} & E\left(t\right) = C\left(t\right) \\ \text{E}_{\max} \cdot E\left(t\right) & IDRM \end{cases}$$

where E_{max}, EC_{50}, and Hill coefficient (HC) are functions of θ and possibly η, and $C(t)$ represents the subject-specific prediction of IgG serum concentration at time t.

A general parameterization considered for the IDRMs was:

$$\frac{\text{d}E\left(t\right)}{\text{d}t} = K \cdot u\left(C\left(t\right)\right) - K \cdot v\left(C\left(t\right)\right)\left[E\left(t\right) + 1\right], \quad E\left(t = 0\right) = 0, \qquad u = \frac{\text{EC}_{50}}{\text{EC}_{50} + C\left(t\right)}, \quad v = 1 + \frac{C\left(t\right)}{\text{EC}_{50}}$$

where $E(t)$ is the solution to the IDRM differential equation, K is a rate constant that is a function of θ and possibly η, and $u(\cdot)$ and $v(\cdot)$ are forcing functions which depend upon IgG concentration $C(t)$.

A full model was developed including covariates of interest (age, race, sex, and baseline IgG) and a covariate selection process using Wald's Approximation Method (WAM)[13] was implemented to derive a parsimonious final

model. The WAM procedure ranked all 2^k models, where k was the total number of covariates in the full model. The top 15 WAM ranked models based on Schwarz's Bayesian Criterion (SBC) were fit using NONMEM for further evaluation and determination of a parsimonious model. The model with the lowest SBC was selected as the final model.

The PATH study had a high degree of dropout at later timepoints, which was likely to yield biased summaries (over-prediction) of the observed data because the subjects withdrawn during the study do not contribute observed data to the summaries after dropout. In order to facilitate a comparison of the observed data and model predictions, an imputation process of the missing data was used. Missing INCAT score data were simulated (imputed) using individual predictions of probabilities from the model.[14] Model diagnostics were based on these imputed complete-case datasets (i.e., all subjects with complete INCAT scores until week 24). Missing baseline covariate data were sourced from a visit prior to baseline. Assessment of goodness-of-fit plots and visual predictive checks (VPCs) were conducted to evaluate the final exposure–response model. Average population mean predictions were computed for Pr(INCAT≤m), m {0,1,…9} by replicate, and 90% prediction intervals were computed across the simulated replicates. These 90% prediction intervals were compared with the averages of the frequency-based means of the observed data. Coverage of these 90% prediction intervals was used to evaluate the quality and performance of the final model.

Last, this model allows interpolation between doses of 0.2 and 0.4 g/kg, with the probability of having a stable or decreased total INCAT falling between 81% and 86%. Based on this analysis, both doses of IgPro20 yield a substantial proportion of subjects with IgG concentrations that exceed the level that would result in a clinically meaningful effect, as measured by total INCAT score after 24 weeks of treatment. The population analysis was performed using NONMEM (version 7.3) software (ICON Development Solutions, Ellicott City, MD, USA). Post-processing of model output was performed using SAS (SAS Institute Inc., Cary, NC, USA) or R software. Graphical analysis of the data or output from the models was performed using R.

RESULTS

Population PK data set

The full PK analysis data set comprised 235 subjects and 1805 observations from PRIMA and PATH. Following exclusion of 234 unevaluable records and 13 outliers, a total of 1558 observations were used in the analysis. Summaries of covariate characteristics are shown in Table S1a and b.

Final population PK model

Different ways of baseline-handling were evaluated: estimating baseline IgG as typical value (θ) and IIV, fixing the baseline IgG concentration to the median observed baseline value with estimated IIV and the "observed baseline as covariate" model. Using the observed baseline as covariate stabilized the model and led to significant improvements of parameter precision. The final model was a two-compartment model with first-order absorption (for SC administration) and elimination and IIV on clearance (CL) and central volume of distribution (V2).

The final ER model equation was:

Baseline + Direct IVIG effect:

$$\text{Probit Pr}\left(\text{INCAT} \le m\right) = f_b\left(m\right) + \eta\text{Base} + \frac{\theta\text{E}_{\max} \cdot C\left(t\right)}{\theta\text{EC}_{50} + C\left(t\right)}$$

where $C(t)$ is the IgG serum concentration at time = t, E_{max} is the maximum drug effect, and EC_{50} is the concentration that achieves 50% of the maximum effect.

The residual error was described with a proportional model. Due to the limited sampling in the absorption phase, the absorption rate constant (KA) was fixed to a previously estimated value in a different patient population.[7] Variability in CL and V2 was modest (<30%). A body weight effect on all CL and volume parameters (CL, intercompartmental clearance [Q], V2, and volume of distribution of peripheral component [V3]) was included in the final model. PK disposition parameter values (CL: 0.45 L/day, V2: 4.7 L, V3: 1.9 L and Q: 0.50 L/day for the reference median body weight of 82 kg) were consistent with earlier analyses of the PK of human IgG, which was characterized by low clearance and a limited volume of distribution. All parameters were estimated with good precision (Table S3). Relative bioavailability of the SCIG formulation compared with IV administration was estimated at 83%. Goodness-of fit plots (Figure S2) and a pcVPC (Figure S3) confirmed the final model was acceptable. Final pharmacometric model paramter estimates are shown in Table S4.

Model-based simulations to evaluate flexible dosing

Using the final pharmacometric model, IgG concentration–time profiles from 300 trials with 25 patients with CIDP each were simulated. Corresponding exposure metrics were calculated from different dose regimens (daily to biweekly dosing) and compared with the weekly dosing regimen. At steady-state, median simulated exposure metrics were 119 g*day/L ($AUC_{days0\text{-}7}$), 17.4 g/L (C_{max}) and 16.5 g/L (C_{min}) for the 0.2 g/kg once a week dose level, and 150 g*day/L ($AUC_{days0\text{-}7}$),

TABLE 1 Median derived PK parameters by simulation scenario

Scenario	$AUC_{days\ 0\text{-}7}$ (g*day/L)	$AUC_{days\ 0\text{-}14}$ (g*day/L)	C_{max} (g/L)	T_{max} (day)	C_{min} (g/L)
0.2 g/kg/week					
Biweekly	123.6 (91.6–177.6)	238.5 (174.6–347.0)	18.2 (13.7–25.9)	3.25	15.7 (11.1–23.4)
Weekly	119.5 (87.4–173.2)	239.1 (174.9–346.6)	17.4 (12.9–25.1)	2.5	16.5 (11.9–24.3)
Twice weekly	119.2 (87.0–172.8)	238.5 (174.2–345.7)	17.2 (12.6–24.8)	1.5	16.8 (12.2–24.5)
Daily	119.7 (87.4–173.2)	239.3 (174.9–346.4)	17.1 (12.5–24.8)	0.5	17.1 (12.5–24.7)
0.4 g/kg/week					
Biweekly	158.9 (119.4–217.7)	301.1 (225.6–419.0)	23.9 (18.2–32.3)	3.25	18.7 (13.3–27.1)
Weekly	150.4 (111.5–209.5)	301.1 (223.3–419.2)	22.2 (16.7–30.6)	2.25	20.4 (14.9–28.9)
Twice weekly	149.7 (111.1–208.8)	299.8 (222.5–417.9)	21.7 (16.2–30.1)	1.5	21.0 (15.4–29.4)
Daily	150.5 (111.9–209.6)	301.1 (223.7–419.2)	21.5 (15.1–30.0)	0.5	21.5 (16.0–29.9)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; C_{min}, minimum concentration; PK, pharmacokinetic; T_{max}, time of maximum concentration.

Numbers are medians of 300 simulated medians, 5th, and 95th percentiles (p5-p95). AUC was calculated as C_{ave}*time (C_{ave} = average concentration over the time interval).

22.2 g/L (C_{max}) and 20.4 g/L (C_{min}) for the 0.4 g/kg once weekly dose level (Table 1). Concentration-time profiles at steady-state following flexible dosing (daily to biweekly) are shown in Figure 1. Ratios of exposure metrics for the various dosing regimens are shown in Table 2. Metrics from daily and biweekly regimens were deemed equivalent with that of a weekly dosing regimen, as ratios were within the common equivalence boundaries of 0.8 and 1.25.

Simulations of IgG concentrations over 6 months after a switch from the original IV dosing regimen (1 g/kg every 3 weeks [q3w]) to 0.2 g/kg qw SC showed essentially stable IgG trough concentration during the entire transition period and beyond (Figure S4a). A switch from the IV regimen to 0.4 g/kg qw SC showed a gradual rise of IgG trough concentrations to a new steady-state (C_{max} 22.2 g/L, C_{min} 20.4 g/L) over a period of ~ 2 months (Figure S4b).

INCAT change correlation with ΔIgG and total IgG levels

When observed changes in INCAT score indicating stability/improvement versus worsening were correlated with ΔIgG, a clear exposure–response relationship was observed (Figure 2a). Lower ΔIgG levels appeared to be a better predictor of worsening INCAT score than lower total IgG levels (Figure 2b) as the trend was clearer, therefore ΔIgG was used as the exposure metric in the exposure–response model.

Final exposure–response model

Data from 171 patients receiving 0.2 g/kg IgPro20, 0.4 g/kg IgPro20, or placebo in the PATH study were used to develop the exposure–response model. Summaries of covariate characteristics of the 171 patients are shown in Table S2a and b. Covariates of interest (age, race, sex, and baseline IgG) in the initial full model are shown in Table S3. The covariates in the final model are listed in Table 3. In terms of covariate demographic characteristics, 64% of subjects were men, ~ 94% of the subjects were non-Japanese. The mean age was 56.4 years (range 24–83 years). Baseline IgG was balanced across treatment groups (mean 12.97). The final model consisted of baseline and drug effects with IIV on baseline. The drug effect was best described by an E_{max} model that was a function of ΔIgG concentration. Age and Japanese race were found to be significant covariates on the baseline parameter of INCAT, which influenced INCAT total score distribution. Older subjects tended to have worse baseline INCAT than younger subjects. Japanese subjects tended to have a better baseline INCAT parameter than non-Japanese subjects. However, none of the tested covariate effects on E_{max} were found to be significant.

The exposure–response relationship from the final model was nonlinear, with an EC_{50} estimated at ~ 2.8 g/L. Goodness-of-fit plots indicated the model was acceptable (Figure S5). VPC results showed that the observed INCAT response rates were largely contained within the 90% prediction intervals, indicating that the final model could accurately simulate INCAT response data that were consistent with the observed data. However, a slight lack of fit was observed for the 0.4 g/kg dose due to a different baseline compared with the other treatment groups (Figure S6).

Model-based predictions of exposure-response relationships

The exposure–response model was leveraged to predict INCAT response in terms of stable/improved disease, improvement in disease, or worsening of disease as a function

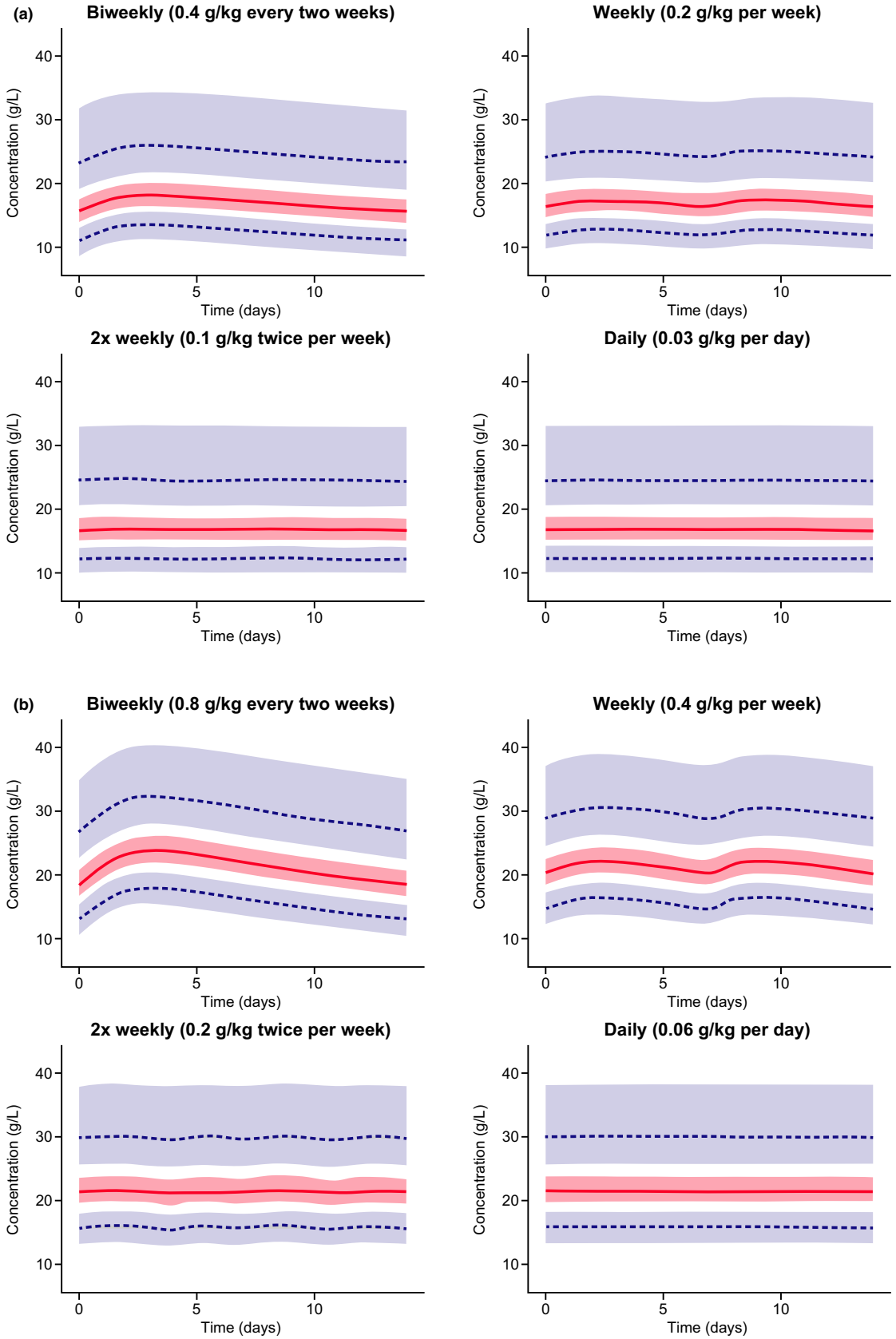

FIGURE 1 Simulated concentration–time plots for (a) 0.2 g/kg and (b) 0.4 g/kg IgPro20. The red line is the median of all median concentrations in 300 simulated trials with 25 subjects each; blue dashed lines are median p5 and p95 concentrations. Red and blue shaded areas are the 95% CI around the median percentiles

TABLE 2 Ratios of exposure metrics (medians and 95% CI)

Exposure metric	Ratio biweekly/weekly	Ratio twice weekly/weekly	Ratio daily/weekly
0.2 g/kg/week			
$AUC_{days\ 0\text{-}7}$	1.034 (1.019–1.058)	0.997 (0.995–0.998)	1.000 (1.000–1.000)
$AUC_{days\ 0\text{-}14}$	0.999 (0.999–0.999)	0.998 (0.997–0.999)	1.001 (1.000–1.001)
C_{max}	1.046 (1.026–1.077)	0.986 (0.976–0.992)	0.981 (0.968–0.989)
C_{min}	0.950 (0.923–0.970)	1.017 (1.010–1.029)	1.033 (1.018–1.055)
0.4 g/kg/week			
$AUC_{days\ 0\text{-}7}$	1.053 (1.030–1.089)	0.995 (0.992–0.997)	1.000 (1.000–1.000)
$AUC_{days\ 0\text{-}14}$	0.999 (0.998–0.999)	0.996 (0.995–0.998)	1.001 (1.000–1.001)
C_{max}	1.073 (1.043–1.119)	0.978 (0.963–0.987)	0.970 (0.951–0.983)
C_{min}	0.918 (0.881–0.949)	1.028 (1.016–1.045)	1.052 (1.031–1.087)

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; C_{min}, minimum concentration.

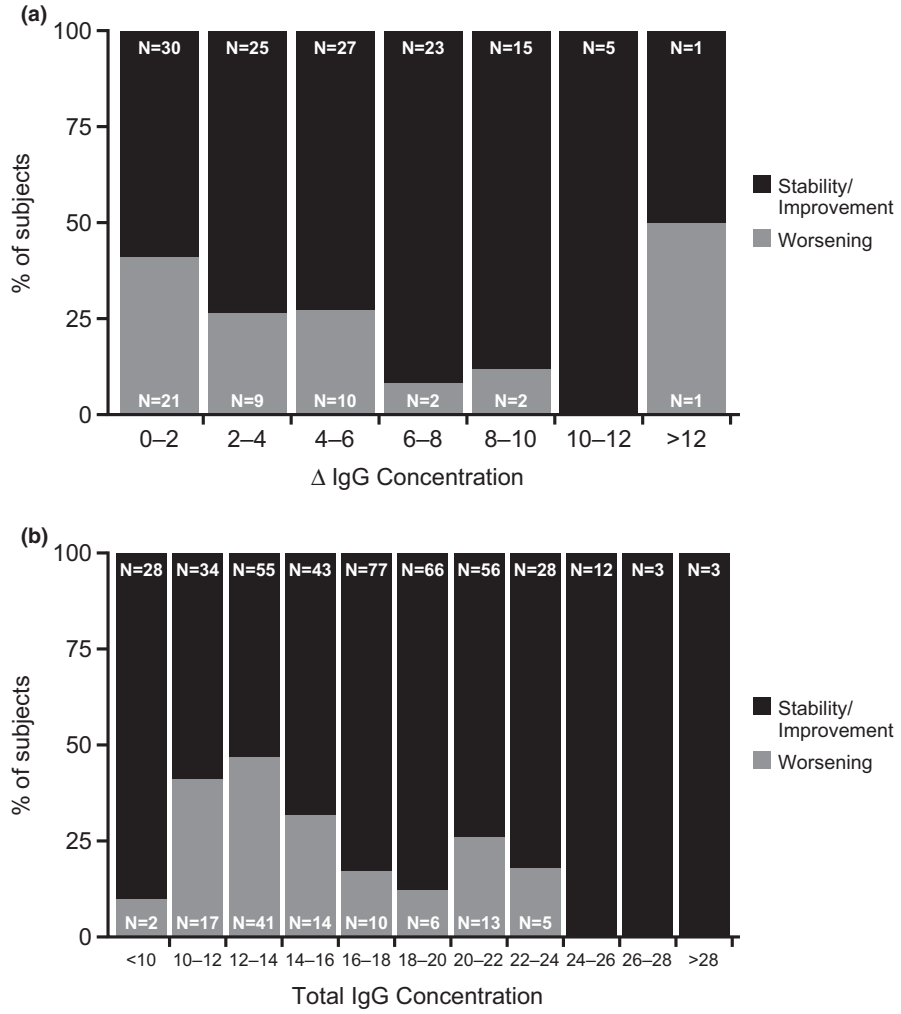

FIGURE 2 Percentage of observed subjects with stable/improved or worsening INCAT scores by (a) ΔIgG levels and (b) total IgG levels. Subjects can appear multiple times. INCAT, Inflammatory Neuropathy Cause and Treatment; IgG, immunoglobulin G

TABLE 3 Parameter estimates for final exposure-response model

Parameter (units)	Estimate	SE	Relative SE (%)	90% CI	Transformed estimate	Transformed 90% CI
Baseline for INCAT ≤ 4	5.26	0.44	8.37	(4.4, 6.13)	–	–
Baseline adjustment for INCAT ≤ 3	1.34	0.0802	5.99	(1.18, 1.49)	–	–
Baseline adjustment for INCAT ≤ 2	1.09	0.0522	4.79	(0.989, 1.19)	–	–
Baseline adjustment for INCAT ≤ 1	0.613	0.0601	9.80	(0.495, 0.731)	–	–
Baseline adjustment for INCAT ≤ 0	0.626	0.064	10.22	(0.5, 0.751)	–	–
Maximum drug effect (E_{max})	2.27	0.463	20.40	(1.36, 3.17)	–	–
EC_{50} (g/L)	1.68	0.562	33.45	(0.578, 2.78)	5.37	(1.78, 16.2)
Age effect on baseline[a]	−0.0862	0.0258	−29.93	(−0.137, −0.0356)	–	–
Japanese effect on baseline[b]	4.06	1.65	40.64	(0.828, 7.3)	–	–
IIV baseline (ω^2)	15.9	2.21	13.90	(11.5, 20.2)	–	–

Abbreviations: SE, standard error; CI, confidence interval; E_{max}, maximum drug effect; EC_{50}, concentration that achieves 50% of the maximum effect; IIV, intersubject variability; INCAT, Inflammatory Neuropathy Cause and Treatment.

[a]Continuous covariate effects: $+\theta_i \bullet (cov_j - cov_{median})$, for i^{th} parameter, j^{th} individual.

[b]Categorical covariate effects: $+\theta_i \bullet I(cov_j = k)$, for i^{th} parameter, j^{th} individual, k = category.

TABLE 4 Model predicted probability of stable/improved disease, improvement of disease, or worsening of disease in terms of change in total INCAT score with various ΔIgG concentrations

		Stable/improved INCAT	Improved INCAT	Worsening INCAT
Ig concentration metric (g/L)	ΔIgG concentration (g/L)	Probability (95% CI)	Probability (95% CI)	Probability (95% CI)
EC_{20}	0.8	0.70 (0.65; 0.74)	0.13 (0.11; 0.15)	0.30 (0.26; 0.35)
EC_{50}	2.8	0.78 (0.77; 0.80)	0.22 (0.20; 0.24)	0.22 (0.20; 0.23)
EC_{80}	8.1	0.87 (0.85; 0.89)	0.31 (0.26; 0.35)	0.13 (0.11; 0.15)
0.2 g/kg weekly SC C_{trough}	3.82	0.81 (0.80; 0.82)	0.18 (0.17; 0.20)	0.19 (0.18; 0.20)
0.4 g/kg weekly SC C_{trough}	7.54	0.86 (0.85; 0.88)	0.25 (0.22; 0.28)	0.14 (0.12; 0.15)
1 g/kg every 3 weeks IV C_{trough}	3.99	0.81 (0.80; 0.83)	0.19 (0.18; 0.20)	0.19 (0.17; 0.20)

Abbreviations: CI, confidence interval; C_{trough}, concentration at the end of the dosing interval; $EC_{20/50/80}$, concentration that achieved 20/50/80% of the maximum effect; INCAT, Inflammatory Neuropathy Cause and Treatment; IV, intravenous; SC, subcutaneous.

of ΔIgG concentrations. There was a higher probability of INCAT stability or improvement and a lower probability of worsening with higher ΔIgG concentrations (Table 4 and Figure 3).

Simulations were performed to assess the effects of the significant covariates (age and Japanese race) on the predicted probabilities of INCAT score changes. Age did not have a meaningful effect on predicted INCAT total score changes from baseline. Similar results were demonstrated in Japanese compared with non-Japanese subjects for a stability/improvement or worsening in INCAT total score. However, Japanese subjects had a slightly lower probability of an improvement, potentially due to the lower baseline INCAT total scores in this subgroup. Note that the Japanese analysis is based on limited data, as only 6% of subjects were Japanese. The covariates only affected the baseline, and neither of the effect-related parameters (EC_{50}, E_{max}), hence a substantial difference in effect is not to be expected.

DISCUSSION

This is the first pharmacometric analysis to characterize the PKs of IgG after SC administration to patients with CIDP and to quantitatively link IgG exposure and clinical outcomes utilizing a latent variable model construct. These analyses, when taken together, provide key insights into multiple aspects of the dosing regimens of SCIG, which include dosing level, frequency of dosing, and achievement of IgG concentrations and how this links to clinical outcomes in patients with CIDP.

The PK of IgG following SC administration was well characterized by a two-compartment model with first order absorption and elimination. Simulations showed that the dosing interval of SCIG administration can be handled flexibly if the total weekly dose remains the same. Tested scenarios included biweekly (every other week), weekly, twice-weekly, and daily administration of SCIG, as these were considered the most typical regimens for patients to choose to fit in with

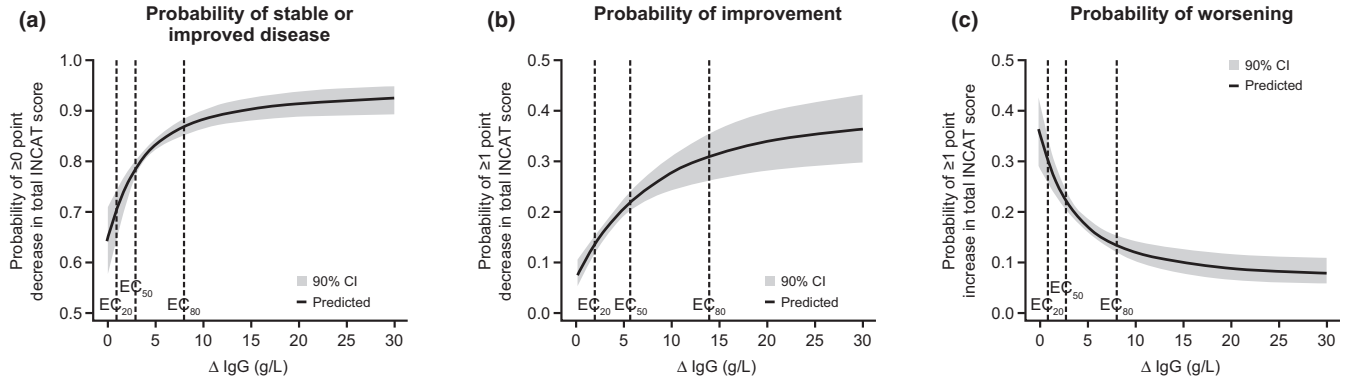

FIGURE 3 Relationship between change in ΔIgG levels and predicted probabilities of (a) a stable or improved disease, (b) improvement of disease, or (c) worsening of disease. Graphs show the relationship between the probability of change in INCAT score and change in ΔIgG; defined as total IgG serum levels at the time of INCAT score assessment minus baseline IgG levels at relapse after IVIG withdrawal, before IVIG restabilization. CI, confidence interval; EC, concentration that achieves a percentage of the maximum effect; IgG, immunoglobulin G; INCAT, Inflammatory Neuropathy Cause and Treatment

their lifestyle. Pharmacometric analysis was previously used to assess flexible dosing regimens,[15] which allow for patient flexibility in how they administer SC IgG in patients with primary immunodeficiency, and a similar approach was taken in the present study. The PATH trial assessed weekly dosing of IgPro20[8] and the present analysis demonstrates the relationship between IgG concentration and total INCAT score. Therefore, exposure matching to the weekly dosing regimen would likely yield a similar relationship to total INCAT score reduction.

Exposure metric ratios (AUC, C_{max}, and C_{min}) of the alternative regimens over the reference dosing regimen stayed well between the equivalence limits of 0.8 and 1.25. Furthermore, simulations demonstrated that trough IgG concentrations are not expected to decline when switching from IVIG at 1 g/kg every 3 weeks to 0.2 g/kg SCIG weekly, and a switch to 0.4 g/kg weekly will lead to a gradual rise in IgG trough concentrations. Our model suggests similar Ig trough exposure for maintenance therapy with IVIG 1 g/kg every 3 weeks and for SCIG 0.2 g/kg every week (i.e., after a 40% dose decrease). Although IVIG and SCIG have not been compared with each other in a clinical head-to-head trial, literature supports that switching from IVIG to SCIG is feasible, and that symptom control can be adequately maintained with SCIG.[16]

Assessing the link between CIDP disability and IgG levels is critical to support the optimization of Ig dosing, as is confirming the flexibility of dosing regimens to suit individual patient needs. Wear-off effects often seen with IVIG treatment suggest that there is a link between IgG levels and disability in CIDP.[17] However, the minimum IgG level needed to maintain stability varies between patients. The drug effect model in this analysis was initially evaluated using total Ig concentration (endogenous + exogenous IgG) as the PK exposure measure, rather than exogenous IgG concentration. This approach was taken as patients with CIDP are likely to have a level of disease with an inherent baseline value of IgG. Objective function values for both the linear and nonlinear drug effect models with total IgG concentration were increased compared with models that used exogenous IgG concentrations. This suggests that the drug effect on total INCAT score is not mediated by endogenous IgG concentration. Our exposure–response model, which analyzed data from subjects in the PATH study, demonstrates that an increase in ΔIgG concentration levels was generally associated with an increased probability of stability or improvement in INCAT score. A previous analysis of data from the PATH study showed no correlation between INCAT score and total IgG levels, both in terms of changes in values or absolute values,[18] highlighting the difficultly in confirming the relationship between IgG levels and function. Total INCAT is an ordered categorical variable, and logistic and probit regressions are the preferred modeling techniques for these types of variables. Furthermore, Ig concentration data were only captured sparsely and therefore a pharmacometric model was necessary to estimate the concentration at each of the timepoints when INCAT was assessed. The baseline used for the ΔIgG calculation in the current analysis was the IgG concentration at relapse after IVIG withdrawal, before IVIG restabilization. This may account for some of the IIV in the IgG level required for CIDP stability. The strength of this exposure–response model is that simulating IgG levels allowed to evaluate a large data set. This is often not possible using observed data, as many patients do not have actual PK sampling on the visits at which INCAT scores are recorded. It must be noted that these exposure–response models used change in total INCAT scores in simulations, whereas the PATH study primary analyses used adjusted INCAT scores to define stability/relapse. Therefore, results may differ between analyses and are not directly comparable.

The exposure-response model estimated that the baseline-corrected IgG concentrations resulting in EC_{20}, EC_{50}, and EC_{80} values associated with the probability of having a stable or decreased total INCAT score would occur at baseline-corrected IgG concentrations of 0.8, 2.8, and 8.1 g/L, respectively. These baseline-corrected target IgG concentrations were then compared with the expected baseline-corrected IgG trough (at the end of the weekly dosing interval) concentrations after SC administration of IgPro20 at a dose of 0.2 g/kg or 0.4 g/kg. The predicted baseline-corrected mean trough concentration was 3.82 g/L for the 0.2 g/kg dose and 7.54 g/L for the 0.4 g/kg dose. These corresponding IgG trough concentrations yield probability estimates of having a stable or decreased total INCAT score of 81% for the 0.2 g/kg dose and 86% for the 0.4 g/kg dose.

The PATH trial demonstrated that a dose of 0.2–0.4 g/kg per week was safe and effective to prevent CIDP relapse.[8] The pharmacometric analysis presented here was used to characterize the relationship between exogenous (baseline-corrected) serum IgG concentrations after administration of IgPro20 and total INCAT scores in subjects with CIDP. Higher serum IgG concentrations resulted in a greater probability of having a stable (no change) or decreased (improvement) total INCAT score.

Based on the ER model, the baseline-corrected IgG trough concentration (C_{min}) that would be expected to produce an EC_{50} (~ 78% probability of having a stable or decreased total INCAT score) was estimated to be 2.8 g/L. The proportion of subjects that would maintain trough concentrations at or above this concentration target would be 72% with 0.2 g/kg IgPro20 and 96% with 0.4 g/kg IgPro20, providing evidence for the use of a dose ranging from 0.2 to 0.4 g/kg. Furthermore, at the mean predicted baseline-corrected IgG trough concentrations after administration of 0.2 g/kg IgPro20 (3.82 g/L) and 0.4 g/kg IgPro20 (7.54 g/L), the probability of having a stable or decreased total INCAT score would be 81% and 86%, respectively. In conclusion, pharmacometric modeling and simulation indicates that dosing intervals of SCIG administration can be handled flexibly if the total weekly dose remains sufficient to maintain symptom control, allowing personalized Ig treatment tailored to patients' preferences.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. H.P.H., D.C., M.T., and T.Y. designed the research. P.J., M.P., and M.T. performed the research. All authors analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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