Pharmacokinetics and Pharmacodynamics of Intravenous Immunoglobulin G Maintenance Therapy in Chronic Immune-mediated Neuropathies

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The regimen for IVIg maintenance treatment varies considerably between patients with chronic immune-mediated neuropathies. Although it is widely recognized that treatment regimens should be improved, detailed pharmacokinetics (PK) of IVIg have not yet been established. We aimed to determine the PK of IVIg maintenance treatment in patients with clinically stable, treatment-dependent, chronic immune-mediated neuropathy. Patients received a median IVIg dose of 30 g (range, 15–70 g) every 14 days (range, 7–28 days) resulting in high IgG peak levels (median, 25.9 g/L; range, 16.7–41.0 g/L) and trough levels (median, 16.1 g/L; range, 9.7–23.6 g/L). IgG PK parameters, including half-life (median, 23.1 days; range, 11–60 days), were constant during subsequent courses in the same patients, but varied considerably between patients. The IgG levels at 1 week after infusion correlated with grip strength. These results provide insight into the PK of IVIg maintenance treatment in patients with chronic immune-mediated neuropathies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Most patients with chronic immune-mediated neuropathy require maintenance treatment with IVIg. The provided dosage and interval of IVIg varies considerably between patients, partly because regimens are adjusted to clinical response. There is no consensus regarding the best strategy to adjust the regimen and no biomarkers are available to monitor the disease activity or treatment, resulting in frequent over- and under-treatment.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What is the PK profile of IVIg maintenance treatment administered to patients with clinically stable but active chronic immune-mediated neuropathy and is there a relation with PDs?

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ Patients with chronic immune-mediated neuropathy show considerable variation in PK parameters of IVIg maintenance treatment associated with fluctuations in grip strength during the treatment course.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These results enable a first understanding of the PK of IVIg maintenance treatment in patients with CIDP. Further studies are required to determine if serum IgG levels can be used to monitor and optimize treatment in patients with chronic immune-mediated neuropathy.

Intravenous immunoglobulin (IgG) is an effective treatment for various acute and chronic forms of immune-mediated peripheral neuropathies, including Guillain–Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and multifocal motor neuropathy (MMN).[1] Although GBS is usually treated with a single course of IVIg, most patients with CIDP require regular infusions for years or even decades.[2] According to international guidelines for treatment of CIDP, the IVIg induction course starts with an arbitrarily set dose of 2 g/kg bodyweight followed by a maintenance regimen of 1 g/kg bodyweight every 3 weeks for 6 months.[3,4] Patients with CIDP show a variable clinical response to this regimen and the treating physician adjusts the treatment dosage and interval accordingly. There is no standard strategy to define the optimal IVIg regimen in these patients and no biomarkers to monitor the disease activity or treatment.[5] As a consequence, the dosage and interval of this maintenance treatment varies considerably between individual patients,[6] and there are reports that patients with CIDP are frequently over- or undertreated.[7–10]

Although in use for decades, little is known about the pharmacokinetics (PK) or pharmacodynamics (PDs) of IVIg in patients with immune-mediated neuropathies. The PK of IVIg is influenced by the serum IgG concentration and PK/PD studies conducted in patients with immune deficiencies with low or absent

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Table 1 Characteristics of 15 patients with clinically stable treatment-dependent chronic immune-mediated neuropathy

Characteristics	No. of patients (%)
Patient characteristics ($N = 15$)	
Gender, male	11 (73)
Age, years	69 (range, 55–75)
Weight, kg	90 (range, 74–97)
Height, cm	173 (range, 168–181)
BMI, kg/m^2	29.05 (range, 21.37–35.55)
Rasch-built overall disability scale 1st/2nd course[19]	36.9 (7.2)/36 (7.8)
Rasch-built Fatique Severity Scale 1st/2nd course[20]	16 (4.6)/14.1 (5.8)
Grip strength dominant hand 1st/2nd course	57.7 (27.8)/58.8 (36.4)
Grip strength nondominant hand 1st/2nd course	48.4 (22.2)/48.7 (20.7)
Treatment characteristics	
Duration of IVIg treatment, years	7 (range, 3–8)
IVIg dose per course, g	30 (range, 15–70)
Interval between IVIg courses, days	14 (range, 7–28)
IVIg dose, g/kg body weight/month	0.77 (range, 0.17–1.85)
Infusion rate, mL/h	157.5 (range, 40–350)

BMI, body mass index; IgG, immunoglobulin G.
Data are presented as number (%), median (interquartile range) or mean (SD).
Grip strength was measured by using the handheld Martin Vigorimeter and shown in kPa.[17,18]

endogenous IgG production, therefore, cannot be extrapolated to patients with CIDP who have normal IgG levels.[11] In addition, it is unknown which factors influence IgG clearance in CIDP and if serum IgG levels can be used to monitor the effect of IVIg treatment. For GBS it was shown that 2 weeks after a standard course of IVIg of 2 g/kg, the serum IgG levels were highly variable between patients and the increase in IgG levels from baseline was related to outcome, suggesting that the PK of IVIg may be used to predict the treatment response.[12] Recent studies in CIDP and MMN also showed that serum IgG levels vary between patients after IVIg.[13–16] However, the limited number of sampling time points was insufficient to assess the PK/PD of IVIg.

To provide a more rational basis for the treatment of chronic immune-mediated neuropathy, we determined the PK/PD of IVIg maintenance treatment in 15 clinically stable and treatment-dependent patients with chronic immune-mediated neuropathies.

RESULTS

Fifteen patients with chronic immune-mediated neuropathy (14 with CIDP and 1 with MMN) were included in this study and all were clinically stable and dependent on IVIg maintenance therapy with either Kiovig (Kiovig, Baxter AG, Vienna, Austria / Baxalta US, Boston, MA; $N = 12$) or Privigen (CSL Behring AG, Bern, Switzerland; $N = 3$). The treatment regimen in this study remained constant during the two courses for each patient, but the dose and interval of IVIg highly differed between patients. The clinical and treatment characteristics are shown in **Table 1**. All patients were monitored frequently during the two consecutive courses of IVIg treatment using several validated and clinically relevant outcome measures for immune-mediated neuropathies. No differences were observed in outcome measures between the two courses except for a minor decrease in the Rasch-built Fatique Severity Scale in the second course (paired samples t-test, $P = 0.036$; **Table 1**). Despite the overall clinical stability, patients denoted a transient increase in grip strength (kPa) in the first week after IVIg, as determined by the validated handheld Martin vigorimeter (**Figure 1**).

After infusion, most patients reached their maximum IgG plasma concentration (C_{max}) of 25.9 g/L (median, interquartile range (IQR) = 19.5–32.2 g/L) within 2 h (time of maximum plasma concentration (T_{max}), median of 90 minutes, IQR = 15–120 min). The median trough level (trough plasma concentration (C_{min})) reached just before the next infusion was 16.4 g/L (IQR = 13.4–19.2 g/L). In individual patients, the peak and trough levels and the PK of IVIg were highly stable over the two courses (**Figure 2**).

Figure 3a shows the course of IgG levels for the whole group. The number of data for the last time points in a treatment course varied because of the difference in the interval between courses in individual patients. Because the trough levels reflected a "steady state" of the total IgG levels under IVIg maintenance treatment, we also defined the ΔIgG as the change in IgG levels for each time point compared to the trough level (**Figure 3b**). Patients showed a maximum median ΔIgG of 8.6 g/L (IQR = 5.6–13.7 g/L). The trough level showed moderate to strong correlations with the levels at subsequent time points, but not with the ΔIgG (**Supplementary Figure S1**). The serum IgG level determined at 15 min after

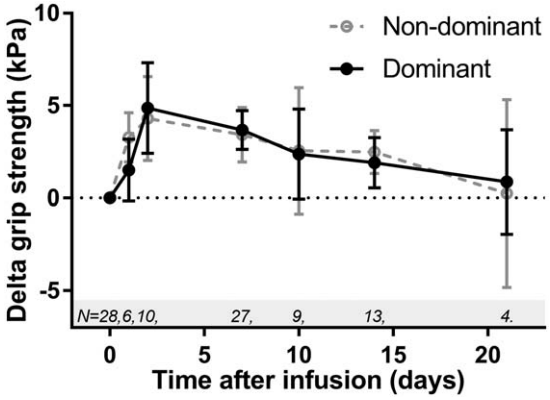

Figure 1 Fluctuations in grip strength during IVIg maintenance treatment in 14 patients with chronic inflammatory demyelinating polyneuropathy (CIDP). Transient increase in grip strength was determined by handheld Martin Vigorimeter, at standard visits when serum was obtained to determine IgG levels. Data are shown as means of two consecutive courses of IVIg and whiskers indicating the EM. The dotted line represents no change in grip strength. Above the X-axis the numbers of data points are indicated.

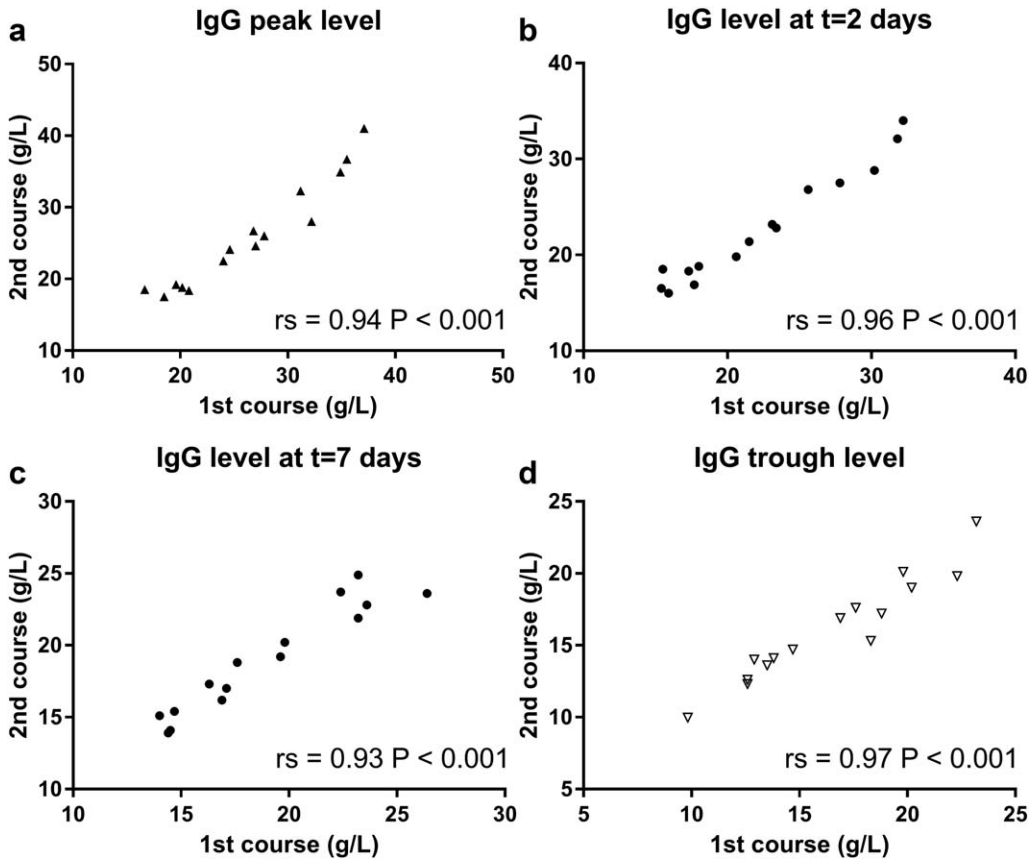

Figure 2 Serum immunoglobulin G (IgG) levels in two consecutive courses of IVIg maintenance treatment in 15 patients with chronic immune-mediated neuropathy. The figure shows stable IgG levels within all patients at standard time points during two consecutive courses of IVIg. (**a**) shows this for the peak plasma concentration, (**b**) 2 days postinfusion, (**c**) 7 days postinfusion, and (**d**) the trough plasma concentration just before the next infusion. Correlation coefficients (rs) were calculated by Spearman Rank correlation analysis.

infusion stop, on the other hand, strongly correlated with both subsequent time points and the ΔIgG up to 7 days after infusion (**Supplementary Figure S1**).

IgG consists of 4 subclasses (IgG1–4), which normally represent 67%, 22%, 7%, and 4%, respectively, of the total serum IgG.[17] The IgG subclasses were tested separately in this study and

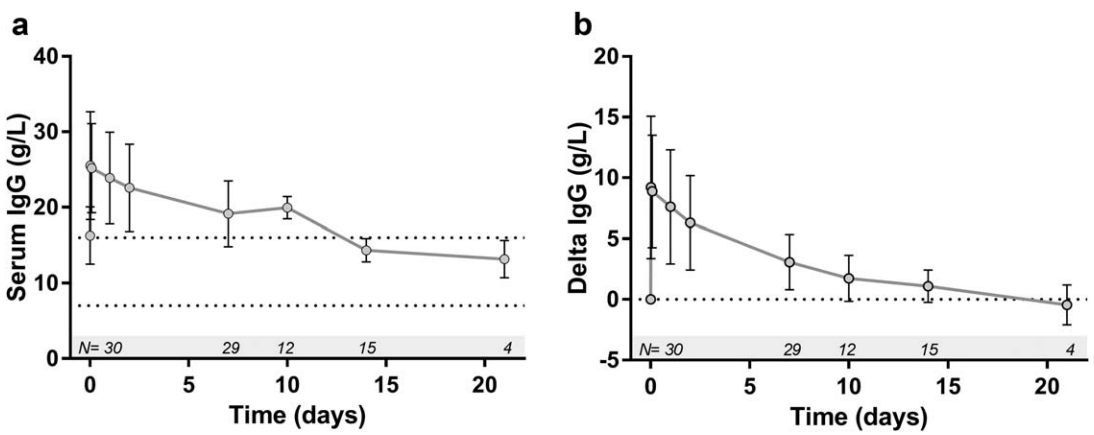

Figure 3 Serum immunoglobulin G (IgG) levels of two consecutive courses of IVIg maintenance treatment in 15 patients with chronic immune-mediated neuropathy. (**a**) Shows the kinetics of the serum total IgG levels shortly before IVIg infusion at steady state (trough plasma concentration) until 21 days after. All patients were sampled at the five first time points, thereafter the number of samples varied with patients on longer intervals being sampled until 3 weeks after infusion. Dotted lines represent the lower (7 g/L) and upper (16 g/L) boundaries of the normal range value for IgG. (**b**) Shows the kinetics of the ΔIgG (the increment of the total serum IgG compared to the steady state shortly before infusion) calculated for each time point separately. Data are shown as mean and whiskers indicate SD. The gray area above the X-axis denotes the number of data points in italics.

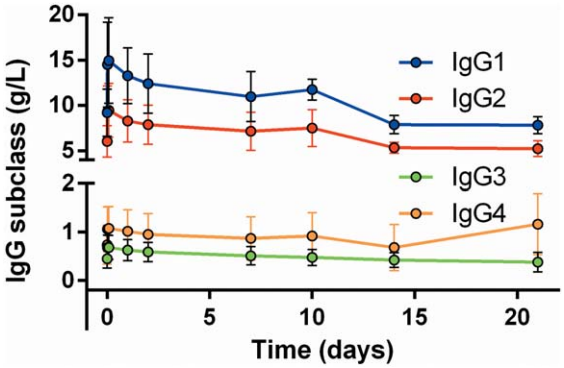

Figure 4 Serum immunoglobulin G (IgG) subclass levels in 15 patients of two consecutive courses of IVIg maintenance treatment. Kinetics of all serum IgG subclasses shortly before infusion at steady state until 21 days after. All patients were sampled at the five first time points, thereafter the number of samples slowly declined with patients on longer intervals being sampled until 3 weeks after infusion (same N as in **Figure 3**). [Color figure can be viewed at wileyonlinelibrary.com]

each IgG subclass demonstrated a PK comparable to the overall IgG levels (**Figure 4**). The minor subclass IgG4 showed a tendency to increase at the last time point for patients with a long infusion interval (>3 weeks). On average, levels of IgG4 were also higher in these patients than IgG3. Total IgG levels correlated with IgG1–3, but not with IgG4. The ΔIgG, however, correlated with all subclasses at all time points with the exception of the ΔIgG at 21 days (not shown). Half-lives of all IgG subclasses were comparable to the half-life of total IgG (**Table 2**). The volume of distribution at steady state was relatively small, but the volume of distribution at steady state of IgG3 exceeded all other subclasses by a factor of 2–3 ($P < 0.001$ Friedman test), similar to the clearance and also apparent from the ΔIgG3. For the ΔIgG, an apparent half-life shorter than a week was calculated; fitting to the infusion intervals that ranged from 1–4 weeks (**Table 2**).

Intravenous IgG is known to follow first order kinetics mostly described by a two-compartmental PK model.[18] In this study, we used the PKSolver's two-compartmental model method for i.v. infusions for the ΔIgG.[19] This allowed for the distinction between the rapid distribution of IVIg (α-phase) shortly after administration, and the more gradual decline of IgG serum levels afterward (β-phase). The ΔIgG median α-half-life was 0.78 days (IQR = 0.1–3.2 days) and the median β-half-life was 6.1 days (IQR = 3.5–9.1 days). The latter elimination phase correlated with the values found for ΔIgG when calculating half-life via noncompartmental analysis approach, albeit shorter (medians differ 1.7 days; $P < 0.001$, Wilcoxon Signed-Rank test).

The ΔIgG has previously been used as a surrogate marker for the kinetics of IVIg. In this study, we found that the half-life of IgG strongly correlated with the peak plasma level reached (C_{max} rs = −0.738; $P < 0.001$), but even stronger with the ΔIgG after 15 min (rs = −0.828; $P < 0.001$). The ΔIgG shortly after infusion also had a moderate to strong correlation with half-lives of all individual IgG subclasses (rs ranging from: 0.563–0.760; $P < 0.01$). Intra-individual variability was minimal (**Figure 2**) and there were no significant differences between the two courses for the PK parameters (**Table 2**), nor the ΔIgG, over all time points (data not shown; Friedman and Wilcoxon Signed-Rank test). In contrast, the variability between patients was considerable with a coefficient of variation (CV) of 48% (coefficient of quartile dispersion (CQD) = 26%) for the half-life of total IgG and a CV of 63% for the ΔIgG after 15 min (CQD = 52%). Stratified for the same dose regimen, the mean CV for the ΔIgG ranged from 18–33% (CQD = 10–22%) for the time points during the first week, but was 79% after 10–14 days (CQD = 41%; $N = 6$; 3 pairs of IVIg regimen-matched patients with CIDP). The interindividual variability for the half-life of total IgG in these patients showed a mean CV of 18% (CQD = 11%) and for the area under the curve (AUC) a mean CV of 4% (CQD = 3%). The

Table 2 Estimation of pharmacokinetic parameters for total immunoglobulin G and subclasses

	Half-life, days (range)	AUC, g/L*days (range)	Vss (L)	Cl (L/day)
IgG				
Total	23.1 (18.5–32.8)	235.1 (206.7–269.0)	1.2 (1.0–1.6)	0.039 (0.020–0.056)
IgG1	21.9 (17.8–36.6)	130.7 (116.3–149.1)	1.3 (1.1–1.9)	0.045 (0.020–0.066)
IgG2	24.0 (16.9–47.6)	92.0 (75.3–97.9)	1.0 (0.8–1.5)	0.027 (0.014–0.054)
IgG3	24.1 (15.5–36.9)	5.8 (5.0–7.8)	2.9 (1.5–4.6)	0.066 (0.034–0.168)
IgG4	23.7 (15.3–49.9)	10.2 (5.7–13.2)	0.8 (0.5–1.2)	0.028 (0.008–0.044)
ΔIgG				
Total	4.4 (3.1–6.6)	34.0 (27.3–65.2)	3.5 (3.2–4.5)	0.590 (0.415–0.758)
IgG1	3.9 (3.0–5.9)	22.9 (13.4–39.3)	3.8 (3.3–4.7)	0.682 (0.511–1.089)
IgG2	4.5 (2.5–8.0)	13.2 (7.9–22.0)	3.4 (2.8–4.0)	0.511 (0.281–0.687)
IgG3	3.5 (2.4–5.5)	0.8 (0.5–1.5)	10.0 (6.9–10.8)	1.508 (0.840–2.430)
IgG4	3.9 (2.6–7.7)	1.2 (0.8–3.4)	2.4 (1.8–2.9)	0.394 (0.194–0.683)

AUC, area under the plasma-concentration curve; Cl, clearance; IgG, immunoglobulin G; Vss, volume of distribution in steady state.
Data presented as median and interquartile range. Noncompartmental pharmacokinetic analysis in all 15 patients incorporating duration of infusion.

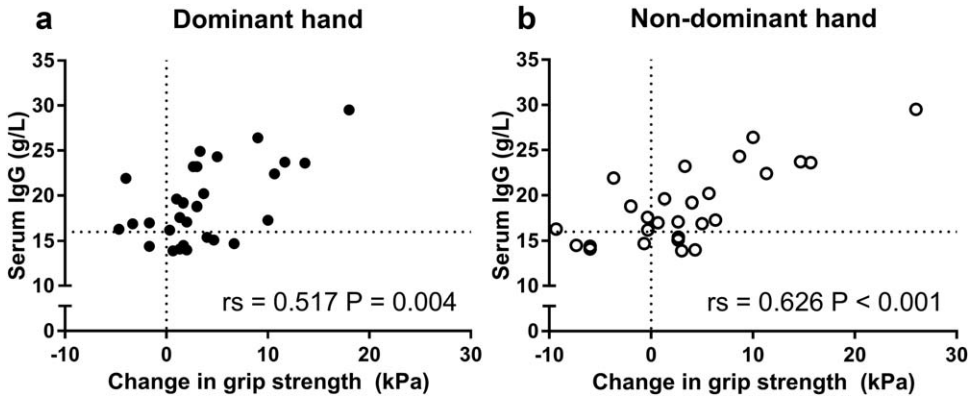

Figure 5 Serum immunoglobulin G (IgG) level and change in grip strength of dominant and nondominant hands at 7 days after IVIg maintenance infusion. Serum IgG levels at 7 days after infusion and the change in grip strength of 29 measurements at 7 days after infusion for (**a**) the dominant hands and (**b**) 27 measurements for the nondominant hands. The dotted lines represents either the upper limit of the normal range for serum IgG (16 g/L, horizontal) or no change in grip strength (vertical). The change in grip strength shortly before the IVIg infusion and 7 days later was measured by the handheld Martin Vigorimeter (kPa).

ΔIgG denoted a mean CV for the AUC of 26% (CQD = 19%) and 31% for the half-life (CQD = 19%).

The observed variability could, in part, be attributed to the administered IVIg dose, with a coefficient of determination of 47% for the IVIg dose on the AUC (adjusted for the interval) and 51% for the half-life of total IgG (i.e., the variation in dose explains roughly half of the variation in PK between patients). Higher dose of IVIg was strongly associated with a higher peak plasma level (rs = 0.870; $P < 0.001$) and lower half-life of IgG (rs = −0.814; $P < 0.001$). Conversely, a longer interval between infusions was associated with a higher half-life of IgG (in days, rs = 0.476; $P = 0.009$), and lower IgG trough level (rs = −0.860; $P < 0.001$). Anthropometrics weakly correlated with IgG PK parameters, but not after adjusting for dose, interval, and gender by Spearman's partial rank-order correlation. Only serum albumin levels (measured concomitantly with the serum IgG) shortly before IVIg infusion were correlated with the AUC (rs = −0.724; $P < 0.001$), even after adjustment for aforementioned variables (rs = −0.415; $P = 0.031$).

Although the grip strength remained stable at the advent of each course, there was a transient increase in grip strength from pretreatment to 1 week after treatment (14 patients with CIDP; **Figure 1**), mean dominant hand strength from 53.9 kPa (21.5) to 57.6 kPa (20.3; $P = 0.002$) and mean nondominant hand strength from 48.8 kPa (21.9) to 52.2 kPa (19.5; $P = 0.029$, paired samples test). Because of the considerable variation in disease severity between patients, we opted to calculate the change in grip strength between these two points for every patient. There was a strong correlation between the change in the dominant and the nondominant hand strength 7 days postinfusion (rs = 0.711; $P < 0.001$). Both the ΔIgG (dominant hand r = 0.455; $P = 0.017$; and nondominant hand r = 0.403; $P = 0.037$) and the serum IgG 7 days after infusion correlated with the grip strength (**Figure 5**). When adjusting for age and gender, this correlation remained significant for the nondominant hand (rs = 0.522; $P = 0.007$), but not for the dominant hand (rs = 0.388; $P = 0.055$; Spearman's partial rank-order correlation).

DISCUSSION

This study, as far as we know, for the first time, provides detailed information on the PK of IVIg maintenance treatment of chronic immune-mediated neuropathies. We found that the PK of IVIg in individual patients remained relatively constant in two subsequent courses of unchanged treatment. The PK of IVIg was variable between these patients and was, in part, related to the administered dose and interval. The serum IgG levels reached at 1 week are related to the transient increase in grip strength that occurred during each course of treatment. These findings may indicate that the PK of IVIg is related to the treatment regimen and effectiveness.

This study was conducted in patients with clinically stable CIDP or MMN who were each dependent on IVIg maintenance treatment with a personalized dosage and interval that remained constant during the study. Intravenous IgG treatment resulted in high steady-state serum IgG levels above the normal range values for IgG (>16 g/L) in half of the patients. Even in this (over)saturated state of vast quantities of IgG, there is a steep increase in IgG levels after every infusion, resulting in a peak level within minutes to hours in all patients. This is followed by a fast drop in IgG levels during 1–2 days, as IgG distributes from the central intravascular compartment to the periphery (α-phase). The higher the peak level reached, the faster the decline in IgG levels in the α-phase, shortening the overall half-life of the infused IgG. The subsequent β-phase resulted in an estimated elimination half-life for total IgG ranging from 11–60 days. All patients returned to the same trough level as in the previous course, indicating a steady-state or equilibrium. When only the surplus of IgG above this steady-state level (ΔIgG) is assessed, a much shorter elimination phase half-life of 4–5 days was observed; reconciling with the treatment interval of 2–3 weeks without accumulation of IgG. The peak plasma level and following decline in total IgG denoted great consistency between the two IVIg courses in individual patients. However, the IVIg PK showed a considerable variation between patients with half-lives differing up to sixfold and interpatient variability calculated as relative dispersion

(CV) often ≥30%. These observed interpatient variations are in accordance with literature for endogenous IgG as well as monoclonal antibodies.[20]

The total IgG half-life of ~23 days observed in the current study is somewhat shorter than reported in literature (28–45 days).[18,21–23] Most of these PK studies of IVIg were conducted in patients with immunodeficiency with a reduced endogenous IgG production. In contrast, patients with untreated immune-mediated neuropathies typically have normal serum IgG levels. Administering additional IgG through IVIg results in high steady-state levels and a relatively low volume of distribution, reflecting the saturation of the body with IVIg. In the current study, all patients reached supraphysiological serum IgG levels after the administration of IVIg with peak levels of up to 41 g/L. The higher this peak, the shorter the IgG half-life, owing to the concentration-dependent PK of IVIg via saturation of the neonatal Fc-receptor.[24] In a study on the safety of an IVIg preparation in healthy volunteers with normal serum IgG levels, an elimination half-life of IgG of 22.4 days was found.[25] Implicating that, compared with healthy controls, patients with active but stable immune-mediated neuropathy do not have a higher IgG turnover.

IgG1 and IgG2 subclass kinetics resembled the total IgG level, in accordance with literature.[18,22] In general, half-lives of IgG3 and IgG4 were also comparable to the major serum subclasses in this study, with some minor deviations. Previous studies demonstrated widely differing half-lives for the two minor serum IgG subclasses.[18,22] Of these, IgG3 is known to have a shorter half-life than other subclasses, owing to the lower affinity binding to the IgG recycling receptor neonatal Fc-receptor.[26] Allotypic variation can bestow the IgG3 molecule with the same binding capacity, and half-life as the other subclasses.[27] Arguably, this rare allotype of IgG3 is present in the pooled IVIg product and could build up. Still, it is more likely that the relatively low serum level for the minor IgG subclasses combined with endogenous production skewed the observed apparent elimination half-lives. This can also be deduced from the higher clearance of IgG3 compared with the other subclasses, and explain the overall slightly higher IgG4 levels.

All PK parameters remained stable between the two courses in individual patients, which are in agreement with the stable peak levels after IVIg found previously.[13] However, the PK of IVIg showed a substantial difference between the patients. About half of the variation could be attributed to the IVIg dose and interval, which differ considerably between patients reflecting the practice to adjust the maintenance treatment based on the clinical response. Still, when adjusting the AUC (the "exposure" to the IVIg) for the infusion interval and matching patients for similar doses, considerable interpatient variability is present. These variations in IVIg PK have been known ever since the first products became available, but, to date, there is no satisfying explanation.[20,28] In the current study, after adjustment of the treatment dose and interval, the PK of IVIg did not correlate with anthropometrics in accordance with previous findings.[13,14] Interestingly, the observed differences in AUC of the surplus IgG correlated with the serum albumin level shortly before the next infusion. Recycling of both proteins is mediated by the same neonatal Fc-receptor-receptor.[29] For GBS, we also found an apparent relationship between serum levels of IgG and albumin.[30]

We conducted an noncompartmental analysis instead of a nonlinear mixed effects data analysis considering that all patients were sampled frequently at standardized time points and the patients were clinically stable on fixed regimens of IVIg. Despite the multiple time points over two courses in the same patients, more frequent sampling and more standardized dosing would have resulted in a higher accuracy of PK values. In addition, to acquire a more accurate estimate of IVIg half-life, a sampling period of at least several half-lives (in this study ~23 days) without administration of IVIg would have been required.[31] All of the above was either logistically or ethically not feasible. The half-lives calculated here do not factor in endogenous IgG production, which could skew elimination half-lives, even when assessing the ΔIgG.[31] In order to mitigate any effects of fluctuating disease severity on the PK of IVIg, we included patients who were dependent on regular infusions, but with a relatively stable disease state. Still, minor fluctuations in grip strength were detected by Vigorimeter during the course interval, with most patients with CIDP slightly increasing in grip strength 7 days after IVIg infusion. At that time point, a higher total serum IgG level correlates with a higher increase in grip strength of both hands. It is appropriate to issue certain caveats with this finding; the number of patients assessed was relatively low and so were the changes in grip strength at day 7 (given their stable disease under maintenance treatment, often lower than the minimum clinically important difference of >8 kPa).[32] In addition, because it was not the primary objective of this study, we did not measure grip strength for all patients at all time points throughout the whole study period. Therefore, no definitive statement can be made whether the interpatient PK differences translate to a variable PD response to IVIg. However, we observed an interesting relationship between the PK of IVIg and the PD defined by grip strength. Further studies are required to determine to what extent serum IgG levels could predict the clinical response to IVIg.

METHODS

Patients

Fifteen patients with chronic immune-mediated neuropathy were included in the study between April 2014 and October 2015. In this group of patients, 14 fulfilled the diagnostic criteria for CIDP and one for MMN.[33–35] All patients had active disease and were dependent on IVIg, as indicated by previous attempts to reduce the dosage in all cases followed by clinical deterioration. During the study period, all patients had a stable clinical condition and the treatment regimen of IVIg was not changed. Intravenous IgG was administered either within the Erasmus University Medical Center or via homecare treatment and, as a standard of care in our expertise center, the regimen was previously tapered down to the minimal effective dose and interval to maintain clinical stability. Intravenous IgG dependency was tested within 1 year before inclusion either by further tapering down the dose or cessation of IVIg treatment. All patients gave written informed consent and the study protocol was approved by the local Medical Ethics Committee.

Sample collection and measurements

Blood samples were collected during two subsequent courses of IVIg, including at seven to nine standard time points per course (depending on the treatment interval): shortly before infusion, after 15 min, 2 and 24 h, and after 2, 7, 10, 14, and 21 days. To assess the clinical stability,

we determined the grip strength by handheld Martin Vigorimeter (values used are an average of three assessments), and the Rasch-built overall disability scale and Rasch-built Fatique Severity Scale at the start of each infusion.[36,37] Blood samples were centrifuged immediately after collection and stored aliquoted at -80°C until use. Aliquots of each of the 220 serum samples were thawed and IgG (including subclasses IgG1 to IgG4) and albumin levels were measured by nephelometry (IMMAGE 800 Immunochemistry System, Beckman-Coulter, Jersey City, NJ).[38] Within run CV was <1% and between run CV 2–4%.

Statistics

The peak increase in serum IgG level was compared to the "steady state" (trough) level shortly before the next infusion and the difference defined as ΔIgG. Primary and secondary PK parameters were calculated using PKSolver's version 2.0 noncompartmental analysis tool for infusion (Linear up – Log down) or the two-compartmental option (ΔIgG).[19] The CV or the CQD (for non-normally distributed data) are defined, respectively, by the ratio of the SD to the mean, or the third quartile minus the first quartile divided by the sum of these $((Q_3-Q_1)/(Q_3+Q_1))$; both multiplied by 100%.[39] In case of non-normal distribution of the data, correlations were assessed using the Spearman Rank-Order correlation with comparisons made using the Wilcoxon Signed-Rank test. Statistical analyses were performed with SPSS version 22.0 and GraphPad Prism version 7.0. A two-sided P value of < 0.05 was considered as significant.

Additional Supporting Information may be found in the online version of this article.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

W.J.R.F., B.C.P.K., P.A.D., T.G., and B.C.J. wrote the manuscript. W.J.R.F., P.A.D., T.G., and B.C.J. designed the research. W.J.R.F. and C.R.B.R. performed the research. W.J.R.F., C.R.B.R., and B.C.J. analyzed the data. C.R.B.R. contributed new reagents/analytical tools.

1. Hughes, R. The role of IVIg in autoimmune neuropathies: the latest evidence. *J. Neurol.* **255** (suppl. 3), 7–11 (2008).
2. Gorson, K.C. An update on the management of chronic inflammatory demyelinating polyneuropathy. *Ther. Adv. Neurol. Disord.* **5**, 359–373 (2012).
3. Hughes, R.A. *et al*. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol.* **7**, 136–144 (2008).
4. Joint Task Force of the, EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First Revision. *J. Peripher. Nerv. Syst.* **15**, 1–9 (2010).
5. Rajabally, Y.A. Long-term immunoglobulin therapy for chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve* **51**, 657–661 (2015).
6. Broyles, R., Rodden, L., Riley, P. & Berger, M. Variability in intravenous immunoglobulin G regimens for autoimmune neuromuscular disorders. *Postgrad. Med.* **125**, 65–72 (2013).
7. Wakerley, B.R. & Yuki, N. Monitoring intravenous immunoglobulin dosing regimens in chronic inflammatory demyelinating polyneuropathy: search for a biomarker. *J. Neurol. Neurosurg. Psychiatry* **84**, 830 (2013).
8. Querol, L. *et al*. Long–term outcome in chronic inflammatory demyelinating polyneuropathy patients treated with intravenous immunoglobulin: a retrospective study. *Muscle Nerve* **48**, 870–876 (2013).
9. Kokubun, N., Sada, T., Yuki, N., Okabe, M. & Hirata, K. Optimization of intravenous immunoglobulin in chronic inflammatory demyelinating polyneuropathy evaluated by grip strength measurement. *Eur. Neurol.* **70**, 65–69 (2013).
10. Iijima, M. *et al*. Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP. *Neurology* **64**, 1471–1475 (2005).
11. Berger, M. & Allen, J.A. Optimizing IgG therapy in chronic autoimmune neuropathies: a hypothesis driven approach. *Muscle Nerve* **51**, 315–326 (2015).
12. Kuitwaard, K. *et al*. Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barré syndrome. *Ann. Neurol.* **66**, 597–603 (2009).
13. Kuitwaard, K. *et al*. Serum IgG levels in IV immunoglobulin treated chronic inflammatory demyelinating polyneuropathy. *J. Neurol. Neurosurg. Psychiatry* **84**, 859–861 (2013).
14. Rajabally, Y.A., Wong, S.L. & Kearney, D.A. Immunoglobulin G level variations in treated chronic inflammatory demyelinating polyneuropathy: clues for future treatment regimens? *J. Neurol.* **260**, 2052–2056 (2013).
15. Vlam, L. *et al*. Pharmacokinetics of intravenous immunoglobulin in multifocal motor neuropathy. *J. Neurol. Neurosurg. Psychiatry* **85**, 1145–1148 (2014).
16. Cocito, D. *et al*. Subcutaneous vs. intravenous immunoglobulin in CIDP: pharmacokinetic and clinical response. *J. Peripher. Nerv. Syst.* **21**, 114–116 (2016).
17. Schroeder, H.W. Jr & Cavacini, L. Structure and function of immunoglobulins. *J. Allergy Clin. Immunol.* **125** (2 suppl. 2), S41–S52 (2010).
18. Bonilla, F.A. Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes. *Immunol. Allergy Clin. North Am.* **28**, 803–819 (2008).
19. Zhang, Y., Huo, M., Zhou, J. & Xie, S. PKSolver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. *Comput. Methods Programs Biomed.* **99**, 306–314 (2010).
20. Gill, K.L., Machavaram, K.K., Rose, R.H. & Chetty, M. Potential sources of inter-subject variability in monoclonal antibody pharmacokinetics. *Clin. Pharmacokinet.* **55**, 789–805 (2016).
21. Koleba, T. & Ensom, M.H. Pharmacokinetics of intravenous immunoglobulin: a systematic review. *Pharmacotherapy* **26**, 813–827 (2006).
22. Wasserman, R.L. *et al*. Pharmacokinetics of a new 10% intravenous immunoglobulin in patients receiving replacement therapy for primary immunodeficiency. *Eur. J. Pharm. Sci.* **37**, 272–278 (2009).
23. Bonilla, F.A. Intravenous and subcutaneous immunoglobulin G replacement therapy. *Allergy Asthma Proc.* **37**, 426–431 (2016).
24. Waldmann, T.A. & Strober, W. Metabolism of immunoglobulins. *Prog. Allergy* **13**, 1–110 (1969).
25. Thürmann, P.A., Sonnenburg-Chatzopoulos, C. & Lissner, R. Pharmacokinetic characteristics and tolerability of a novel intravenous immunoglobulin preparation. *Eur. J. Clin. Pharmacol.* **49**, 237–242 (1995).
26. Stapleton, N.M. *et al*. Competition for FcRn-mediated transport gives rise to short half-life of human IgG3 and offers therapeutic potential. *Nat. Commun.* **2**, 599 (2011).
27. Vidarsson, G., Dekkers, G. & Rispens, T. IgG subclasses and allotypes: from structure to effector functions. *Front. Immunol.* **5**, 520 (2014).

28. Pirofsky, B., Campbell, S.M. & Montanaro, A. Individual patient variations in the kinetics of intravenous immune globulin administration. *J. Clin. Immunol.* **2** (2 suppl.), 7S–14S (1982).
29. Roopenian, D.C. & Akilesh, S. FcRn: the neonatal Fc receptor comes of age. *Nat. Rev. Immunol.* **7**, 715–725 (2007).
30. Fokkink, W.R., Walgaard, C., Kuitwaard, K., Tio-Gillen, A.P., van Doorn, P.A. & Jacobs, B.C. Association of albumin levels with outcome in intravenous immunoglobulin-treated Guillain-Barré syndrome. *JAMA Neurol.* **74**, 189–196 (2017).
31. Schiff, R.I. & Rudd, C. Alterations in the half-life and clearance of IgG during therapy with intravenous gamma-globulin in 16 patients with severe primary humoral immunodeficiency. *J. Clin. Immunol.* **6**, 256–264 (1986).
32. Merkies, I.S., van Nes, S.I., Hanna, K., Hughes, R.A. & Deng, C. Confirming the efficacy of intravenous immunoglobulin in CIDP through minimum clinically important differences: shifting from statistical significance to clinical relevance. *J. Neurol. Neurosurg. Psychiatry* **81**, 1194–1199 (2010).
33. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. *Neurology* **41**, 617–618 (1991).
34. Van den Bergh, P.Y. *et al*. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision. *Eur. J. Neurol.* **17**, 356–363 (2010).
35. Van den Berg–Vos, R.M., Franssen, H., Wokke, J.H., Van Es, H.W. & Van den Berg, L.H. Multifocal motor neuropathy: diagnostic criteria that predict the response to immunoglobulin treatment. *Ann. Neurol.* **48**, 919–926 (2000).
36. van Nes, S.I. *et al*. Improving fatigue assessment in immune-mediated neuropathies: the modified Rasch-built fatigue severity scale. *J. Peripher. Nerv. Syst.* **14**, 268–278 (2009).
37. van Nes, S.I. *et al*. Rasch-built overall disability scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology* **76**, 337–345 (2011).
38. Benard, C., Chauzeix, J., Blancher, A. & Puissant–Lubrano, B. Analytical performances of SPAPLUS® turbidimeter for the quantification of albumin and IgG in serum and cerebrospinal fluid. *Clin. Biochem.* **49**, 828–831 (2016).
39. Bonett, D.G. Confidence interval for a coefficient of quartile variation. *Comput. Stat. Data Anal.* **50**, 2953–2957 (2006).