A Prospective, Two-Phase Study of Intravenous Immunoglobulin (IVIG) in Hypogammaglobulinemia: Pharmacokinetic Characterization and a Dosing Nomogram

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ABSTRACT

Background: Shortages of IV immunoglobulin (IVIG) and other blood products are a concern. Individualized IVIG dosing is needed to ensure optimal patient outcomes and to minimize wasting of IVIG.

Objective: To characterize IVIG pharmacokinetics in patients with primary hypogammaglobulinemia and to apply this information in testing the validity of a dosing nomogram.

Methods: In phase I of the study, the pharmacokinetics of IVIG were determined by obtaining blood from 15 patients for testing of serum immunoglobulin G (IgG) concentration 30 min before an IVIG dose and 30 min and 1, 2, 3, and 4 weeks after. In phase II of the study, steady-state trough serum IgG concentration was measured for 16 patients, and individualized doses were determined according to a nomogram designed to target a serum IgG concentration of 7 g/L. Serum IgG concentrations were determined before each of 6 infusions of IVIG, and the IVIG dose was adjusted if necessary. A health-related questionnaire was completed by each patient.

Results: The decline in serum IVIG concentrations was monoexponential (displaying first-order pharmacokinetics). In phase II, the IVIG dose was decreased for 7 patients and increased for 1 patient on the basis of the nomogram. There was a significant relationship between predicted and actual trough serum IgG concentrations (r^2 = 0.656, $p < 0.05$), with a relatively low percent prediction error (8.7%). No notable trends were observed in the answers to health-related questions for the patients in the study.

Conclusions: The sampling strategy used in this study indicated that IVIG elimination follows first-order pharmacokinetic principles. A nomogram derived from these pharmacokinetic data can be used to individualize IVIG dosing.

Key words: hypogammaglobulinemia, IV immunoglobulin, pharmacokinetic parameters, nomogram

RÉSUMÉ

Historique : Les pénuries d'immunoglobuline pour administration intraveineuse (IGIV) et d'autres produits du sang soulèvent des inquiétudes. Il est essentiel d'individualiser les posologies d'IGIV pour optimiser l'évolution de l'état de santé des patients et pour réduire au minimum le gaspillage d'IGIV.

Objectif : Caractériser la pharmacocinétique de l'IGIV chez les patients présentant une hypogammaglobulinémie primaire et utiliser les renseignements obtenus pour tester la validité d'un nomogramme posologique.

Méthodes : Au cours de la phase I de l'étude, on a déterminé la pharmacocinétique de l'IGIV chez 15 patients en évaluant les concentrations plasmatiques d'immunoglobuline G (IgG) à partir d'échantillons de sang obtenus 30 minutes avant puis 30 minutes et 1, 2, 3 et 4 semaines après l'administration de la dose d'IGIV. Au cours de la phase II de l'étude, on a mesuré la concentration plasmatique minimale de l'IgG à l'état d'équilibre chez 16 patients, puis déterminé la posologie individuelle selon un nomogramme conçu pour atteindre une concentration plasmatique d'IgG de 7 g/L. Les concentrations plasmatiques d'IgG ont été mesurées avant chacune des six perfusions d'IGIV, et la dose d'IGIV a été ajustée, au besoin. Chaque patient a rempli un questionnaire lié à la santé.

Résultats : La diminution des concentrations plasmatiques d'IGIV était monoexponentielle (suivant une cinétique de premier ordre). Dans la phase II, la dose d'IGIV a été réduite chez 7 patients et augmentée chez 1 patient, d'après le nomogramme. On a observé une relation significative entre les concentrations plasmatiques minimales d'IgG prévues et réelles (r^2 = 0,656, $p < 0.05$), et un taux d'erreur de prévision relativement faible (8,7 %). On n'a cependant observé aucune tendance remarquable dans les réponses des patients de l'étude au questionnaire lié à la santé.

Conclusion : La stratégie d'échantillonnage utilisée dans cette étude montre que l'élimination de l'IGIV suit les principes de cinétique de premier ordre. Un nomogramme dérivé de ces données pharmacocinétiques peut être utilisé pour individualiser la posologie de l'IGIV.

Mots clés : hypogammaglobulinémie, immunoglobuline intraveineuse, paramètres pharmacocinétiques, nomogramme

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INTRODUCTION

The role of immunoglobulin preparations has expanded immensely over the past 2 decades, since development of products that are safe for IV administration.[1] IV immunoglobulin (IVIG) is now widely used for the treatment of primary immunodeficiency diseases such as X-linked agammaglobulinemia, common variable immunodeficiency, and immunoglobulin G (IgG) deficiency with increased immunoglobulin M (IgM).[1-3] The success of IVIG therapy in the management of these deficiencies has led to investigations for its use in secondary immunodeficiency diseases developing from malignancy, nephrotic syndrome, trauma, surgery, shock, burns, and prematurity and after bone marrow transplantation.[3,4] Several case reports and preliminary studies have also reported the use of IVIG in noninfectious diseases including myasthenia gravis, coagulopathies, and neuropathies.[4]

Currently, IVIG is the mainstay of treatment for hypogammaglobulinemia. The development of advanced purification techniques, fewer reports of adverse effects, and the use of higher doses has led to a dramatic increase in IVIG usage for this type of immunodeficiency. Widespread use of this blood product, however, has led to worldwide shortages and, consequently, high acquisition costs. For an adult patient requiring immune-modulating therapy, the cost of IVIG regularly exceeds Can$10,000 per treatment course.[5] These shortcomings have led to research directed at improving prescribing patterns and preventing overuse.

Dose selection of IVIG for hypogammaglobulinemia is largely empiric. Several studies comparing doses have reported various results, with clinical response occurring in a dose range of 200 to 600 mg/kg administered every 4 weeks.[6-8] Current recommendations suggest that IVIG be administered on a milligram per kilogram basis, and therefore dosing is entirely weight-based.[1] The disadvantage of this method is that it does not take account of the differing degrees of gammaglobulin deficiencies that exist or the wide variation in pretreatment serum IgG concentrations.[3] In addition, the IVIG dose required for prevention of symptoms varies greatly between patients.[2,3,9] Therefore, individualization of IVIG doses is highly desirable.[3] Moreover, dosage adjustments are currently based solely on subjective responses, and dose increments are arbitrary. As a result, there is a potential for misuse of IVIG and excess drug administration to some patients.

Serum IVIG concentrations can be used to monitor a patient's response to therapy. While there is general agreement in the literature that serum IVIG concentrations should be greater than 5 g/L, the optimal target serum concentration to minimize the risk of infection in primary antibody deficiencies is not known.[9,10] Studies have shown a decrease in the incidence of infections associated with trough serum IgG concentrations of >4 g/L,[7] 5 g/L[6,11] 5–8 g/L[12] and >8 g/L.[13] However, there is no evidence that even if trough serum IgG concentrations are elevated to normal physiologic values, there is a reversal of long-term damage.[3] For patients who experience more than 2 infections per year, Eijkhout and others[12] recommended initiation of a standard IVIG dose (300 mg/kg every 4 weeks); they also suggested using serum IVIG concentrations to guide dosage titration to achieve serum concentrations of up to 9.4 g/L (increasing by increments of 1 to 1.5 g/L). Higher doses were not recommended for initial therapy because of the risk of adverse effects, as well as the cost implications.

The half-life of IgG ranges from 23 to 32 days. IgG is primarily cleared by cells of the reticuloendothelial system.[3,14] The catabolism of IgG is extremely variable in patients with primary immunodeficiency diseases, and therefore the half-life may sometimes be longer.[3] Few studies of IVIG clearance, half-life, or other pharmacokinetic characteristics have been performed in this population. Such information is needed to explore alternative ways to individualize dosing of IVIG according to each patient's metabolic response. If a target trough serum concentration is identified before initiation of therapy, knowledge of the drug's pharmacokinetic characteristics will facilitate prediction of the IVIG dose required by specific patients to achieve the desired target serum concentration. In addition, knowledge of the pharmacokinetic characteristics of IVIG will provide data with which to predict trough serum IgG concentrations expected as a result of a dosage change in patients for whom serum IVIG concentration is at steady state. Furthermore, some patients may be receiving more IVIG than necessary to remain symptom-free, as a result of the absence of methods to optimally individualize dose selection. Development of a nomogram with which to select individualized doses, based on a desired target trough serum concentration, would allow IVIG therapy to be individualized and IVIG overuse to be minimized.

The purposes of this study were to characterize the pharmacokinetics of IVIG in patients with primary hypogammaglobulinemia and to use this information to test the validity of a dosing nomogram for tailoring IVIG dose selection to achieve a common trough serum IgG concentration of 7 g/L.

METHODS

Design

Following approval from the ethics review board at St Paul's Hospital in Vancouver, British Columbia, a convenience sample of 15 patients was enrolled in phase I of this study between May 1999 and June 2000. Separate approval from the review board was obtained for phase II of the study, into which a convenience sample of 16 patients was enrolled between April 2001 and August 2002.

Population

All patients in both study phases were enrolled from within the Department of Hematology at St Paul's Hospital and provided written informed consent. Inclusion criteria were prior confirmed diagnosis of primary hypogammaglobulinemia, older than 19 years of age, currently receiving between 15 and 30 g (0.3 and 0.4 g/kg) IVIG (Gamimune N, Bayer Healthcare, Toronto, Ontario; or Gammagard, Baxter Corporation, Mississauga, Ontario) every 3 or 4 weeks, and no dosage change within the previous 6 months. Patients were excluded if they were receiving IVIG for indications other than primary hypogammaglobulinemia or if they had conditions such as a chronic active disease (AIDS, hepatitis, malignant condition, gastrointestinal disorder) that might alter pharmacokinetic parameters.

Study Protocol

Phase I was a prospective, open-label study. Blood for determination of trough serum IgG concentrations was collected into serum separator Vacutainer tubes (Becton-Dickson, Franklin Lakes, New Jersey) within 30 min before administration of the patient's regularly scheduled IVIG dose. Patients received IVIG over 2 to 6 h at the regularly scheduled time of administration. Additional blood samples were obtained at 30 min and 1, 2, 3, and 4 weeks after administration of the dose (but the 4-week post-dose sample was not available for patients who regularly received IVIG every 3 weeks). These sampling times were selected to obtain a minimum of 4 samples throughout one estimated half-life or dosing interval. Specimens were centrifuged at approximately 3500 rpm for 10 min, after which the serum was harvested and refrigerated at 2°C to 8°C until analyzed. Serum IgG concentrations were measured by rate nephelometry using a nephelometer analyzer (Beckman Array model 360, Behring).[15] Rate nephelometry involves detecting the amount of light scattered by bound haptoglobulin and comparing it to a reference range to determine IgG concentration. The exact analyzer range varies slightly with reagent lot, but varies from approximately 0.40 to approximately 47.0 g/L for IgG. Assay performance was monitored with 4 quality control serum samples with known IgG concentration, all with coefficients of variation less than 5%.

Pharmacokinetic parameters (area under the curve [AUC], maximal concentration [C_{max}], minimal or trough concentration [C_{min}], apparent elimination rate constant [k], and apparent elimination half-life [$t_{1/2}$]) were calculated by traditional noncompartmental analyses. Specifically, AUC was determined via the trapezoidal rule, C_{max} and C_{min} were determined by direct observation of the data, k was calculated by least-squares regression of the log serum concentrations in the log-linear phase (i.e., the last 4 or 5 log concentration–time points), and $t_{1/2}$ was calculated as 0.693/k.

Phase II was a prospective, single-blind study. Blood for determination of trough serum IgG concentration was obtained before administration of each patient's regularly scheduled IVIG dose. Trough serum concentration data were used to determine each patient's study dose at the next scheduled infusion date. The study dose was determined according to the nomogram shown in Table 1. The nomogram was developed using first-order pharmacokinetic principles (confirmed from data obtained in phase I of the study) and was designed to achieve target trough serum IgG concentrations of 7 g/L (range 6.4–7.6 g/L). For the purposes of this study, the target trough serum IgG concentration of 7 g/L was chosen on the basis of clinical experience at St Paul's Hospital and because it is the median value of the recommended ranges in the literature.[6,7,11-13] Using each patient's prestudy dose and the measured trough serum IgG concentration, a new dose for a target trough serum concentration of 7 g/L was calculated by direct proportion. According to this principle, a set of multiplication factors was calculated for any given trough serum IgG concentration and used to develop the nomogram presented in Table 1.

Implementation of the calculated study dose resulted in an increase, decrease or no change in the current dose. Doses were rounded to the nearest 5 g because of product availability. To ensure that patients remained blinded to the dose of IVIG that they were receiving, the blood bank did not print the study dose on the IVIG label. Gamimune N IVIG was administered over 4 to 6 h, and this infusion was designated as infusion 1. Patients received the study dose for a total of 6 infusions according to their usual 3- or 4-week administration

Table 1. IV Immunoglobulin Dosing Nomogram (for Starting Doses of 15 g, 20 g, 25 g, 30 g)

Trough Serum Concentration (g/L)	Current Dose Multiplication Factor
<3.3	2.30
3.3–3.6	2.00
3.7–3.8	1.85
3.9–4.1	1.75
4.2–4.3	1.65
4.4–4.6	1.55
4.7–4.9	1.45
5.0–5.1	1.40
5.2–5.3	1.35
5.4–5.5	1.30
5.6–5.9	1.25
6.0–6.1	1.15
6.2–6.3	1.12
6.4–7.6	1.00
7.7–7.8	0.90
7.9–8.0	0.88
8.1–8.3	0.85
8.4–9.3	0.75
9.4–10.0	0.70
10.1–11.2	0.65
11.3–12.0	0.60
12.1–14.1	0.55
14.2–18.8	0.40
>18.8	0.35

schedule. Blood for determination of trough serum IgG concentrations was obtained within 30 min before the scheduled infusion time for each of the 6 infusions. All serum IgG concentrations were measured and analyzed as described for phase I.

Patients were asked to complete health-related questionnaires at the time of each IVIG infusion (Appendix 1). At the end of the study, patients were given the choice to remain on the study dose or return to the prestudy dose.

The correlation between predicted and measured trough concentrations was assessed by simple linear regression. Statistical significance was defined a priori as $p < 0.05$. Percent prediction error (%PE) in trough serum concentrations was used to assess predictive performance. The %PE was calculated according to the following formula:

$$\%PE = 100 \times \frac{(\text{predicted trough} - \text{actual trough})}{\text{actual trough}}$$

A mean %PE greater than 15% was arbitrarily defined as unacceptable. Because the health-related questionnaire was used to complement the pharmacokinetic data and was not measuring a primary study objective, descriptive statistics were used to characterize its results.

Table 2. Patient Characteristics

Characteristic	Phase I (n = 15)	Phase II (n = 16)
Age (years)		
Range	37–66	27–84
Mean ± SD	50 ± 10	59 ± 14
Sex		
Female	12	10
Male	3	6
IVIG Dose (g)		
Range	15–35	20–25
Mean ± SD	22.0 ± 4.6	21.2 ± 2.2
Dose Frequency		
Every 3 weeks	3	5
Every 4 weeks	12	11

SD = standard deviation, IVIG = intravenous immunoglobulin.

RESULTS

Patient Characteristics

The characteristics of the 15 participants in phase I and the 16 participants in phase II are summarized in Table 2. Seven of the patients who participated in phase I were also participants in phase II. Altogether, data from 14 patients in phase I and 14 patients in phase II were used in the final pharmacokinetic analyses. Fourteen patients completed phase I of the study; the 15th patient did not return to have blood samples drawn at 3 and 4 weeks after the IVIG infusion, and this patient's data were excluded from the pharmacokinetic analysis. One patient voluntarily withdrew from phase II of the study after the third infusion of the study dose because of a persistent sinus infection. Data for this patient were not included in the phase II analysis. Another patient did not adhere to scheduled infusion dates and times during phase II, and this patient's data were also excluded from the phase II analysis. Serum IgG concentrations were determined to be at steady state in all patients, because trough serum IgG trough concentrations were within 10% of one another before 2 consecutive IVIG doses.

Phase I

The pharmacokinetic parameters calculated from the 14 patients who participated in phase I are presented in Table 3. There was wide interpatient variability in IVIG pharmacokinetic parameters. The plot of serum IgG concentration versus time (Figure 1) showed a monoexponential decline (i.e., first-order pharmacokinetics). However, the dosing interval was shorter than the calculated $t_{1/2}$ in 9 patients.

Table 3. Pharmacokinetic Parameters of IV Immunoglobulin (n = 14)

	C_{max} (g/L)	C_{min} (g/L)	k (h^{-1})	$t_{1/2}$ (days)	AUC (g • h/L)	Dose-Normalized AUC* (g • h/L)
Mean	14.7	8.0	0.0009	34.9	6382.4	300.6
Median	15.2	8.5	0.0008	37.5	5950.0	290.9
SD	2.0	2.2	0.0004	12.4	1688.9	96.2
Minimum	11.8	4.8	0.0005	16.2	3699.7	148.0
Maximum	19.1	12.9	0.0018	56.4	9866.1	493.3

C_{max} = maximum serum concentration of immunoglobulin G (IgG) , C_{min} = minimum (trough) serum IgG concentration,
k = elimination rate constant, $t_{1/2}$ = elimination half-life, AUC = area under the serum concentration–time curve, SD = standard deviation.
*Determined as the quotient of AUC and the actual dose.

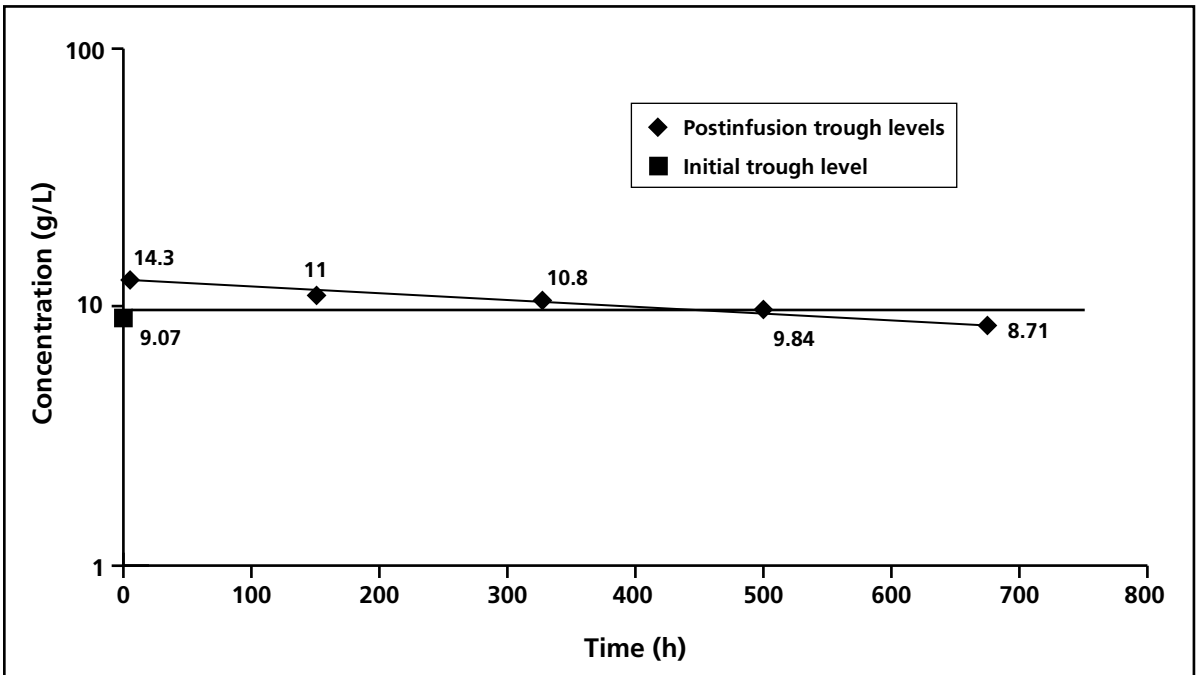

Figure 1. Concentration of immunoglobulin G as a function of time for a representative patient in phase I of the trial (analysis of pharmacokinetic parameters).

In 5 patients, trough serum IVIG concentrations were lower than the target trough concentration of 7 g/L (range 4.8 to 6.9 g/L). In 2 patients, trough serum IgG concentrations were 7.2 and 7.4 g/L, respectively. In the remaining 8 patients, trough serum IgG concentrations were above the target (range 8.6 to 12.9 g/L).

Phase II

Study doses were selected according to the dosing nomogram in Table 1. For 8 patients, serum IgG concentrations were within the target range of 6.4 to 7.6 g/L, and therefore a dose adjustment was not performed. For the 7 patients with trough serum IVIG concentrations above the target range, the IVIG dose was decreased. For the single patient whose serum IgG concentration was below the target range, the dose was increased. For the patients for whom dose adjustments were performed, the IVIG dose was either decreased or increased by 5 g. The patient who withdrew from the study because of a persistent sinus infection had undergone a decrease in IVIG dose. The serum IgG concentrations after the first 3 infusions for this patient were 8.73, 7.61, and 8.08 g/L, respectively.

The results for the 14 patients whose data were analyzed in phase II are presented in Table 4. The mean %PE was 8.7%. Simple linear regression analysis revealed a significant correlation between predicted and measured trough serum IgG concentrations (r^2 = 0.656, $p < 0.05$). No trends were noted in the results of the health-related questionnaire (Table 5). Patients were

Table 4. Accuracy of Dosing Nomogram for Predicting Serum Immunoglobulin G (IgG) Concentrations (*n* = 14)

	Predicted Trough Serum [IgG]	Actual Trough Serum [IgG]	% Prediction Error
Mean	7.4	8.0	8.7
Median	7.5	8.1	7.7
SD	0.6	1.2	6.8
95% CI	7.1–7.7	7.1–8.9	6.1
Minimum	6.5	6.3	0.8
Maximum	8.5	10.2	23.5

SD = standard deviation, CI = confidence interval.

Table 5. Results of Health-Related Questionnaire (*n* = 14)

Visit no.	Self-Rated Health*		No. of Colds		No. of Infections		No. of Admissions to Hospital	
	Median	SD	Mean	SD	Mean	SD	Median	SD
1	3.0	–	0.5	0.7	0.2	0.4	0.0	–
2	2.0	–	0.7	0.9	0.2	0.4	0.0	–
3	3.5	–	0.5	0.7	0.1	0.3	0.0	–
4	3.0	–	0.7	1.0	0.2	0.6	0.0	–
5	3.0	–	0.7	1.0	0.3	0.6	0.0	–
6	3.5	–	0.5	0.7	0.2	0.4	0.0	–

SD = standard deviation.
*Rated from 0 (worst) to 5 (best).

asked to state the duration of each episode of cold symptoms; however, the responses to this part of question 2 were inconsistent or missing altogether, and therefore no analysis was possible.

After completion of the study, 6 of the 7 patients who underwent an IVIG dose decrease asked to remain on the lower study dose. One of these 6 patients requested a further 5-g decrease. The seventh patient was the one who withdrew from the study and reinitiated his prestudy dose. Patients asked to remain on the lower dose (or to have the dose reduced even more) because they detected no increase in symptoms at the lower dose and did not feel it was necessary to increase the dose again. The one patient who underwent a dose increase asked to revert to the lower prestudy dose after completion of the study because there was no perceived additional benefit from the higher dose.

DISCUSSION

The results of this 2-phase study have confirmed that IVIG follows a linear elimination profile and that a dosing nomogram can be derived to guide dose adjustments to achieve a target trough serum IgG concentration in patients with primary hypogammaglobulinemia. The nomogram was validated by the predictability of actual (measured) trough serum concentrations. No serious life-threatening illnesses or admissions to hospital occurred in the patients while they were participating in the study. For all patients, serum IgG concentrations were confirmed to be at steady state, as indicated by the relative consistency (i.e., within 10%) of concentrations between visits (before any dose adjustments).

Eight of the 15 patients in phase I had measured trough serum IgG concentrations that were higher than the chosen target of 7 g/L. This finding confirmed the authors' suspicion that there is a potential overuse of IVIG, since more than half of the patients in this phase of the study were receiving doses that yielded serum IgG concentrations in excess of that required for therapeutic efficacy.[3,12,13]

The nomogram was validated by the significant correlation between predicted and actual trough serum IgG concentrations and by a relatively low percent prediction error. Continued control of symptoms was evident during the study, as indicated by the number of reported cold symptoms (runny nose, cough, fever), antibiotic prescriptions, and admissions to hospital. One patient withdrew from this phase of the study and could not be included in the statistical analysis. This patient

developed persistent flu-like symptoms, which might have been attributable to the 5-g reduction in IVIG dose during the study. It was postulated that this patient might have been extremely sensitive to any dosage change in IVIG or the persistent flu might have developed at the prestudy dose, because serum IgG concentrations were fairly consistent over the course of this patient's 3 study infusions.

A study duration of 6 infusions was deemed appropriate for phase II, given the findings in phase I. The average half-life of IVIG was 35 days, and ranged from 16 to 56 days. Therefore, time to reach steady state after a dosage change is approximately 5 months on average (5 half-lives). Moreover, it is likely that less time was required to achieve therapeutic serum IgG concentrations than would be the case for patients initiating IgG therapy, because patients in this study had previously been receiving IVIG and therefore were beyond the loading stage.

Serum IgG concentrations were not above the target trough serum concentration of 7 g/L in all patients. Specifically, 5 patients (33%) in phase I and 1 patient (6%) in phase II had trough serum concentrations below the target level. According to the nomogram, these patients required an increase in dose. Theoretically, however, the potential for identifying patients with serum IgG concentrations below the target trough serum concentration is greater than that for patients with serum IgG concentrations above the target. If a patient's serum IgG concentration is subtherapeutic, there is a greater likelihood that signs and symptoms of disease will be apparent between doses, which would lead the patient to return to the physician for a dose increase. Conversely, if the patient's serum IgG concentration is above the target, but not so high as to result in symptoms of toxicity, the patient would probably not be aware of the situation and might receive more drug than needed for symptom control. Dose adjustment using the nomogram presented here has the potential to minimize overuse of IVIG.

This dosing nomogram is potentially useful when initiating or adjusting a patient's IVIG dose. In addition, this nomogram could be employed throughout the duration of therapy with IVIG. As a standard, trough serum IgG concentration may be measured at particular intervals to ensure that it remains near the target concentration. An interval of every 6 months is suggested as appropriate for follow-up once the serum IgG concentration has reached the target range. As in usual clinical practice, trough serum concentrations can also be measured if there is a change in the patient's clinical status. However, despite adequate IVIG replacement, infections may occur periodically (as in the general population). Trough serum IgG concentration should be determined when these infections occur more frequently than normal.

Several limitations of this study deserve mention. The sample size was relatively small. In addition, sampling times were limited; the calculated $t_{1/2}$ may not represent purely elimination characteristics; and 7 patients participated in both phase I and phase II. The sampling times were selected to represent at least 4 data points throughout one estimated half-life (or dosing interval). However, because the calculated $t_{1/2}$ was longer than the dosing interval for 9 patients, this value may not represent pure elimination and the $t_{1/2}$ was denoted as "apparent." Similarly, the limited number of blood samples may have precluded observation of a distribution phase (i.e., biphasic, rather than the observed monophasic, decline). Because of the limited study time frame, 7 patients participated in both phases. However, when these 7 patients were excluded from analysis, the predictive performance of the nomogram was relatively unchanged (%PE = 8.4, r^2 = 0.510, $p < 0.05$).

Much previous research has focused on determining the dose of IVIG for optimal therapeutic efficacy. Some studies have assessed relationships between dose and infection rates,[16,17] others have compared methods of administration,[18] and yet others have compared high and low doses of IVIG.[6-8,12] To the authors' knowledge, no studies have focused on determining the optimal serum IgG concentration to achieve the best possible therapeutic efficacy in patients with primary hypogammaglobulinemia. As shown in this study, IVIG dosing by the traditional weight-based method has limitations because of interpatient pharmacokinetic variability. Further research is needed to optimize therapeutic efficacy on the basis of trough serum IgG concentrations and, more specifically, to determine the optimal serum concentration or therapeutic range for achieving the best possible clinical response. This study was designed to establish a method of more accurately estimating target serum IgG concentrations; subsequent studies can build on this work to determine the optimal target serum concentration.

This study has validated a nomogram that uses trough serum IgG concentrations as the basis for dose adjustment for achieving target concentrations in patients with primary hypogammaglobulinemia. This nomogram is patient-specific rather than weight-specific. The advantages of this novel method of dosing are

2-fold. First, the patient benefits from individualized dosing, which potentially minimizes adverse effects by preventing excess exposure to IVIG. Second, by streamlining the use of IVIG, the nomogram may minimize overuse of a drug that is in short supply. Future work is warranted to determine the cost-effectiveness of this approach and to evaluate whether IVIG dose adjustments to attain targeted IgG concentrations lead to improvements in patient health outcomes.

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Appendix 1. Health-Related Questionnaire

1. How do you rate your health since your last infusion? (0 = worst you have ever felt; 5 = best you have ever felt)
2. How many times since your last infusion have you experienced a period of cold symptoms (runny nose, cough, fever) that has affected your daily activities? (State the number of times and the number of days each time lasted.)
3. How many infections have you had requiring antibiotics since your last infusion? (Please explain)
4. How many infections have you had requiring hospitalization since your last infusion? (Please explain)