Serum IgG levels in IV immunoglobulin treated chronic inflammatory demyelinating polyneuropathy

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ABSTRACT

Objective: To determine the variability of serum IgG in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods: All 25 CIDP patients had active but stable disease and were treated with individually optimised fixed dose IVIg regimens. IgG was measured by turbidimetry and variability was defined as coefficient of variation (CV).

Results: The intra-patient variability of the pre-treatment IgG levels, post-treatment levels and increase in serum IgG shortly after IVIg (ΔIgG) was low (mean CV = 3%, 4%, 10%). The inter-patient variability between patients treated with the same dose and interval was low in pre-treatment, post-treatment and ΔIgG level (mean CV = 13%, 11%, 20%). The ΔIgG levels were associated with IVIg dosage ($r_s = 0.78$, $p<0.001$).

Conclusion: Clinically stable CIDP patients show a steady-state in serum IgG after serial IVIg infusions. The low intra- and inter-patient variability in IgG may indicate that constant levels are required to reach this stability.

INTRODUCTION

Intravenous immunoglobulin (IVIg) has been proven effective for Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The precise mechanisms of action are unknown, but the pleiotropic immune-modulating effects of IgG are assumed to be responsible for the therapeutic effect.[1] The optimum dosage and frequency of IVIg to reach a clinically stable situation in CIDP during maintenance treatment differs between patients and varies between 0.4-1.2 g/kg body weight every 2-6 weeks.[2] Currently, the optimum regimen has not been defined and cannot be predicted and needs to be established empirically in clinical practice.[2, 3] The variation in the required dosage and frequency of administration might be partially explained by individual differences in catabolism of IVIg. The aim of this study was to determine the intra-patient and inter-patient variability of serum IgG levels in clinically stable but IVIg-dependent CIDP patients receiving fixed dose maintenance treatment of IVIg.

METHODS

All patients fulfilled the American Academy of Neurology criteria for CIDP and participated in a randomised controlled trial comparing freeze-dried IVIg (Gammagard S/D) with a liquid preparation (Kiovig).[4, 5] All were treated in neuromuscular centers and the dosage and frequency of IVIg was determined by neurologists experienced in treating CIDP. Muscle weakness was defined by the Medical Research Council (MRC) sum score (range 0-60) and Vigorimeter, disability by the overall disability sum score (ODSS) and sensory dysfunction by the INCAT sensory sum score (ISS).[5] Medical ethical approval and informed consent was obtained.[5]

Patients had active CIDP and worsening of symptoms following IVIg reduction within the year before the start of the trial, confirming IVIg dependency.[5] All were treated according to their own individually optimised IVIg dosage and frequency prior to trial entry and these regimens remained constant throughout the trial. To establish the optimal regimen of IVIg, the dosage was increased to achieve the maximal clinical response and the infusion frequency was shortened when patients were experiencing end-of-dose symptoms and signs.[6] Regular attempts to decrease the dose were made as recommended.[6]

Serum IgG concentration (g/L) was determined by turbidimetry. At total IgG levels of 9.0 g/L and 21.5 g/L, the between-run coefficients of variation were respectively 1.6% and 2.6% and the within-run coefficient of variation was <1%.[7] Prior to this study, we had established that peak serum IgG levels were reached 1 minute after infusion, and

remained stable for at least 30 minutes after infusion. In this study, IgG levels were determined in serum samples obtained immediately before and 5 minutes after every infusion. The peak increase in serum IgG after IVIg (ΔIgG) was defined as the IgG level after treatment minus the level just before treatment. The coefficient of variation (CV) was calculated as the ratio of the standard deviation to the mean multiplied by 100 (%). High variability in drugs is generally defined as a CV ≥ 30%.[8]

The ΔIgG of both preparations was compared using Wilcoxon matched-pairs signed-rank test. Correlation was tested with Spearman correlation coefficient (r_s). Analysis was performed using SPSS V.17.0. Two-sided p values <0.05 were regarded significant.

RESULTS

Twenty-seven patients were originally included in the trial. One patient was excluded from this study because of an unusual treatment regimen potentially influencing IgG levels (every other infusion a double dosage) and another because of premature termination of participation. All had been treated successfully with maintenance IVIg before starting the trial (mean 5 years, range 5 months to 13 years).

The ΔIgG after Gammagard infusion was smaller than after Kiovig (median 6.1 g/L (IQR 5-9) vs. 6.8 g/L (6-9), p<0.001), which may in part be attributed to the lower IgG content in Gammagard (95%) compared to Kiovig (~100%). Because of these differences in IgG content and the higher number of Kiovig infusions throughout the trial we focused on the analysis of the IgG values after Kiovig infusions, although a similar low variability in IgG levels was observed after Gammagard. The lowest serum IgG level reached prior to infusion was 9.70 g/L (mean 15.0 g/L; median 15 g/L IQR 13-17) and the minimum ΔIgG level was 3.7 g/L (mean ΔIgG 7.8 g/L; median 7 g/L IQR 6-9). After serial infusions, intra-patient variability was low in pretreatment IgG levels (mean CV 3%, median 4 IQR 3-5), post-treatment levels (mean CV 4%, median 4 IQR 3-4) and ΔIgG levels (mean CV 10%, median 8 IQR 6-12) (Figure 1). Although somewhat larger than the intra-patient variability, the inter-patient variability was small in pre-treatment IgG levels (mean CV 13%, median 8 IQR 4-28), post-treatment IgG levels (mean CV 11%, median 5 IQR 3-20) as well as ΔIgG levels (mean CV 20%, median 14 IQR 9-28) between those patients receiving the same dose and frequency of Kiovig (N = 17, Figure 1, Supplementary Table 1). When we calculated the increase in serum IgG 2 weeks after IVIg in the 13 patients with a frequency of one infusion every 2 weeks the delta IgG was very low and close to zero (mean 0.09 g/L, median 0.07 g/L, range -0.61 till 0.7 g/L), whereas it was much larger in GBS (mean 7.8 g/L) due to the use of a larger dosage in GBS than used in the maintenance IVIg treatment in our CIDP cohort. The 2 week level was unsuitable for this cohort, and therefore, the peak IgG levels were determined shortly after infusion.

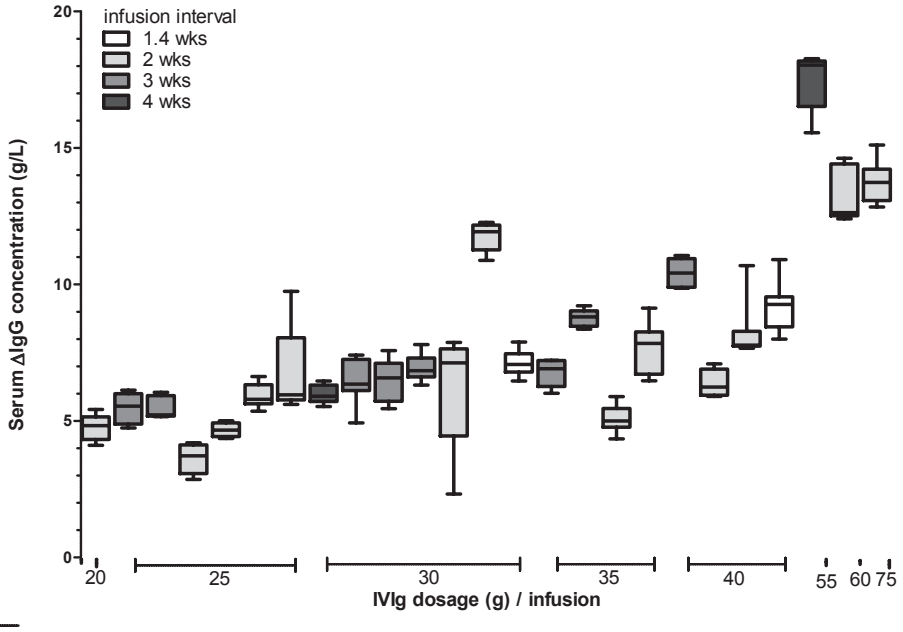

Figure 1. Serum ΔIgG levels in patients receiving maintenance intravenous immunoglobulin (IVIg) treatment (Kiovig, N=25)

ΔIgG = peak increase in serum IgG 5 min after IVIg infusion compared to pretreatment. Box and whisker plots show ΔIgG in 25 different patients, the box indicates 25th-75th percentiles; horizontal line indicates median value and the whiskers indicate minimum and maximum values. Patients are grouped by dosage. The colours of the boxes represent the infusion interval; patients receiving the same dosage and interval are displayed next to each other.

The post-treatment IgG levels and ΔIgG levels were related to the IVIg dosage administered per infusion (r_s = 0.405, p<0.05; r_s = 0.78, p<0.001), but not to the infusion frequency. The total dosage per infusion required to reach a stable clinical state and ΔIgG did not correlate with age, sex, body weight, lean body mass, muscle strength, disability or sensory dysfunction (Supplementary Table 2).[5, 7]

DISCUSSION

We showed that the serum IgG levels before and shortly after serial IVIg infusions were remarkably constant over time in patients with active but stable CIDP on constant maintenance treatment. This indicates that these patients have reached a steady state with a constant distribution rate and turnover of IgG without accumulation over time.

The dosage and frequency of IVIg required to maintain a clinically stable condition differs between CIDP patients, which might be due to interindividual differences in IVIg metabolism. Although there is some inter-patient variability between CIDP patients treated with the same IVIg dose and frequency, the mean CV can still be considered low from a pharmacological perspective which leads us to a different conclusion than previously reported.[9] A higher inter-patient variability in serum IgG levels 2 weeks after a standard course of IVIg has been observed in GBS (CV 31%) and primary immunodeficiency patients.[7, 10] This variation may depend on the activity of the disease, immunological host factors, baseline IgG levels, IgG glycosylation and Fc-receptor polymorphisms.[3, 11, 12] The low inter-patient variability in serum IgG levels we found in CIDP may be explained by the different study design in which none of the CIDP patients were treatment naïve, and all were already known to be IVIg responsive and clinically stable after a previous adjusted regimen of maintenance IVIg treatment. Variation in half-life of IgG is greater among patients with abnormal baseline IgG levels due to its concentration-dependent catabolism. [13, 14] The mean CV in baseline serum IgG level was somewhat lower in the CIDP patients treated with the same dose and interval (CV 13% N = 17) than in GBS (mean CV 28% N=174) (Kuitwaard K, 2009, unpublished data) which might have contributed to the low variability seen in CIDP.[7] Furthermore, the CIDP patients were treated with a lower IVIg dosage than the 2 g/kg used in GBS patients.

In patients with primary immunodeficiency, a minimum level of serum IgG may be required to prevent infections.[10] In GBS, an increase of serum IgG level (about 7.30 g/L) 2 weeks after 2 g/kg IVIg may be required for a better recovery since the increase in the IgG level was independently associated with the ability to walk unaided at 6 months.[7] The results of the current study suggest that a minimum serum IgG level and a minimum increase in serum IgG may be required to induce a clinical response and to reach a stable clinical condition in CIDP. This laboratory finding may be in line with the clinical observation that more than one IVIg course may be required to show improvement in CIDP.[15] We did not include non-responsive or clinically unstable patients in this study; these patients may not have reached this minimum serum IgG level and may benefit from a higher IVIg dosage. Research in these patients is required to define if serum IgG levels can be used as a biomarker to monitor the effect of IVIg treatment.

No factors have been identified so far to predict the optimum regimen for maintenance IVIg treatment in CIDP. [2, 3] Body weight and the degree of disability were not related to the required dose of IVIg, confirming previous reports.[2] Factors other than body weight might determine the optimum dosage, and maintenance IVIg treatment can probably be started at a low dose and should only be increased if required by the clinical situation.[2]

The dose administered was the only factor related to the ΔIgG. The IVIg dosages or ΔIgG levels were not associated with body weight, lean body mass, or severity of disease.

In GBS, we demonstrated an association between disease severity and the increase in serum IgG level at 2 weeks after standard IVIg treatment.[7] This difference may be explained by the fact that in the current study, all patients were in a stable and good neurological condition being treated with optimised regimens.

We have shown that in active but stable CIDP, the inter-patient variability was larger than the intra-patient variability but still considered small. More studies are needed to determine whether unselected treatment-naïve CIDP patients do show a large variability in serum IgG levels after IVIg and if monitoring of serum IgG levels can be used to optimise IVIg treatment regimens in CIDP. Until such time, the reason why CIDP patients require different dosages in their IVIg maintenance treatment remains uncertain.

Supplementary Table 1. Intra- and inter-patient variability in IgG level per subgroup of patients treated with the same dose and interval of IVIg (Kiovig)

	Patient 1	**Patient 2**			**CV of IIV**
Dose/interval (g/wks)	25/3	25/3			
Pre-treatment IgG (g/L)	16.3 (16-17)	15.4 (15-16)			
CV of IOV	3%	2%			4%
Post-treatment IgG (g/L)	22.0 (21-22)	21.1 (20-21)			
CV of IOV	2%	3%			3%
ΔIgG (g/L)	5.5 (5-6)	5.2 (5-6)			
CV of IOV	11%	8%			0.3%
	Patient 3	**Patient 4**	**Patient 5**	**Patient 6**	**CV of IIV**
Dose/interval (g/wks)	25/2	25/2	25/2	25/2	
Pre-treatment IgG (g/L)	15.2 (15-16)	13.6 (13-14)	15.7 (14-16)	16.8 (16-17)	
CV of IOV	5%	7%	6%	3%	9%
Post-treatment IgG (g/L)	21.6 (21-24)	19.3 (19-20)	20.2 (19-21)	20.8 (20-21)	
CV of IOV	7%	4%	4%	3%	6%
ΔIgG (g/L)	6.0 (6-8)	5.8 (6-6)	4.7 (4-5)	3.7 (3-4)	
CV of IOV	25%	7%	6%	15%	26%
	Patient 7	**Patient 8**	**Patient 9**		**CV of IIV**
Dose/interval (g/wks)	30/3	30/3	30/3		
Pre-treatment IgG (g/L)	17.5 (17-18)	12.1 (12-13)	14.3 (14-15)		
CV of IOV	4%	3%	2%		28%
Post-treatment IgG (g/L)	24.1 (24-24)	19.4 (19-20)	20.8 (20-21)		
CV of IOV	2%	3%	6%		20%
ΔIgG (g/L)	6.6 (6-7)	6.8 (7-7)	6.4 (6-7)		
CV of IOV	12%	7%	15%		9%
	Patient 10	**Patient 11**			**CV of IIV**
Dose/interval (g/wks)	30/2	30/2			
Pre-treatment IgG (g/L)	11.1 (11-12)	18.5 (18-19)			
CV of IOV	5%	3%			35%
Post-treatment IgG (g/L)	17.4 (16-19)	30 (30-31)			
CV of IOV	13%	2%			38%
ΔIgG (g/L)	6.3 (5-7)	11.8 (11-12)			
CV of IOV	35%	5%			43%
	Patient 12	**Patient 13**			**CV of IIV**
Dose/interval (g/wks)	35/3	35/3			
Pre-treatment IgG (g/L)	13.5 (13-14)	13.0 (13-13)			
CV of IOV	6%	3%			3%
Post-treatment IgG (g/L)	20.3 (20-21)	21.8 (21-22)			
CV of IOV	4%	2%			5%
ΔIgG (g/L)	6.8 (6-7)	8.8 (8-9)			
CV of IOV	8%	4%			18%

Supplementary Table 1. Intra- and inter-patient variability in IgG level per subgroup of patients treated with the same dose and interval of IVIg (Kiovig) (continued)

	Patient 14	**Patient 15**	**CV of IIV**
Dose/interval (g/wks)	35/2	35/2	
Pre-treatment IgG (g/L)	16.3 (16-17)	14.6 (14-15)	
CV of IOV	2%	3%	8%
Post-treatment IgG (g/L)	21.4 (21-22)	22.2 (22-23)	
CV of IOV	3%	4%	3%
ΔIgG (g/L)	5.1 (5-6)	7.6 (7-8)	
CV of IOV	9%	12%	28%
	Patient 16	**Patient 17**	**CV of IIV**
Dose/interval (g/wks)	40/2	40/2	
Pre-treatment IgG (g/L)	14.4 (14-15)	13.2 (13-14)	
CV of IOV	4%	3%	7%
Post-treatment IgG (g/L)	20.8 (20-21)	21.4 (21-22)	
CV of IOV	4%	4%	2%
ΔIgG (g/L)	6.4 (6-7)	8.2 (8-8)	
CV of IOV	8%	12%	18%

ΔIgG = peak increase in serum IgG 5 minutes after IVIg infusion compared to pre-treatment. Data are presented as medians (IQR). CV = coefficient of variation (mean, %); IIV = inter-individual patient variability; IOV = inter-occasion or intra-patient variability.

Supplementary Table 2. Correlations of IVIg dose and ΔIgG and various patient characteristics

	IVIg dosage (g)	ΔIgG (g/L)
age	r_s = 0.054, p = 0.80	r_s = 0.004 p = 0.98
sex	r_s = -0.120 p = 0.57	r_s = 0.253, p = 0.22
Body weight	r_s = 0.248, p = 0.23	r_s = -0.099, p = 0.64
Lean body mass	r_s = 0.093, p = 0.66	r_s = -0.297, p = 0.15
MRC sum score	r_s = 0.090, p = 0.67	r_s = -0.128 p = 0.54
Vigorimeter	r_s = -0.026, p = 0.90	r_s = -0.18 p = 0.93
ISS	r_s = 0.222, p = 0.29	r_s = 0.336 p = 0.10
ODSS	r_s = 0.101, p = 0.63	r_s = 0.260 p = 0.21
Infusion frequency (days)	r_s = -0.006, p = 0.98	r_s = 0.019, p = 0.93

r_s = Spearman correlation coefficient; MRC = Medical Research Council; ISS = INCAT sensory sum score; ODSS = overall disability sum score

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