# Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barré syndrome

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## ABSTRACT

**Objective:** Intravenous immunoglobulin (IVIg) is the first choice treatment for the Guillain-Barré syndrome (GBS). All patients initially receive the same arbitrary dose of 2 g per kg body weight. Not all patients, however, show a good recovery after this standard dose. IVIg clearance may depend on disease severity and vary between individuals, implying that this dose is suboptimal for some patients. In this study, we determined whether the pharmacokinetics of IVIg is related to outcome in GBS.

**Methods:** We included 174 GBS patients who had previously participated in 2 randomised clinical trials. At entry, all patients were unable to walk unaided and received a standard dose of IVIg. Total IgG levels in serum samples obtained immediately before and 2 weeks after the start of IVIg administration were determined by turbidimetry and related to clinical outcome at 6 months.

**Results:** The increase in serum IgG (ΔIgG) 2 weeks after IVIg treatment varied considerably between patients (mean 7.8 g/L; standard deviation 5.6 g/L). Patients with a low ΔIgG recovered significantly more slowly, and fewer reached the ability to walk unaided at 6 months (log-rank $p<0.001$). In multivariate analysis adjusted for other known prognostic factors, a low ΔIgG was independently associated with poor outcome ($p=0.022$).

**Interpretation:** After a standard dose of IVIg treatment, GBS patients show a large variation in pharmacokinetics, which is related to clinical outcome. This may indicate that patients with a small increase in serum IgG level may benefit from a higher dosage or second course of IVIg.

## INTRODUCTION

Guillain-Barré syndrome (GBS) is a postinfectious polyradiculoneuropathy leading to a rapidly progressive flaccid paresis, followed by a slow and often incomplete recovery. Treatment of GBS is focused on the acute phase of the disease, when the activated immune system damages the peripheral nerves. Plasma exchange (PE) and intravenous immunoglobulin (IVIg) are equally effective in GBS, but IVIg is more widely available and has less side-effects.[1-3] IVIg is also an important treatment for patients with immune deficiencies and various other forms of autoimmune disease.[4,5] IVIg has pleiotropic immune-modulating effects, including saturation of Fcγ-receptors, neutralisation of autoantibodies and cytokines and inhibition of complement activation.[6] Which, if any, of these immunological actions provide the therapeutic effect of IVIg in GBS is as yet unknown.

IgG is the major component of IVIg and probably responsible for most of the immune-modulating effects.[4] Pharmacokinetic studies on serum IgG levels after IVIg treatment have been conducted predominantly in patients with immune deficiencies. These studies suggest that IgG levels peak at 3 days after IVIg treatment and have a half-life of 18 to 32 days.[6] However, patients show a considerable variability in pharmacokinetics after treatment, which may influence the efficacy of IVIg.[7] The variability in pharmacokinetics in patients with normal immunoglobulin levels, as in GBS, has been less well defined and the optimum therapeutic serum IgG concentration is unknown.[7] The pharmacokinetics might partly explain the diversity in clinical course and outcome of GBS.

The therapeutic dose of IVIg for GBS was empirically set at 2g per kg body weight, based mainly on the clinical experience in patients with immune deficiencies.[6] There is circumstantial evidence that this standard dosage of IVIg is too low for some patients with GBS. First, 10% of GBS patients treated with IVIg show early relapse after initial improvement or stabilisation, and these patients often improve after a second dose of IVIg.[8] Second, some patients show no sign of improvement or further deteriorate in the first weeks after IVIg. Third, a case study suggested that a second course of IVIg might be beneficial in these patients,[9] but this observation requires confirmation in a randomised controlled trial. More effective treatment for GBS is needed, considering the high mortality of 5% and high morbidity with 25% of patients needing artificial ventilation and 20% remaining severely disabled.[10] A subgroup of patients with GBS that shows a more rapid clearance of IgG may have received a suboptimal dose of IVIg, and may benefit from a higher dosage or second course.

The aim of this study was to determine serum IgG levels in patients with GBS after standard IVIg treatment in relation to clinical course and outcome. GBS is an ideal disease for studying the pharmacokinetics of IVIg, because it is acute and monophasic, and all patients are treated with the same dose of IVIg. Pharmacokinetic information may be useful to optimise treatment in GBS and other autoimmune diseases responsive to IVIg.

## PATIENTS AND METHODS

### Patients

The patients in this study had previously participated in 2 randomised controlled trials investigating the therapeutic effect of IVIg.[11,12] The first trial compared the effect of IVIg with PE in 147 patients.[11] The second trial studied the additional effect of methylprednisolone (500mg per day for 5 days) when added to IVIg in 225 patients.[12] All patients fulfilled the diagnostic criteria for GBS,[13,14] were unable to walk 10m unaided, and received a standard IVIg dosage of 0.4g per kg body weight per day for 5 consecutive days within 2 weeks of onset of weakness. Furthermore, all patients received the same brand of IVIg (Gammagard or Gammagard S/D, Baxter Bioscience). These trials have been described in detail previously.[11,12]

To be included in the current study, sufficient amounts of serum taken pretreatment and 2 weeks after start of treatment had to be available to measure total IgG levels. Additionally, in some patients serum was available to determine total IgG levels at 4 weeks, 3 months and 6 months after the start of treatment. Serum levels obtained after treatment with an additional or second IVIg course were excluded. Patients who had a previous episode of GBS or who developed chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) were excluded. Approval of the local Medical Ethical Committee was obtained and all patients gave informed consent.

### Data collection

All clinical and laboratory data were collected prospectively at standardised time points during a follow-up of 6 months.[11,12] The Medical Research Counsel (MRC) sum score[15] and the GBS disability scale[16] were used to indicate the level of severity of the disease. The MRC sum score ranges from zero (quadriplegic) to 60 (normal strength). The GBS disability scale ranges from zero (normal = no disability) to six (death). Good outcome was defined as a GBS disability scale of ≤ 2, indicating the ability to walk unaided, at a follow-up of 6 months. The 6-month endpoint was defined before the start of the current study based on our previous prognostic study in GBS,[17] although not recorded in writing. Body weight at the start of treatment and the dosage of IVIg were recorded.

Serum samples were stored at -80°C until use. Serum sodium and albumin levels were determined to check the quality of the samples after long-term storage. Total serum IgG levels were determined by routine automated turbidimetry on the Hitachi 917 clinical chemistry analyser or the Modular P clinical chemistry analyser with the same Tina-quant IgG assay, according to the manufacturers' instructions (Roche, Almere, The Netherlands). At total IgG levels of 9.0g/L and 21.5g/L, the between-run coefficients of variation were respectively 1.6% and 2.6%. The within-run coefficient of variation of the Tina-quant IgG assay was <1%.

### Statistical analysis

The variability of serum IgG levels between patients was expressed as a mean and standard deviation (SD). The coefficient of variation (CV) was defined as the ratio of the SD to the mean multiplied by 100 (%). Spearman correlation coefficient ($r_s$) was used to analyse the correlation between serum IgG levels. A paired *t* test was used to compare the change in IgA and IgM after IVIg treatment.

Patients were divided into quartiles based on the increase in serum IgG ($\Delta$IgG) at 2 weeks after IVIg treatment from their pretreatment level. Clinical characteristics of these quartiles were compared using analysis of variance for linear trend or $\chi^2$ test for trend. Time to reach the ability to walk unaided during the follow-up of 6 months for these quartiles was analysed using the Kaplan-Meier method and the log-rank test for trend. The effect of $\Delta$IgG on the likelihood of walking unaided after 6 months, in relation to previously established prognostic factors including age, preceding diarrhoea, and GBS-disability score, was determined by multivariate logistic regression. The Hosmer and Lemeshow test was used to check for goodness-of-fit of the model. SPSS for Windows (V.15.0, SPSS Inc., Chicago) was used for all statistical analyses. A 2-sided p value $< 0.05$ was regarded as significant.

## RESULTS

Of the 372 patients included in these 2 trials, 298 patients were treated with IVIg. Sufficient quantities of serum to perform pharmacokinetic studies were available from 174 patients. Of these patients, 57 had participated in the first trial (IVIg vs. PE) and 117 in the second trial (IVIg and placebo vs. IVIg and methylprednisolone). These 174 patients did not differ significantly from the excluded patients in age, sex, body weight, symptoms of a preceding infection (diarrhoea or upper respiratory tract), MRC sum score or GBS disability score at entry or at 6 months.

Total IgG levels were determined in serum samples obtained pretreatment and 2 weeks after the start of treatment in all patients. In addition, in some of these patients total IgG levels were determined in samples obtained at 4 weeks (N = 91), 3 months (N = 86) and 6 months (N = 83) after the start of treatment. As expected, the serum IgG levels were higher in the samples obtained at 2 weeks and (to a lesser extent) at 4 weeks after IVIg administration as compared with the pretreatment level (Figure 1). There was a strong positive correlation between serum IgG levels obtained pretreatment, and those taken at 3 months ($r_s$=0.73; p<0.001) and 6 months post-treatment ($r_s$ =0.73; p<0.001), indicating an individual constant baseline level of serum IgG.

The largest variability in IgG level was found in serum samples obtained 2 weeks after IVIg treatment (mean 18.8g/L; SD 5.8; CV 31%). The variability was less pronounced 4

weeks after IVIg (mean 14.0g/L; SD 3.1; CV 22%). There was no association between serum IgG levels at baseline or at 2 weeks and age, body weight or symptoms of a recent infection. The IgG level at 2 weeks correlated weakly with pretreatment level ($r_s$=0.28; p<0.001) and the level at 4 weeks ($r_s$=0.55; p<0.001), indicating that to some extent the IgG level 2 weeks after treatment can be attributed to the level at baseline. IgA and IgM levels were determined from 46 patients in serum obtained before and 2 weeks after treatment, showing no significant change in either level after IVIg. IgG levels in 59 serum samples from 42 patients were also determined at time of admission, before storage at -80°C, and this initial measurement showed a high correspondence with the IgG levels determined for the current study ($r_s$=0.958; p<0.001).

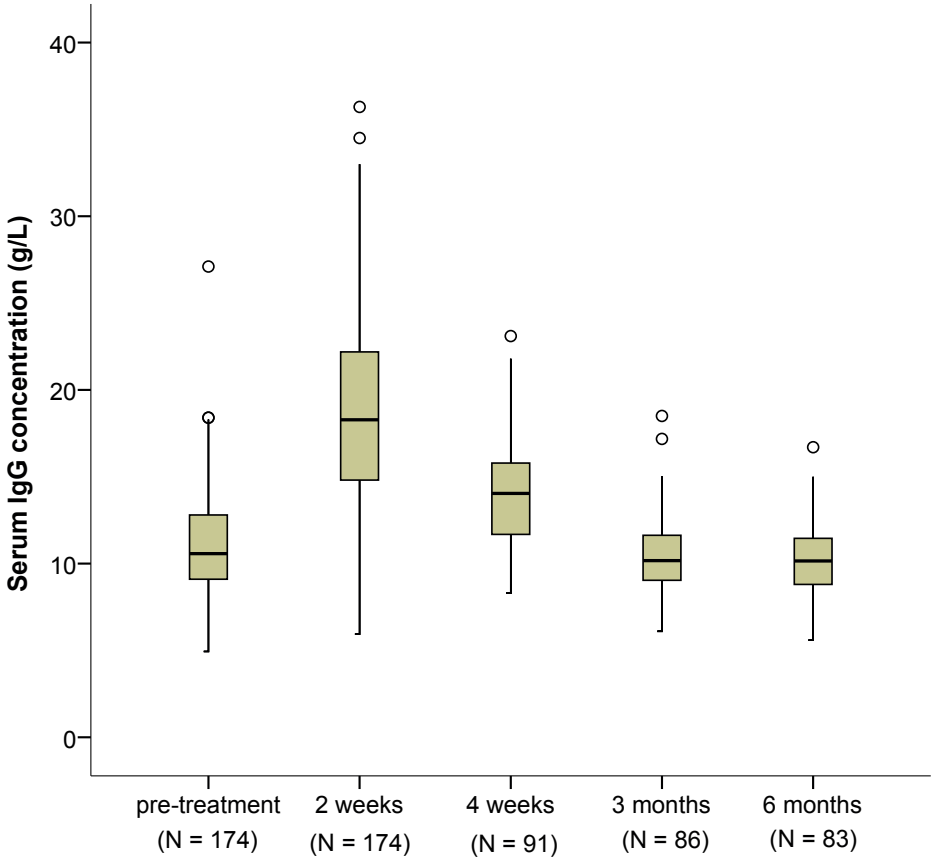


**Figure 1. Variability of serum immunoglobulin (Ig)G levels in Guillain-Barré syndrome patients before and at 4 time points after treatment with a standard high dose of intravenous immunoglobulin (2g per kg body weight)**

Boxes indicate interquartile range (IQR), horizontal bars within boxes indicate medians, and whiskers indicate range without outliers. Observations more than 1.5 times IQR from the box are indicated as open dots.

To investigate the pharmacokinetics of IVIg, the change in serum IgG was calculated by subtracting the pretreatment level from the level at 2 weeks after IVIg treatment (ΔIgG). There was a large variability in ΔIgG 2 weeks after IVIg treatment (mean 7.8 g/L; SD 5.6). Patients were clustered into quartiles according to the ΔIgG levels (cutoff value for the 25$^{th}$ percentile was 3.99g/L, for the 50$^{th}$ percentile it was 7.30g/L, and for the 75$^{th}$ percentile it was 10.92 g/L). Comparing clinical characteristics and prognostic factors between these quartiles showed no significant difference in age, body weight or the presence of preceding infection (Table 1). Furthermore, there was no difference between these quartiles regarding IVIg dosage or the presence of additional methylprednisolone treatment.

Patients with a low ΔIgG 2 weeks after IVIg had a more severe course of disease, expressed as the GBS disability score and MRC sum score at entry and nadir (Table 1). In addition, the Kaplan-Meier curves of the quartiles of patients based on this ΔIgG showed a significant difference in the time required to reach the ability to walk unaided (GBS disability score of ≤ 2) (log-rank test for trend; p<0.001) (Figure 2). When adjusted for the GBS disability score at entry, the stratified log-rank test remained significant (p=0.004). Of the 27 patients who were not able to walk unaided after 6 months, 12 (44%) were from the quartile with the lowest ΔIgG level, and 23 (85%) were from the lowest 2 quartiles. The time required to improve 1 grade on the GBS disability scale was also significantly longer in the quartile of patients with the lowest ΔIgG (log-rank test for trend; p=0.001).

The relation between IgG levels and outcome was determined in multivariate analysis. Previously identified prognostic factors in GBS that predict the chance to walk unaided at 6 months -age, preceding diarrhoea and GBS disability score- were included in the model.[17] A forward stepwise approach was used. The IgG level pretreatment (p=0.74) or the IgG level at 2 weeks after treatment (p=0.32) were not significantly associated with the outcome; therefore, these variables were not included in the final model. The GBS disability score at entry was entered as a categorical variable (GBS disability score 3, 4 or 5) in the multivariate analysis. After adjusting for age, preceding diarrhoea, and the GBS disability score at entry, the ΔIgG 2 weeks after IVIg treatment was still associated with the outcome in the final model (N=173; p=0.022). One patient was not included in this analysis, because there was no information available about the presence of preceding diarrhoea. Compared to the reference ΔIgG quartile 4, the odds ratio (OR) was 0.26 for quartile 1, 0.25 for quartile 2 and 3.90 for quartile 3. Comparing the combined quartiles 1-2 with the combined quartiles 3-4 resulted in an OR of 0.148 (95% CI 0.05-0.48; p=0.001).

When adjusting for the Erasmus GBS outcome score (EGOS), a prognostic model based on a scoring system for age, preceding diarrhoea and GBS disability score at 2 weeks,[17] the ΔIgG was also associated with the outcome after 6 months (p= 0.020).

**Table 1. Baseline characteristics, clinical course, and outcome in quartiles of patients based on the increase in serum IgG levels (ΔIgG) two weeks after treatment with a standard high dose of intravenous immunoglobulin**

| | Quartiles based on ΔIgG at two weeks | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | p Value |
| Serum ΔIgG (g/L) | < 3.99 | 3.99-7.30 | 7.31-10.92 | > 10.92 | |
| N | 43 | 45 | 43 | 43 | |
| **Serum IgG level (g/L)** | | | | | |
| Pretreatment | 12.5 (3.8) | 10.8 (2.4) | 10.4 (2.6) | 10.4 (3.0) | |
| 2 wk after treatment | 13.5 (4.2) | 16.6 (2.7) | 19.4 (2.8) | 25.7 (4.8) | |
| **Baseline characteristics** | | | | | |
| **Demographic features** | | | | | |
| Age, y | 52.1 (22.9) | 49.2 (20.6) | 51.8 (17.2) | 45.4 (19.2) | 0.20 |
| Males | 23 (54%) | 29 (64%) | 24 (56%) | 23 (54%) | 0.79 |
| Body weight, kg | 71.0 (19.7) | 74.4 (15.1) | 75.2 (13.9) | 75.2 (16.1) | 0.24 |
| **Preceding infections** | | | | | |
| Diarrhoea | 9 (21%) | 8 (18%) | 11 (26%) | 13 (31%) | 0.19 |
| Upper respiratory tract infection | 17 (40%) | 17 (38%) | 13 (30%) | `13 (31%) | 0.31 |
| **Clinical severity at entry** | | | | | |
| GBS disability score | 4.0 (0.44) | 3.8 (0.56) | 3.7 (0.58) | 3.7 (0.56) | 0.007 |
| ≥ 4 | 39 (91%) | 34 (76%) | 29 (67%) | 28 (65%) | 0.004 |
| MRC sum score | 35.8 (11.3) | 39.0 (13.0) | 42.7 (10.1) | 43.7 (9.8) | <0.001 |
| ≤40 | 25 (58%) | 19 (42%) | 14 (33%) | 12 (28%) | 0.003 |
| **Outcome characteristics** | | | | | |
| **Clinical severity at nadir** | | | | | |
| GBS disability score | 4.6 (0.7) | 4.0 (0.7) | 3.9 (0.7) | 4.0 (0.5) | <0.001 |
| > 4 | 25 (58%) | 10 (22%) | 7 (16%) | 5 (12%) | <0.001 |
| MRC sum score | 23.0 (16.0) | 32.9 (17.3) | 37.9 (14.4) | 39.1 (15.3) | <0.001 |
| ≤ 40 | 36 (84%) | 25 (56%) | 20 (47%) | 16 (37%) | <0.001 |
| **Mechanical ventilation** | | | | | |
| Frequency * | 22 (52%) | 9 (23%) | 5 (12%) | 5 (13%) | <0.001 |
| **Outcome at 6 mo** | | | | | |
| GBS disability score > 2 | 12 (28%)[#] | 11 (24%)[†] | 1 (2%)[‡] | 3 (7%)[˙] | 0.001 |

Data are presented as means (standard deviation) and compared using analysis of variance for linear trend or as numbers (percentage) and compared using $\chi 2$ test for trend. * at any time
[#] 95% CI=15%-44%, [†] 95% CI=13%-40%, [‡] 95% CI=0.1%-12%, [˙] 95% CI= 1%-19%.
ΔIgG = increase in serum immunoglobulin G; IgG = immunoglobulin G; GBS = Guillain-Barré syndrome; MRC = medical research council; CI = confidence interval.

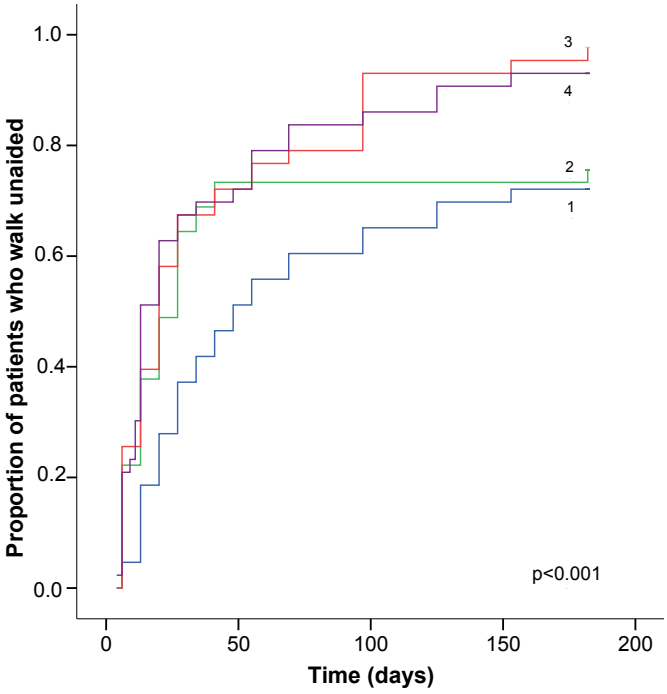


**Figure 2. Proportion of patients who regained the ability to walk unaided in quartiles based on increase in serum immunoglobulin (Ig)G 2 weeks after treatment with a standard high dose of intravenous immunoglobulin**

The Kaplan-Meier curves show the cumulative fractions of patients walking unaided along time grouped according to the quartiles (1-4) of increase in serum IgG (ΔIgG)**.**

Cutoff values ΔIgG for quartile 1: < 3.99 g/L (N=43), quartile 2: 3.99-7.30 g/L (N=45), quartile 3: 7.31-10.92 g/L (N=43), and quartile 4: ΔIgG > 10.92 g/L (N=43). p Value is based on the log-rank test for trend.

## DISCUSSION

We determined the pharmacokinetics of IVIg treatment in patients with GBS in relation to the clinical course and outcome. Infusion with a standard regime of 2g per kg body weight resulted in a considerable variability in increase of serum IgG levels (ΔIgG) between patients. Two weeks after commencing treatment, the ΔIgG ranged from -5g/L to 26g/L, with <4 g/L in the lowest quartile of patients and >10 g/L in the highest quartile. The ΔIgG levels were determined in a representative group of 174 GBS patients with regard to demographic characteristics, preceding infections, disease severity and outcome. The variation in ΔIgG in these patients was unrelated to sex, age, body weight, presence of symptoms of preceding infections, or additional treatment with methylprednisolone. IgG levels were defined by turbidimetry, which is a routine and highly accurate method for determining the levels of IgG in serum. Previous studies

have shown that the IgG level in frozen serum samples is not influenced by long-term storage (up to 25 years).[18] Various control studies were conducted in the current study to verify the quality of the tested serum samples and reproducibility of the tests. Based on these results, we concluded that there is a considerable variation between GBS patients in the pharmacokinetics of IVIg.

Previous studies in patients with other diseases have shown that after infusion with the standard high dose of IVIg, the serum IgG level increases 5-fold, declines within 72 hours to 50%, and returns to pretreatment levels after 21 to 28 days.[6] The initial rapid decline in IgG levels is largely influenced by redistribution, whereas the slower catabolism in the next phase follows a first-order kinetic.[6] The half-life of IVIg is approximately 18-32 days, which is similar to that of native serum IgG.[6] In our study, a low ΔIgG was associated with more extensive disability and weakness at the start of treatment, as defined by the GBS disability score and MRC sum score. A higher disease activity, with more extensive immune activation and nerve damage, may result in a higher consumption of IgG. This subgroup may also be exposed to a higher rate of (intensive care unit--related) infections that may further increase the catabolism of IgG. Accordingly, in patients with sepsis and severe trauma needing artificial ventilation, the consumption of IgG is increased.[19,20] A second factor in this study associated with a low ΔIgG was a high baseline level of serum IgG before treatment. Patients with a high serum IgG concentration are known to have a higher catabolism of IgG.[21] When the plasma IgG concentration reaches 200% of its normal value, the half-life of IgG decreases from 21 to 12 days.[22] It is possible that this dose-dependent clearance can be explained by saturation of the neonatal Fc receptor (FcRn), which protects IgG from degradation.[23] The FcRn is present in many adult tissues, especially in vascular endothelial cells, suggesting that these cells are a major site of IgG catabolism. Variable numbers of tandem repeats promoter polymorphisms influence the expression of FcRn, leading to differences in IgG binding,[24] and possibly contribute to the individual clearance rates of IVIg. Part of the therapeutic effect of IVIg may be attributed to the saturation of these receptors, which results in a higher clearance of auto-antibodies.[25] The efficacy of IVIg in immune thrombocytopenia has been shown to be FcRn dependant.[26] IVIg may also inhibit the production of auto-antibodies and cytokines, although no general immunoregulatory feedback on IgG synthesis by IVIg has been demonstrated.[27] The variability in IgG kinetics between individual GBS patients, as found in the current study, may be explained by the combination of disease severity and these host genetic factors involved in IgG turnover.

The current study suggests that GBS patients with a low ΔIgG have a more severe clinical course and poor outcome after a standard dose of IVIg, independent of other prognostic factors. A low ΔIgG 2 weeks after IVIg treatment was related to more severe clinical deficits at nadir, defined by the MRC sum score and GBS disability score, and a higher frequency of mechanical ventilation. In these patients, the time to reach a GBS

disability score of ≤ 2 and to improve 1 grade on the GBS disability score was prolonged. In addition, a low ΔIgG was associated with a higher chance to remain disabled at 6 months after treatment. Multivariate analysis confirmed that the association between ΔIgG at 2 weeks and poor clinical outcome was independent of the disease severity before treatment and other main prognostic factors in GBS. When adjusted for the EGOS, which contains the GBS disability score at 2 weeks, the ΔIgG was still significantly associated with the chance of reaching independent walking after 6 months. This may indicate that the ΔIgG has an additional value in predicting outcome in GBS, although this should be confirmed in an independent prospective study. Very recently, IVIg-related plasmacytosis 7 days after initiation of treatment was reported as a prognostic marker in GBS patients receiving IVIg treatment.[28]

The optimal dosage of IVIg for treatment of GBS is unknown. The current standard regime of 2g per kg body weight was set arbitrarily, and is not defined in dose-finding studies in subgroups of patients. If the immune modulating effects of IVIg are dose dependent, a low ΔIgG may result in suboptimal immune suppression, more extensive or prolonged damaging of peripheral nerves, and worse outcome. In a multicentre controlled trial comparing two IVIg regimens, GBS patients treated with 2.4g per kg body weight in 6 days showed faster and better recovery than patients treated with 1.2g per kg body weight in 3 days.[29] A small case study suggested that a second course of IVIg might be beneficial in GBS patients who show no sign of improvement or further deteriorate in the first weeks after IVIg.[9] There is circumstantial evidence that the number of plasma exchanges in GBS should be adjusted to the initial severity of the disease.[30] From clinical practice in the treatment of chronic forms of immune mediated neuropathy, it is known that patients who show an insufficient response may further improve after a higher dosage of IVIg. This may also indicate that in GBS patients treated with IVIg, a certain threshold of ΔIgG is needed for a substantial effect, or that a subgroup of patients may further improve after a higher dosage of IVIg. In the current study, decisions about further treatment could only be made based upon a IgG level determined at 2 weeks. It is possible that this delay is too long to improve outcome, although the time window in which (additional) IVIg treatment is still effective is unknown. It is known that PE may be effective in up to 30 days after admission.[1,31] A controlled trial is needed to demonstrate the additional therapeutic benefit of a higher dosage or second course of IVIg in these patients.

IVIg is used in the treatment of a wide spectrum of immune disorders, including various autoimmune neuromuscular diseases.[5] The pharmacokinetics of IVIg treatment have been evaluated in healthy controls and patients, showing a considerable intra- and interpopulation variability.[7] Patients may be subject to more pronounced individual variation than normal persons if disease activity or disease-predisposing factors influence IgG catabolism. GBS is a model disease to determine the pharmacokinetics of

IVIg, because GBS is an acute monophasic disorder, usually affecting persons with an unremarkable immune history, who are treated with the same standard regime of IVIg. The current study suggests that the high variability of IVIg pharmacokinetics in patients with GBS is related to clinical course and outcome. Prospective studies are required to determine if monitoring of serum IgG levels can be used to optimise the use of IVIg treatment in GBS patients on an individual basis.

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