ORIGINAL ARTICLE

Randomized trial of intravenous immunoglobulin maintenance treatment regimens in chronic inflammatory demyelinating polyradiculoneuropathy

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Background and purpose: High peak serum immunoglobulin G (IgG) levels may not be needed for maintenance intravenous immunoglobulin (IVIg) treatment in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and such high levels may cause side effects. More frequent lower dosing may lead to more stable IgG levels and higher trough levels, which might improve efficacy. The aim of this trial is to investigate whether high frequent low dosage IVIg treatment is more effective than low frequent high dosage IVIg treatment.

Methods: In this randomized placebo-controlled crossover trial, we included patients with CIDP proven to be IVIg-dependent and receiving an individually established stable dose and interval of IVIg maintenance treatment. In the control arm, patients received their individual IVIg dose and interval followed by a placebo infusion at half the interval. In the intervention arm, patients received half their individual dose at half the interval. After a wash-out phase patients crossed over. The primary outcome measure was handgrip strength (assessed using a Martin Vigorimeter). Secondary outcome indicators were health-related quality of life (36-item Short-Form Health Survey), disability (Inflammatory Rasch-built Overall Disability Scale), fatigue (Rasch-built Fatigue Severity Scale) and side effects.

Results: Twenty-five patients were included and were treated at baseline with individually adjusted dosages of IVIg ranging from 20 to 80 g and intervals ranging from 14 to 35 days. Three participants did not complete the trial; the main analysis was therefore based on the 22 patients completing both treatment periods. There was no significant difference in handgrip strength change from baseline between the two treatment regimens (coefficient −2.71, 95% CI −5.4, 0.01). Furthermore, there were no significant differences in any of the secondary outcomes or side effects.

Conclusions: More frequent lower dosing does not further improve the efficacy of IVIg in stable IVIg-dependent CIDP and does not result in fewer side effects.

Introduction

Patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have limb muscle weakness, often with proximal involvement, and

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decreased or absent reflexes [1]. The majority of patients with CIDP have moderate to severe symptoms and disability, which requires treatment [2]. Controlled studies have shown the efficacy of intravenous immunoglobulin (IVIg) in 54–76% of patients [3–6]. IVIg can already be effective after 8–10 days [3,5]. Although 15–30% of patients only need a single IVIg course, most patients need long-term maintenance treatment [1]. In a long-term follow-up study in 106 patients with CIDP, 11% had stable disease without any treatment for ≥5 years [7]. In clinical practice, CIDP patients are treated with different IVIg maintenance schedules [8]. These non-evidence-based maintenance schedules are usually based on body weight, even though body weight does not seem to correlate with the IVIg dosage required in CIDP [9–11]. Randomized controlled trials (RCTs) comparing different dose schedules are lacking and much needed [12–14]. In general, it is recommended to adjust the dose and interval of IVIg maintenance treatment in CIDP patients individually, but the best way to do this is unclear [1,14]. Lunn *et al.* [15] developed a straightforward and practical algorithm in order to achieve an individual IVIg maintenance dose and interval. It is unknown what is the best approach: keeping the plasma level of immunoglobulin G (IgG) relatively constant and above a threshold with lower dosages and more frequent infusions, or providing spiking of the immune system with higher and less frequent infusions [16,17]. The half-life of IVIg depends on the serum IgG level, probably influenced by the limited capacity of the pool of neonatal Fc receptor that protects IgG from degradation [18,19]. Treatment with a higher dose of IVIg could therefore lead to a higher serum IgG peak level and a shorter half-life of IVIg [20]. A small case series reported a higher IgG trough level and better efficacy when IVIg was given more frequently in CIDP [21]. When IVIg is given more often this will likely lead to less fluctuation in serum IgG levels and possibly also less fluctuation in disease activity, which might improve clinical stability. If this turns out to be a more efficient way to treat patients, it could lead to a reduction of the total IVIg dose required over time.

The aim of the present study was to assess whether high-frequency low-dose IVIg treatment is more effective and results in fewer side effects than low-frequency high-dose maintenance treatment for CIDP.

Patients and methods

Trial design

Patients were treated with IVIg at home or at the hospital day-care according to where they were treated prior to trial entry. A computer-generated list of random assignments was prepared by the study statistician (H.L.). Randomization was stratified by study centre, and allocation sequence concealment was ensured via sequentially numbered, opaque sealed envelopes. The investigator (K.K.) allocated the next available number when a patient was eligible and gave written informed consent. Thereafter an unmasked neurologist (E.B.) randomized patients according to the computer-generated list. Neither the patients nor the nurses or investigators knew the treatment sequence. The laboratory analysts were also unaware of the treatment sequence.

The trial consisted of one baseline infusion, four blinded infusions, two wash-out infusions and thereafter another four blind infusions. Each patient was treated at baseline according to their own individually adjusted dose and interval of IVIg. During the double-blind phases, each patient was allocated to either half of their normal individual dose at half of their normal interval first (intervention), or their normal dose and interval first, with intermittent placebo infusions to maintain the blinding (control). A low dose of albumin 0.5% was chosen as the placebo because of its identical appearance to IVIg and because it has been used as a placebo in various trials, including the largest RCT confirming the efficacy of IVIg in CIDP [6]. After a wash-out phase of two infusions, patients crossed over to the opposite treatment regimen. This period seemed reasonable because the half-life of IVIg is 18–32 days [12,22] and the efficacy of IVIg can often be determined within 2 weeks [3,23]. The total amount of IVIg that was given during the double-blind phases remained the same in individual patients. When half the dose of IVIg was given, placebo was subsequently given to maintain the blinding by using the same total volume. Blinded study medication was always divided over two EVA bags during the whole study so that IVIg did not have to be diluted and in order to maintain the blinding. Allocation was revealed after all patients completed the trial, whereupon data entry was declared complete. Further details regarding the trial design and the process of randomization and blinding have been described previously [24].

Patients

Patients aged 18 years or older fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society diagnostic criteria for CIDP and who were receiving a stable dose and interval of 10% liquid IVIg maintenance treatment (Kiovig; Takeda Manufacturing Austria AG, Vienna, Austria) were eligible

for inclusion [1,24]. Concomitant other immunosuppressive drugs were only allowed if the dose remained unchanged in the 8 weeks before start of the trial and the daily dose of prednisone did not exceed 20 g [24]. Patients were only included when they showed either an objective deterioration (a decrease in muscle strength as measured by a Martin Vigorimeter) following reduction of IVIg dose or lengthening of the IVIg interval, or an objective improvement following an increase in IVIg dose or shortening of the IVIg interval at some time during the 9 months before randomization [24]. Importantly, to be able to capture an improvement in the primary outcome, patients were only eligible when their handgrip strength score, as measured with the Vigorimeter, was less than the median value for an age- and sex-matched healthy control [25]. A complete list of the inclusion and exclusion criteria is provided in the previous publication of the protocol [24].

Outcomes

The primary outcome measure was the score on the Martin Vigorimeter (handgrip strength) [26,27]. The Martin Vigorimeter is a simple assessment tool that tended to parallel or precede initial improvement in the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score in a placebo-controlled trial that confirmed the efficacy of IVIg in CIDP [26]. Prior to every infusion, handgrip strength was measured (mean of the three measurements of both hands was used) by the nurse administrating the IVIg. The same Vigorimeter was used for individual patients throughout the whole study. The mean Vigorimeter measurements for the two infusions before the double-blind phases were taken as baseline measurements.

Secondary outcome indicators included clinical (disability, fatigue and quality of life), laboratory and safety variables measured according to: (1) the Inflammatory Rasch-built Overall Disability Scale (I-RODS) [28]; (2) the modified Rasch-built Fatigue Severity Scale (R-FSS) [29]; (3) the 36-item Short-Form Health Survey (SF-36), Dutch language acute version 2 [30]; (4) serum IgG level as determined by turbidimetry; and (5) serious adverse events (SAEs) and side effects.

Questionnaires were completed after every infusion (except for the SF-36, which was administered only four times). Before and 5 min after every infusion, a blood sample was drawn for determination of the serum IgG level. Previous studies have established that peak IgG levels are already reached minutes after an infusion and remain stable for 30 min [11,31]. The percentages of patients with at least one SAE were compared. In addition, the most common reported side effects were described and the number of patients reporting these was compared between the two groups.

Sample size

A difference in the (mean of the four) Vigorimeter score changes from baseline between the two treatment regimens of >8 kPa was considered clinical relevant [32]. A difference of >8 kPa in Vigorimeter score change from baseline in favour of the group treated with half the dose and interval as compared with the control group was considered a clinically relevant improvement. The value of 8 kPa was based on the minimum clinically important difference cut-off value of 8 kPa for handgrip strength (Vigorimeter) using the ½ SD technique [32]. Historical data [33] showed an SD value of 7.65 kPa for the change from baseline of Vigorimeter score of the mean value after four subsequent infusions (ΔVigorimeter score) in stable but IVIg-dependent CIDP patients. To demonstrate a difference in the mean ΔVigorimeter score 15 patients are required who complete both treatments (assumed difference: 8 kPa, two-sided $\alpha = 0.05$, $\beta \geq 80\%$) [24,33]. To account for some unevaluable patients and to increase power, more patients were included.

Statistical analysis

The main analysis of the present trial consists of a comparison of the change from baseline in Vigorimeter values (kPa) between the two treatment regimens. Patients who did not complete both treatments in this crossover trial are described but excluded from the analysis according to the statistical analysis plan, as published online in the Dutch Trial Registry (NTR3705) before the process of database locking and unblinding occurred. The mean Vigorimeter score changes from baseline as well as the changes in secondary outcome measures were compared using mixed model analysis to account for repeated measurements per patient. Mixed model analysis was also used to perform a *post hoc* subgroup analysis on the effect of the intervention on the primary outcome for patients stratified by infusion interval. A paired *t*-test was used to compare baseline Vigorimeter values for both treatment regimens. To further check for a carry-over effect in the primary outcome, linear mixed model analysis was used.

To test if the serum IgG trough levels in the intervention regimen were different we fitted a linear mixed model, with IgG level as the outcome, using all measurements of IgG just before administering the IVIg in the blinded phase. We included the covariates

infusion number and treatment regimen and a random intercept for patient. The coefficient of treatment regimen measured the average difference in serum IgG trough level across the four blinded infusions.

The percentage of patients with at least one SAE (for which a doctor was consulted) was compared using McNemar's test. The most common reported side effects were described and the number of patients reporting these in both groups was compared using McNemar's test.

Analysis was performed using SPSS v. 24 and R statistical software.

Ethics

This study was approved by the Medical Ethics Committee of the Erasmus MC (MEC-2014-407). Ethical approval was further obtained from the participating centres and all patients provided written informed consent before inclusion. This trial complies with the Declaration of Helsinki. Trial monitoring was conducted according to the local guidelines by an Association of Clinical Research Professionals accredited monitor. This trial (DRIP) was registered in the Dutch trial register (Netherlands Trial Register) as NTR3705 (NL3555) and the statistical analysis plan was published online.

Results

Between 2015 and 2018, 49 patients were screened for eligibility in three centres in the Netherlands. From these 49 screened patients, 25 were included (Fig. 1). Main reasons for non-eligibility in the screening process were handgrip strength that exceeded the median value for age- and sex-matched healthy controls, no treatment with IVIg required on a regular basis, and no signs of active disease (Fig. 1). In total, 25 patients were randomized from three neuromuscular disease centres. Most of the included patients were from the Erasmus medical centre (n = 17); the other two university medical centres included four patients each. From these 25 patients, 22 patients completed both treatment regimens of this crossover trial. Three patients showed an exacerbation of CIDP during the second blinded phase, one patient during treatment with half the dose and interval, and two patients during the normal dose and interval treatment. These three patients were excluded from the analysis of this crossover trial as planned beforehand.

The median age was 67 years and the median duration of IVIg treatment was 4 years (Table 1). The individual adjusted IVIg dosages ranged from 20 to 80 g and intervals between 14 and 35 days (Figure S1). None of the patients received other immunosuppressive or immunomodulatory medication during the trial or in the period before IVIg dependency was established. There were no missing values for the primary outcome measurement. Missing items responses on the SF-36 were handled according to the user's manual for the SF-36 version 2 when possible [34].

Treatment efficacy

Overall mean (SD) handgrip strength (Vigorimeter) before the start of the trial was 63 (46) kPa. Baseline handgrip strength with the intervention treatment (mean 64, SD 21) was not different from the control regimen [mean 64, SD 22; difference −0.11, 95% confidence interval (CI) −2.85, 2.65; P = 0.94]. Mean (SD) handgrip strength after the intervention treatment [61 (22)] was statistically significantly different compared to the handgrip strength after the control regimen [64 (21); difference −2.9, 95% CI −4.9, −0.78; P = 0.009]. There was no significant difference in Vigorimeter score change from baseline between the treatment regimens (Fig. 2; Table 2). Furthermore, there were no significant differences between the treatment regimens in the secondary outcome indicators (Table 2). A subgroup analysis on the effect of the intervention on the change in Vigorimeter value from baseline stratified by infusion frequency showed no difference (Table S1). There was a non-significant interaction between period and treatment (P = 0.26) in a linear mixed model. Furthermore, baseline Vigorimeter scores between the two treatment regimens showed no significant differences, implying no carry-over effect from one period to the next.

Treatment tolerance and preference

Both treatments were well tolerated and no SAEs occurred. There were no significant differences between the treatment regimens in the number of patients who reported one of 10 most common side effects (Table 3). Most patients had no preference for either of the two treatments, but two patients did prefer the intervention treatment regimen and three patients preferred the control regimen.

Serum IgG levels

The peak serum IgG levels were lower after the half-dose than after the normal dose, and the difference between peak and trough levels was smaller in the half-dose group (Fig. 3). The IgG trough level was not higher in the half-dose and interval group (Fig. 3). Overall, the IgG trough level was slightly higher in the

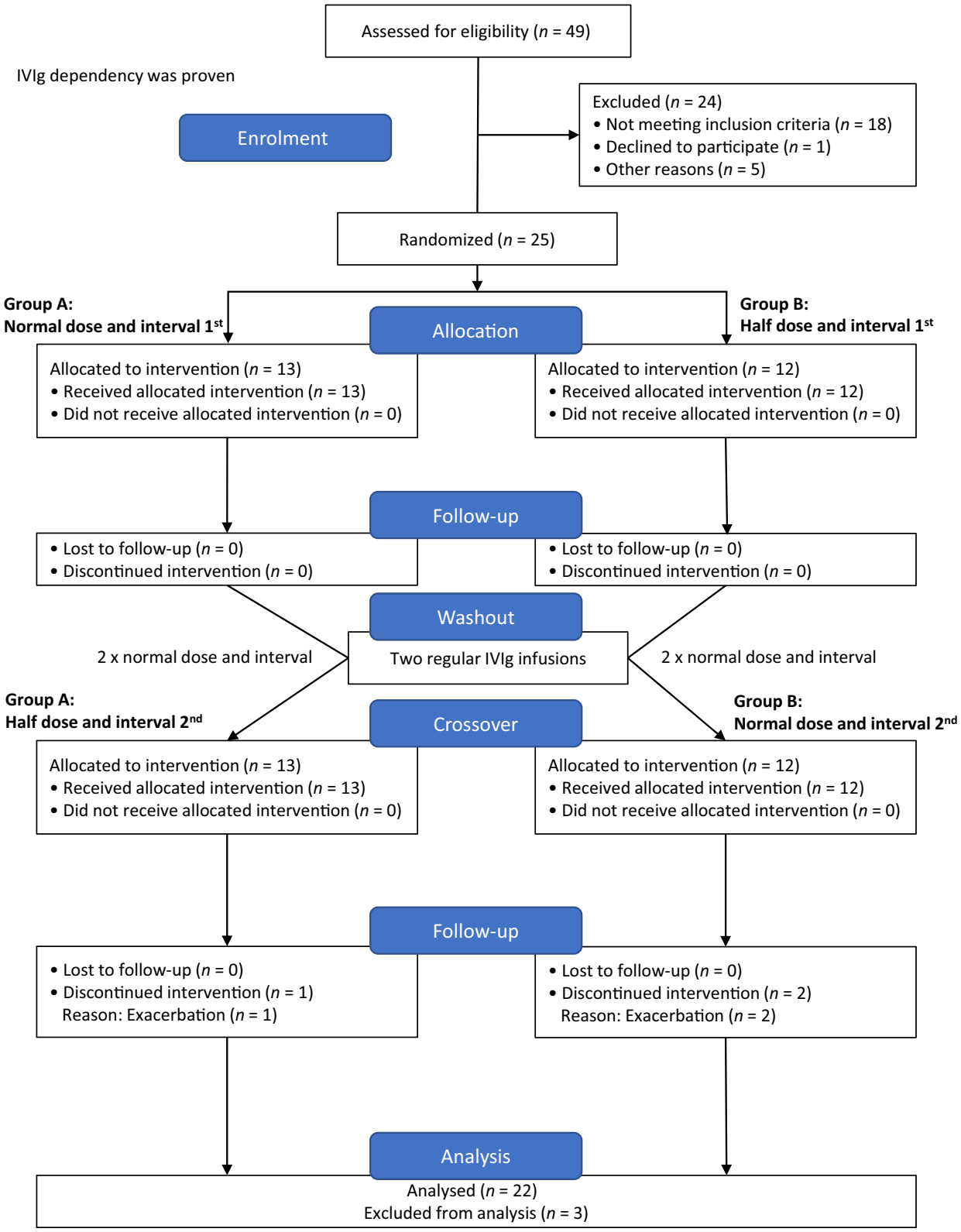

Figure 1 Flow diagram illustrating the crossover study design. IgG, immunoglobulin G. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1 Baseline demographics and characteristics (N = 22)

Characteristic	
Age, years	67 (27–81)
Men, *n* (%)	16 (73)
Body weight, kg	81 (19)
Duration of IVIg treatment, years	4 (0–31)
IVIg dosage per infusion, g	43 (17)
IVIg dosage per kg bodyweight, g	0.55 (0.24)
IVIg dose per week, g	14 (5–40)
IVIg interval, days	14 (14–35)
Vigorimeter value[a], kPa	63 (46)
Serum IgG trough level, g/L)	16 (4)
Serum IgG peak level, g/L	28 (7)

IgG, immunoglobulin G; IVIg, intravenous immunoglobulin. Data are mean (SD), or median (range), unless otherwise indicated. Higher Vigorimeter scores indicate greater strength. [a]Value before first infusion (mean of three measurements of both hands; range 0–160).

normal dose and interval regimen (coefficient 0.67, 95% CI 0.3, 1.1; P = 0.002). The serum IgG levels were quite constant over time in individual patients, whereas there were relatively large inter-individual differences between patients treated with the same dose and interval.

Blinding

To check whether blinding was successful, patients and nurses were asked what medication they thought they were given in which phase. Both patients and nurses were right five times about the order in which each treatment had been given, whereas they were wrong eight times. On most occasions, the patients responded that they had no idea or they simply did not answer the question.

Discussion

This trial showed that patients with stable CIDP on optimized IVIg maintenance treatment appreciated no further clinical benefit from more frequent lower dosing. Furthermore, more frequent but lower dosing did not result in higher IgG trough levels or fewer side effects. The patients with CIDP included in this trial were mainly middle-aged men, which is similar to the general CIDP population. Furthermore, we included patients with a broad range of dosages and intervals of IVIg improving the generalizability of the study. A possible explanation for this result could have been that the IVIg infusion frequency in the patients enrolled in this trial was already relatively high and that therefore further shortening of the intervals did not result in improvement. The infusion frequency of IVIg maintenance treatment of CIDP is reported to be shorter in the Erasmus Medical Centre than in some other centres, which was also the case in this multicentre trial [24,35]. Although approximately half of the patients included in the present study indeed had a short IVIg infusion interval, a subgroup analysis of patients divided by their infusion interval (2 weeks or ≥ 3 weeks) did not reveal differences in outcome. Wearing-off weakness or end-of-dose complaints are reported by many CIDP patients when the effects of IVIg are waning just before the next infusion is due [35]. Whether these end-of-dose complaints require a change of IVIg dose or infusion interval is unknown. We only included patients who had handgrip strength less than the median value for an age- and sex-matched control, indicating that they could potentially improve from a better treatment regimen. However, it is possible that the patients in our study were already at a steady-state because of an individually optimized infusion schedule with no or hardly any end-of-dose complaints, so that further improvement could not be reached. Patients were not formally assessed for end-of-dose complaints before trial entry. All three hospitals that included patients in this trial were neuromuscular disease centres with special

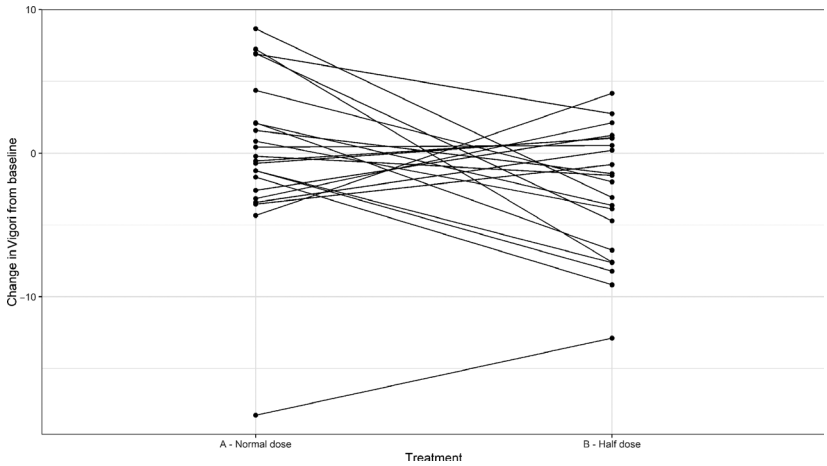

Figure 2 Mean change in Vigorimeter score from baseline per treatment regimen.

Table 2 Effect of the intervention on the outcome

	Coefficient	95% CI	*P*
Primary outcome			
Vigorimeter score[a] (kPa)	−2.71	−5.4, 0.01	0.07
Secondary outcomes			
R-FSS	−0.01	−0.2, 0.2	0.90
I-RODS	−0.02	−0.4, 0.4	0.93
SF-36			
Physical functioning	−2.98	−8.0, 2.1	0.25
Role-physical	−5.32	−12, 1.3	0.13
Bodily pain	−0.77	−22, 21	0.95
General health	−0.28	−10, 9.4	0.96
Vitality	−3.48	−7.3, 0.3	0.08
Social functioning	−3.70	−15, 8.2	0.55
Role emotional functioning	−4.40	−13, 4.1	0.32
Mental Health Score	−4.22	−10, 2.2	0.22

CI, confidence interval; I-RODS, Rasch-built Overall Disability Score (range 0–100 centile metrics; higher value indicates fewer limitations); R-FSS, Modified Rasch-built Fatigue Severity Scale (range 0–21; higher score indicates more fatigue); SF-36, 36-item Short-Form health survey (range 0–100; higher score indicates better health or less bodily pain). Data shown are a comparison (difference) of the change from baseline between the two treatment schedules (half-dose and interval vs. normal dose and interval) using mixed model analysis. [a]Score range 0–160 kPa; higher value indicates better muscle strength.

Table 3 Number of participants who reported common adverse events during the double-blind phase

Adverse events (blinded phase)	Normal IVIg dose and interval	Half IVIg dose and interval	*P*
Fatigue	19 (86)	20 (91)	1.0
Muscle and joint ache	17 (77)	16 (73)	1.0
Headache	11 (50)	13 (59)	0.69
Warm feeling	13 (59)	11 (50)	0.69
Backache	12 (55)	10 (46)	0.63
Shortness of breath	11 (50)	9 (41)	0.63
Itching	8 (36)	8 (36)	1.0
Cold shivers	8 (36)	7 (32)	1.0
Dizziness	10 (46)	6 (27)	0.13
Malaise	4 (18)	6 (27)	0.76

IVIg, intravenous immunoglobulin. Data are *n* (%) and were compared using McNemar's test.

expertise in the treatment of CIDP, which might have contributed to the optimal individual adjusted maintenance treatment before enrolment in the study. Although this trial did not show that more frequent but lower IVIg dose is better than less frequent higher IVIg dosing, it is important to mention that we do not encourage treatment with very infrequent IVIg infusions, such as once every 6 or even 8 weeks, considering the half-life of IVIg.

We used Vigorimeter score as the primary outcome measurement because it has been proven in an RCT to be a sensitive tool to measure the clinical effects of IVIg in CIDP [36]. Although the Vigorimeter score does not address lower limb function or proximal muscle weakness, improvement in Vigorimeter values does translate into better functionality for patients [27].

More frequent lower dosing of IVIg did not result in fewer side effects. This might be attributable to the stable situation of the patients or mean that adverse events may not be caused by peak serum IgG levels, as has been previously suggested [37]. The long-term safety and efficacy of subcutaneous immunoglobulin (SCIg) in CIDP has been established (PATH trial) [38]. SCIg is generally given more frequently and in lower dosages than IVIg, similar to the comparison of treatment schedules in our trial. In the PATH trial, treatment with 0.4 g/kg per week of SCIg led to more side effects than treatment with half of this dose (0.2 g/kg per week), whereas the opposite was true for the rate of adverse events per infusion, which was lower in the high dose group compared to the low dose [38].

Three patients in our trial did not complete both treatment regimens and were excluded. Since two of these patients had an exacerbation whilst being treated with the normal dose and interval of IVIg and because there was no carry-over effect, this was likely attributable to a fluctuation of the CIDP itself instead of treatment failure whilst receiving the half-dose and interval treatment. In the extension study of the PATH trial, some patients showed a relapse when they were treated with high-dose SCIg and recovered without further intervention, which indicated that this was likely to be attributable to a disease fluctuation of CIDP and not to treatment failure [38]. CIDP is a chronic disorder in which some either spontaneous or infection-related instability in muscle strength or sensory disturbances can occur over time. The double-blind phases of four infusions each seemed reasonable because of the half-life of IVIg and because the efficacy of IVIg can often be determined already within 2 weeks [12,22,23,39]. Extending the treatment phases would probably have increased the risk of spontaneous fluctuations unrelated to treatment, making it more difficult to attribute changes related to the treatment arm.

Whether there is an association between serum IgG levels and clinical efficacy in IVIg-treated CIDP patients remains to be determined [40,41]. Although more frequent lower dosing leads to more stable serum IgG levels, we showed that it did not increase the trough level as suggested by previous reports [21,42]. It is possible that the IgG trough level can only be increased due to a dose-dependent

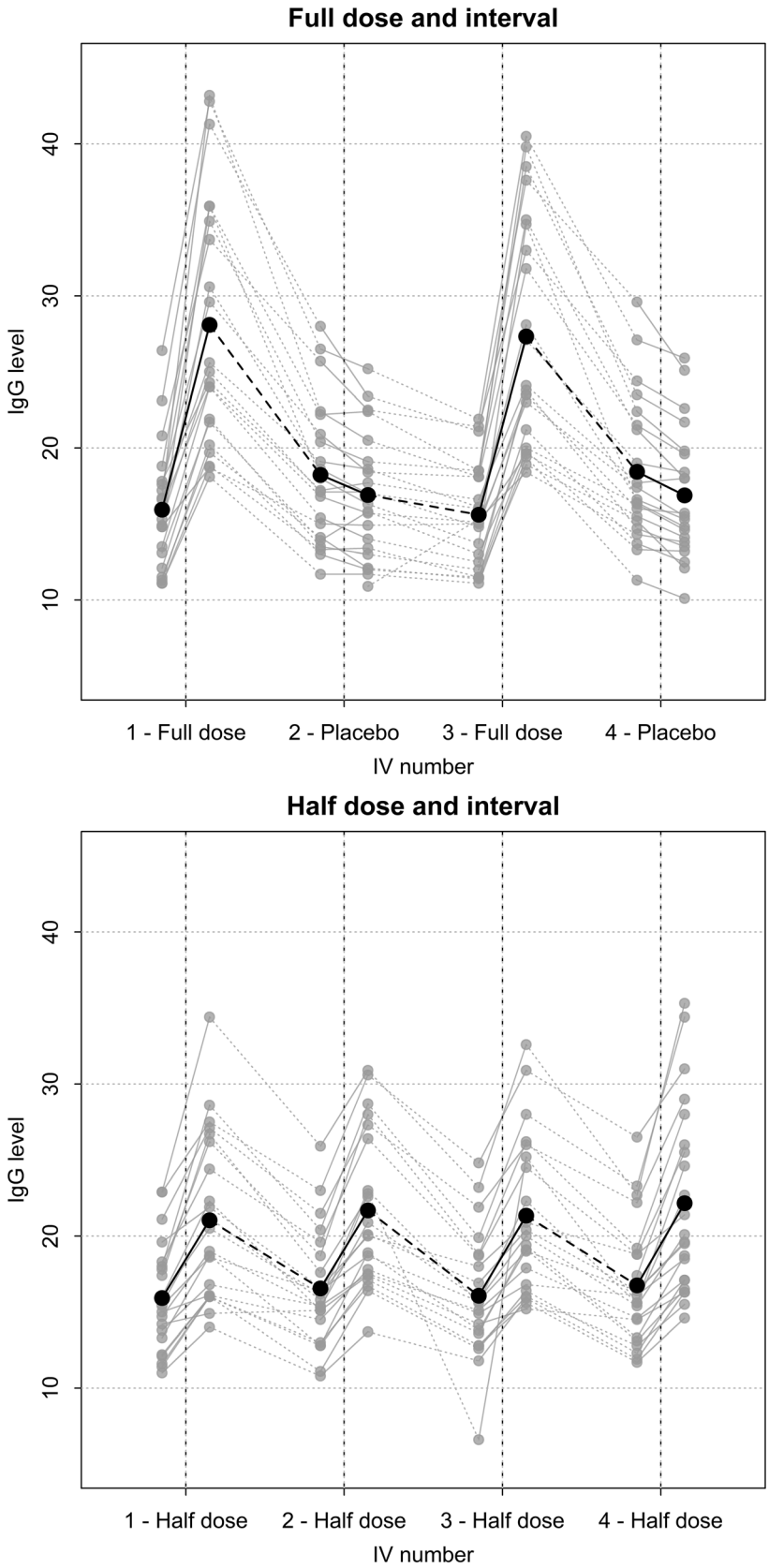

Figure 3 Serum immunoglobulin G (IgG) levels before and after four blind infusions per treatment regimen.IVIg, intravenous immunoglobulin.

relationship in a population with lower baseline IgG levels. Serum IgG or changes in IgG levels might not be useful as a biomarker in a chronic disorder treated with maintenance IVIg such as CIDP [11,38].

Overall, patients who were treated with the more frequent lower IVIg dose schedule did not show more exacerbations. This suggests that high IgG peak levels are not needed for successful IVIg maintenance treatment, and this finding is in accordance with previous studies that showed SCIg could be used as maintenance treatment for CIDP [38,43]. As high peak serum IgG levels are not needed during maintenance IVIg treatment of CIDP, more personalized IVIg treatment schedules are preferred over treating all patients with expensive high maintenance dosages such as 1 g/kg every 3 weeks [44]. Furthermore, the risk of thrombotic complications of high-dose maintenance IVIg treatment with 1 g/kg every 3 weeks over time is not negligible [44–46]. Therefore, individually adjusted maintenance dosages and intervals should be used in clinical practice [1,6].

Limitations of the present study, apart from the low number of included patients and infusions, include the use of quite strict inclusion and exclusion criteria, which limits generalizability, the fact that no treatment-naïve patients were enrolled, and the fact that we only compared two maintenance schedules. Currently, a randomized study is investigating three different IVIg maintenance doses dosages in CIDP [47]. We hope this trial will provide further insights regarding maintenance treatment of CIDP with IVIg.

The present trial showed that giving IVIg more frequently at a lower dose does not lead to an improvement in efficacy or a decrease in side effects and should therefore not be recommended in patients with stable disease receiving IVIg once every 2–5 weeks. We also showed that more stable serum IgG levels did not result in an improvement of clinical efficacy and indicate that higher peak serum IgG levels are not needed in the IVIg maintenance treatment of CIDP.

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Disclosure of conflicts of interest

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Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Supporting Information

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

Table S1. Effect of the intervention on the primary outcome by infusion interval.

Figure S1. Baseline doses and intervals of intravenous immunoglobulin.

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