

Protocol of a dose response trial of IV immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy (DRIP study)

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ABSTRACT

High peak levels of serum IgG may not be needed for maintenance treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with intravenous immunoglobulin (IVIg). More frequent dosing of IVIg leads to more stable IgG levels and higher trough levels which may be related with improved clinical efficacy. More frequent lower dosing leads to lower peak levels and may induce less systemic side-effects. The DRIP study is a double-blind randomised controlled cross-over intervention study. CIDP patients ≥ 18 years old, proven IVIg dependent and receiving an individually established but stable maintenance dose and interval of IVIg (Kiovig) can be included. One group (A) will be treated with their normal dosage and interval of IVIg and receive a placebo (albumin 0.5%) infusion in between their regular IVIg infusions, for a total of four infusions. The other group (B) will be treated with half their normal IVIg dosage (with the same volume of placebo to maintain the total volume) at half their interval (double their frequency) for four infusions. After a wash-out phase (2 infusions), patients will cross-over to the other treatment group. During the study the total dose of IVIg administered will remain unchanged as before start of the trial. The main objective is to investigate whether high frequent low dosage IVIg treatment is more effective than low frequent high dosage IVIg treatment as maintenance treatment for CIDP. Hand grip strength, as measured by the Martin Vigorimeter, will be used as the primary outcome measure. Secondary objective is to investigate whether high frequent low dosage of IVIg results in less adverse events compared to low frequent high dosage treatment. The DRIP study is currently ongoing and the protocol is presented.

INTRODUCTION

Intravenous immunoglobulin (IVIg) is a proven effective treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).¹ It is unknown whether high serum IgG peak levels are required to induce a clinical response and to reach and maintain a stable clinical condition in CIDP patients when treated with IVIg. The question how to treat CIDP patients most effectively with IVIg during the course of disease remains and randomised trials comparing different dosage schedules are needed.²⁻⁶ The pharmacokinetics of IgG differs when more frequent lower dosages are given in comparison to a less frequent higher IVIg dosage regimen. A lower dose more frequent IVIg regimen likely results in lower peak and higher trough levels of serum IgG, and may therefore be a preferable treatment schedule (Figure 1).⁷ More frequent dosing leads to more stable IgG levels without very high peak levels which have been held responsible for the systemic side effects.^{7,8} Whether more frequent, but lower IVIg dosing, leads to better clinical efficacy with less systemic side-effects, will be investigated in a dose-response RCT in CIDP (DRIP study). The results of the DRIP study may help to develop a more evidence based guideline regarding the optimal dose and frequency of maintenance IVIg treatment in CIDP. This trial has been registered in the Dutch Trial register as NTR3705. The background and outline of this study is described.

MATERIAL AND METHODS

Patients

CIDP patients responsive to IVIg who need regular IVIg treatment and who are in a stable condition with regular maintenance treatment of liquid 10% (100 g/l) IVIg (Kiovig, Baxter AG, Vienna, Austria) can be included. In all patients the diagnosis of CIDP or acute-onset CIDP (A-CIDP) has to be established by a consultant neurologist. The patients need to fulfil the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) clinical diagnostic criteria for CIDP.^{9,10} To indicate that each patient is still IVIg dependent and has active CIDP, he/she must have shown either an objective deterioration (decrease in muscle strength as measured with the Martin Vigorimeter and/or MRC sum score) 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 randomisation. To be able to measure a meaningful improvement in the primary outcome measurement, patients are only eligible when their hand grip strength as measured by the Martin Vigorimeter was < the median value (kPa) for an age and sex matched healthy control.¹¹ Patients with an infusion interval < 14 days will be excluded because we consider an infusion frequency of more than once a week (during the trial) not feasible for patients. The in- and exclusion criteria are displayed in Table 1.

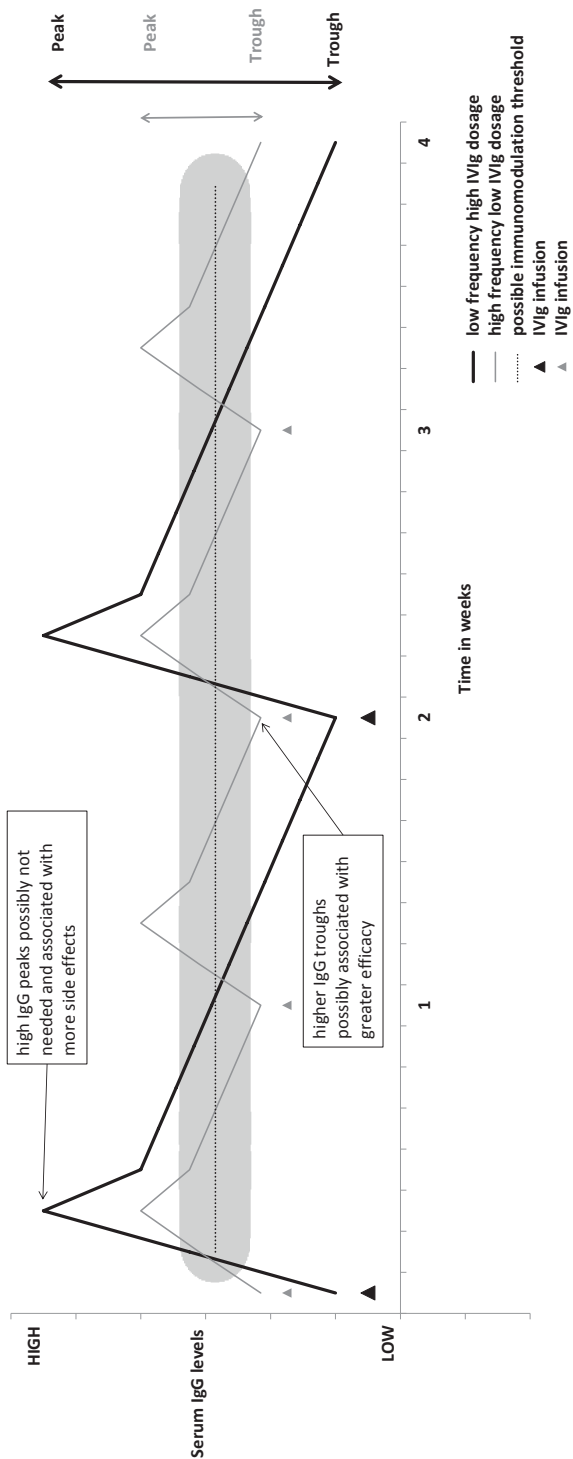


Figure 1. Serum IgG levels in high versus low frequency of IVIg maintenance treatment

Table 1. In- and exclusion criteria DRIP study

Inclusion criteria	Exclusion criteria
1. Diagnosis of CIDP or acute-onset CIDP made by a consultant neurologist, fulfilling EFNS/PNS clinical diagnostic criteria. ^{9,10}	1. Known IgA deficiency or known allergic reaction to IVIg.
2. Age \geq 18 years.	2. Hand grip strength (Martin-Vigorimeter ¹¹) \geq the median value (kPa) for an age and sex matched healthy control. ¹¹
3. Significant improvement following the first use of IVIg. (decrease \geq 1 modified Rankin scale) ²⁶	3. Maintenance dose < 15g of IVIg every infusion or an infusion interval < 14 days.
4. IVIg dependency. (objective* deterioration following IVIg reduction or improvement following an increase in IVIg < 9 months before randomisation)	4. Known hereditary neuropathy or severe concomitant diseases (HIV, Lyme, hepatitis, heart failure, SLE, drug or toxin induced neuropathy, vasculitis, malignancy)
5. Ongoing intermittent treatment with 10% liquid IVIg (Kiovig) for at least 2 infusions. The dose must have been not changed within the 8 weeks prior to the study.	5. Multifocal motor neuropathy. (fulfilling EFNS/PNS criteria) ²⁷
6. EMG findings compatible with CIDP showing peripheral nerve demyelination at least once during their illness. [#]	6. IgM paraprotein with anti- MAG antibodies.
7. Signed informed consent.	7. Atypical CIDP. (pure sensory, persistent unifocal, CNS involvement)
	8. Participation in a controlled trial of an investigational medicinal product \leq 12 weeks prior.
	9. Severe known abnormalities in liver, kidney function or serum glucose level.
	10. Treatment with > 20mg prednisone a day.
	11. Treatment with other immunosuppressive drugs if the dosage has been changed within 8 weeks prior to start of the study.

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CNS, central nervous system; EFNS/PNS; European Federation of Neurological Societies/Peripheral Nerve Society; EMG, electromyography; HIV, human immunodeficiency virus; INCAT, inflammatory neuropathy cause and treatment group; IVIg, intravenous immunoglobulin; MAG, myelin-associated glycoprotein; MRC, medical research council; SLE, systemic lupus erythematosus.

* Martin Vigorimeter¹¹ or MRC sum score²⁸

[#] Preferentially fulfilling the electro diagnostic criteria proposed by the INCAT²⁹ or EFNS/PNS.⁹

Treatment allocation and randomisation

Random assignments will be provided via a computer-generated list produced by the study statistician. A block randomisation will be made for each centre. The pharmacist will hold treatment codes for all the participants in the study. One investigator (KK) will allocate the next available number on entry after informed consent is given. Another unmasked neurologist (EB) will randomise patients according to the computer-generated list. Allocation concealment will be ensured via sequentially numbered, opaque sealed envelopes. Allocation will be revealed after all patients have completed the trial and data entry has been declared complete.

Treatment and blinding

In the DRIP trial every patient will be treated at baseline (one infusion) according to their own individual established IVIg dosage and interval prior to start of the trial. During the double-blind phase (4 infusions) one group (A) will be treated with their normal dosage and interval of IVIg, followed by a placebo infusion between their regular infusions, so that they receive an infusion of either IVIg or placebo at half of the interval. The other group (B) will be treated with half of their normal dosage of IVIg (with placebo added to maintain the total volume) at half of the interval (Figure 2). Blinded study medication will always be divided over two infusion bags during the whole study so that IVIg as well as placebo will be given separately and the IVIg does not have to be diluted (in case of half the dose and interval) and in order to maintain the blind. Albumin 0.5% has been chosen as placebo because of its identical appearance to IVIg during visual inspection. Albumin has been used as a placebo in various IVIg trials including the largest IVIg treatment trial in CIDP.¹²

After a wash-out phase (2 infusions), patients will cross-over to the other treatment group (Figure 2). This study period seems reasonable because the half-life of IVIg is 18-32 days^{3, 13} and the efficacy of IVIg can be determined within 1-2 weeks after start of treatment.^{14, 15} The total amount of IVIg given during the whole double-blind phase will remain the same in both groups.

A two-period, double-blind cross-over design was chosen because of its statistical efficiency. In this design, each patient acts as his/her own control, enabling a more precise estimate of the treatment effect. Due to the extended wash-out period (2 infusions) and the short half-life of IVIg a carry-over effect will be very unlikely. Patients will receive their treatment at home or at the hospital day-care according to where they were treated prior to trial entry. IVIg will be administered at home or in the hospital day-care setting by a nurse who is trained in administering IVIg and the treatment of (S)AEs. The study period will be approximately 14-26 weeks, depending on infusion frequency prior to randomisation.

	Group A		Group B
BASELINE	30g IVIg	Week 0	30g IVIg
DOUBLE-BLIND PHASE 1	30g IVIg	Week 4	15g IVIg+Placebo*
	Placebo	Week 6	15g IVIg+Placebo*
	30g IVIg	Week 8	15g IVIg+Placebo*
	Placebo	Week 10	15g IVIg+Placebo*
	30g IVIg	Week 12	30g IVIg
WASHOUT	30g IVIg	Week 16	30g IVIg
	15g IVIg+Placebo*	Week 20	30g IVIg
DOUBLE-BLIND PHASE 2	15g IVIg+Placebo*	Week 22	Placebo
	15g IVIg+Placebo*	Week 24	30g IVIg
	15g IVIg+Placebo*	Week 26	Placebo
	15g IVIg+Placebo*		

Example of the study outline for a patient treated with 30 grams of IVIg every 4 weeks.

**Placebo is added to maintain the total volume.*

Figure 2. Study outline

Outcome measures

The primary objective of this study is to investigate whether high frequency low dosage IVIg treatment is more effective than low frequency high dosage as maintenance treatment for CIDP. Secondary objectives are to investigate whether high frequency low dosage of IVIg results in less adverse events, as well as higher IgG trough levels compared to low frequency high dosage. Hand grip strength (Martin Vigorimeter) will be used as the primary outcome measure. The Martin Vigorimeter is a simple assessment tool measuring hand grip strength that tended to parallel or precede initial improvement in inflammatory neuropathy cause and treatment (INCAT) disability score in a placebo controlled trial that confirmed the efficacy of IVIg.¹⁶ Stronger grip strength has been reported to translate into better functionality for patients.¹⁷ Prior to every infusion, hand

grip strength will be measured (mean of three measurements of both hands) by the nurse administrating the IVIg under standard and stable conditions. To eliminate possible (minor) differences between Vigorimeters, patients will use the same Vigorimeter throughout the whole study. The mean of the two Vigorimeter measurements before the first infusion of each double blind phase will be taken as a baseline measurement. A difference of > 8 kPa in the mean of the four Vigorimeter changes from baseline in favor of the group treated with half the dosage and interval as compared with the other group will be considered a clinical relevant improvement. Patients additionally will complete questionnaires regarding disability (R-ODS)¹⁸⁻²⁰, fatigue (R-FSS)^{21, 22}, quality of life (SF-36)²³, and side effects (side effects questionnaire) 2-5 days after every infusion. Blood samples will be drawn before and after every infusion to investigate serum IgG levels. Changes in the R-ODS, R-FSS, and SF-36 and the occurrence of side-effects will be used as secondary outcome measures.

Statistical analysis

Historical data, from a similar population of stable but IVIg dependent CIDP patients, showed a SD =7.65 kPa for the mean Vigorimeter change from baseline after 4 subsequent infusions (Δ Vigorimeter).²⁴ To demonstrate a clinically relevant difference in Vigorimeter measurements, at least 15 patients are required who complete both treatment arms (two-sided alpha 0.05, power $\geq 80\%$). A difference of > 8 kPa in the mean of the four Vigorimeter changes from baseline in favor of the group treated with half the dosage and interval as compared with the other treatment group will be considered a relevant clinical improvement.²⁵ The value of 8 kPa is based on the minimum clinically important difference cut-off value of 8 kPa for grip strength (Vigorimeter) using the $\frac{1}{2}$ SD technique.²⁵ The mean Vigorimeter change from baseline will be compared between both treatments using ANOVA for cross-over studies. Repeated measurements ANOVA will be used to explore changes in Vigorimeter and serum IgG levels. Data will primarily be analysed according to the intention-to-treat principle. The percentage of patients with at least one serious adverse event will be compared using McNemar's test. The most common reported side-effects will be described and the amount of patients reporting these in both groups will be compared.

CONCLUSION

Currently it is unknown how IVIg maintenance treatment should be given in CIDP in order to be most effective and convenient. The DRIP study may give more insight into what constitutes a preferable dosage regimen for IVIg maintenance treatment of CIDP.

REFERENCES

1. Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2013; (12): CD001797.
2. Koski CL. Initial and long-term management of autoimmune neuropathies. *CNS drugs* 2005; 19(12): 1033-48.
3. Donofrio PD, Berger A, Brannagan TH, 3rd, et al. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee. *Muscle Nerve* 2009; 40(5): 890-900.
4. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004; 291(19): 2367-75.
5. Negi VS, Elluru S, Siberil S, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. *J Clin Immunol* 2007; 27(3): 233-45.
6. Querol L, Rojas-García R, Casanovas C, et al. Long-term outcome in chronic inflammatory demyelinating polyneuropathy patients treated with intravenous immunoglobulin: a retrospective study. *Muscle Nerve* 2013; 48(6): 870-6.
7. Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clinical immunology* 2004; 112(1): 1-7.
8. Eftimov F, Vermeulen M, de Haan RJ, van den Berg LH, van Schaik IN. Subcutaneous immunoglobulin therapy for multifocal motor neuropathy. *J Peripher Nerv Syst* 2009; 14(2): 93-100.
9. Joint Task Force of the EFNS and PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—First Revision. *J Peripher Nerv Syst* 2010; 15(1): 1-9.
10. Ruts L, van Koningsveld R, van Doorn PA. Distinguishing acute-onset CIDP from Guillain-Barré syndrome with treatment related fluctuations. *Neurology* 2005; 65(1): 138-40.
11. Merkies IS, Schmitz PI, Samijn JP, Meché FG, Toyka KV, van Doorn PA. Assessing grip strength in healthy individuals and patients with immune-mediated polyneuropathies. *Muscle Nerve* 2000; 23(9): 1393-401.
12. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol* 2008; 7(2): 136-44.
13. Dalakas MC. Mechanisms of action of IVIg and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. *Neurology* 2002; 59(12 Suppl 6): S13-21.
14. van Doorn PA, Brand A, Strengers PF, Meulstee J, Vermeulen M. High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo-controlled, crossover study. *Neurology* 1990; 40(2): 209-12.
15. van Doorn PA. Treatment of Guillain-Barré syndrome and CIDP. *J Peripher Nerv Syst* 2005; 10(2): 113-27.
16. Latov N, Deng C, Dalakas MC, et al. Timing and course of clinical response to intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *Arch Neurol* 2010; 67(7): 802-7.
17. Merkies IS, Schmitz PI, van der Meché FG, Samijn JP, van Doorn PA. Connecting impairment, disability, and handicap in immune mediated polyneuropathies. *J Neurol Neurosurg Psychiatry* 2003; 74(1): 99-104.

18. Merkies IS, Schmitz PI. Getting closer to patients: the INCAT Overall Disability Sum Score relates better to patients' own clinical judgement in immune-mediated polyneuropathies. *J Neurol Neurosurg Psychiatry* 2006; 77(8): 970-2.
19. Merkies IS, Schmitz PI, van der Meché FG, Samijn JP, van Doorn PA. Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies. *J Neurol Neurosurg Psychiatry* 2002; 72(5): 596-601.
20. van Nes SI, Vanhoutte EK, van Doorn PA, et al. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology* 2011; 76(4): 337-45.
21. Merkies IS, Schmitz PI, Samijn JP, van der Meché FG, van Doorn PA. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. *Neurology* 1999; 53(8): 1648-54.
22. van Nes SI, Vanhoutte EK, Faber CG, Garssen M, van Doorn PA, Merkies IS. Improving fatigue assessment in immune-mediated neuropathies: the modified Rasch-built fatigue severity scale. *J Peripher Nerv Syst* 2009; 14(4): 268-78.
23. Merkies IS, Schmitz PI, van der Meché FG, Samijn JP, van Doorn PA. Quality of life complements traditional outcome measures in immune-mediated polyneuropathies. *Neurology* 2002; 59(1): 84-91.
24. Kuitwaard K, van den Berg LH, Vermeulen M, et al. Randomised controlled trial comparing two different intravenous immunoglobulins in chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry* 2010;81(12):1374-9.
25. Merkies IS, van Nes SI, Hanna K, Hughes RA, Deng C. Confirming the efficacy of intravenous immunoglobulin in CIDP through minimum clinically important differences: shifting from statistical significance to clinical relevance. *J Neurol Neurosurg Psychiatry* 2010; 81(11): 1194-9.
26. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; 19(5): 604-7.
27. Joint Task Force of the EFNS and PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Peripher Nerv Syst* 2006; 11(1): 1-8.
28. Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve* 1991; 14(11): 1103-9.
29. Hughes R, Bensa S, Willison H, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 2001; 50(2): 195-201.

Chapter 4