

Maintenance IV immunoglobulin treatment in chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients treated with intravenous immunoglobulin (IVIg) usually start with a standard dosage of 2 g/kg body weight. Only a minority of patients have a sustained improvement, and most require ongoing maintenance treatment. Preferred IVIg regimens, however, vary considerably between doctors and at present it is unknown which is optimal. As there are also large differences in IVIg dosage and interval requirements between patients, optimal IVIg maintenance treatment of CIDP is even more complex. The lack of evidence-based guidelines on how IVIg maintenance treatment should be administered may potentially lead to under- or overtreatment of this expensive therapy. We provide an overview of published practical IVIg maintenance treatment regimens, IVIg maintenance schedules used in randomised controlled trials and one based upon our own long-term experience on how this treatment could be given in CIDP.

INTRODUCTION

In 1980, 13 children with idiopathic thrombocytopenia were treated successfully with 2 g/kg of IV immunoglobulin (IVIg).¹ In 1985, the first report was published on a group of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) that were being treated with infusions of fresh-frozen plasma and later with IVIg in the Erasmus MC.² Improvements in these patients were seen within 8 days after start of treatment with IVIg.² The first randomised controlled trial (RCT) showing that IVIg is effective compared to placebo came from a small cross-over trial in seven CIDP patients who previously improved after IVIg.³ The largest RCT showing that IVIg is effective in CIDP is the IVIg for the treatment of CIDP (ICE) trial.⁴ Next to IVIg, both corticosteroids and plasma exchange are proven to be effective in CIDP.⁵⁻⁷ We, as well as others, found that about 15% of CIDP patients only need one or two courses of IVIg to achieve a sustained improvement, but most need treatment for many years.^{8,9} Since the first reports, CIDP patients have been treated with IVIg for over 30 years now.^{2,3} Its efficacy on a somewhat longer term has also been confirmed in the ICE trial.⁴ Considering its long-term use and its reported success rate of around 54-76% it is remarkable that hardly any prospective studies have been published on how maintenance treatment with IVIg should be given.^{4,10-12} An optimal treatment regimen is needed not only to improve and maintain muscle strength, but also to prevent permanent disability due to ongoing demyelination and secondary axonal loss.¹³ Furthermore, optimal use of IVIg is important to avoid overtreatment.¹⁴ This paper provides an overview on published information about IVIg maintenance treatment in CIDP and our experience at the Erasmus MC with IVIg maintenance treatment in CIDP over the years.

TREATMENT OF CIDP WITH IVIG

Current practice of IVIg maintenance treatment in CIDP

The half-life of IVIg ranges from 18-33 days, and most of the variation can probably be explained by individual differences in the speed of diffusion to the extravascular space and concentration-dependent catabolism.^{15,16} The efficacy of IVIg can be determined quickly after infusion, most often within 1-2 weeks after start of treatment.^{3,9} In some patients, however, more than one treatment course over a period of 6 weeks (2 g/kg followed by 1g/kg after 3 weeks) may be required to identify clear objective clinical improvement.¹⁷ In our experience, one full course of IVIg (2 g/kg, divided over 5 days) is usually sufficient to determine whether IVIg is effective in typical CIDP patients.^{9,10,18} In case of doubt, a course of IVIg can be repeated to be sure that this treatment results in an improvement or not. Empirical evidence has shown that attempts to lengthen the

treatment interval between IVIg infusions in CIDP patients are unsuccessful most of the time.^{18,19} The dosage and frequency of maintenance IVIg treatment in CIDP varies per patient, usually ranging from 0.4 to 1.2 g/kg once every 2-6 weeks.^{20,21} This variation is likely to be caused by differences in IVIg catabolism between patients but may also be due to variations in disease activity.²² A similar large variation in IVIg dosage level requirement and frequency has been reported in multifocal motor neuropathy (MMN) and primary immunodeficiencies.^{23,24} Therefore, the optimum dosage and frequency of maintenance IVIg must be individually established for every CIDP patient.^{8,11,13,19} How this can best be achieved is currently unclear and is done by trial and error.^{15,25}

Traditionally, the initial IVIg loading dose and to some extent maintenance treatment is based on an arbitrary and simplistic "dose per kg body weight" principle. Several studies have shown evidence that this principle is inappropriate.^{19,26} Individually established effective dosages per infusion do not correlate with body weight or body mass index challenging the current practice of weight-dependant dosage adaptations.^{19,22,26,27} It has been suggested that ideal or actual (calculated/adjusted) body weight should be used instead of (measured) body weight.²⁶ The amount of muscle strength, disability or sensory disturbances does not seem to determine the dosage of IVIg required.^{19,22,28} In clinical practice, however, dosages and intervals are individualised usually based upon clinical response and practical reasons.²⁹ Randomised controlled trials comparing different dosage schedules are still urgently needed.^{12,15,30-34}

A small study regarding IVIg maintenance treatment in CIDP reported a large variability in "lowest" effective dose, although no formal dose reduction schedules were used and in almost half of the patients' dose reductions were performed due to the subjective impressions of patients themselves instead of using objective assessment scale parameters.¹⁹ An example of a practical treatment regimen to optimise the use of IVIg in CIDP has recently been published.¹¹ In this schedule, one standard course of IVIg (2 g/kg) is given and the response is assessed 3 and 6 weeks thereafter.¹¹ If the patients' situation has not "normalised" six weeks after the initial course, another standard course will be given.¹¹ Again the response will be assessed after 3 weeks and the period of time in which deterioration develops thereafter will be used to set the individual dosing interval.¹¹ Patients are stabilised with two standard IVIg courses according to their established dosing interval.¹¹ The dose is then reduced with 20% per course until a relapse occurs.¹¹ Patients are then maintained at the dose prior to the relapse.¹¹ Although this approach has not been the subject of an RCT, it is a straight forward and efficient way to provide a guideline in how to personalise IVIg treatment in CIDP. The mean dosing interval was 4 weeks with a broad range of 0.5-10 weeks. Although, considering the half-life of IVIg, it is hard to understand that in some patients this algorithm will set an interval of 10 weeks. This study further underlines that IVIg treatment should be individualised.¹¹ It is remarkable that the mean dosage was quite high (1.4 g/kg) explaining why in most

patients this IVIg dosage had to be infused over more than 1 day.¹¹ In the Erasmus MC, we initially treat CIDP patients with a loading dose of IVIg of 2 g/kg (usually over 5 days) and when a patient improves and subsequently deteriorates, another IVIg dosage of 0.4-2 g/kg over 1-5 days is given depending on the severity of disability and speed of deterioration. When a patient does not respond at all after at least 2 dosages of 2 g/kg of IVIg it is concluded that the patient is an IVIg non-responder and either corticosteroids or plasma exchange should be given. When a patient improves and subsequently deteriorates at least two times after each course of IVIg, we usually start maintenance IVIg treatment with a dosage of 0.4 g/kg every 3-4 weeks before we increase the dose until a maximal response is obtained. It is known that patients with CIDP may show some day-to-day variation in clinical performance in between IVIg infusions.^{12, 35} The GRIPPER study (ClinicalTrials.gov NCT02414490) is currently investigating wear-off or other treatment-related fluctuations by measuring daily grip strength in CIDP patients on IVIg.³⁶ When clear end-of-dose effects are observed, we usually shorten the infusion frequency, especially when the IVIg dosage is already relatively high, for example, >40 g IVIg per infusion.¹² If a clear fluctuation occurs adding an extra dose in between the normal infusions could be considered. When a relatively severe level of weakness remains despite improvement after IVIg, we usually give a higher dose of IVIg.^{21, 22} This approach allows us to administer infusions of maximum 1 g/kg on a single day, avoiding infusion over two consecutive days. An alternative approach would be to start with a high dose of IVIg and then try to lower the dosage to find the lowest effective dose.^{19, 37} The strategy to find the lowest effective dose in MMN patients resulted in under-treatment and therefore finding the highest effective dose with the shortest interval might be a better approach.^{12, 38} In the ICE-study a standard, and relatively high, IVIg maintenance dose of 1 g/kg every 3 weeks was used for CIDP patients during a period of 24 weeks in the first phase and another 24 weeks in the extension phase.⁴

Figure 1 gives an overview of three different ways to administer IVIg maintenance treatment in CIDP: the algorithm of Lunn, et al.¹¹, the ICE trial treatment schedule⁴, and the way we usually treat CIDP patients in the Erasmus MC.

It is important that improvement after start of IVIg as well as IVIg dependency is proven objectively using proper assessment scales.³⁹ IVIg dependency should be proven on a regular basis, for example, at least once every 6 months via dose reduction to avoid overtreatment.¹⁴ It is unlikely that the response to treatment of IVIg is dependent on the brand of IVIg used, but side effects may vary between different brands.^{28, 40, 41} Table 1 gives a short guideline regarding IVIg treatment in CIDP.

Some concerns have arisen whether IVIg leads to treatment dependency.^{42, 43} Three factors appear to support the idea that IVIg treatment does not create treatment dependency. First, some patients require only one or two IVIg courses to recover. Second, remission occurs in a substantial proportion of patients after treatment with IVIg over

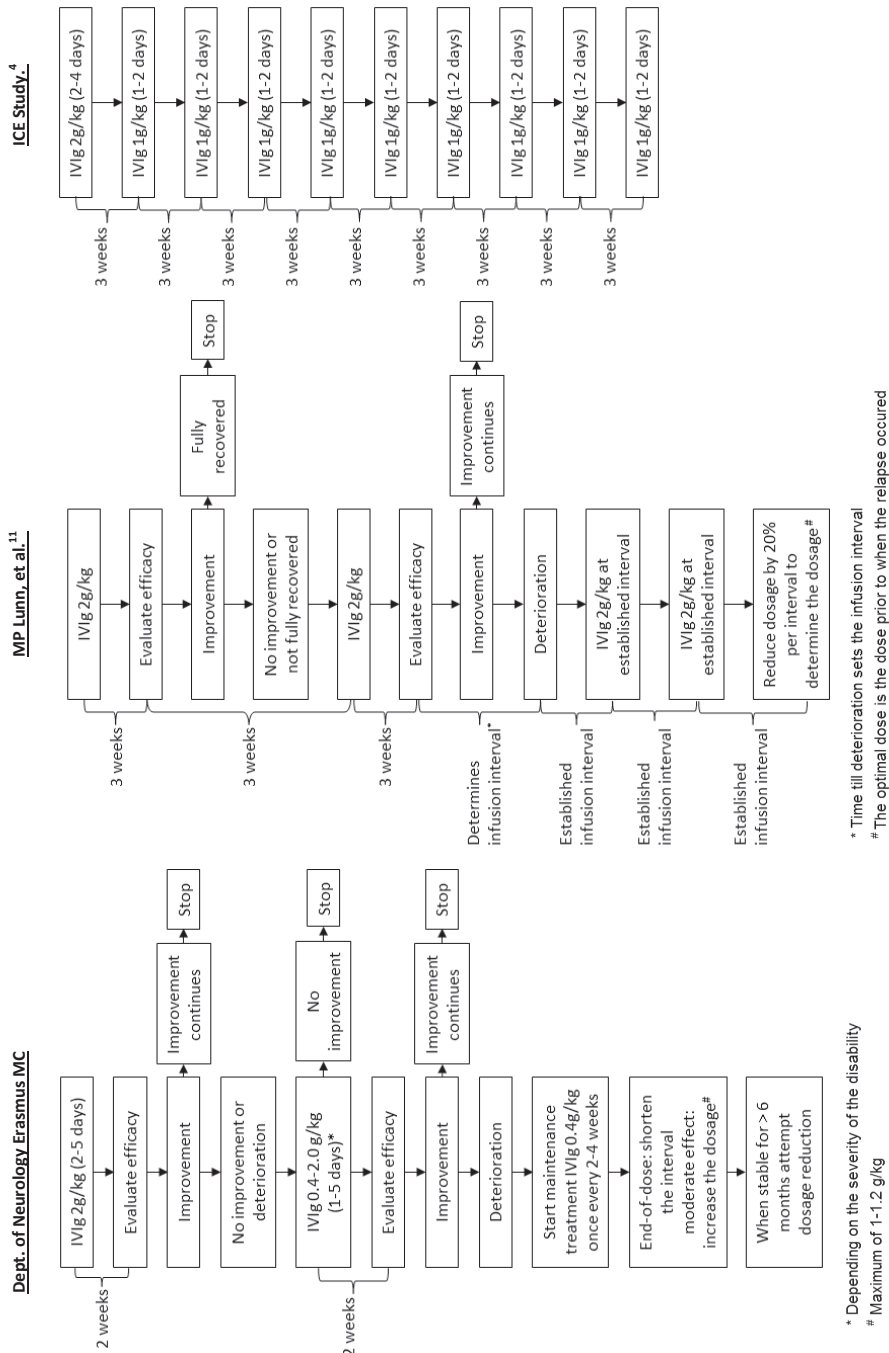


Figure 1. Alternative maintenance regimens of intravenous immunoglobulin (IVIg) treatment in chronic inflammatory demyelinating polyradiculoneuropathy



Table 1. Guideline for IVIg treatment in CIDP

Initial IVIg loading dose	Standard: 2 g/kg (2-5 days) Number of days depending on age and body weight. Consider lower IVIg dosages in case of impaired renal function
No improvement after first IVIg course	Check diagnosis Repeat 2 g/kg (2-5 days)
No improvement after second IVIg course	Check diagnosis Start corticosteroids, in case of pure motor CIDP give plasma exchange
Improvement followed by deterioration (first time)	Repeat IVIg treatment usually 0.4-2 g/kg, depending on severity and rate of deterioration
Improvement followed by deterioration (second time)	Start maintenance treatment: either fixed (1g/kg once every 3 weeks) or individualised*
Suboptimal improvement	Increase the dose (or shorten the interval)
Clear end-of-dose effects	Shorten the interval
Deterioration during period of relative stable course of disease	Consider giving an "extra dose of IVIg" (e.g. 0.4 g/kg) in between the usual interval
Stable for 6 months	Check IVIg dependency [#]

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; IVIg, intravenous immunoglobulin;

*Using either the "start low and increase till maximum effect" or the "start high and decrease till minimum effective dose" approach, usually 0.4-1.0 g/kg once every 2-6 weeks.

[#]By lowering the dose (or lengthen the interval).

several years. Third, patients do not need a continuous increase in dosage with prolonged treatment with IVIg.^{10,44} Investigation if IVIg treatment leads to treatment dependency is difficult because reasons why CIDP patients go into remission and predictors of remission are unfortunately still unknown.²⁴ In our experience the median time on IVIg treatment before it successfully can be stopped is about five years.

High peaks or high troughs?

Immunoglobulin G (IgG) is the major component of IVIg and is probably responsible for most of the immunomodulating effects.⁴⁵ In Guillain-Barré syndrome (GBS), we have reported that a higher increase in serum IgG 2 weeks after IVIg treatment was associated with a better outcome.⁴⁶ This study suggested that an increase in IgG above a certain threshold level is needed to gain a substantial effect of IVIg in GBS.⁴⁶ It is also reported that the serum IgG level needs to increase above a certain threshold level in CIDP patients treated with IVIg in order to be effective.⁴⁷

It is currently not known how to reach optimal immunomodulation in CIDP; whether keeping the plasma level of IgG high for prolonged periods is better than spiking the immune system intermittently with high doses of IVIg.⁴⁸ It is known that the catabolism of IgG is proportional to its serum concentration.^{49, 50} When the plasma IgG concen-

tration reaches 200% of its normal value, the half-life of IgG decreases from 21 to 12 days.⁵¹ A high peak dose may therefore result in greater catabolism of IgG which might be avoided by giving smaller doses more often.⁵² Very high peak levels, however, may not be needed in either the induction or maintenance treatment of CIDP or MMN.^{19, 53-55} Shortening the interval between IVIg infusions in CIDP results in a higher IgG trough level which appears to correspond to clinical efficacy.^{50, 56} Subcutaneous immunoglobulin therapy (SCIg) has been shown to be effective as maintenance treatment of CIDP.⁵⁷ It is administered at lower dosages and at more frequent intervals compared to IVIg, resulting in higher trough and more stable serum IgG levels.^{50, 58, 59} The most frequently used dosage when switching from IVIG to SClg is 1:1, although some studies suggest that a higher dosage is needed.⁵³ In general dosages of up to 50 g per week are tolerated, using 2-3 weekly injections.⁵³ Two trials comparing SClg to IVIg in CIDP or MMN suggested a somewhat better effect of SClg on muscle strength than IVIg which might be the result of the more stable IgG levels due to the more frequent infusions.⁵⁹⁻⁶¹ A recent trial comparing the efficacy of IVIg to SClg in treatment-naïve CIDP patients reported similar effects on muscle strength, with an earlier maximum effect after IVIg treatment.⁶² The disease duration of CIDP before enrolment although was much longer in the IVIg treated group.⁶² Results of this study suggest that a loading dose of IVIg might not be needed to initiate a therapeutic response.⁶² It is nowadays a question whether more patients should be shifted from IVIg to SClg for health-economic reasons or convenience.⁵³

In primary immunodeficiencies, serum IgG levels are used to optimise the dosage and interval of the IVIg maintenance treatment.⁶³ At present it is unknown if serum IgG levels can also be used as a reliable biomarker in CIDP. The most likely purpose of IVIg maintenance treatment in CIDP is to maintain a constant serum IgG level above a certain threshold in order to control the inflammatory process and to reach a stable clinical situation.^{22, 47, 64} Relapses are reported to correspond with a drop in serum IgG level.⁴⁷ It has been speculated that both patients with CIDP or immunodeficiencies being treated with regular immunoglobulin treatment prefer regimens with shorter IVIg intervals due to the fact that they often experience wear-off effects before their next dose.²⁹ Considering its half-life it is not surprising that the effect of IVIg is not always maintained over a 3-4 week interval.^{35, 61} A recent study on patients who were referred to a neuromuscular clinic with the diagnosis of refractory CIDP showed that the most frequent intervention required for a response to IVIg was increasing the frequency of IVIg maintenance treatment from once every 4 weeks to once every 2 weeks.⁶⁵ Another report regarding patients who were considered to be IVIg unresponsive were in fact patients who showed a very short response to IVIg and were in need of IVIg maintenance treatment with a very short treatment interval.⁴⁷ This indicates that some CIDP patients misclassified as non-responders to IVIg might in fact be undertreated.

How to optimise or individualise IVIg treatment?

Currently there are no biomarkers to predict disease activity and to avoid over- as well as under-treatment in CIDP. Serum IgG levels may be helpful in finding the best dose and interval. Clinically stable patients with CIDP on fixed IVIg maintenance treatment reach a certain steady-state IgG level, which confirms the fact that patients do not need higher (or lower) dosages over time in long-term IVIg treatment.²² Ideally, one would be able to predict individual pharmacokinetics of IVIg based on simple clinical characteristics of patients in order to optimise and individualise IVIg treatment.

Two studies have shown how daily self-monitoring of muscle strength can be very useful in establishing the optimal dose and interval in individual patients.^{35, 66} A good instrument for this is the Martin-Vigorimeter which measures handgrip strength.⁶⁷ It is a simple assessment tool providing indicators that tended to parallel or precede initial improvement in inflammatory neuropathy cause and treatment disability score in a placebo-controlled trial that confirmed the efficacy of IVIg.¹⁷ Stronger grip strength has been reported to translate into better functionality for patients.⁶⁸ The Vigorimeter is recommended for use in studies in inflammatory neuropathy based on its reliability, responsiveness, validity and patient satisfaction.⁶⁹

A small study suggested that serum IgG concentrations correlate with the clinical condition in CIDP patients on IVIg maintenance treatment.⁴⁷ Patients seem to have their own individual threshold level and a decrease in serum IgG level beneath this threshold led to clinical fluctuations.⁴⁷ Monitoring of serum IgG level as well as clinical scores were used to guide IVIg dosage and frequency in four CIDP patients.⁴⁷ The effect of different IVIg dosages during maintenance treatment of CIDP will be investigated in a new international RCT (ProCID study) that is currently recruiting patients (ClinicalTrials.gov NCT02638207). Whether more frequent, but lower IVIg dosing leads to more stable IgG levels with higher trough levels and better clinical efficacy is currently being investigated in The Netherlands in a dose-response RCT in CIDP (DRIP study). This trial has been registered in the Dutch Trial register as NTR3705.

CONCLUSIONS

There is limited evidence how to determine the optimal IVIg maintenance treatment regimen for a CIDP patient. The current weight-based dosing is probably inappropriate. IVIg dosages and intervals vary substantially between individuals and to give the optimal dosage and interval, treatment should be personalised. How this can be achieved best is currently unknown. To obtain the maximum effect of IVIg, it is unknown whether high peak levels of IgG are needed, whether IgG levels should reach a certain threshold above which an effect appears, or if more constant serum IgG levels are pre-

ferred. Potential biomarkers to achieve optimal maintenance treatment are: serum IgG levels and/or pharmacokinetics analysis, yet to be determined specific autoantibodies, genetic polymorphisms influencing IVIg pharmacokinetics, or simple and easy to use muscle strength dynamometry. The results of new trials or the testing and validation of proposed dosing algorithms will hopefully help to unravel the long-lasting discussions on IVIg dose and frequency requirements in CIDP.

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