

<http://hdl.handle.net/1765/105969>



Discussion



GBS and CIDP show many similarities but are usually considered separate disorders mainly based on differences in duration of onset, subsequent disease course and response to treatment. There are other differences, like the occurrence of preceding infections or antiganglioside antibodies but many similarities also exist. In clinical practice the distinction between GBS or CIDP may not be straightforward and some patients do not fulfil the strict diagnostic criteria for GBS (duration of progression less than 4 weeks) or CIDP (duration of progression at least 8 weeks).¹⁻³ First, there are patients with an onset phase of 4-8 weeks that have been described as subacute idiopathic demyelinating polyradiculoneuropathy (SIDP).⁴ Second, some patients initially fulfil the criteria for GBS and are diagnosed as such, and then show secondary deteriorations after initial improvement or stabilisation with IVIg or PE treatment, or show further progression for a period exceeding 8 weeks without these treatment-related fluctuations (TRFs). These patients are eventually diagnosed with an acute-onset (A-CIDP). Third, although GBS is in general a monophasic disorder, some patients do have recurrences of acute weakness and should be diagnosed with recurrent GBS and treated accordingly. Fourth, some CIDP patients have a monophasic course, needing only one IVIg treatment course before they get into remission. Fifth, some cases have been reported in which individual patients had separate episodes of both GBS and CIDP. These clinical observations may suggest that GBS and CIDP share common host susceptibility factors and/or form a continuous spectrum of inflammatory polyradiculoneuropathies. An accurate diagnosis has major implications for both the monitoring and treatment of individual patients.

For GBS, IVIg is usually the first choice treatment since plasma-exchange (PE) requires good vascular access and specific facilities and may be difficult to perform when patients have autonomic disturbances, and because PE is less convenient treatment with PE is less likely to be completed.⁵ All patients treated with IVIg receive the same initial arbitrary dose of 2 g IVIg per kg body weight (usually divided over a five-day course). This dosage is based mainly on the clinical experience of treating patients with idiopathic thrombocytopenic purpura. Not all GBS patients, however, have a good recovery after this standard dose and some show an end-of-dose effect with deterioration after initial improvement, a so called TRF, which can be treated successfully with another course of IVIg. The severity of GBS as well as the outcome (after four weeks or six months) varies considerably between patients and therefore it is likely that this standard course of IVIg might not be optimal for all. Although the exact working mechanism of IVIg is still unknown, IgG is the major component of IVIg and probably responsible for most of the immune modulating effects. IVIg clearance and consumption may vary between individual patients with GBS, suggesting that some patients may show better recovery after a higher dosage or second IVIg course. In contrast to CIDP, corticosteroids (given either oral or IV) are not effective in GBS.⁶ There might be a limited short-term additional effect of IV methylprednisolone added to IVIg after correction for prognostic factors.⁷

For treatment of CIDP, IVIg, PE, and corticosteroids have all proven to be beneficial. Corticosteroids and IVIg differ in terms of cost, speed of action and adverse events. There is no consensus on which is the best treatment for individual patients of CIDP. In CIDP, IVIg treatment is started with the same arbitrary standard dosage of 2 g/kg as in GBS. Most patients with CIDP require maintenance treatment for a prolonged period of time, some even till up to more than 30 years. IVIg maintenance treatment regimens vary considerably between CIDP patients and between institutions. IVIg treatment schedules seem to be dependent on both disease activity but may also be related to individual differences in catabolism of IVIg. Fast IgG metabolisers may require a shorter infusion interval than slow metabolisers. How maintenance IVIg treatment should be given and how treatment should be individualised by defining the optimum dosage and interval is currently unknown and is usually done by trial and error and seems to be related to the preference of local neurologists or departmental guidelines.

In this thesis we investigated the diversity of GBS and CIDP with its overlapping forms as well as the variation in response to treatment, with a focus on the treatment with IVIg. Defining the variation in subtypes of inflammatory neuropathy patients as well as the diversity in treatment response is important in order to be able to individualise treatment regimens.

In this chapter the main results of these studies, as described in chapter 2-4, will be discussed in relation to the available literature. Based on these results, recommendations for clinical practice are provided and suggestions for further research will be given.

THE SPECTRUM OF GBS AND CIDP

Recurrences of GBS have been reported in small case series to occur in about 2-5% of patients.^{8,9} In **chapter 2.2** we describe the largest group of recurrent GBS patients published so far. This was the first study comparing the characteristics of recurrent GBS with those of non-recurrent GBS patients. Since we identified 32 patients with recurrent GBS out of a total of 524 GBS patients, the crude estimated prevalence is around 6%. In these patients, the clinical symptoms in a first episode were often similar to the following episodes (either GBS or MFS; pure motor or sensory-motor) but the severity of the symptoms and the nature of the preceding infections varied between episodes. There was a trend towards a shorter interval between episodes and a more severe deficit with each recurrence. A later study from the Gothenburg region confirmed that the frequency of recurrent GBS is 6%.¹⁰ This study that used our definition of recurrent GBS, found that there was a trend towards similar viral infections in recurrences.¹⁰ Some patients in our study had very specific recurrent symptoms during subsequent episodes, such as unilateral cranial nerve palsy at the same site. Replicated laterality of cranial nerve dysfunction

has been described before in MFS.^{11,12} The results from our study suggest that some patients have a susceptibility to have an abnormal immune reaction to certain types of infection, resulting in a person-specific immune-mediated nerve injury. The finding of similar symptoms in individual recurrent GBS patients has been reproduced later in an Asian cohort.¹³ In our cohort, recurrences of GBS occurred more frequently in young patients (<30 years), in those with milder symptoms and in patients with the MFS variant. Age as a risk factor for a recurrent GBS was not described in the literature before. After the publication of our study another study group confirmed that the mean age in the recurrent GBS patients was significantly lower than in the non-recurrent ones (35 vs. 51 years).¹⁰ Why a younger age predisposes for a recurrent course is unknown. It is possible that an immunological host factor is involved and that younger GBS patients in general have more time ahead to encounter infections that results in an immune-response to nerves causing a recurrence. Furthermore, in younger patients the immune system might be more active and vulnerable to develop a recurrence. In addition, patients with a specific genetic and or immunological predisposition to develop GBS might develop the disease at an earlier age. The mean age of patients with a relapsing course of CIDP has been reported to be lower compared with CIDP patients with a non-relapsing (monophasic or progressive) course (27 vs. 51 years).¹⁴ This further strengthens the idea that GBS, recurrent GBS, relapsing CIDP and other varieties of CIDP all form parts of the same spectrum of inflammatory neuropathies. Patients with the MFS subtype were also found to be more likely to have a recurrence than GBS patients in an Asian cohort.¹⁵

Interestingly, other autoimmune diseases were more common in recurrent GBS than in non-recurrent GBS patients although this did not reach the conventional level of statistical significance ($p = 0.05$). Despite its retrospective nature, our study provides important information that patient-specific genetic and/or immunological host factors likely play an important role in recurrent GBS and are probably more important in determining the clinical phenotype than external factors such as preceding infections.

The rare case descriptions of patients who had had separate episodes of both GBS and CIDP (**Chapter 2.1 and 2.3**) further suggests that GBS and CIDP may constitute a clinical continuum and that there are common host specific factors that influence the susceptibility for inflammatory polyneuropathies. After our publication, a Swedish publication described two recurrent GBS patients who developed a progressive clinical course similar to CIDP.¹⁰ The fact that these patients were published in a paper on recurrent GBS shows that differentiation between GBS and CIDP can be difficult and perhaps they should be considered as part of a continuum.

In **Chapter 2.1** the results of a survey among 461 members of the Dutch society of neuromuscular disorders are described. A total of 245 GBS and 76 CIDP patients were included. Nineteen of these 245 (7%) GBS patients reported a recurrence and in 9 of these we could verify the recurrence by screening of medical letters (4%). Two patients

had separate episodes in which they both had GBS and CIDP. Other autoimmune diseases were present in 9% of GBS patients (23/245) in this cohort which is higher than the prevalence of 5% reported in the general population.¹⁶ Another study reported a higher frequency of other autoimmune diseases in multifocal motor neuropathy (MMN) another inflammatory neuropathy.¹⁷ In a large Dutch and Canadian cohort of CIDP patients as described in **Chapter 3.3**, other autoimmune diseases were present in 13% of CIDP patients (35/281), and 5 of these 35 patients even had multiple autoimmune disorders.

GBS is an immune-mediated disease that can be triggered by preceding infections but potentially also by vaccinations. The possible association of inflammatory polyneuropathies with vaccination causes considerable uncertainties among patients and society. To help answer the question of whether patients with GBS or CIDP may be vaccinated, we studied the recurrence of GBS after receiving a vaccination. In our study, described in **Chapter 2.1**, none of the 106 GBS patients who received a flu vaccination (range 1-37 times, with a total of 775 vaccinations) in the years after they developed GBS reported a recurrence thereafter. Of the 24 patients who received a flu vaccination (range 1-17 times) after being diagnosed with CIDP, five reported an increase in symptoms after one or more vaccinations. The results of our study indicate that the risk of developing a recurrence of GBS after a flu vaccination is small, and that flu vaccinations seem relatively safe in patients who have had GBS or still have active CIDP. In 1976 the American vaccination programme against the swine flu virus, an influenza virus, was stopped prematurely due to an increase of cases developing GBS after vaccination.¹⁸ In 2009 the world witnessed the emergence of another influenza virus of swine origin that was a serious public health threat. After the quick development and start of the vaccination campaign against the Mexican flu (H1N1) the question was raised whether GBS and CIDP patients could receive a vaccination safely.¹⁹ The results of our study and the fact that the chance of getting (recurrent) GBS after a vaccination is probably much smaller than the chance of getting (recurrent) GBS after a flu infection itself resulted in our recommendation, as well as that from others, that GBS or CIDP is no absolute contraindication for a flu vaccination.¹⁹⁻²² In GBS or CIDP patients with a reason for a flu vaccination, due to advanced age or comorbidity, the risk of getting GBS after flu infection is probably higher than the risk of the vaccination itself. This recommendation has been further supported by other studies.²³⁻²⁵ It is important to mention that GBS or CIDP patients who do not belong to this risk group, should not have vaccinations. When a CIDP patient receives a vaccination one should be aware that a temporary increase of symptoms may occur but this is usually minor and does not require extra treatment.^{20,22,26} A flu vaccination is relatively contraindicated in patients who had GBS recently (past 6 weeks) or in patients with a history of GBS in the six weeks after a flu vaccination. A large multinational study in Europe, including the Netherlands, did not observe an associa-

tion between the influenza H1N1 vaccine and GBS, after adjustment for confounders.²⁷ Although our survey (**Chapter 2.1**) provided useful information regarding the safety of vaccinations it has several methodological limitations due to its retrospective nature such as selection as well as recall bias. Strong aspects however are the large numbers of patients included (response rate of 70%) with an extended follow-up time and the fact that we confirmed the diagnosis of recurrence.

**Recurrences and vaccinations in patients within the spectrum of GBS and CIDP:
some key-points for clinical practice**

1. Recurrence of GBS is rare, with a recurrence rate of around 6%.
2. Recurrences of GBS are more likely in patients under 30 years of age, in those with initial milder symptoms and in patients with MFS.
3. CIDP patients can experience a temporary minor increase of symptoms after a flu vaccination.
4. Seasonal flu vaccinations seem relatively safe in GBS or CIDP patients. GBS or CIDP itself is no reason to have a flu vaccination.

TREATMENT OF CIDP

IVIg, PE and corticosteroids are effective treatments for CIDP, but each treatment may be more or less effective in certain individuals or a subgroup of patients and may cause treatment specific side-effects.²⁸ In **Chapter 3.1** we give an overview of their efficacy, side effects, costs and availability in order to guide clinicians in their choice of treatment. An update of the Cochrane reviews is given in **Table 1**. The fact that the proof of evidence for IVIg is better than for corticosteroids even on the long-term, its faster speed of action and better (long-term) side-effect profile is probably the main reason that IVIg is often the first treatment choice in countries where IVIg is available and affordable. The main advantage of corticosteroids is its low price and ease of administration. A recent study has found that high-dose (pulsed) treatment with corticosteroids is likely to induce a more long-lasting effect than IVIg, since the time to relapse is longer after discontinuing steroids than after IVIg.^{29,30} On the other hand, IVIg was shown to be superior over high-dose corticosteroids because it was effective more often and better tolerated.²⁹ Our study, as described in **Chapter 3.3**, indicates that IVIg is a very effective treatment and that (long-term) adverse events are minor and hardly ever a reason to withdraw treatment. High-dose corticosteroids given as pulsed therapy may result in less side-effects than daily oral steroids although this has not yet been proven.³¹ Not much is known about the risk of side-effects of corticosteroids in CIDP because most trials have an insufficient follow-up period to capture these on the long-term.³² PE has the advantage of a fast speed of action, similar to IVIg. In a retrospective study, side-effects leading to therapy interruption, occurred more often after PE (19%), than in steroid (12.5%) or IVIg (4%) treatment.³³ The disadvantage of PE is that PE is less convenient and special

Table 1. Cochrane reviews in the treatment of CIDP

Study	Treatment	Efficacy	Speed of action	Potential long-term adverse effects	Availability	Costs
Eftimov ³⁸	IVIg	Proven	Fast	Minor	Good	High
Hughes ³⁹	Corticosteroids	Proven	Moderate	Severe	Very good	Low
Mehndiratta ⁴⁰	Plasma exchange	Proven	Fast	Minor	Variable	High
Mahdi-Rogers ³⁵	Other immunomodulatory drugs	Unknown	Variable	Severe/variable	Good/variable	Moderate/variable

equipment is needed for the procedure. Therefore, PE is usually given only when both IVIg and steroids have shown to be ineffective. There is no evidence so far from RCTs for the effectiveness of other immunomodulatory drugs in CIDP.^{28,34,35} Patients diagnosed with CIDP, who do not improve after IVIg, corticosteroids or PE, should have their diagnosis reconsidered.³⁶ Patients who become unresponsive to treatment should be re-evaluated for the appearance of a monoclonal protein or other signs of malignancy.³⁷

Since some CIDP patients reported that one brand of IVIg seemed more efficacious than another; we compared the efficacy of two immunoglobulin brands in a RCT (CIC study).^{41,42} The results of this trial are described in **Chapter 3.2**. This trial did not find any differences in efficacy between two different IVIg products (a liquid and a freeze-dried product). The limitations of this study are that it was an equivalence study and that for practical reasons only two products were compared (both manufactured by the same pharmaceutical company and likely from the same donor population). Our study was the first RCT to compare various IVIg brands in inflammatory neuropathies. After this publication, another study showed similar results.⁴³ Although different IVIg brands all contain similar amounts of IgG, they differ slightly in composition, purification and virus elimination process.⁴⁴ In patients with renal failure, preparations with a low sugar or sucrose content are recommended and patients with thromboembolic risk factors are likely better off being treated with preparations with a lower osmolality and protein level infused over a longer period of time.⁴⁴ Currently another RCT is comparing two different IVIg preparations in CIDP.^{28,45} Different IVIg brands did not seem to differ much in respect to IgG Fc-glycosylation as well.⁴⁶ Since IVIg brands are similar in efficacy, trying a different brand of IVIg in patients who show no response to IVIg is unlikely to be useful. It may however be tried when patients experience more than usual side-effects related to IVIg treatment.

In **Chapter 3.3** we describe a study that included 281 CIDP patients from two neuromuscular disease centres that all received IVIg as a first treatment. These patients were followed for a mean duration of 5 years (median 3.8 years, range 20 days-28 years). A clear and significant response to IVIg (improvement ≥ 1 grade on the mRankin scale)

was achieved in 76% of patients. The higher response rate to IVIg in our study compared to the ICE trial (response rate of 58%) is likely due to the fact that the diagnosis in our study was always established by a senior neurologist with long-term experience in the diagnosis and treatment of CIDP.^{47,48} Although most patients required long-term treatment, 16% of the treatment responders who achieved a documented clinical remission needed only one IVIg course, a similar percentage has been reported before.² If these patients had been treated with corticosteroids as a first treatment they probably would have been on steroids for many months due to the need for slow tapering with steroids. In the largest clinical trial of IVIg in CIDP side effects were also an infrequent reason to stop treatment even over the long term.^{48,49} In our study, most of the IVIg non-responders received an alternative subsequent treatment successfully; 66% improved after plasma exchange and 58% with corticosteroids. Of the IVIg non-responders who were treated with at least one other treatment modality, about three quarters improved after either PE, corticosteroids or both. The response rate to second as well as third treatment modalities (corticosteroids or PE) we found was higher compared to what has been reported in the literature.^{33,50} Although our study was non-blinded, it provided an important implication for clinical practice, as it seems very useful to try one or even two of the other three evidence based efficacious treatments before moving to other immunomodulatory treatments since efficacy of these treatments has not been proven in CIDP.³⁵ Given the high success rate of IVIg, PE and corticosteroids, combining two treatments is rarely necessary and might cause an unnecessary risk of (more) side effects. In CIDP both corticosteroids and IVIg are in general efficacious, but some patients for unknown reasons do not respond to either one of the two treatments. In multivariate analysis, the presence of pain or a difference in level of weakness between arms and legs was associated with a lack of response to IVIg in our study. Whether these patients are better off when treated with corticosteroids still needs to be investigated. Some of the patients from our cohort have been included in a previous study from the Erasmus MC that already showed an association between no response to IVIg and a discrepancy between weakness of the arms and legs.⁵¹ In patients with pure motor CIDP, IVIg is generally recommended as a first choice because corticosteroids can lead to a dramatic clinical deterioration, as we have experienced several times.^{2,52} A post-hoc analysis of the PREDICT trial, comparing dexamethasone with prednisolone in CIDP, reported an association of less sensory electrophysiological abnormalities with early deterioration in CIDP patients treated with corticosteroids.⁵³ In our cohort, 46% of pure motor CIDP patients however did show a significant improvement after steroids; therefore this treatment should not be omitted in pure motor CIDP if IVIg is not efficacious.

In our cohort, there were only 3 patients who did not respond to any of the three proven effective treatments, all were screened again but no alternative diagnosis was found. The high response rate to the first as well as the second or third treatments mo-

dalities in our study is likely due to the short interval (median 4 months) from symptom onset to start of treatment and the fact that patients were treated in neuromuscular centres with a long experience and expertise in diagnosing and treating CIDP by experienced doctors. This may be important because recent studies from the USA showed that the diagnosis of CIDP is often made incorrectly, especially by non-neuromuscular specialists, in patients with another cause of neuropathy or no neuropathy at all.^{54,55}

Important limitations of our study (**Chapter 3.3**) are its retrospective nature and the fact that some items, such as pain or other autoimmune disease, were not assessed in a standardised manner. Subgroups of patients who only improved after a third treatment modality were relatively small, and therefore offer limited information. Currently it is not possible to predict whether an individual CIDP patient will improve after IVIg or steroids or whether a treatment failure is more likely. Animal models of CIDP are being developed and used to continue the search for biomarkers in order to be able to predict the response to IVIg.⁵⁶ CIDP patients with antibodies of the IgG4 isotype against paranodal proteins contactin-1 (CNTN1) and neurofascin-155 (NF155) share specific clinical features and are less likely to respond to IVIg.^{57,58} Although specific autoantibodies can be detected only in a small group of CIDP patients so far, they can be useful in guiding treatment choice. It has been suggested that rituximab might be useful in these patients with IgG4 antibodies.⁶⁰ Recently it has been reported that CIDP patients with contactin-associated protein1 (CASPR1) are less responsive to IVIg and they show severe neuropathic pain, since the presence of pain was associated with no response to IVIg in our cohort it will be interesting to check these patient for these antibodies.⁵⁹ Furthermore it is possible that the discrepancy in weakness between arms and legs that we found to be associated with no response to IVIg, can be explained by axonal changes due to certain antibodies.

Although IVIg, corticosteroids and plasma exchange are all proven efficacious in CIDP, many questions still remain. Maintenance treatment regimens vary largely between patients and the best strategy to adjust maintenance IVIg treatment in individual patients with CIDP is unknown. In **Chapter 3.4** we give an overview of what is currently known regarding IVIg maintenance treatment and give guidance on how maintenance treatment can be given in clinical practice. We are currently investigating in an RCT whether more frequent low IVIg dosing is more effective than low frequency high dosing as maintenance treatment in CIDP (DRIP study) which is briefly pointed out in **Chapter 3.5**.

Treatment of CIDP: practical key-points

1. Around three quarters of treatment-naïve CIDP patients is responsive to IVIg.
2. In CIDP patients who do not respond to one or two courses of IVIg, trying a different brand of IVIg is unlikely to be useful.
3. In IVIg non-responders, the response rate to steroids or PE is still quite high. Therefore, these treatments should both be tried first before trying other immunosuppressive drugs that have not been proven to be efficacious.
4. Although there is a risk of deterioration, pure motor CIDP patients can show a good response to corticosteroids. This implies that when IVIg is not efficacious, treatment with corticosteroids should not be omitted.
5. Patients without a difference in weakness between arms and legs and those without pain are more likely to improve after IVIg.
6. From the patients who are IVIg responsive and who reach a clinical remission, about 15% only needs one course of IVIg.
7. Most CIDP patients need IVIg for a long period of time, but side effects are hardly ever a reason to stop treatment, even on the long-term.

SERUM IGG LEVELS IN IVIG-TREATED GBS AND CIDP

The working mechanism of IVIg in GBS and CIDP is still unknown and patients are treated with the same standard induction dose (2 g/kg in 2-5 days) for many years based on studies in idiopathic thrombocytopenia.^{61,62} Not all patients recover well after this standard dose, but studies comparing different IVIg dosages have not been done in GBS. It has been shown that the number of plasma exchanges could be adjusted to the severity of GBS, and that in CIDP the response (rate and magnitude) can be improved by either repeating or increasing the dosage.^{63, 64} In the treatment of CIDP it is known that at least two IVIg courses may be required before patients show an improvement.⁶⁵ A small case series suggested that a second IVIg course might be beneficial in severe unresponsive GBS patients.⁶⁶ Although not formally investigated, re-treatment with IVIg is recommended in GBS patients who show a treatment-related fluctuation (TRF).^{67, 68} These findings indicate that patients with inflammatory neuropathy may not respond equally to a standard IVIg dosage and that some patients may benefit from a higher dosage or additional course of IVIg. The differences in treatment response may be related to a variation in the clearance or consumption of IVIg. In patients with primary immunodeficiency the pharmacokinetics of IVIg have been reported to show considerable variability, which may suggest that a similar variability is present in patients with inflammatory neuropathies.⁶⁹

In **Chapter 4.1** we describe a study that was conducted with 174 GBS patients, who had all participated in one of two previous RCTs and were treated with a standard course of IVIg (2 g/kg in 5 days).^{7,70} We found considerable variation between GBS patients in the pharmacokinetics of a standard course of IVIg. Patients with a low increase in serum IgG two weeks after standard IVIg treatment (delta IgG level) had a more severe course of disease expressed as a higher GBS-disability score and a lower MRC sum score both

at entry and nadir. The time required to improve one grade on the disability scale was significantly longer in the patients with the lowest increase in serum IgG. A low increase in serum IgG two weeks after IVIg was associated with a worse outcome, independent of other prognostic factors. Our data suggest that a certain threshold of delta IgG (> 7.30 g/L) is required for a substantial therapeutic effect in GBS. When adjusted for the Erasmus GBS Outcome scale (EGOS) prognostic model,⁷¹ the delta IgG level was still associated with the outcome at six months (**Chapter 4.1**). From these results, it can be concluded that a subgroup of GBS patients may likely benefit from a second course of IVIg. Whether some patients, for example those who metabolise IVIg faster, have a better outcome when treated with a second course of IVIg requires further investigation in a RCT. Based upon the results of our study, the second IVIg dose trial in GBS patients with a poor prognosis was started (SID-GBS trial), registered in the Dutch trial register as NTR2224.⁷² Although some GBS patients with a poor prognosis are already treated in clinical practice with another course of IVIg, results from a RCT are needed to prove whether this is justified.⁷³

In our study, GBS patients with a higher pre-treatment serum IgG level had slightly more disability in the acute stage. A higher disease activity with more extensive immune activation and nerve damage may result in a higher consumption of IVIg. Patients with a higher serum IgG level are known to have a higher catabolism of IgG, probably caused by the saturation of the pool of neonatal Fc receptors that protects IgG from degradation.⁷⁴⁻⁷⁶ The expression level of the neonatal Fc receptor (FcRn) is influenced by the number of gene copies, but a recent study found no difference between this genetic polymorphism and the pharmacokinetics of IVIg or outcome in GBS.⁷⁷ It is interesting that the serum IgG level at a three and six month time period did show statistically significant differences between groups of GBS patients with different FcRn polymorphisms.⁷⁷ It is possible that the “baseline” serum IgG level, before the administration of IVIg, is influenced by the acute stage of the disease suggesting that serum IgG levels being measured much later are more representative for the individual “baseline” IgG level.⁷⁷ This means that a relationship between FcRn polymorphisms and serum IgG levels cannot be ruled out. Serum IgG levels are associated with serum albumin levels which may be explained by the fact that both IgG and albumin are protected against degradation by the FcRn.^{78,79} Patients with a mutation in the β 2-microglobulin chain of the FcRn have been reported to have a higher catabolism of IgG.⁸⁰ The higher IgG baseline level that we found in our GBS study only had a small effect on the variation observed in delta IgG level, and in multivariate analysis the pre-treatment serum IgG level was not associated with the outcome. After the publication of our results, the MMN research group in Utrecht investigated the pharmacokinetics of IVIg in MMN.⁸¹ Serum samples were obtained at somewhat different time-points before and after a standard course of IVIg (2 g/kg) in 23 treatment-naïve MMN patients.⁸¹ Similar to our results the authors

found a large variation in serum IgG level as well as in delta IgG between patients.⁸¹ Furthermore baseline IgG levels were higher and the mean delta IgG level was lower in IVIg non-responders but due to the low patient numbers it is likely that this study could not provide sufficient power to detect significant differences.⁸¹

The optimum dosage and frequency of maintenance IVIg treatment varies widely between CIDP patients.⁸² This variation might be partially explained by individual differences in IVIg catabolism and disease activity. In **Chapter 4.2** we describe a study in which we investigated serum IgG levels in CIDP patients with active but stable disease obtained from a previous RCT comparing two different immunoglobulin preparations in CIDP (**Chapter 3.2**). All patients were IVIg responsive and had been treated according to their own individual established optimum regimen of IVIg.² Similar to what has been reported in the literature, the total dosage of IVIg per infusion required to reach a stable clinical situation did not correlate with body weight.^{82, 83} This is of interest since at least the loading dose of IVIg is still based on body weight. Disability did not correlate with the IVIg dosage required, which is similar to what we observe in clinical practice where initially more severely affected CIDP patients do not seem to require a higher dosage than mildly affected patients of the same body weight. It has been reported previously that the dosage of IVIg required does not correlate with (initial) disability in CIDP.⁸² Although the inter-patient variability in increase in serum IgG immediately after IVIg was higher than the intra-patient variability in these CIDP patients (**Chapter 4.2**), both were considered low. Serum IgG levels remained relatively constant over time during subsequent courses of maintenance IVIg treatment in stable CIDP patients. More or less constant serum IgG levels (above a certain threshold) are probably needed to reach and maintain a clinical stable situation in CIDP. Different from our pharmacokinetic study in GBS (**Chapter 4.1**) is that all CIDP patients were known to be IVIg responders, and all were in a clinically stable situation receiving maintenance IVIg treatment according to individual established dosages and intervals. A limitation of this study is the relatively low number of patients that received exactly the same dosage and frequency of IVIg, reducing the amount of patients that could be compared. Two other studies published later on, found constant serum IgG levels during two courses of IVIg in CIDP.^{79,83} Both these studies reported large inter-patient variability, although the study by Rajabally et al. does not report whether they only compared patients with the same dosage and interval.^{79,83}

High peak levels of serum IgG may not be needed for maintenance treatment of CIDP with IVIg. Whether more frequent dosing of IVIg leads to more stable IgG levels and higher trough levels corresponding with an improvement in efficacy and less side effects is currently being investigated in an RCT in a cohort of CIDP patients (DRIP study) (**Chapter 3.5**).⁸⁴ It is reported that a decrease in serum IgG level seems to correspond with a higher level of clinical disability in MMN and CIDP.^{79,85,86} Serum IgG levels have

been used to guide dosage and interval of IVIg in CIDP for the first time in a small study.⁸⁶ If high peak levels are needed for the efficacy of immunoglobulins IVIg would be preferred above SCIg. If high peak levels are not needed and the efficacy is more dependent on stable serum levels as well as high trough levels, SCIg would be more favourable. The fact that a loading dose of IVIg (0.4 g/kg/day over 5 days) improved motor function to a similar degree as SCIg in treatment-naïve CIDP (0.4 g/kg every week) suggests that a loading dose is not always needed to initiate a therapeutic response.⁸⁷ In this study patients did show an earlier maximal improvement after treatment with IVIg compared to when treated with SCIg, which might be explained by the higher peak serum levels of IgG after the loading dose of IVIg.⁸⁷ Results of future trials are required to investigate whether monitoring of serum IgG levels can be used to improve the clinical efficacy of IVIg treatment in GBS or CIDP. Till then monitoring of serum IgG levels to adjust the IVIg dosage and interval cannot be recommended.

IgG levels in IVIg treated GBS and CIDP: practical key-points

1. GBS patients show considerable variation in the pharmacokinetics of IgG (after IVIg treatment) which is associated with the outcome at six months.
2. A low increase in serum IgG two weeks after start of IVIg is associated with a worse outcome in GBS, independent of other prognostic factors.
3. A subgroup of GBS patients may benefit from a higher dosage or second course of IVIg.
4. Body weight by itself does not seem to influence the IVIg dosage required for effective CIDP maintenance treatment.
5. In CIDP patients on maintenance IVIg treatment more constant serum IgG levels above a certain threshold level are probably required to reach and maintain a stable clinical situation.
6. Standard monitoring of serum IgG levels cannot be recommended until future trials provide more evidence that these levels are related to treatment response and outcome.

FUTURE PERSPECTIVES

To further investigate the whole spectrum of inflammatory polyneuropathies, including the rare subtypes such as GBS-TRF, recurrent GBS and A-CIDP; large prospective cohort studies are very helpful. The prospective International GBS Outcome Study (IGOS) started in May 2012 and by May 2017 included more than 1500 participants from 19 countries across 5 continents.⁸⁸ The IGOS is a perfect platform to gain a large amount of data regarding these rare subtypes of GBS from different geographical parts all over the world.⁸⁸ Large international studies such as IGOS will provide opportunities to study genetic susceptibility factors in the development of these inflammatory neuropathies possibly via techniques such as genome wide association studies or whole exome sequencing. Understanding why some patients develop recurrent GBS or chronic forms of inflammatory polyradiculoneuropathy might give more insight how to improve and personalise treatment.

Over the past 10-15 years, a lot of new information has been gathered that shed more light on the pathogenesis of GBS. A recent study has shown that former GBS patients show a stronger response to pathogen-associated molecules compared to healthy controls.⁸⁹ The next step could be to investigate whether patients with recurrent GBS show even stronger responses to pathogen-associated molecules compared to patients with a monophasic GBS. It is important to realise that GBS is highly diverse with respect to clinical course and outcome. Some less severely affected patients show spontaneous and complete recovery even without treatment, while others remain severely handicapped despite repeated IVIg treatment. Further studies are needed to understand what mechanisms influence this clinical diversity and how treatment can be personalised in such a way that each patient receives the optimal treatment for their own personal situation. The IGOS aims to define biomarkers for disease activity and recovery and to develop prognostic models to predict the clinical course and outcome in individual patients with GBS.⁸⁸ Partially based upon the results of our study, as described in **Chapter 4.1**, showing that GBS patients with a higher increase in serum IgG level two weeks after IVIg showed a better outcome, the SID-GBS trial was started.⁷² In this SID-GBS trial, GBS patients treated with a standard dose of IVIg that have a poor prognosis at day 7 defined by the modified EGOS prognostic model⁹⁰ are randomised to receive either a placebo or a second course of IVIg. Results of this RCT are expected by the end of 2018. If this trial can prove that a second IVIg dose is more effective in patients with a poor prognosis and/or a lower increase in serum IgG after the first course, this will lead to an improvement in treatment and outcome in GBS and as such will be a first step towards more personalised medicine in GBS. In the SID-GBS trial serum IgG levels will also be determined from an earlier time point (one week after the start of treatment) which is different from the study we have published (**Chapter 4.1**). Although the time window in which additional IVIg treatment is effective is unknown, it is likely that an early start of a second IVIg course is better (“time is nerve”) to avoid axonal damage or (para)nodal disruption. In CIDP a quick start of effective treatment is associated with a higher chance to be able to stop treatment later on.⁹¹

A prospective international observation study (I-SID GBS study, as part of the IGOS) is currently investigating whether a second course of IVIg (started within the first four weeks after onset of GBS) is more effective than treatment with one standard course of IVIg. The results of this observational study are likely to be published prior to the results of the Dutch RCT (SID-GBS trial). In large parts of the world, especially in low income countries, IVIg is not readily available or too expensive and GBS patients are left untreated or are treated with PE (or modified PE). The decrease in serum IgG level has been reported to differ between patients treated with (standard) PE.⁹² The French PE trial indicated that the number of plasma exchanges could be adjusted to the severity of GBS.⁶⁴ These papers together with the results of our study (**Chapter 4.1**) showing

an association between the delta IgG and outcome of GBS after a standard IVIg course, make it worth investigating whether patients with a poor outcome after PE have a lower decrease in serum IgG after standard plasma exchange (e.g. 4 sessions) and therefore would potentially benefit from more sessions of PE.⁶⁴ The IGOS study will provide more information on a very large scale regarding multiple topics studied in this thesis, including longitudinal serum IgG levels after IVIg in relation to outcome. In the IGOS study, serum IgG levels are determined at multiple time-points to determine IVIg pharmacokinetics. Additionally, DNA polymorphisms will be investigated to determine potential genetic susceptibility factors involved related to the response to treatment. These data likely will be available within the next few years.

It is unknown why some CIDP patients do not respond to IVIg. Future research should focus on finding explanations for this lack of response, but also on why some patients after being treated with IVIg successfully over many years at some point do not need treatment anymore. Why CIDP patients who do respond to IVIg require different dosages and frequencies is currently unknown and requires further investigation. A large scale international study similar to the IGOS is currently being prepared for in CIDP (ICOS study). This study will provide a large amount of data regarding the occurrence of A-CIDP, the response to IVIg treatment, as well as IVIg pharmacokinetics. These large international studies (IGOS and ICOS) provide unique opportunities to study genetic polymorphisms and other potential biomarkers that may explain why some patients do not respond to IVIg, require a higher dosage or prolonged IVIg treatment. The recent discovery of new antibodies in a small group of CIDP patients has led to an advance in understanding of the diversity of CIDP and its subforms and differences in the response to therapy. It is expected that over the next years new antibodies will be discovered in subgroups of CIDP patients that can be related to the treatment response which may further support the development of personalised treatment. Some concern has arisen recently whether IVIg leads to treatment dependency in CIDP when compared to corticosteroid treatment.³⁰ Some CIDP patients however only need one or two IVIg courses, and patients who have been treated with IVIg for years can still reach a remission without the need for further treatment. Treatment dependent patients were more often responsive to IVIg and resistant to corticosteroids compared to patients whose treatment could be withdrawn and were not treatment dependant.⁹¹

Future studies in CIDP will hopefully give an answer whether treatment dependency is due to clinical features or to the therapy used. Since IVIg acts fast, and high-dose steroids potentially may induce more frequent remissions, the Optimal Induction Treatment In CIDP study (OPTIC trial) has been initiated. This study will investigate whether the addition of methylprednisolone to IVIg will lead to an earlier remission. Future studies investigating serum IgG levels in CIDP patients treated with IVIg are expected. It is of interest to investigate serum IgG levels in treatment-naïve CIDP patients who receive their

first IVIg course and to compare responders versus non-responders in order to predict response and individualise therapy as early as possible. Currently we are investigating in a RCT (DRIP-study) whether high frequent low dosage IVIg treatment is more effective than low frequent high IVIg dosage as maintenance treatment for CIDP (**Chapter 3.5**). If our hypothesis is true that more stable IgG levels lead to a better efficacy, subcutaneous IgG (SCIg) might potentially be more effective than IVIg because it is usually given in smaller dosages more often over time. A recent small study found similar efficacy on the short-term after SCiG compared to IVIg in treatment-naïve CIDP patients, with an earlier improvement following IVIg treatment.⁸⁷ Very recently a large placebo controlled trial was published showing that SCiG is effective as maintenance treatment in CIDP.⁹³ In the future, more studies are needed to compare the efficacy and pharmacokinetics of SCiG versus IVIg.^{94,95} Since CIDP patients have been treated with IVIg for over 30 years it is remarkable that so many questions still remain regarding its working mechanism, what determines the response, and how IVIg treatment can be optimised.

FINAL REMARKS

GBS and CIDP, connected by their overlap forms such as recurrent GBS, GBS-TRF, monophasic CIDP and A-CIDP, should be considered parts of a spectrum of immune-mediated polyradiculoneuropathies instead of completely separate entities. Three facts appear to underline the importance of genetic and host-specific immune responses in GBS and CIDP; 1st only a small proportion of patients develop GBS after exposure to an identical infection, 2nd GBS and CIDP can co-occur in a single patient and 3rd GBS can reoccur at a higher rate than expected, showing similar symptoms after different infections.

Descriptions of specific individual cases can be relevant since these may give more insight into the clinical course and outcome of GBS and CIDP, especially in atypical patients who are often not covered in clinical trials. Since individual patients with GBS or CIDP can vary largely in clinical characteristics, severity, duration of progression, metabolism, and outcome, it is unlikely that one standard treatment regimen will fit every patient. It is important to choose the best treatment option in each individual as soon as possible in order to prevent secondary axonal degeneration, side-effects and unnecessary costs. Treatment with a standard IVIg dosage based on body weight alone does not fulfil the needs of every patient. More personalised treatment based on an individual's clinical subtype as well as genetic and metabolic factors instead of a one-size-fits-all approach can hopefully be applied in GBS and CIDP patients in the near future. Serum IgG levels may predict the clinical response to IVIg, but whether these levels can be used as biomarkers to improve IVIg treatment regimens needs to be determined in a RCT. Hopefully the results of the SID-GBS trial, that are expected by the end of 2018, will give

an answer as to whether a second IVIg course improves the outcome in patients with a poor prognosis. If it can be proven that monitoring of serum IgG levels can be used as a biomarker to optimise IVIg therapy this might also have an impact for other diseases that are currently treated with IVIg.

REFERENCES

1. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. *Ann Neurol* 1990; 27 Suppl: S21-4.
2. 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.
3. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet* 2016; 388(10045): 717-27.
4. Hughes R, Sanders E, Hall S, Atkinson P, Colchester A, Payan P. Subacute idiopathic demyelinating polyradiculoneuropathy. *Arch Neurol* 1992; 49(6): 612-6.
5. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev* 2014; (9): CD002063.
6. Hughes RA, Brassington R, Gunn AA, van Doorn PA. Corticosteroids for Guillain-Barré syndrome. *Cochrane Database Syst Rev* 2016; (10): CD001446.
7. van Koningsveld R, Schmitz PI, Meché FG, et al. Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barré syndrome: randomised trial. *Lancet* 2004; 363(9404): 192-6.
8. Grand'Maison F, Feasby TE, Hahn AF, Koopman WJ. Recurrent Guillain-Barré syndrome. Clinical and laboratory features. *Brain* 1992; 115 (Pt 4): 1093-106.
9. Das A, Kalita J, Misra UK. Recurrent Guillain Barre' syndrome. *Electromyogr Clin Neurophysiol* 2004; 44(2): 95-102.
10. Mossberg N, Nordin M, Movitz C, et al. The recurrent Guillain-Barré syndrome: a long-term population-based study. *Acta Neurol Scand* 2012; 126(3): 154-61.
11. Uchihara T, Ikeda M, Tsukagoshi H. Recurrent Fisher's syndrome with immunological abnormalities and replicated laterality. *Eur Neurol* 1991; 31(4): 270-2.
12. Orr CF, Storey CE. Recurrent Miller-Fisher syndrome. *J Clin Neurosci* 2004; 11(3): 307-9.
13. Pyun SY, Jeong JH, Bae JS. Recurrent Guillain-Barré syndrome presenting stereotypic manifestations, positive antiganglioside antibodies, and rapid recovery. *Clin Neuro Neurosurg* 2015; 139: 230-3.
14. McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy. A clinical and electrophysiological study of 92 cases. *Brain* 1987; 110 (Pt 6): 1617-30.
15. Ishii J, Yuki N, Kawamoto M, Yoshimura H, Kusunoki S, Kohara N. Recurrent Guillain-Barré syndrome, Miller Fisher syndrome and Bickerstaff brainstem encephalitis. *J Neurol Sci* 2016; 364: 59-64.
16. Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun* 2007; 29(1): 1-9.
17. Cats EA, Bertens AS, Veldink JH, van den Berg LH, van der Pol WL. Associated autoimmune diseases in patients with multifocal motor neuropathy and their family members. *J Neurol* 2012; 259(6): 1137-41.
18. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976--1977. *Am J Epidemiol* 1979; 110(2): 105-23.
19. Price LC. Should I have an H1N1 flu vaccination after Guillain-Barré syndrome? *BMJ* 2009; 339: b3577.

20. Kuitwaard K, Bos-Eyssen ME, Blomkwist-Markens PH, van Doorn PA. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. *J Peripher Nerv Syst* 2009; 14(4): 310-5.
21. Jacobs BC Wijnans L, Sturkenboom M, van der Maas N. Guillain-Barré syndrome en het nieuwe influenza A (H1N1)-virus. *Ned Tijdschr Geneesk* 2009; 153: A1490.
22. Jacobs BC WC, Drenthen J, Kuitwaard K, van Nes SI, van Doorn PA. Wel of niet vaccineren tegen het nieuwe influenza A (H1N1)-virus bij het syndroom van Guillain-Barré en CIDP? *Tijdschr Neurol Neurochir* 2010; 111: 17-9.
23. Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A, Rodrigues LC. Guillain-Barré syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. *PLoS one* 2007; 2(4): e344.
24. Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barré syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. *Am J Epidemiol* 2009; 169(3): 382-8.
25. Sivadon-Tardy V, Orlikowski D, Porcher R, et al. Guillain-Barré syndrome and influenza virus infection. *Clin Infect Dis* 2009; 48(1): 48-56.
26. Pritchard J, Mukherjee R, Hughes RA. Risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation. *J Neurol Neurosurg Psychiatry* 2002; 73(3): 348-9.
27. Romio S, Weibel D, Dieleman JP, et al. Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccines: a multinational self-controlled case series in Europe. *PLoS one* 2014; 9(1): e82222.
28. Oaklander AL, Lunn MP, Hughes RA, van Schaik IN, Frost C, Chalk CH. Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews. *Cochrane Database Syst Rev* 2017; 1: CD010369.
29. Nobile-Orazio E, Cocito D, Jann S, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. *Lancet Neurol* 2012; 11(6): 493-502.
30. Nobile-Orazio E, Cocito D, Jann S, et al. Frequency and time to relapse after discontinuing 6-month therapy with IVIg or pulsed methylprednisolone in CIDP. *J Neurol Neurosurg Psychiatry* 2015; 86(7): 729-34.
31. Gorson KC. A new trick for an old dog: pulsed dexamethasone treatment for chronic inflammatory demyelinating polyneuropathy. *Lancet Neurol* 2010; 9(3): 228-9.
32. Press R, Hiew FL, Rajabally YA. Steroids for chronic inflammatory demyelinating polyradiculoneuropathy: evidence base and clinical practice. *Acta Neurol Scand* 2016; 133(4): 228-38.
33. Cocito D, Paolasso I, Antonini G, et al. A nationwide retrospective analysis on the effect of immune therapies in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *Eur J Neurol* 2010; 17(2): 289-94.
34. Mahdi-Rogers M, van Doorn PA, Hughes RA. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2013; (6): CD003280.
35. Mahdi-Rogers M, Brassington R, Gunn AA, van Doorn PA, Hughes RA. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2017; (5): CD003280.
36. Eftimov F, Vermeulen M, van Doorn PA, Brusse E, van Schaik IN, Predict. Long-term remission of CIDP after pulsed dexamethasone or short-term prednisolone treatment. *Neurology* 2012; 78(14): 1079-84.

37. Kuitwaard K, van Doorn PA. Newer therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy. *Drugs* 2009; 69(8): 987-1001.
38. 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.
39. Hughes RA, Mehndiratta MM, Rajabally YA. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2017; (11): CD002062.
40. Mehndiratta MM, Hughes RA, Pritchard J. Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2015; (8): CD003906.
41. Elluru S, Duong Van Huyen JP, Prost F, et al. Comparative study of the anti-inflammatory effect of two intravenous immunoglobulin preparations manufactured by different processes. *Immunol Lett* 2006; 107(1): 58-62.
42. Zhang G, Lopez PH, Sheikh KA. Comparison of different brands of IVIg in an in vitro model of immune neuropathy. *J Neuroimmunol* 2006; 173(1-2): 200-3.
43. Gallia F, Balducci C, Nobile-Orazio E. Efficacy and tolerability of different brands of intravenous immunoglobulin in the maintenance treatment of chronic immune-mediated neuropathies. *J Peripher Nerv Syst* 2016; 21(2): 82-4.
44. Abolhassani H, Asgardoost MH, Rezaei N, Hammarstrom L, Aghamohammadi A. Different brands of intravenous immunoglobulin for primary immunodeficiencies: how to choose the best option for the patient? *Expert Review Clinical Immunol* 2015; 11(11): 1229-43.
45. Pouget J DC, Antoine J-C, Lacour A, de Seze J, Vial C, et al. A comparative, double-blind, randomized, multicentre clinical trial to assess the efficacy and safety of clairyg vs. tegeline in maintenance treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Inflammatory Neuropathy Consortium of the Peripheral Nerve Society Meeting Programme* 2016.
46. Fokkink WJ, Falck D, Santbergen TC, Huizinga R, Wuhrer M, Jacobs BC. Comparison of Fc N-Glycosylation of Pharmaceutical Products of Intravenous Immunoglobulin G. *PLoS one* 2015; 10(10): e0139828.
47. Kuitwaard K, Hahn AF, Vermeulen M, Venance SL, van Doorn PA. Intravenous immunoglobulin response in treatment-naïve chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry* 2015; 86(12): 1331-6.
48. 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.
49. Donofrio PD, Bril V, Dalakas MC, et al. Safety and tolerability of immune globulin intravenous in chronic inflammatory demyelinating polyradiculoneuropathy. *Arch Neurol* 2010; 67(9): 1082-8.
50. Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. *Neurology* 1997; 48(2): 321-8.
51. van Doorn PA, Vermeulen M, Brand A, Mulder PG, Busch HF. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy. Clinical and laboratory characteristics associated with improvement. *Arch Neurol* 1991; 48(2): 217-20.
52. Donaghy M, Mills KR, Boniface SJ, et al. Pure motor demyelinating neuropathy: deterioration after steroid treatment and improvement with intravenous immunoglobulin. *J Neurol Neurosurg Psychiatry* 1994; 57(7): 778-83.

53. Eftimov F, Liesdek MH, Verhamme C, van Schaik IN, PREDICT Study Group. Deterioration after corticosteroids in CIDP may be associated with pure focal demyelination pattern. *BMC neurology* 2014; 14: 72.
54. Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. *Neurology* 2015; 85(6): 498-504.
55. Allen JA, Ney J, Lewis RA. Electrodiagnostic errors contribute to CIDP misdiagnosis. *Muscle Nerve* 2017.
56. Meyer Zu Horste G, Cordes S, Pfaff J, et al. Predicting the Response to Intravenous Immunoglobulins in an Animal Model of Chronic Neuritis. *PLoS one* 2016; 11(10): e0164099.
57. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. *Neurology* 2014; 82(10): 879-86.
58. Querol L, Illa I. Paranodal and other autoantibodies in chronic inflammatory neuropathies. *Curr Opin Neurol* 2015; 28(5): 474-9.
59. Querol L, Devaux J, Rojas-Garcia R, Illa I. Autoantibodies in chronic inflammatory neuropathies: diagnostic and therapeutic implications. *Nat Rev Neurol* 2017; 13(9): 533-47.
60. Querol L, Rojas-Garcia R, Diaz-Manera J, et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. *Neurol Neuroimmunol Neuroinflamm* 2015; 2(5): e149.
61. Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981; 1(8232): 1228-31.
62. Fehr J, Hofmann V, Kappeler U. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. *N Engl J Med* 1982; 306(21): 1254-8.
63. Raphaël JC, Chevret S, Harboun M, Jars-Guinestre MC, French Guillain-Barré Syndrome Cooperative G. Intravenous immune globulins in patients with Guillain-Barré syndrome and contraindications to plasma exchange: 3 days versus 6 days. *J Neurol Neurosurg Psychiatry* 2001; 71(2): 235-8.
64. Appropriate number of plasma exchanges in Guillain-Barré syndrome. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. *Ann Neurol* 1997; 41(3): 298-306.
65. 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.
66. Farcas P, Avnun L, Frisher S, Herishanu YO, Wirguin I. Efficacy of repeated intravenous immunoglobulin in severe unresponsive Guillain-Barré syndrome. *Lancet* 1997; 350(9093): 1747.
67. Irani DN, Cornblath DR, Chaudhry V, Borel C, Hanley DF. Relapse in Guillain-Barré syndrome after treatment with human immune globulin. *Neurology* 1993; 43(5): 872-5.
68. Verboon C, van Doorn PA, Jacobs BC. Treatment dilemmas in Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry* 2017; 88(4): 346-52.
69. Koleba T, Ensom MH. Pharmacokinetics of intravenous immunoglobulin: a systematic review. *Pharmacotherapy* 2006; 26(6): 813-27.
70. van der Meché FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. Dutch Guillain-Barré Study Group. *N Engl J Med* 1992; 326(17): 1123-9.
71. van Koningsveld R, Steyerberg EW, Hughes RA, Swan AV, van Doorn PA, Jacobs BC. A clinical prognostic scoring system for Guillain-Barré syndrome. *Lancet Neurol* 2007; 6(7): 589-94.
72. van Doorn PA. Diagnosis, treatment and prognosis of Guillain-Barré syndrome (GBS). *Presse Med* 2013; 42(6 Pt 2): e193-201.
73. Godoy DA, Rabinstein A. Is a second cycle of immunoglobulin justified in axonal forms of Guillain-Barré syndrome? *Arq Neuropsiquiatr* 2015; 73(10): 848-51.

74. Waldmann TA, Strober W. Metabolism of immunoglobulins. *Prog Allergy* 1969; 13: 1-110.
75. Masson PL. Elimination of infectious antigens and increase of IgG catabolism as possible modes of action of IVIg. *J Autoimmun* 1993; 6(6): 683-9.
76. Yu Z, Lennon VA. Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. *N Engl J Med* 1999; 340(3): 227-8.
77. Fokkink WJ, Haarman AE, Tio-Gillen AP, et al. Neonatal Fc receptor promoter gene polymorphism does not predict pharmacokinetics of IVIg or the clinical course of GBS. *Ann Clin Transl Neurol* 2016; 3(7): 547-51.
78. Fokkink WR, Walgaard C, Kuitwaard K, Tio-Gillen AP, van Doorn PA, Jacobs BC. Association of Albumin Levels With Outcome in Intravenous Immunoglobulin-Treated Guillain-Barré Syndrome. *JAMA neurology* 2017; 74(2): 189-96.
79. Fokkink W, Koch B, Ramakers C, van Doorn PA, van Gelder T, Jacobs BC. Pharmacokinetics and Pharmacodynamics of Intravenous Immunoglobulin G Maintenance Therapy in Chronic Immune-mediated Neuropathies. *Clinical Pharmacol Ther* 2017; 102(4): 709-716.
80. Wani MA, Haynes LD, Kim J, et al. Familial hypercatabolic hypoproteinemia caused by deficiency of the neonatal Fc receptor, FcRn, due to a mutant beta2-microglobulin gene. *Proc Natl Acad Sci USA* 2006; 103(13): 5084-9.
81. Vlam L, Cats EA, Willemsse E, et al. Pharmacokinetics of intravenous immunoglobulin in multifocal motor neuropathy. *J Neurol Neurosurg Psychiatry* 2014; 85(10): 1145-8.
82. Rajabally YA, Seow H, Wilson P. Dose of intravenous immunoglobulins in chronic inflammatory demyelinating polyneuropathy. *J Peripher Nerv Syst* 2006; 11(4): 325-9.
83. Rajabally YA, Wong SL, Kearney DA. Immunoglobulin G level variations in treated chronic inflammatory demyelinating polyneuropathy: clues for future treatment regimens? *J Neurol* 2013; 260(8): 2052-6.
84. Lucas M, Hugh-Jones K, Welby A, Misbah S, Spaeth P, Chapel H. Immunomodulatory therapy to achieve maximum efficacy: doses, monitoring, compliance, and self-infusion at home. *J Clin Immunol* 2010; 30 Suppl 1: S84-9.
85. Dacci P, Riva N, Scarlato M, et al. Subcutaneous immunoglobulin therapy for the treatment of multifocal motor neuropathy: a case report. *Neurol Sci* 2010; 31(6): 829-31.
86. Debs R, Reach P, Cret C, et al. A new treatment regimen with high-dose and fractionated immunoglobulin in a special subgroup of severe and dependent CIDP patients. *Int J Neurosci* 2017; 127(10): 864-72.
87. Markvardsen LH, Sindrup SH, Christiansen I, et al. Subcutaneous immunoglobulin as first-line therapy in treatment-naïve patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study. *Eur Neurol* 2017; 24(2): 412-8.
88. Jacobs BC, van den Berg B, Verboon C, et al. International Guillain-Barré Syndrome Outcome Study: protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome in Guillain-Barré syndrome. *J Peripher Nerv Syst* 2017; 22(2): 68-76.
89. Huizinga R, van den Berg B, van Rijs W, et al. Innate Immunity to *Campylobacter jejuni* in Guillain-Barré Syndrome. *Ann Neurol* 2015; 78(3): 343-54.
90. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barré syndrome. *Neurology* 2011; 76(11): 968-75.
91. Rabin M, Mutlu G, Stojkovic T, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: search for factors associated with treatment dependence or successful withdrawal. *J Neurol Neurosurg Psychiatry* 2014; 85(8): 901-6.

92. Yuki N, Tagawa Y, Hirata K. Minimal number of plasma exchanges needed to reduce immunoglobulin in Guillain-Barré syndrome. *Neurology* 1998; 51(3): 875-7.
93. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2018;17(10:35-46.
94. Markvardsen LH, Debost JC, Harbo T, et al. Subcutaneous immunoglobulin in responders to intravenous therapy with chronic inflammatory demyelinating polyradiculoneuropathy. *Eur Neurol* 2013; 20(5): 836-42.
95. Cocito D, Romagnolo A, Peci E, et al. Subcutaneous vs. intravenous immunoglobulin in CIDP: pharmacokinetic and clinical response. *J Peripher Nerv Syst* 2016; 21(2): 114-6.

