GBS AND CIDP

SPECTRUM AND IVIG TREATMENT

Krista Kuitwaard

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CHAPTER 1

General introduction

Immune-mediated polyneuropathies cover a spectrum of potentially treatable disorders of the peripheral nervous system leading to variable levels of weakness and sensory disturbances. Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are important disorders in this spectrum. Both GBS and CIDP show a diversity in clinical symptoms, response to treatment and outcome. In the papers in this thesis we investigate what determines this variation in disease course and treatment response. The focus of the first part of this thesis is on the spectrum of GBS and CIDP as well as its subtypes such as recurrent GBS, acute-onset CIDP (A-CIDP), and GBS with treatment-related fluctuations (GBS-TRF). The second part of the thesis focusses on the treatment of GBS and CIDP with IV immunoglobulins (IVIg).

GUILLAIN-BARRÉ SYNDROME

In 1916, two French soldiers with acute flaccid paralysis and a high cerebrospinal fluid (CSF) protein level with a normal cell count were described by Guillain, Barré and Strohl.[1] This syndrome became known as the Guillain-Barré syndrome (GBS) and nowadays it is the most common severe acute paralytic neuropathy worldwide.[2] The diagnosis of GBS is based mainly on the clinical characteristics of progressive symmetric muscle weakness with reduced or absent tendon reflexes of the arms and legs.[3, 4] Other common symptoms are cranial nerve dysfunction (resulting in facial palsy, double vision or swallowing difficulties), sensory symptoms and pain. Important symptoms to recognise and monitor closely are weakness of respiratory muscles and autonomic dysfunction which may require ICU admittance and artificial ventilation. GBS is often a severe disease, and about 25% of patients require artificial ventilation for some period of time.[2] A variant of GBS is the Miller Fisher syndrome (MFS), characterised by ophthalmoplegia, ataxia and areflexia.[5] MFS patients in general show a milder disease course than GBS, but progression to GBS can occur (GBS-MFS overlap syndrome).[6] GBS is often preceded by an infection such as a respiratory tract - or gastrointestinal infection, and sometimes by a vaccination, which may induce an autoimmune response attacking the peripheral nerves and spinal roots. Whether vaccinations can lead to recurrences of GBS is unknown. Preceding infections of GBS are *Campylobacter jejuni (C. jejuni)*, cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, *Haemophilus influenza*, hepatitis E virus, and recently Zika virus has also been suggested to be associated with GBS as well.[7 8-11] Molecular mimicry between microbial agents and peripheral nerve antigens (gangliosides) play an important role in the pathogenesis of GBS after infection with *C. jejuni*.[12] Although *C. jejuni* infections are common, only one in 2000-5000 individuals with a *C. jejuni* infection will eventually develop GBS.[13] Since only a small subset of individuals develops this post-infectious polyneuropathy, host susceptibility factors are likely to play an important role

as well in the development of the disease.[14] A key factor in the development of GBS after *C. jejuni*-infection in many patients is the production of antibodies to gangliosides that cross-react against neural antigens. These antibodies are neurotoxic and their fine specificity is associated with the type of clinical deficits: antibodies to GM1 are associated with pure motor GBS and antibodies to GQ1b are related to MFS or oculomotor dysfunction in GBS, which is in accordance with the spatial distribution of these gangliosides in the peripheral nervous system.[15]

On a yearly basis, about 200-250 individuals in the Netherlands develop GBS, which can occur at all ages, although the frequency increases with age. The annual incidence rate of GBS in Europe and North America is 1-2 per 100.000.[13] The main clinical symptom of GBS is rapidly developing limb weakness which should by definition reach its maximum within 4 weeks of onset, but most patients already reach their maximum weakness within 2 weeks.[7] This is followed by a plateau phase of variable duration (generally weeks to months), followed by a recovery phase which can take years (Figure 1).[2] Patients often have an increased CSF protein level but this is not mandatory for the diagnosis. The CSF protein level might be normal especially in the early phase of the disease.[16] CSF examination is more important to rule out an increased cell count which should lead to further investigation for other diseases that can mimic GBS such as Lyme's disease, cytomegalovirus or HIV-infection, or leptomeningeal malignancies.

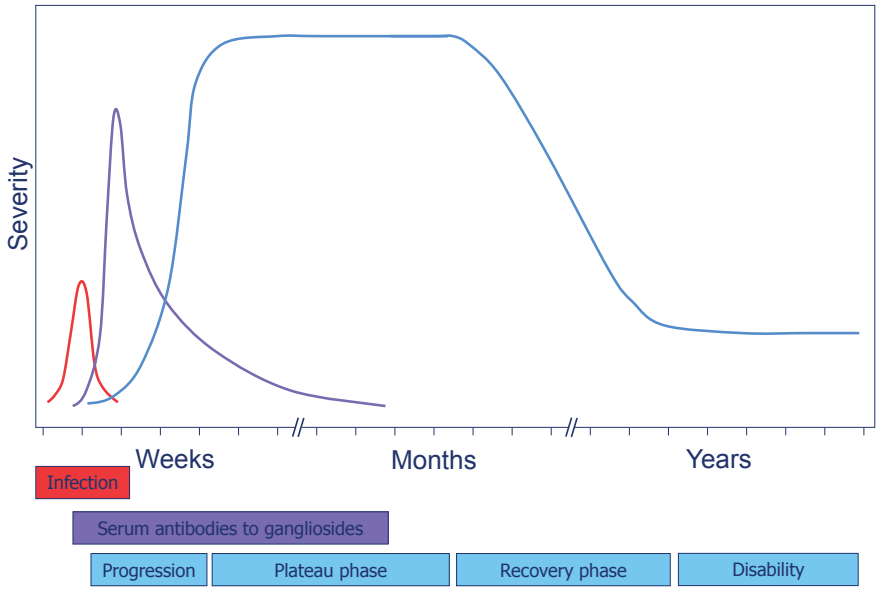

Figure 1. Guillain-Barré syndrome time course[2]

Electromyography (EMG) can be helpful to confirm the diagnosis and to distinguish the demyelinating subtype from the pure axonal form. Currently, the distinction between an axonal and a demyelinating subtype of GBS is of predominant importance for research purposes. In Europe and North America the demyelinating form (acute inflammatory demyelinating polyradiculoneuropathy or AIDP) is the most common form whereas the axonal form (acute motor axonal neuropathy or AMAN or acute motor and sensory axonal neuropathy or AMSAN) is more common in China and Japan.[17, 18] It is important to recognise that the results of EMG in GBS can be normal in the early phase of the disease, and therefore the usefulness of EMG is often limited in the acute phase. EMG however can be helpful, especially when there are abnormalities indicating a polyneuropathy, or when there is doubt about the diagnosis. Criteria supporting the diagnosis of GBS as well as criteria that function as a "red flag" for the diagnosis are listed in Table 1. Table 2 shows differential diagnostic possibilities of GBS.

Table 1. Diagnostic criteria for Guillain-Barré syndrome[3, 21]

Features required for the diagnosis
Progressive motor weakness of arms and legs
Reduced or absent tendon reflexes
Features strongly supportive of the diagnosis
Progression of symptoms over days till maximum of 4 weeks
Relative symmetry
Mild sensory symptoms or signs
Cranial nerve involvement
Autonomic dysfunction
Pain
Increased CSF protein level
Typical electro diagnostic features
No other identifiable cause
Features that should raise doubt about the diagnosis
Fever at onset
Bladder or bowel dysfunction at onset
Sharp sensory level
Increased CSF cell count (>50×10^6/L) or polymorph nuclear cells in CSF
Marked persistent asymmetry
Sensory signs with limited weakness at onset
Severe pulmonary dysfunction at onset
Slow progression with limited weakness and no respiratory involvement
Another identifiable cause of acute polyneuropathy

Table 2. Differential diagnosis of GBS [2, 22, 23]

Metabolic
Diabetic polyradiculopathy/plexopathy
Vitamin deficiency (B1, B12)
Hypophosphatemia
Hypermagnesaemia
Hypokalaemia
Inflammatory or autoimmune
A-CIDP
Myasthenia Gravis
LEMS[1]
Poly- or dermatomyositis
Vasculitis
Transverse myelitis
ADEM[2]
Infectious
Lyme's disease
HIV
Poliomyelitis
West-Nile virus myelitis
Diphtheria
Botulism
Rabies
Cytomegalovirus
Neoplastic
Leptomeningeal carcinomatosis/malignancies
Drug induced
Disulfiram
Nitrofurantoin
Chemotherapeutic drugs
Hereditary
Porphyria
Intoxication
Arsenic neuropathy
Thallium
Shell fish or puffer fish poisoning
Tick paralysis
Alcoholic neuropathy
Spinal cord or brainstem injury
Spinal stenosis or disc prolapse
Epidural abscess or haematoma

Table 2. Differential diagnosis of GBS [2, 22, 23] (continued)

Anterior spinal artery occlusion
Atlantoaxial dislocation
Brain stem stroke
Other
ICU-acquired weakness
Acute rhabdomyolysis

[1] Lambert-Eaton myasthenic syndrome
[2] Acute disseminated encephalomyelitis

Even after full recovery of muscle strength, many patients are bothered, even years later, by severe fatigue interfering with their daily activities.[19, 20] A multidisciplinary practical guideline has been published in 2010 in the Netherlands that covers many aspects of GBS; regarding its diagnosis and treatment, including physiotherapy and revalidation. This guideline (multidisciplinaire richtlijn Guillain-Barré syndrome) can be downloaded at www.vsn.nl. It also contains information about long-term symptoms such as pain and fatigue. We evaluated the levels of pain and fatigue experienced by patients long after the initial phase of their disease.

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

The first case of chronic and recurrent neuritis was probably already described in 1890, but the concept of steroid-responsive chronic or relapsing neuritis followed much later in 1958.[24, 25] Various names have been used since then until in 1982 the term chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) was given to the disorder and this description has been used ever since.[26] The features of CIDP are in many ways similar to those in GBS, but weakness is usually less severe in CIDP. Patients with CIDP have limb muscle weakness, most often with clear proximal involvement, and decreased or absent reflexes.[27] Most patients have sensory involvement as well, but CIDP can manifest as a pure motor neuropathy.[28] Although pain is present in many GBS patients, not much is known about the occurrence of pain in CIDP.[29-31]

In CIDP about one third of patients report a preceding infection or vaccination as a trigger which is considerably lower than in GBS where two-third reports such a trigger.[32] Not much is known regarding the safety of vaccinations in CIDP patients. CIDP is a chronic polyradiculoneuropathy that develops by definition over more than 8 weeks, distinguishing this disorder from its acute counterpart: GBS. The disease course of CIDP can be either monophasic, chronic or relapsing. The diagnosis of CIDP is based on clinical characteristics combined with electro diagnostic findings.[33] EMG examination is

essential and must display features of demyelination to establish the diagnosis of CIDP.[33] Similar to GBS, the CSF protein level is most often increased in CIDP and an increased CSF protein level supports the diagnosis.[33] A normal CSF protein level can occur in CIDP but an increased cell count should raise the suspicion for other diagnostic possibilities. Criteria supporting the diagnosis of CIDP as well as criteria that function as a "red flag" for the diagnosis are listed in Table 3. CIDP can be difficult to diagnose and has a very broad differential diagnosis (Table 4). In difficult diagnostic cases, a MRI scan of the brachial plexus or a nerve ultrasound can be helpful.[34-37] A nerve biopsy can be used to exclude another diagnosis such as amyloidosis or vasculitis, but is rarely needed.[33, 38] Diabetes or the presence of another autoimmune disease or a monoclonal gammopathy

Table 3. Diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy[3]

Features required for the diagnosis
Progressive motor weakness of arms and legs
Reduced or absent tendon reflexes
Electro diagnostic criteria for primary demyelination
Features strongly supportive of the diagnosis
Progression of symptoms over more than 8 weeks
Sensory symptoms or signs
Increased CSF protein level
Proximal muscle weakness
Features that should raise doubt about the diagnosis
Respiratory muscle weakness
Bladder or bowel dysfunction at onset
Sharp sensory level
Increased CSF cell count (>50×10^6/L) or polymorph nuclear cells in CSF
Marked persistent asymmetry
Autonomic dysfunction
Severe ataxia or tremor at onset
Family history of (hereditary) neuropathies or clear muscle atrophy at onset
Systemic complaints (weight loss, lymphadenopathy, skin changes)
Another identifiable cause of chronic polyneuropathy
Features that rule out the diagnosis
IgM paraprotein with anti-MAG antibodies[1]
Paraprotein related haematological disorders such as POEMS syndrome[2] (often increased VEGF[3]), Waldenström's macroglobulinemia, multiple myeloma, lymphoma
Alternative diagnosis; such as MMN[4], amyloidosis, hereditary neuropathy

[1] Myelin-Associated Glycoprotein
[2] Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes
[3] Vascular Endothelial Growth Factor
[4] Multifocal Motor Neuropathy

Table 4. Differential diagnosis of CIDP

Metabolic
Diabetic polyradiculopathy/plexopathy
Uremic polyneuropathy
Hepatic polyneuropathy
Vitamin deficiency (B1, B6, B12)
Tangier disease
Inflammatory
Recurrent GBS
GBS-TRF
MMN[1]
Paraprotein with anti-MAG antibodies
POEMS[2] syndrome
CANOMAD[3]
Sarcoidosis
SLE[4]
Sjögren's syndrome
Amyloidosis
Vasculitis
Infectious
Lyme's disease
Syphilis
HIV
Hepatitis C
Varicella zoster virus
Cytomegalovirus
Neoplastic
Multiple myeloma or osteosclerotic myeloma
Leptomeningeal carcinomatosis
Lymphoma
Leukaemia
Cryoglobulinemia
Drug induced
Amiodarone
Intrathecal methotrexate
Tacrolimus
Hereditary
CMT[5] type 1A, B, C, CMTX
HNPP[6]
Metachromatic leucodystrophy or adrenomyeloneuropathy
Porphyria

Table 4. Differential diagnosis of CIDP (continued)

Refsum's disease
Intoxication
Lead or arsenic neuropathy
Idiopathic
CIAP[7]

[1] Multifocal Motor Neuropathy
[2] Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes.
[3] Chronic sensory Ataxic Neuropathy, Opthalmoplegia, IgM paraprotein, cold Agglutinins, Disialosyl antibodies
[4] Systemic Lupus Erythematosus
[5] Charcot-Marie-Tooth
[6] Hereditary Neuropathy with susceptibility to Pressure Palsies
[7] Chronic Idiopathic Axonal Polyneuropathy

of undetermined significance (MGUS) does not exclude the diagnosis of CIDP as long as the clinical and EMG features are compatible with CIDP. It is unknown whether CIDP patients more often have other autoimmune disorders. In case of an IgM paraprotein, the presence of anti-MAG (myelin-associated glycoprotein) antibodies should be examined. If a patient has a more slowly progressive disease with predominantly distal weakness and sensory symptoms, the presence of anti-MAG antibodies rule out the diagnosis of CIDP. These patients should be classified as an IgM anti-MAG related polyneuropathy and treated accordingly.

This differential diagnosis list as presented represents the most common differential diagnostic possibilities. It should be noted that some disorders are probably associated with CIDP (mainly in case reports) such as HIV, hepatitis, SLE, connective tissue disease, sarcoidosis, thyroid gland disorders, inflammatory bowel disease, glomerulonephritis and bone marrow transplantation and therefore do not rule out the diagnosis of CIDP.

THE SPECTRUM OF GBS AND CIDP

GBS has traditionally been separated from its chronic counterpart CIDP by the duration of progressive weakness.[4] Preceding infections, involvement of cranial nerves or weakness of respiratory muscles are more often encountered in GBS than in CIDP, but can occur in both. Several subforms of GBS and CIDP exist; such as recurrent GBS, GBS with treatment-related fluctuations (GBS-TRF) and acute-onset CIDP (A-CIDP). Although GBS is generally a monophasic disorder, TRFs and recurrences can occur. How often GBS patients show a recurrence and what predisposes them for a recurrent GBS is currently unknown. CIDP usually runs a progressive or relapsing course but may be monophasic resembling GBS, and requiring only a single course of treatment. How often this happens

is unknown. Additionally, CIDP patients with an acute or subacute onset, resembling GBS, do exist. Although it can sometimes be difficult to distinguish GBS from CIDP it is important to do so because treatment and prognosis can be different.

CASE 1

"A 42-year-old woman complained of severe pain and soon thereafter she developed progressive weakness and sensory disturbances, which reached their nadir in less than 4 weeks. She showed a near complete recovery. Seven years later, after a flu, she had similar symptoms that peaked in less than 2 weeks. Sixteen years later she had another episode of progressive weakness after a flu-like infection that developed in one week. Five years after the previous episode, she developed a 4th episode after a bout of diarrhoea of progressive weakness that developed over a few hours.

Despite treatment with IVIg, she needed artificial ventilation and had severe autonomic dysfunction complicated by an asystole. She was successfully resuscitated and eventually discharged to a rehabilitation centre. A year later she was using a walker but was independent in her daily life activities. "

Although GBS is most often a monophasic disorder, recurrences like in case 1 can occur. Five patients who fully recovered from an initial episode of GBS have been described who had another acute episode years later. [39] The clinical features of rapid progressive weakness, return of normal reflexes as well as the long asymptomatic intervals distinguished them from CIDP. [39] All had similar antecedent infections as well as similar symptoms over time. [39] Another 12 patients with recurrent GBS have been reported with a total of 32 episodes (1-6 recurrences). [40] Vaccinations may be associated with the recurrence of GBS as well.[41] It is unknown why only some patients develop a recurrence of GBS and whether symptoms and triggers may differ between episodes.

CASE 2

"A twenty-year-old man complained of muscle aches after a flu infection. Two days later he had tingling in his limbs. Whilst at the general practitioner he fell off the examination couch and could not get up by himself. At hospital admission a few hours later he had a tetraparesis and areflexia. CSF showed a normal protein level. He was treated with IVIg and over the following week his muscle strength of arms and legs improved quickly. Just a few days later he developed bilateral facial palsy and progressive weakness, and he was successfully re-treated with another IVIg course."

Most often GBS follows a monophasic course but some patients like the one described in case 2, experience a worsening after an initial improvement to treatment; the so called treatment-related fluctuations (TRFs).[42] Ten out of 95 GBS patients who had been treated with a course of plasma exchange (PE) showed worsening after an initial improvement. [43] Eight of these patients were treated with a repeated course of PE which was then followed by a clinical improvement, and during follow-up none of these patients developed CIDP. [43] Similar worsening after treatment was seen in GBS patients treated with IVIg.[42] Re-treating these TRF patients with another IVIg course also led to an improvement. [42] The prospective GRAPH study showed that a diagnosis of A-CIDP is more likely than GBS-TRF if a patient deteriorates after ≥ 8 weeks of onset or ≥ 3 times. [44]

CASE 3
*"A 52-year-old woman developed sen**s**ory disturbances after a flu infection. Two days later she was unable to walk. Maximum disability was reached in 6 days. Over the next few months she had several exacerbations needing IVIg treatment, and she was treated subsequently with IVIg once every month for the next 7 years."*

Case 3 describes a patient who was diagnosed initially with GBS due to the onset phase of less than 4 weeks but who turned out to have acute-onset CIDP (A-CIDP). A prospective study found that 5% of patients initially diagnosed with GBS actually had A-CIDP, all with an onset phase of < 4 weeks.[44] Seven patients with a monophasic episode of progressive weakness over the course of 4-8 weeks have been classified as subacute idiopathic demyelinating polyneuropathy (SIDP).[45] These patients had predominantly motor dysfunction and were relatively mildly affected, none needed artificial ventilation.[45] All patients clearly responded to prednisone or had a spontaneous recovery.[45] An acute-onset has been reported in 15% of CIDP patients.[32] It can be difficult to distinguish GBS-TRF from A-CIDP, but a diagnosis of A-CIDP is more likely when a patients deteriorates after 8 weeks from onset or 3 times or more.[44] Whether GBS and CIDP can co-occur in the same patient has not been determined yet. The whole spectrum of GBS and CIDP including its overlap or sub forms including some of our research questions of this thesis are shown in Figure 2.

TREATMENT OF GBS AND CIDP

In GBS, both PE and IVIg are proven to be beneficial, but in recent years most patients are treated with IVIg.[46, 47, 48, 49] IVIg contains a huge number of different human immunoglobulins (IgG antibodies) derived from pooled blood of several thousands of blood donors and is given by IV infusion. The exact working mechanism is unknown but probably multifactorial. IVIg has only proven its benefit so far when given within two weeks from onset of weakness in GBS patients who are unable to walk independently.[47, 50] IVIg is usually the first treatment choice; it is readily available and had a better side-effect profile and because of its convenience patients are more likely to complete the course.[47] Despite the clinical variation between GBS patients, all are treated with one standard IVIg course (2 g/kg over 5 days). Not all GBS patients however respond in a similar way and it is unknown whether this standard course is appropriate for all, irrespective of their clinical course, severity or prognosis.

It has not yet been investigated whether mildly affected patients or patients with MFS may benefit from IVIg treatment.[51] Despite the absence of proof from RCTs, and more based upon expert opinion, it has been recommended to treat severely affected MFS patients and MFS patients who develop a GBS-MFS overlap syndrome with IVIg.[52] The same has been advocated for mildly affected GBS patients who show fast progression

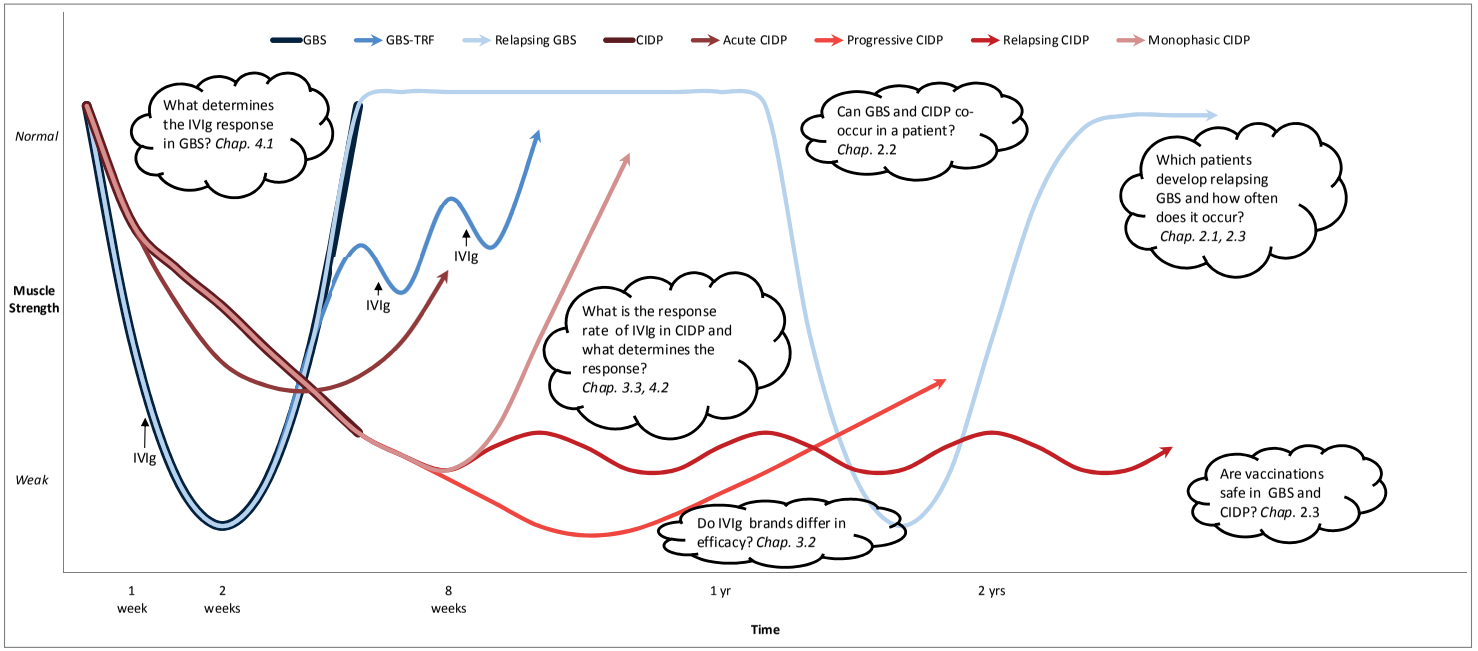

Figure 2. The spectrum of GBS and CIDP

within the first two weeks or who develop severe autonomic dysfunction, bulbar or facial weakness.[52] When GBS patients develop a TRF, another full IVIg course (2 g/kg) is recommended (expert opinion). Despite IVIg treatment, GBS has a high morbidity, with 25% of patients needing artificial ventilation and 20% of patients remaining severely disabled after half a year, and a mortality rate of about 3-5%. [53] Surprisingly, steroids alone are ineffective in GBS. When added to IVIg, intravenous methylprednisolone might have a small positive effect on the short-term outcome compared to IVIg alone.[54]

In CIDP, IVIg, PE and corticosteroids are proven to be effective; although the evidence for a positive treatment effect of corticosteroids is less strong.[55-59] It is currently unknown why some patients do not respond to IVIg and if various IVIg brands differ in clinical efficacy. CIDP patients are treated initially with a loading course of IVIg (2 g/kg) but most patients need intermittent IVIg treatment for several years, for a median duration of about 5 years, ranging up to even more than 30 years (P.A. van Doorn, personal communication). In contrast to GBS, monotherapy with corticosteroids can be effective in CIDP. IVIg is the first choice of treatment in many hospitals because of its convenience and better side-effects profile. IVIg however is an expensive treatment and the time to reach a clinical remission (without treatment) might be longer with IVIg compared to IV corticosteroid treatment.[60] As most CIDP patients improve after IVIg, steroids or PE, the diagnosis should be reconsidered in a patient that does not respond to one of these treatments.[61] CIDP patients who become unresponsive to therapy should be checked again for the appearance of a monoclonal protein or signs of malignancy.[62] Effective dosages and the frequency of IVIg administration required seem to vary largely between patients and it is not known what determines this variation. Variation in the required dose and interval of IVIg in CIDP might be due to differences in IVIg catabolism. It is unknown if high peak serum IgG levels are needed, or if more constant serum IgG levels are preferable.

OBJECTIVES

The research described in this thesis focusses on GBS and CIDP including its overlapping variants.

The aims of this thesis are:

1. To gain a better understanding of the spectrum of GBS and CIDP
2. To obtain more information about the presence of (other) autoimmune diseases and the risk of vaccinations in GBS and CIDP
3. To study the efficacy of IVIg in GBS and CIDP in more detail
4. To improve treatment options in GBS and CIDP

In order to study questions related to these objectives we use GBS and CIDP cohorts (Dutch GBS study group, the Erasmus MC cohort of inflammatory neuropathies, and a Canadian CIDP cohort), as well as a survey of GBS and CIDP members of the Dutch society of neuromuscular disorders.

The studies in this thesis are intended to answer the following questions (related to aim 1 and 2):

1) Can GBS and CIDP co-occur in a single patient?
2) How often does GBS reoccur, and why do some patients have recurrences? Do patients with recurrences show the same symptoms and triggers each time?
3) What is the chance of developing a recurrence of GBS or an increase of symptoms of CIDP after a vaccination?
4) Do (other) autoimmune diseases occur more frequently in GBS and CIDP?

Although treatment with IVIg is relatively successful in most GBS and CIDP patients, many questions remain (related to aim 3 and 4):

1) How often is IVIg effective as a first treatment in CIDP? What is the chance that an IVIg non-responder improves after a second or third treatment modality? Why do not all GBS and CIDP patients improve after a standard course of IVIg?
2) Is one brand of IVIg more effective than another product?
3) Is the standard IVIg dose (2 g/kg) suitable for all GBS patients, or do some patients need a higher dosage or another course?
4) What determines the variation in dosage and frequency of IVIg maintenance treatment required and how should maintenance IVIg treatment be given? How can the efficacy of IVIg maintenance treatment in CIDP be improved?
5) What is the variation in serum IgG levels before and after IVIg in GBS and CIDP? Are serum IgG levels useful to monitor or predict the treatment response?

These questions are investigated in the following studies as described in this thesis.

OUTLINE

Chapter 2 covers the spectrum of GBS and CIDP. In **Chapter 2.1** the clinical characteristics of 32 recurrent GBS patients are described and compared with those of 476 non-recurrent patients. Four patients who had separate episodes of both GBS and CIDP that fulfilled the clinical and diagnostic criteria of these disorders are presented in **Chapter 2.2**. In **Chapter 2.3** the results of a survey of 461 members of the Dutch society of neuromuscular disorders with the diagnosis of GBS or CIDP are described. Recurrences, vaccinations and long-term symptoms such as pain, fatigue and quality of life are described.

Chapter 3 covers the treatment of CIDP. An overview of different treatment options in CIDP is given in **Chapter 3.1**. In **Chapter 3.2** the results of a RCT comparing two different brands of immunoglobulins in CIDP is given (CIC study). In **Chapter 3.3** the results of a retrospective study in 281 patients from two large university hospitals (Erasmus MC, University Medical Centre Rotterdam, the Netherlands and London Health Sciences Centre London Ontario, Canada) being treated with IVIg as a first treatment modality are described. The response to IVIg as well as the response to second or even third treatment modalities was studied. In addition, clinical factors that were associated with a good response to IVIg were assessed. **Chapter 3.4** contains a review regarding maintenance treatment of IVIg in CIDP. The rationale and outline of a dose response trial of IVIg in CIDP (DRIP study) that we are currently performing is described in **Chapter 3.5**. This multi-centre randomised placebo-controlled trial investigates whether high frequency low dosage IVIg treatment is more effective than low frequency high dosage as maintenance treatment for CIDP.

Chapter 4 describes serum IgG levels in IVIg-treated GBS and CIDP. **Chapter 4.1** shows the results of a study of serum IgG levels in 174 GBS patients treated with a standard course of IVIg (2 g/kg). We investigated whether serum IgG levels are related to the outcome. The variability of serum IgG levels in clinically stable but IVIg-dependent CIDP patients receiving maintenance treatment of IVIg is described in **Chapter 4.2**.

In **Chapter 5**, the results of these chapters are discussed in a broader perspective and in relation to the current literature, and suggestions for further research are given.

In **Chapter 6** the observations from the studies, as described in **Chapter 2-4**, are summarised.

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CHAPTER 2

The spectrum of GBS and CIDP

Chapter 2.1

Recurrent Guillain-Barré syndrome

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ABSTRACT

Background: Guillain-Barré syndrome (GBS) is generally considered to be monophasic, but recurrences do occur in a presently undefined subgroup of patients.

Objectives: To determine which subgroup of patients develops a recurrence and to establish whether preceding infections and neurological symptoms are similar in subsequent episodes.

Methods: A recurrence was defined as two or more episodes that fulfilled the NINCDS criteria for GBS, with a minimum time between episodes of two months (when fully recovered in between) or four months (when only partially recovered). Patients with a treatment-related fluctuation or chronic inflammatory demyelinating polyneuropathy with acute onset were excluded. The clinical characteristics of recurrent GBS patients were compared with those of 476 non-recurrent patients.

Results: 32 recurrent GBS patients, who had a total of 81 episodes, were identified. The clinical symptoms in a first episode were similar to the following episodes in individual patients, being GBS or its variant Miller Fisher syndrome (MFS) but never both. While neurological symptoms in subsequent episodes were often similar, the severity of the symptoms and the nature of the preceding infections varied. Recurrent patients (mean age 34.2 years) were younger than non-recurrent patients (mean age 46.9; $p = 0.001$) and more often had MFS ($p = 0.049$) or milder symptoms ($p = 0.011$).

Conclusions: Genetic or immunological host factors may play an important role in recurrent GBS, since these patients can develop similar symptoms after different preceding infections. Recurrences occur more frequently in patients under 30, with milder symptoms and in MFS.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy leading to flaccid paresis. Its annual incidence rate is 0.75 to 2 per 100.000.[1, 2] GBS is a heterogeneous disease in which approximately two-thirds of patients report a preceding incident, usually an infection, such as diarrhoea or an upper-respiratory-tract infection.

Although GBS is considered to be monophasic, recurrences are reported in 2-5% of patients.[3, 4] It is unknown why some patients have a recurrence and whether this occurs more frequently in a distinct subgroup of patients. It is suggested that recurrent GBS patients may have similar clinical symptoms in subsequent episodes, while having the same or different triggering events.[4] It is important to distinguish between recurrent GBS patients and GBS patients with treatment-related fluctuations (GBS-TRF) or chronic inflammatory demyelinating polyneuropathy with acute onset (A-CIDP) especially because the treatment regimen for CIDP is different.[5]

The purpose of this study is to establish whether recurrent GBS patients have similar neurological symptoms in subsequent episodes and to determine whether these patients can be distinguished from non-recurrent patients based on their clinical characteristics. We additionally investigate whether recurrent GBS patients have similar infections prior to each episode, if the severity varies in subsequent episodes and if the interval between episodes tends to get longer or shorter. By analysing these features, we also aim to determine the relevance of host susceptibility factors in GBS.

METHODS

Subjects and methods

To determine whether the type of neurological symptoms or the type of preceding infections are similar in subsequent episodes, we studied 32 recurrent GBS patients. These patients were identified from the Erasmus MC GBS databank, which contains information on patients enrolled in clinical studies between 1985-2008. Additional patients came to our attention on patient meetings organized by the Dutch Society for Neuromuscular disorders (VSN). Medical records or letters were screened and missing or indistinct items were clarified by contacting the patients or treating doctors.

All cases were re-evaluated (by KK and PD) using the criteria of the National Institute of Neurological and Communicative Diseases and Strokes (NINCDS) for GBS.[6] Patients were also included when they fulfilled the criteria for Miller Fisher syndrome (MFS), a GBS variant characterized by areflexia, ataxia and opthalmoplegia.[1] The severity of each episode was graded according to the GBS disability scale.[7]

The GBS disability scale is a seven-point disability scale, ranging from no symptoms (zero points) to death (six points). Patients who were able to walk with or without support (GBS disability scale ≤ 3) were considered as "mildly affected", whereas patients who were bedbound (GBS disability scale ≥ 4) were categorised as "severely affected".

We defined a recurrent patient as one having two or more episodes that fulfilled the NINCDS criteria for GBS, either with a minimum interval ≥ 4 months between the episodes if the patient did not recover completely (GBS disability scale ≥ 2); or ≥ 2 months when there was a complete or near-complete recovery (GBS disability scale ≤1) after the previous episode.

We excluded GBS-TRF and A-CIDP patients.[5] GBS-TRF was defined as (1) improvement in the GBS disability scale of at least one grade or improvement in the MRC sum score more than five points after completion of therapy (2 g IVIg/kg body weight in 2-5 days), followed by a worsening of the GBS disability scale of at least one grade or a decrease in the MRC sum score of more than five points within the first 2 months after the disease onset or (2) stabilisation for more than 1 week after completion of therapy, followed by a worsening of the GBS disability scale of more than one grade or more than five points on the MRC sum score within the first 2 months after disease onset.[5, 8] A-CIDP was defined as a CIDP patient in whom the nadir of the first episode was within 8 weeks of onset and the consecutive course was chronic, as in CIDP.[9]

Information was obtained concerning age, sex, cranial nerve involvement, preceding type of infection and/or trigger, GBS disability scale at nadir, and time between recurrences. Antecedent infections were classified clinically either as upper-respiratory tract or as diarrhoea/gastrointestinal. Reported influenza or flu-like infections were classified as upper-respiratory-tract infections. Information was also obtained about the presence of other autoimmune or immune-mediated disease.

To investigate whether recurrent patients can be distinguished from non-recurrent patients, we compared the clinical characteristics with those of non-recurrent GBS patients admitted with a diagnosis of GBS between 1987 and 1996 in The Netherlands.[2]

We compared the groups with respect to age, sex, MFS, cranial nerve dysfunction, the need for artificial respiration, severity of the symptoms and preceding triggers.

Statistical analysis

For statistical analyses, an unpaired t test and χ^2 test were performed, to compare characteristics of recurrent and non-recurrent GBS patients. If appropriate, the Fisher exact test was used. SPSS for Windows (version 15.0, SPSS, Chicago) was used for all statistical analyses, and p values < 0.05 were regarded as significant.

RESULTS

Forty-eight patients were considered as potentially eligible. Sixteen patients were excluded: three with GBS-TRF and six with A-CIDP; three due to missing information about clinical symptoms during one of the possible episodes, and four because they did not fulfill the diagnostic criteria for GBS.

We identified 32 recurrent patients, 21 males and 11 females, who had a total of 81 episodes of GBS. Of these 32 patients, four had recurrent MFS, and three were known with another autoimmune disease (two inflammatory bowel disease and one hyperthyroidism). In the group of non-recurrent GBS patients, 11 were known to have one of the following autoimmune disorders: rheumatoid arthritis, polyarthritis nodosa, spondylitis ankylopoetica, sarcoidosis, thyroid gland disease or inflammatory bowel disease. The clinical characteristics of the recurrent GBS patients during their first episode are listed in Table 1.

Table 1. Comparison of baseline characteristics of recurrent and non-recurrent Guillain-Barré syndrome (GBS) patients

	GBS patients		
	Recurrent (during first episode) (n =32)	Non-recurrent (n = 476)	p value
Age, years, mean (SD)	34.2 (23.9)	46.9 (21.5)	0.001
Age < 30 years	44%	22%	0.006
Male	66%	60%	0.505
Cranial nerve dysfunction	38%	42% (472)	0.654
Miller Fisher syndrome	13%	4%	0.049
Sensory-motor symptoms	72%	62% (474)	0.275
Artificial respiration needed	16%	18% (472)	0.691
Mildly affected*	59%	37% (450)	0.011
Known with other autoimmune disease	9%	2%	0.051
Preceding vaccination	6%	3% (475)	0.219
Preceding gastrointestinal infection	13%	17% (475)	0.541
Preceding respiratory infection	28%	37% (475)	0.299

The number in parentheses is number of patients on whom information was available (if different from the total).

* GBS disability scale ≤ 3

Seven recurrent GBS patients had three episodes, two had four episodes, and two had five episodes. All patients with at least four episodes were female. The mean age during the first episode was 34.2 (range: 1-87) and of the first recurrence 42.1 (range: 5-88). The interval between recurrences ranged from 2 months to 37 years. The mean interval

between all recurrences was 7 years. Most patients had a long interval between subsequent episodes, only two patients had an interval of 2 months in between episodes with near complete recovery. The mean GBS-disability score at nadir was 3.1 for the first two episodes, increasing to 3.8 for the fourth episode. The characteristics of all episodes are shown in Table 2.

Table 2. Characteristics per Guillain-Barré syndrome (GBS) episode

	No of patients	Age, years, mean (SD)	Time between recurrences, years, mean (SD)	GBS disability scale nadir, mean (SD)	Mean GBS disability scale after 6-12 months
1st episode	32	34.2 (23.9)	-	3.1 (1.2)	1.0 (29)
1st recurrence	32	42.1 (23.2)	7.9 (10.8)	3.1 (1.1)	1.1 (24)
2nd recurrence	11	48.0 (25.8)	6.0 (6.3)	3.4 (1.2)	1.4 (8)
3rd recurrence	4	46.0 (24.3)	5.8 (3.1)	3.8 (1.0)	1.5 (4)
4th recurrence	2	30.0	4.0	3.0	2.0 (2)

The number in parentheses is the number of patients on whom information was available (if different from the total).

The GBS disability scale, type of preceding infection and neurological symptoms (pure motor or sensory-motor) were compared with the previous episode. The characteristics during a recurrence were compared with those during the previous episode (Figure 1).

In individual patients, a preceding infection in two subsequent episodes was reported 17 times. Eleven times the infections were reported as either respiratory or gastrointestinal, whereas six times a gastrointestinal infection was reported prior to one episode and a respiratory infection before the other. Two patients had an upper-respiratory-tract infection preceding three episodes and a gastrointestinal before another. Four patients had a serologically confirmed infection prior to one episode; one patient had a varicella zoster virus and a *Mycoplasma pneumoniae*; one a herpes simplex virus infection and two a *Campylobacter infection*.

One patient reported a tetanus vaccination as a trigger in two subsequent episodes. Another patient, with inflammatory bowel disease, had two episodes of GBS after starting treatment with the drug Salazopyrine. In the two patients, reporting the same trigger in subsequent episodes, neurological symptoms developed faster in the second episode. Two other patients reported a vaccination (influenza/flu virus or hepatitis virus) as a trigger prior to one of the episodes.

In 18 out of 49 successive episodes (36%) there was a more severe GBS disability scale at nadir; in 16 (33%) a less severe GBS disability scale and in 15 (31%) the GBS disability scale was equal in comparison with the previous episode.

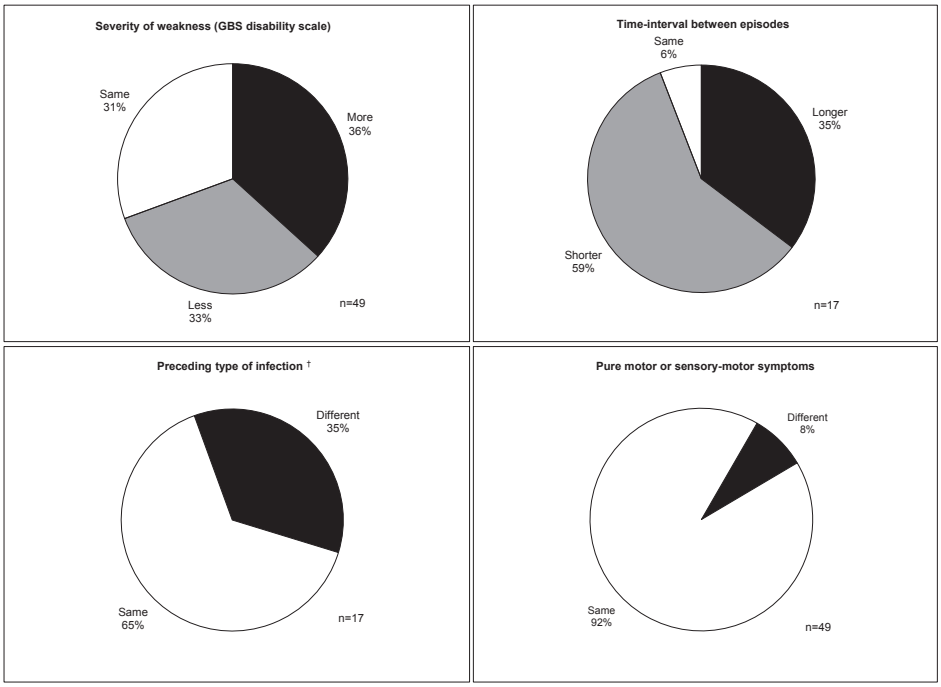

Figure 1. Recurrence characteristics, compared with the previous episode of Guillain-Barré syndrome (GBS)

† Gastrointestinal or upper-respiratory-tract infection.

n = number of two subsequent episodes from which information was available.

For example:

n = 17 means patients reported an infection 17 times before two sequential episodes.

n = 49 means the GBS disability scale was reported in two sequential episodes 49 times.

Most patients had either pure motor or sensory-motor symptoms in subsequent episodes (Figure 1). None of the patients initially had GBS in one episode followed by MFS in a subsequent episode.

One patient had right-sided oculomotor nerve dysfunction in four subsequent episodes, and another patient had three episodes with right-sided oculomotor nerve and abducens nerve palsy, accompanied by dysphagia. One patient had acute motor axonal neuropathy (AMAN) with moderate recovery five times over a period of 14 years.

In the recurrent group, patients more often had MFS (13% vs 4%, $p = 0.049$) and were more frequently < 30 years (44% vs 22%, $p = 0.006$) and more often had a mild course (59% vs. 37%, $p = 0.011$) compared with the non-recurrent group. The mean age was lower in the recurrent group than in the non-recurrent group (34.2 vs 46.9, 95% CI: -20.4 to -4.9, $p = 0.001$). Clinical characteristics of recurrent and non-recurrent patients are listed in Table 1.

DISCUSSION

The patients with a recurrent GBS in our study showed similar signs and symptoms during every episode despite having different types of symptoms of a preceding infection. This may indicate that genetic and immunological host factors partly determine the clinical phenotype irrespective of the preceding infection. The recurrent patients were younger and more often had MFS and a milder course of disease, which suggests that a distinct subgroup of patients has a higher susceptibility of recurring.

To our knowledge, this is the largest group of recurrent GBS patients described so far, and a comparison with non-recurrent patients has not been documented before. We excluded GBS-TRF and A-CIDP patients. One study reported 12 "recurrent" patients with a progressive phase of less than 8 weeks, therefore not excluding the possibility that some of these patients had A-CIDP or subacute GBS.[3] Distinguishing between recurrent GBS, GBS-TRF and A-CIDP can be difficult but is clinically relevant because treatment may differ. In a previous study, we found that nine out of 11 patients with GBS-TRF had their TRF within 9 weeks from onset, and most patients having an exacerbation after 9 weeks eventually developed CIDP.[5]

Whether clinical symptoms and preceding infections differ in recurrent patients has already been addressed in other case studies and is controversial.[10-12] Two studies have reported different antecedent events in individual recurrent GBS patients.[10, 11] In contrast, another study described similar antecedent illnesses in individual recurrent GBS patients.[12] Unfortunately, infection serology in this group of patients was not always testable since serum was not systematically obtained. Two of our patients appeared to have had recurrences after the same specific triggers, one after the drug Salazopyrine and one after a tetanus vaccination; both showed a shorter time between trigger exposure and symptom onset the following episode. Tetanus toxoid vaccination as a trigger for GBS with a shorter symptom onset in subsequent episodes has been reported previously.[13] The drug Salazopyrine has not previously been described as a trigger for GBS, but ulcerative colitis has.[14] We cannot exclude that these events occurred coincidental or that there had not been a subclinical preceding infection in this patient.

In subsequent episodes, most of the recurrent GBS patients had either pure motor or sensory-motor symptoms. Some patients had very specific symptoms during subsequent episodes, such as unilateral cranial nerve palsy at the same site. We cannot explain this specific finding, but it could be related to a local susceptibility of neural tissue related epitopes as replicated laterality of cranial nerve dysfunction has been described before in MFS.[15, 16]

Our observations identify a trend towards shorter intervals between subsequent recurrences, and a more severe deficit with each recurrence. The GBS disability scale is not a linear scale, but a tendency to accumulate neurological deficits after each episode has

been reported previously.[4] It has been established that patients over 50 years of age are more likely to have a worse recovery, which may explain that disability becomes worse after each subsequent recurrence.[17] Recurrent patients are more likely to have MFS than non-recurrent patients. The presence of anti-GQ1b antibodies in almost all MFS patients highlights the importance of immunological factors in this disorder. Since females are more susceptible to autoimmune diseases, it is of interest that the recurrent patients with at least four episodes were all female. Three of the recurrent GBS patients were known with another autoimmune disease, which suggests that genetic host factors are relevant.

The mean age was significantly lower in the recurrent group compared with non-recurrent GBS patients. Age as a risk factor for a recurrent GBS has not been described before, but it has for CIDP. The mean age of relapsing CIDP patients (27 years) is reported to be significantly lower compared with CIDP patients with a non-relapsing course (51 years).[18]

Due to the retrospective nature of our study, we cannot estimate unbiased the exact incidence of recurrent GBS, but as there were 32 recurrent patients out of a total of 524, the crude estimated prevalence will be around 6%. We cannot exclude the fact that some non-recurrent GBS patients have developed a recurrence outside the geographic boundary of the study area or after the 10-year study period. It is possible that some "non-recurrent" patients had their first GBS episode just before the end of the study period, which would have limited the chance of recording a recurrence.

Individual patients developed either GBS during all episodes or MFS, never both. Because recurrent GBS patients were significantly younger, more mildly affected and more often had MFS, neurologists should be aware that these patients are more prone to recurrences. Since similar neurological symptoms can occur after different infections, this study further indicates that immunological and genetic host factors play a role in determining the clinical phenotype in recurrent GBS.

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Chapter 2.2

Individual patients who experienced both Guillain-Barré syndrome and CIDP

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INTRODUCTION

Although Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) have been considered as separate entities, some authors have argued that they may be part of a continuum of inflammatory demyelinating neuropathies.[1 2, 3] GBS is defined as having a progressive onset phase of less than 4 weeks; CIDP of at least 2 months. [4-6] However, some CIDP patients have an acute onset, resembling GBS, and some patients with GBS may relapse or experience treatment-related fluctuations (TRFs).[1, 7] We describe four patients all having had separate episodes of both GBS and CIDP that fulfilled the clinical and diagnostic criteria.[4-6] These four patients came to our attention during a period of twenty years in which over 700 GBS and 150 CIDP patients were seen or enrolled in clinical studies. Most GBS patients were followed up for a period of 1 year, the majority of CIDP patients for many years.

RESULTS

Patient 1

A 46-year-old man developed weakness and numbness in his limbs, worsening over 1 year. He fulfilled the clinical and electrodiagnostic criteria for CIDP and responded well to intravenous immunoglobulin (IVIg) treatment, every two weeks. The IVIg dosage was reduced several times with immediate deterioration as a result. Treatment was continued for 6 years and then stopped; thereafter he remained in remission. Twelve years later, he developed tetraparalysis and facial palsy within 48 hours, 2 weeks after a bout of diarrhoea. He fulfilled criteria for GBS. He was treated with IVIg, and he required artificial ventilation for 2 months. He reached a near complete recovery and no new episodes occurred (Table 1).

Patient 2

A 33-year-old man developed progressive weakness and paraesthesia in all limbs over the course of 1 week. Three days later he was unable to walk. He fulfilled diagnostic criteria for GBS. After IVIg, he initially improved, but 9 days later, he developed facial palsy and opthalmoplegia and he was re-treated with IVIg. He subsequently became tetraplegic needing artificial ventilation. Initially it was thought that he had TRFs, although after five exacerbations all rapidly responding to IVIg, a diagnosis of CIDP was more appropriate. His symptoms required maintenance IVIg treatment for two and a half years. Electrodiagnostic studies were compatible with CIDP (Table 1).

Table 1. Case characteristics

Case	Episode	Sex	Age	Diagnosis	Preceding infection/ incident	Cranial nerve dysfunction	Need for artificial respiration
1	1	M	46	CIDP	-	-	-
1	2	M	64	GBS	Gastrointestinal	VII	+
2	1	M	33	GBS	Cytomegalovirus	VII,ophtalmoplegia	+
2	2	M	34	CIDP	-	-	-
3	1	M	34	GBS	Gastrointestinal	-	-
3	2	M	39	Recurrent GBS with TRF	-	-	-
3	3	M	40	CIDP	-	-	-
4	1	M	39	GBS	Flu-vaccination	VII	+
4	2	M	68	CIDP	-	-	-

GBS, Guillain-Barré syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy; TRF, treatment-related fluctuation.

Patient 3

A 34-year-old man developed a rapidly progressive tetraparesis after an episode of diarrhoea. He was diagnosed with GBS and recovered fully after IVIg treatment. Five years later, he was readmitted with similar symptoms that had developed over 1 week. A lumbar puncture showed a normal protein level of 0.43 g/l. Two to three months later his symptoms returned and were successfully treated with IVIg. One and a half years later he experienced another relapse over a 2-month period. His disease course suggested CIDP, and during another IVIg treatment his symptoms stopped and did not recur (Table 1). Electrodiagnostic studies were compatible with the diagnosis of CIDP.

Patient 4

A 39-year-old man developed tingling sensations and weakness in his limbs after a flu vaccination earlier that month. He then developed bilateral facial palsy and fulfilled diagnostic criteria for GBS. Within 3 days he needed artificial ventilation, which continued for 6 weeks. He recovered slowly. Twenty-nine years later, he developed progressive weakness and numbness over a period of 2 months, compatible with CIDP. No preceding illness or vaccination was reported. Electrodiagnostic studies were compatible with the diagnosis of CIDP. He has been successfully treated with maintenance IVIg treatment, every 4 weeks, for a period of 1 year so far (Table 1).

DISCUSSION

These case histories show that GBS and CIDP can occur in the same patient, and underline the difficult differential diagnosis of GBS or acute CIDP. Patient 1 initially had a course fully compatible with CIDP. Many years later he developed an acute polyneuropathy with severe weakness and respiratory failure after a gastrointestinal infection, a classic example of GBS. Patient 2 had a GBS-like acute onset with respiratory insufficiency, but finally developed CIDP. He experienced five exacerbations and needed maintenance IVIg for more than 2 years thereafter, which suggests that the diagnosis of CIDP with acute and severe onset was more appropriate.[7] Patient 3 experienced two episodes of weakness with acute onset after an infection, suggesting recurrent GBS. The minor deteriorations after each IVIg treatment were considered to be TRFs. The progressive symptoms which developed 1 year later over a longer period of 2 months were compatible with CIDP. [5] Patient 4 had rapidly progressing symptoms of GBS after a flu vaccination. Twenty-nine years later weakness gradually returned: this episode was compatible with CIDP. The patient improved but required intermittent IVIg treatment.

Case histories of patients with multiple episodes of weakness and characteristics of both GBS and CIDP are rare.[3, 8] One patient with GBS-like deterioration after administration of IVIg for CIDP has been reported.[9] These four case histories in which individual patients were affected with both GBS and CIDP suggest that in a proportion of patients GBS and CIDP may constitute a clinical continuum, or that there are common host factors which influence susceptibility to these disorders. Apart from striking similarities, GBS and CIDP also show clear differences. Anti-ganglioside antibodies are frequently detected in GBS, but generally absent in CIDP.[10] Preceding infections are less frequently reported in CIDP, but infections during the course of CIDP may clearly worsen symptoms.[10] It should be noted that most CIDP patients improve after steroids, whereas GBS patients do not.[11] On the other hand, most GBS and CIDP patients improve after IVIg or plasma-exchange. Patients with subacute idiopathic demyelinating polyradiculoneuropathy with progressive weakness of 4-8 weeks have been described, and this entity bridges the gap between GBS and CIDP.[2, 12]

Although we are aware that most patients clearly fit the diagnostic criteria of GBS or CIDP alone and that patients having separate episodes of GBS and CIDP are extremely uncommon, it is important to be aware of the possibility that both GBS and CIDP can co-occur in a single patient and should be diagnosed and treated accordingly. Although it can not be excluded that individuals get both GBS and CIDP by chance, these case descriptions may indicate that in some patients CIDP and GBS are part of a clinical and pathophysiological continuum instead of fully separate entities.

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Chapter 2.3

Recurrences, vaccinations and long-term symptoms in GBS and CIDP

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ABSTRACT

We determined the frequency of recurrent Guillain-Barré syndrome (GBS), whether vaccinations led to recurrences of GBS or an increase of disability in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and we assessed the prevalence of pain, fatigue and the impact on quality of life after GBS and CIDP. Additionally, we assessed the presence of common auto-immune disorders.

Four hundred and sixty-one members of the Dutch society of neuromuscular disorders received a questionnaire. Two hundred and forty-five GBS and seventy-six CIDP patients were included (response rate 70%). Nine patients had a confirmed recurrent GBS, and two patients had experienced both GBS and CIDP. Common auto-immune diseases were reported in 9% of GBS and 5% of CIDP patients. None of the 106 GBS patients who received a flu vaccination (range 1-37 times, total 775 vaccinations) reported a recurrence thereafter. Five out of twenty-four CIDP patients who received a flu-vaccination (range 1-17 times) reported an increase in symptoms. Pain or severe fatigue was reported in about 70% of patients after the diagnosis of GBS (median 10 years) or after onset of CIDP (median 6 years), and quality of life was significantly reduced.

Flu-vaccinations seem relatively safe. GBS and CIDP patients often experience pain, fatigue and a reduced quality of life for many years after the diagnosis.

INTRODUCTION

Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are immune-mediated polyneuropathies associated with a variable clinical course and outcome. GBS patients usually reach their maximum disability within 4 weeks of onset compared to at least 2 months for CIDP patients.[1,2]

Although GBS is considered as a monophasic disorder, some patients experience a recurrence of GBS or even develop a separate episode of CIDP.[3,4] Additionally, some CIDP patients may develop GBS.[4] In this study, we aimed to obtain more information about the frequency of recurrent GBS and the occurrence of both GBS and CIDP in single patients. Additionally, we evaluated the levels of pain, fatigue and quality of life experienced by patients for an extended period after the initial phase of their disease. Pain has been documented as one of the symptoms that can precede and accompany GBS but in CIDP this has hardly been studied.[5-7]

Reports about recurrences of GBS or relapses of CIDP following vaccinations are rare, which suggests that this risk is low.[8] As we aimed to study a large number of patients that might have had multiple vaccinations over time, this information would add to the discussion whether GBS and CIDP patients could safely have vaccinations or not.

MATERIALS AND METHODS

In June 2008, 461 members of the Dutch society of neuromuscular disorders (Vereniging Spierziekten Nederland) with GBS or CIDP were sent a combined set of questionnaires composed by the researchers. Patients were asked to return the questionnaires only if they were diagnosed with GBS, the cranial nerve variant Miller Fisher syndrome (MFS) or CIDP. Furthermore, they were asked to report the disorder they were diagnosed with. To increase the response rate, patients were sent two reminder letters. The study was approved by the Medical Ethical Committee of the Erasmus MC, Rotterdam, The Netherlands.

The questionnaires concentrated on 4 areas; preceding vaccinations (within 8 weeks before the onset of GBS or CIDP), family members with GBS or CIDP, the occurrence of common auto-immune diseases and persistent symptoms at a variable time-point after the diagnosis (the moment of completing the questionnaire). The combined set of questionnaires contained various standardised and well evaluated subquestionnaires to be filled in for the present situation at the time of completion: the numeric pain rating scale (NPRS) for pain, the fatigue severity scale (FSS) for fatigue, the hospital anxiety and depression scale (HADS) for anxiety and depression and the short form (36) health survey (SF-36, Dutch acute version 1) for quality of life.

Severe pain was defined as a score of ≥ 7 on the NPRS.[9] The FSS ranges from one (no signs of fatigue) to seven (most disabling fatigue score). Severe fatigue was defined as a mean FSS score of ≥ 5.0 (≥ 95th percentile in healthy controls), and corrected for depression as scored on the HADS.[10]

SF-36 percentage scores were transformed to norm-based scores using a T-score transformation (mean = 50, SD = 10), giving the opportunity to compare the results from one domain meaningfully with those from other domains, and in particular to compare these with the distribution of scores in the general Dutch population (n = 1742).[11-13] A high SF-36 score is an indication of a better health status, and scores below 50 are interpreted as below average in the general Dutch population. Missing values that could not be traced were substituted with person-specific estimates if the respondent answered at least 50% of the items in a domain according to the half-scale rule from the SF-36 developers.[12] In the case of missing values in the other standardised questionnaires or when other major items were lacking, such as diagnosis or severity at nadir, patients were contacted to obtain missing information. Data were checked by two researchers (K.K. and M.B.E.). When patients reported having had recurrent GBS, both GBS and CIDP, or having relatives with GBS or CIDP, medical information was obtained and verified by the researchers (K.K. and P.D.). When evaluating fatigue, patients were considered mildly affected by their disease when they were able to walk unaided (GBS-disability scale score ≤ 2) at nadir.[14]

Differences in characteristics, and self-reported pain, fatigue, and quality of life were calculated using the χ^2 test, Fisher exact test, Mann-Whitney *U* test or t-test. Spearman's correlation coefficient (r_s) was used to analyse the correlation between fatigue and GBS disability score or the time since diagnosis. A p value < 0.05 was considered significant. Data were analysed using SPSS version 15.0.

RESULTS

A total of 323 questionnaires were returned: a response rate of 70%. Two patients were excluded; one with a chronic idiopathic axonal polyneuropathy and one with an unknown diagnosis. Patients completed the questionnaire after a variable time from onset of GBS (median 10 years, range 0-62) or CIDP (median 6 years, range 0-29).

Of the 321 patients, 245 were diagnosed with GBS and 76 with CIDP. Of the 245 GBS patients, four had MFS and five had an MFS/GBS overlap. One patient had Bickerstaff encephalitis. Nineteen GBS patients reported recurrent GBS, and in nine of these patients (4%) we could confirm this, but in the other 10 it remained unclear from the medical information available whether these patients had indeed had another GBS episode. Two patients had both GBS and CIDP. One of these patients has been described previously.[4]

Eight GBS patients and one CIDP patient had a relative with an immune-mediated polyneuropathy, which was verified by checking medical records. Six GBS patients had a first till fourth degree relative with GBS. One GBS patient had a grandson with CIDP and another had a cousin with multifocal motor neuropathy. One CIDP patient had a brother with CIDP.

Twenty-three GBS (9%) and eight (11%) CIDP patients reported a preceding vaccination, within 8 weeks form onset of symptoms. The most often reported vaccination was a flu vaccination (Figure 1).

None of the 106 GBS patients who received a flu vaccination (range 1-37 times, in total 775 vaccinations) in the years after they experienced GBS reported a recurrence of GBS. 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.

Twenty-three patients with GBS (9%) and four patients with CIDP (5%) are currently diagnosed with a common auto-immune disease, most often a thyroid disorder (Figure 2).

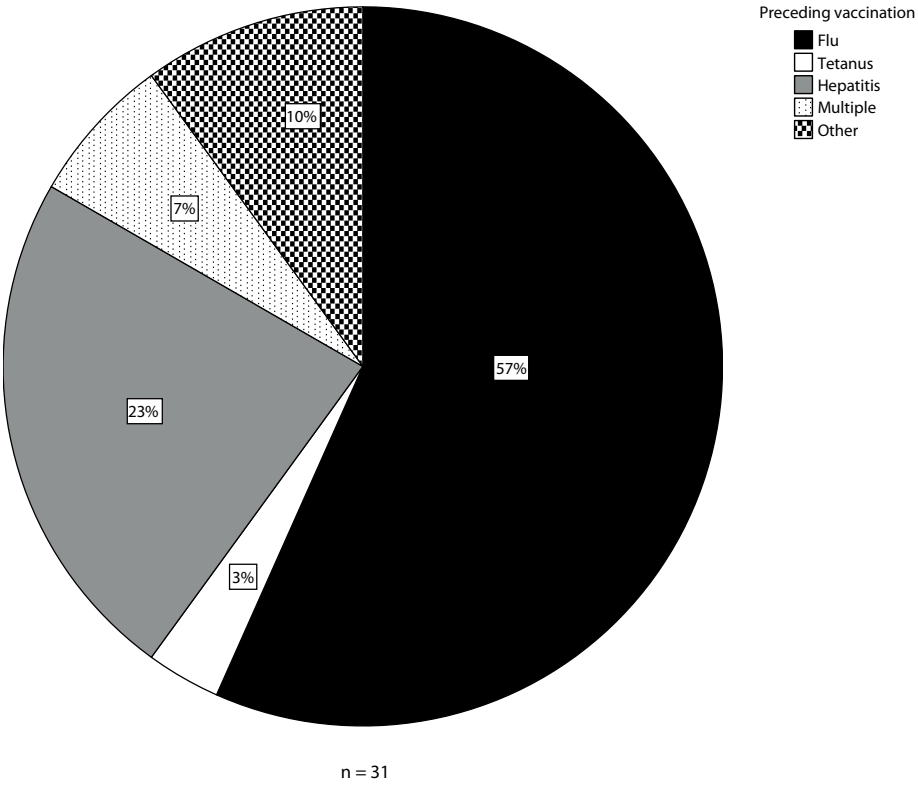

Figure 1. Reported vaccinations prior to onset of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy

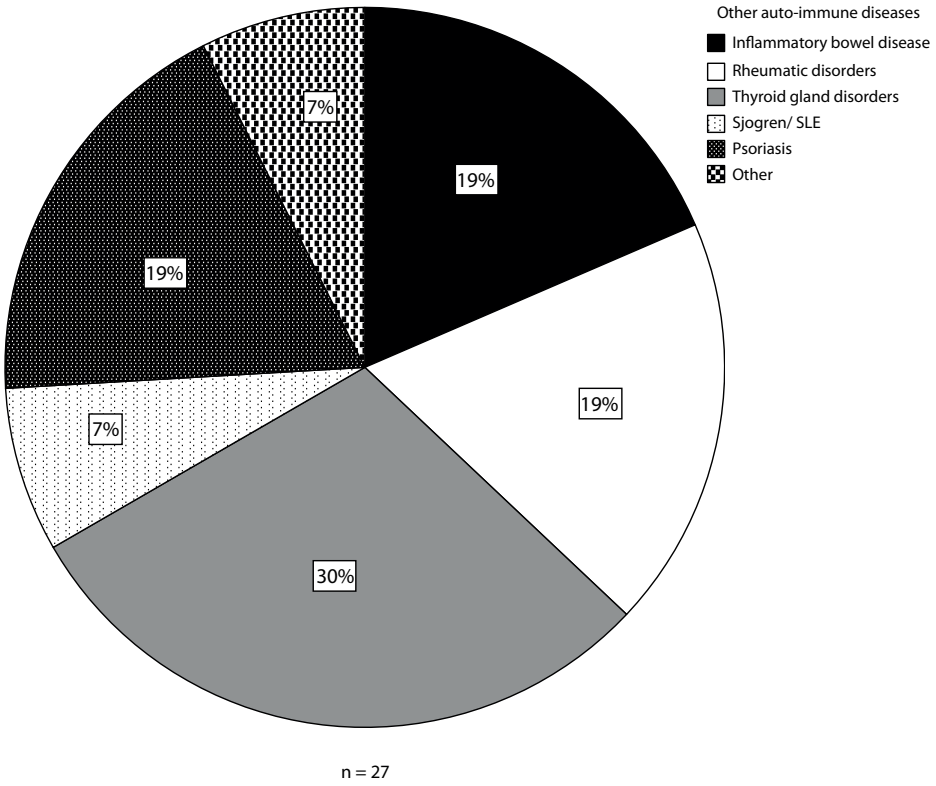

Figure 2. Reported auto-immune diseases in patients with Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy

Pain was reported in 71% of GBS and in 72% of CIDP patients long after the diagnosis, and severe pain in 8% of GBS and 17% of CIDP patients. Several years after the diagnosis, severe fatigue was still prominent, and 45% of GBS and 25% of CIDP patients experienced fatigue as their most disabling symptom (Table 1). Severe fatigue was more pronounced in the patients who were still severely affected as assessed with the GBS-disability scale, than in the mildly affected patients (85% vs 68%, p=0.008), and the GBS-disability score correlated weakly with the FSS score ($r_s = 0.5$, $p < 0.01$). Fatigue was not significantly related to the time since start of the GBS symptoms ($r_s = 0.04$, $p = 0.5$).

CIDP patients scored significantly lower than the GBS patients on three items of physical functioning (Table 1). GBS and CIDP patients scored significantly lower in all physical health items of the SF-36 as well as in two items of mental health (vitality and social functioning) when compared with the normal Dutch population (Figure 3).[13]

Table 1. Long-term symptoms in Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

	Patients		
	GBS (n = 245)	CIDP (n = 76)	p value
Time since diagnosis, y	10 (0-62)	6 (0-29)	0.001
Age when participating in this study, y	59 (7-94)	59 (9-85)	NS
Disability (GBS-disability score)			
Median (range)	2 (0-4)	2 (0-4)	NS
Pain (NPRS)			
Median (range)	2.2 (0-10)	2.3 (0-8)	NS
Severe pain[#]	8%	17%	0.028
Depression (HADS)			
Depressed	6%	9%	NS
Fatigue (FSS)			
Median (range)	5.8 (1-7)	5.9 (1-7)	NS
Severe fatigue*	69%	74%	NS
Quality of Life (SF-36)			
Physical functioning	36.2 (13.7)	32.6 (13.2)	0.046
Role-physical	41.7 (11.8)	38.6 (11.2)	0.042
Bodily pain	46.5 (10.7)	45.3 (12.0)	NS
General health	44.6 (11.5)	39.1 (11.7)	<0.001
Vitality	43.6 (10.6)	41.2 (10.2)	NS
Social functioning	45.8 (9.0)	46.2 (9.2)	NS
Role-emotional	50.0 (10.0)	50.0 (10.8)	NS
Mental health	50.0 (9.3)	50.1 (9.8)	NS

NS = not significant ($p > 0.05$)
Continuous or categorical variables presented as median (range) and compared using Mann-Whitney *U* test.
Numeric variables presented as percentage and compared using χ^2- test or Fisher exact test.
Continuous variables regarding the SF-36 are presented as norm-based mean scores (SD) using a T-score transformation (mean = 50, SD 10) according to the general Dutch population and compared using t-test.
NPRS = numeric pain rating scale
HADS = hospital anxiety and depression scale
FSS = fatique severity scale
SF-36 = Short Form (36) health survey
[#] NPRS ≥ 7.
* FSS ≥ 5.0 corrected for depression.

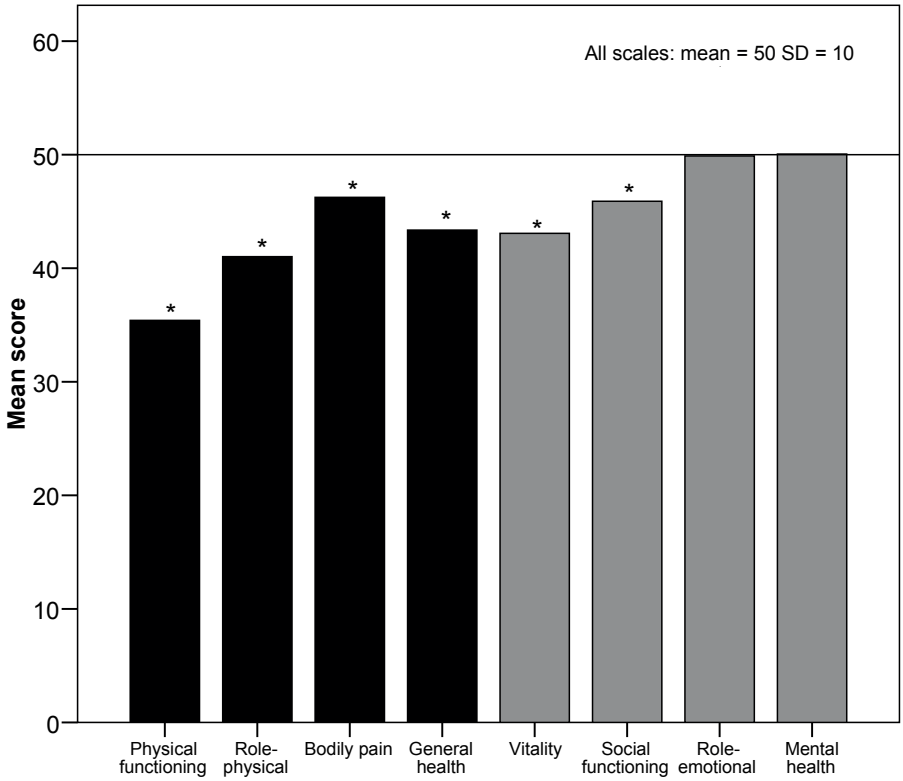

Figure 3. SF-36 health survey in Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy patients (norm-based scoring)
* = $p < 0.001$.

DISCUSSION

The frequency of recurrent GBS (4%) in the current study is comparable with the 2-6% that has been described previously.[3,15] We found two patients who had had both GBS and CIDP. Although the combination of having both GBS and CIDP could be by chance, these patients support the hypothesis that GBS and CIDP may constitute a clinical continuum or that there are common host factors which influence susceptibility to these disorders.[4] We identified nine patients (eight GBS and one CIDP) having a relative with an immune-mediated polyneuropathy, which may suggest, but does not prove, a genetic susceptibility factor; some of these patients have been described previously.[16] The GBS and CIDP patients included in our study had a slightly higher prevalence of common auto-immune diseases than the 5% previously reported in the general population.[17]

Our study indicates that the risk of developing another GBS episode after a flu vaccination is small. This confirms a recent study that found no evidence of an increased

risk of GBS after seasonal influenza vaccination.[18] Another study has also suggested a low risk following vaccination, where only 4% (11/311) of GBS patients and 8% (5/65) of CIDP patients experienced a recurrence of symptoms following a vaccination.[19]

The occurrence of pain long after the diagnosis of GBS in our study was similar to the 69% that has been described before in 50 GBS patients long after the diagnosis (median 10 years).[20] Severe fatigue was also a major complaint even long after the diagnosis of GBS or CIDP. Fatigue is reported to occur more often in patients with an immune-mediated neuropathy than in healthy controls (median 6.1 vs. median 2.9, $p < 0.0001$).[10] In a group of 113 patients with an immune-mediated neuropathy, severe fatigue appeared to be present in 80% of patients several years (median 5.1 years) after the diagnosis.[10] Some of these patients were probably also included in our study, but our study contained three times more GBS as well as CIDP patients and the median time from disease onset was longer. We did not find a correlation between the time since diagnosis and the presence of fatigue. In contrast to what has been reported previously, our study suggests that severe fatigue was more pronounced in patients who were more severely affected by the disease at the time of completing the questionnaire. Both GBS and CIDP patients scored significantly lower on the SF-36 than the general Dutch population, except for two items regarding mental health, which has been described before.[20,21] When we compared GBS patients with those having CIDP, CIDP patients scored significantly lower on three items regarding physical health. This has not been reported before but can be explained by the chronic and often still active course of disease in CIDP.

Our study was a survey of members of a patient organisation, which may have given rise to several methodological limitations. As only members from a patient organisation were included, selection bias could have occurred. Patients who are or remain a member of a patient organisation are probably more likely to be severely affected. Patients were asked to return the questionnaire if they were diagnosed with GBS or CIDP. As we could not verify the diagnosis in all patients, some patients with another diagnosis might have been included. The retrospective nature of part of the questionnaires could have introduced recall bias. It is difficult to draw firm conclusions from a questionnaire in which patients report their recurrences after vaccinations themselves. It seems that patients are more likely to respond to a questionnaire when they did experience a recurrence.

Furthermore, the fact that not all patients responded to our questionnaire might have introduced some bias, although some members might have not replied due to the fact that they had been diagnosed with another disease or were healthy relatives of a patient. Strong points of our study are the large number of GBS and CIDP patients and the extended length of time between diagnosis and questionnaire completion.

The occurrence of recurrent GBS, GBS and CIDP in single patients or in families, and the slightly higher rate of common auto-immune diseases in GBS and CIDP patients may indicate a certain, possibly genetic, susceptibility factor. The common seasonal flu

vaccinations seem relatively safe in patients who have had GBS or still have active CIDP. Several years after the diagnosis of GBS (median 10 years) or CIDP (median 6 years) a significant number of patients still have residual symptoms, such as pain and severe fatigue, as well as a reduced quality of life, which clearly warrants recognition and support when possible.

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CHAPTER 3

Treatment of CIDP

Chapter 3.1

Newer therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disorder with variable symptoms and severity that can be difficult to diagnose. Intravenous immunoglobulin, plasma exchange and corticosteroids have all been proven to be beneficial in randomised controlled trials, although the proof for steroids is less clear. Although these treatments are likely to be similar in efficacy they differ in terms of their cost, availability and adverse effects. These characteristics should be taken into account when deciding which treatment to offer a patient. If there is no response to the first treatment option, one of the other treatments should be tried. Patients with a pure motor CIDP may deteriorate after steroid treatment.

Some patients do not respond or become refractory or intolerant to these conventional treatments. Those who become unresponsive to therapy should be checked again for the appearance of a monoclonal protein or other signs of malignancy. Over the years, small non-randomised studies have reported possible beneficial effects of various immunosuppressive agents. A Cochrane review concluded that currently there is insufficient evidence to decide whether these immunosuppressive drugs are beneficial in CIDP. When giving immunosuppressive drugs, one should be aware that some might even cause demyelinating disease. It is difficult to prove beneficial effects of these newer treatments since they are only tried in small groups of patients, who are refractory to other treatments, and often in combination with other treatments. CIDP patients can deteriorate during or after infections or improve spontaneously, making it more difficult to judge treatment efficacy. Various treatments for CIDP are described such as azathioprine, cyclosporin, cyclophosphamide, interferons, methotrexate, mycophenolate mofetil, rituximab, and etanercept. An overview of these newer treatments, their mode of action, adverse effects and potential place in the spectrum of treatments for CIDP based on previous reports and their level of evidence is given.

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is characterized by proximal and distal weakness of the extremities, sensory disturbances, and reduced or absent tendon reflexes.[1, 2] It is a relatively rare disorder with an estimated prevalence of 1-2 per 100.000.[3, 4] The course of CIDP can be relapsing-remitting or chronic and progressive.[5] Many patients with CIDP have a chronic disease course lasting several years. Some patients with active CIDP have been receiving immunomodulatory treatment for over 25 years (personal observations). The diagnosis of CIDP is made based on clinical and electrodiagnostic criteria.[1, 2] An elevated protein level in cerebrospinal fluid without pleiocytosis or the findings on nerve biopsy may support the diagnosis but are not mandatory.[1] CIDP can be associated with various other concomitant diseases, such as diabetes mellitus.[1, 5] In general, CIDP has a progressive phase of >8 weeks.[1, 2] The duration of progression differentiates CIDP from Guillain-Barré syndrome (GBS), a rapidly progressive polyneuropathy, which has a progressive phase of <4 weeks.[6] However, about 16% of CIDP patients do have an acute onset like GBS.[7, 8]

CIDP is a heterogeneous disorder that can be difficult to diagnose.[5] There are numerous chronic polyneuropathies and making the diagnosis of CIDP can be difficult; however, it is important to make the diagnosis because CIDP is a potentially treatable disorder.

Mildly affected patients should not always be treated since spontaneous recovery can occur and the risk of adverse effects may not outweigh the potential benefits of treatment.[9] The treatment of CIDP consists of anti-inflammatory, immunosuppressive and immunomodulating drugs. The following three treatments have been shown to be effective in randomised controlled trials: intravenous immunoglobulin (IVIg)[10-13], plasma exchange (PE)[14, 15] and corticosteroids[16]. Only 60-80% of patients with CIDP improve with one of these three treatments[17] and some patients, for unknown reasons, respond better to one treatment than to another.[18] In a group of 44 CIDP patients, 39% responded to initial therapy, and of the non-responders, 35% responded to second treatment and 27% of the patients who needed a third treatment showed a response.[19] Overall, 66% responded to one of the three main treatments.[19]

CIDP patients can have a spontaneous improvement of muscle weakness and sensory disturbances, making it difficult to judge efficacy of treatment in single patients. Whatever treatment is given, regular assessments should be carried out as needed, based upon the clinical response and adverse effects, to see if treatment can be reduced or discontinued, if the patient is in remission.[9] Patients who initially respond and subsequently become unresponsive to therapy should be checked again for the appearance of another disorder, such as paraproteinemia.[20] When treating and evaluating patients with CIDP, it is important to realise that infections and febrile conditions may worsen

symptoms. Although, anecdotally, CIDP patients have been described who showed a spectacular improvement after sepsis.[21]

In autoimmune diseases (e.g. rheumatoid arthritis) and immune-mediated disorders (e.g. multiple sclerosis) new therapeutic drugs are tested and evaluated relatively quickly. Although not proven, CIDP probably is an autoimmune disorder; therefore, immunosuppressive or immunomodulating agents are expected to be beneficial. Transferring experimental therapeutics from animal models to humans has not been always successful.[22] Over the years, small non-randomised studies have reported possible beneficial effects of various immunosuppressive agents in CIDP. Since these were all small non-controlled studies a Cochrane review concluded that there was insufficient evidence to decide whether these immunosuppressive drugs were beneficial in CIDP (Table 1).[23-26] It is difficult to prove beneficial effects of these newer treatments because (i) they are generally administered to small groups of patients who are refractory to all other treatments; (ii) they are often tried in combination with other treatments; and (iii) because CIDP is such a rare disorder, it is difficult to recruit large numbers of patients for clinical trials. In prescribing these immunosuppressive agents, one should be aware of the possibility that some of these might even cause demyelinating disease.[27]

Table 1. Cochrane reviews in the treatment of chronic inflammatory demyelinating polyradiculoneuropathy

Study	Treatment	Efficacy	Speed of action	Potential long-term adverse effects	Availability	Costs
Eftimov et al. [24]	Intravenous immunoglobulin	Proven	Fast	Minor	Good	High
Mehndiratta and Hughes[25]	Corticosteroids	Proven	Moderate	Severe	Very good	Low
Mehndiratta et al. [26]	Plasma exchange	Proven	Fast	Minor	Variable	High
Hughes et al.[23]	Cytotoxic drugs and interferons	Unknown	Variable	Severe/ variable	Good/ Variable	Moderate/ Variable

Levels of evidence and dosage regimens for various treatments are listed in Table 2.[9, 22, 28-30] Since some patients are non-responsive, or become refractory or intolerant to the conventional treatments, newer therapeutic options are potentially important in the treatment of CIDP and randomised-trials are urgently needed.

Table 2. Drug regimens for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy

Treatment	Evidence level[a]	Regimen
Proven efficacy in RCTs		
Intravenous immunoglobulin	1a	Induction: 2 g/kg, divided over 2-5 d Maintenance: 0.4-1 g/kg every 2-6 wk
Plasma exchange	1a	Induction: 3-5 PE sessions (2-2.5 L/session) Maintenance: 1 PE session every 1-3 wk
Prednisolone	1b	Induction: 60 mg/d or 1-1.5 mg/kg Maintenance: slowly tapering over mo to y
Unproven efficacy in RCTs		
Intravenous methylprednisolone	III	Induction: 500 mg/d for 5 d, or 1 g/d for 3 d Maintenance: once a mo, slowly tapering
Azathioprine	III	1.5-3 mg/kg/d
Cyclosporin	III	2.5-5.0 mg/kg/d divided into 2 doses
Mycophenolate mofetil	III	1.0-2.0 g/d divided into 2 doses
Cyclophosphamide	III	Pulsed 1g/m^2 IV over 1.5 h each mo, 3-6 mo
Methotrexate	III	7.5-15 mg once a wk
Interferon-α	III	3 MIU 3 x/wk SC
Interferon-β	III	6 MIU 3 x/wk SC
Rituximab	IV	375 mg/m^2 IV once a wk for 4 wk
Tacrolimus	IV	0.1-0.3 mg/kg/d divided into 2 doses
Etanercept	IV	25 mg SCtwice a wk
Alemtuzumab	IV	30 mg/d IV 5 d

[a] Levels of evidence: Ia = meta-analysis of more than one RCT of good quality; Ib = RCT of good quality; II = controlled study without randomisation or randomised study with low patient numbers;
III= uncontrolled study; IV = one or more case reports.
MIU = million international units; RCT = randomised controlled trial; SC = subcutaneous.

CURRENT PROVEN EFFECTIVE TREATMENTS

Intravenous immunoglobulin (IVIg)

Several placebo-controlled trials have shown that IVIg is an effective treatment for CIDP.[10-13] In one of these trials, IVIg was effective in 50 previously untreated CIDP patients.[12] Another randomised, double-blind, crossover trial showed a positive effect of IVIg in three of seven CIDP patients. This trial was prematurely stopped after the benefits of IVIg were proven in another trial and continuing was considered unethical.[11, 31]

One randomised, double-blind, placebo-controlled study could not demonstrate a beneficial effect of IVIg in 28 CIDP patients.[32]

A Cochrane review confirmed the efficacy of IVIg and concluded that there is evidence that IVIg improves disability for at least 2-6 weeks compared with placebo.[24]

Recently, the largest randomised, placebo-controlled trial in CIDP patients has proven the benefits of IVIg.[13] This randomised, double-blind, placebo-controlled, response-conditional, crossover trial conducted in 117 patients also showed the first evidence for long-term efficacy and safety of IVIg in CIDP patients.[13] In the IVIg group, 54% improved in adjusted inflammatory neuropathy cause and treatment (INCAT) disability score[33] compared with 21% out of the placebo group. Results were confirmed during the cross-over period. During the extension phase, patients who received IVIg had a longer time to relapse than patients who were treated with placebo. The frequency of adverse events and the incidence of serious adverse events on the long-term did not differ generally from placebo.[13]

If CIDP patients do improve after IVIg, clinical improvement can be expected within 1-2 weeks after starting treatment.[9] The maximum effect may last from several weeks to months.[34] The exact mechanism of action of IVIg is unknown. IVIg has various immuno-modulating effects such as neutralisation of autoantibodies, inhibition of complement, modulating phagocytosis through blockage of Fc receptors.[18] In general, IVIg is well tolerated, and has only mild infusion-related adverse effects such as chills, headache and myalgias, which are probably caused by complement activation.[18] However, some rare serious adverse events can occur, such as anaphylaxis, thrombo-embolic events or renal failure. Therefore, in patients known with cardiac failure or kidney failure, IVIg should be used with caution.[18]

The disadvantage of IVIg is its high cost and need for intravenous infusions. It is time consuming to administer and most patients require the treatment for a long period. Since it has few adverse effects, it is frequently considered as an initial treatment.[9]

The initial dosage of IVIg is usually 0.4 g IVIg/kg body weight for 5 days. It is unknown whether a higher infusion dosage (1 g/kg body weight for 2 days) is more effective. The best treatment schedule, dose and frequency in CIDP are still unknown and randomised trials comparing several dosage schedules are needed.[35, 36]

A flowchart for treatment of CIDP with IVIg is given in Figure 1.[9] Also, it is unknown whether different brands of immunoglobulin are similar in efficacy. We are currently conducting a randomised controlled trial comparing two different immunoglobulins in CIDP patients receiving maintenance IVIg treatment.

Plasma exchange (PE)

Two trials have shown that PE is an effective treatment for CIDP.[14, 15]

In the first double-blind sham-controlled trial, 5 of 15 patients who received PE experienced greater improvements on the neurological disability scale from baseline than the 14 patients who received sham exchange. These results were reproduced during an open-label phase. This study showed that PE can be beneficial in some CIDP patients. In the patients who responded to the treatment, the effect began to fade 10-

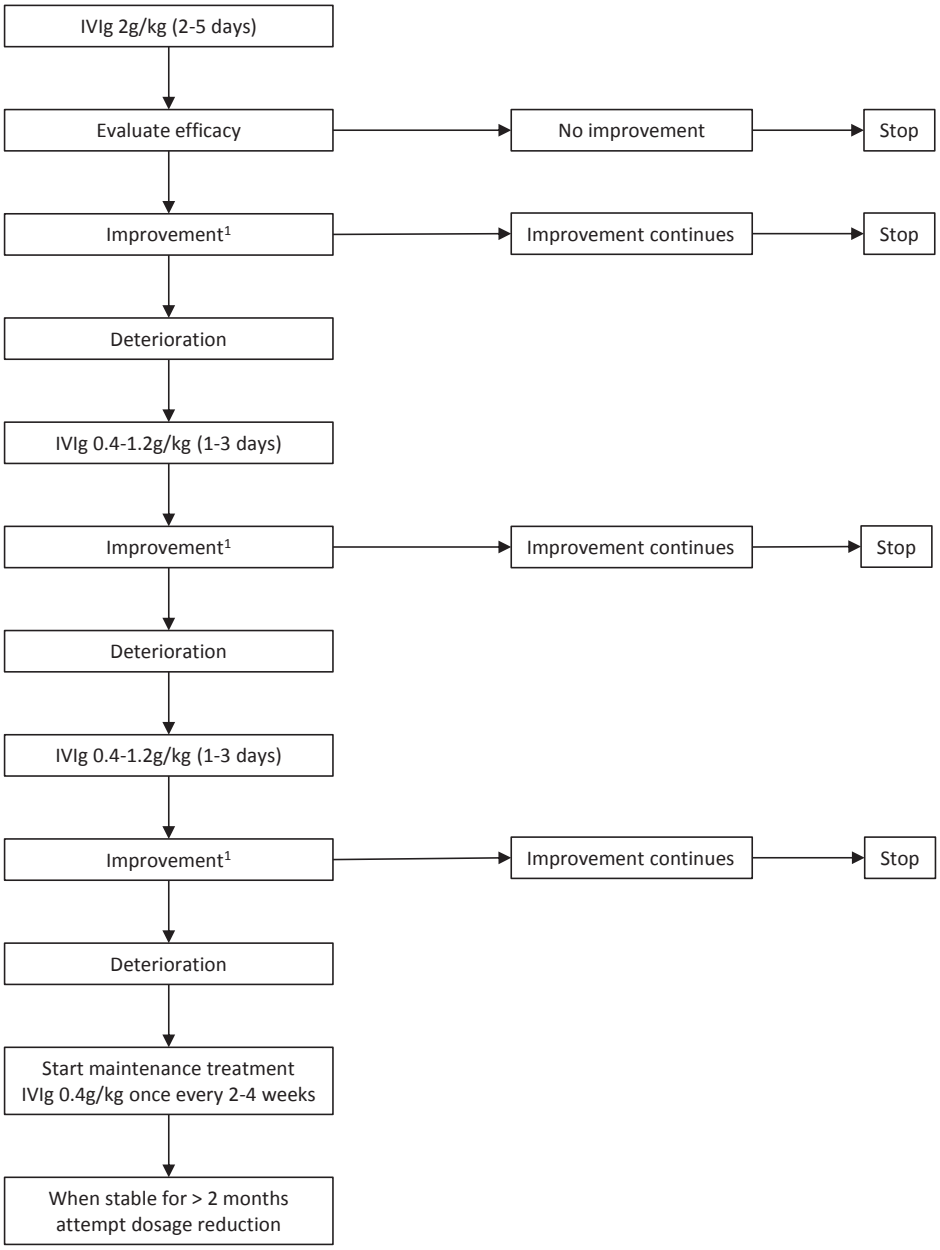

Figure 1. Intravenous immunoglobulin (IVIg) treatment in chronic inflammatory demyelinating polyradiculoneuropathy

[1]Clinical assessment 1-2 weeks after onset of IVIg therapy.

14 days after treatment. Limitations of this trial are its short duration of 3 weeks and possible interactions with other immunosuppressive drugs.[14] In another double-blind, sham-controlled, cross-over study, 12 of 15 patients who completed the trial improved substantially with PE. These patients were all newly diagnosed with CIDP, either chronic relapsing or progressive, and did not receive other immunosuppressive drugs. Eight of the 12 responders relapsed after stopping PE, and prednisolone therapy was needed to maintain long-term remission. The three patients who did not respond to PE responded to prednisolone. The authors concluded that PE is a very effective therapy in CIDP, but adjuvant immunosuppressive drug treatment is often needed in the long term. Three patients in this trial withdrew; one because of problems with venous access, one had a stroke and another patient quit to receive open treatment elsewhere.[15] On the basis of these two trials, a Cochrane review concluded that PE provides short-term benefits in about two-thirds of patients with CIDP.[26]

PE is normally started with a frequency of five exchanges per 2-week period. When the patient improves, a maintenance regimen (e.g. once every 1-3 weeks) can be adopted. PE is probably effective because it removes pathogenic antibodies and other substances like cytokines directly from the circulation. Whether this is the exact mechanism of PE is presently unknown.[37] PE is an invasive procedure that is not always available. Furthermore, it is time-consuming, requires hospitalisation and is often needed for a prolonged period. Severe cardiac disease or coagulopathy are relative contraindications for PE. The most reported adverse effects are hypotension, fluid overload, electrolyte imbalances, infection, bleeding or thrombosis at the venous access site. Myocardial infarction is a rare adverse effect. Adverse events relating to, for example, difficulty with venous access, use of citrate and haemodynamic changes occur in 3-17% of patients.[26] Although most patients respond within several days after starting, rapid deterioration may occur after therapy is stopped.[26]

Prednisolone

Only one randomised controlled trial considering the treatment of CIDP with prednisolone has been conducted to date.[16] In this study, 35 patients were randomised between prednisolone, starting with 120 mg/day and tapering over 12 weeks, and no treatment. The conclusion from this study was that corticosteroids significantly reduced impairment and improved nerve conduction measurements.[16] However, it should be noted that it was an open-label study without concealed allocation. A Cochrane review concluded that this trial provided weak evidence that oral steroids reduce impairment in CIDP.[25]

Several case series support the general opinion that corticosteroids are beneficial.[1] Ten CIDP patients were given pulsed high-dose dexamethasone, three of these discontinued treatment -one as a result of adverse effects and two due to neurological deterioration. Of the two patients who deteriorated, one had a pure motor form of CIDP

and the other showed no response to IVIg or PE. All seven patients who completed the treatment improved in functional health status.[38]

The results from a randomised trial comparing pulse-dosed dexamethasone with prednisolone are eagerly awaited.[39]

About 65% of CIDP patients seem to respond after corticosteroid treatment.[7] The generally accepted dosage for prednisolone is 60 mg/day or 1.5 mg/kg body weight on alternate days as induction, with maintenance therapy slowly tapering over months to years.

For an as yet unknown reason, patients with pure motor CIDP may deteriorate after corticosteroids; therefore, IVIg is advised in this group.[38, 40]

Corticosteroids have various effects on cellular immunity such as reducing the number of lymphocytes, decreasing the levels of cytokines and inhibition of macrophages. Corticosteroids have been used for a long time, are widely available and are not time-consuming. Long-term adverse effects such as hypertension, hyperglycaemia, osteoporosis, infections, gastrointestinal ulcers, obesity, cataracts and psychiatric disturbances are very common. Corticosteroids are inexpensive, but adverse effects can be severe. Another disadvantage of corticosteroids is a time-lag of several weeks that can occur between the start of treatment and clinical improvement. Also, corticosteroid treatment is often needed for a long period ranging from 6 weeks to several years.

Comparing IVIg, PE and steroids

The choice of the best agent to use to treat patients with CIDP is difficult. One single-blind, crossover trial compared PE with IVIg.[41] Twenty CIDP patients were randomly assigned to either PE (twice a week for 3 weeks then once a week for 3 weeks) or IVIg (0.4 g/kg once a week for 3 weeks then 0.2 g/kg once a week for the next 3 weeks). This treatment regimen was chosen because it had an approximately similar cost and was thought to be effective. No significant difference between the two treatments was found.[41] Some limitations of this trial are its unusual regimen of IVIg, and lack of an intention-to-treat analysis and inadequate allocation concealment.[42]

A double-blind crossover trial compared IVIg (2 g/kg) with a 6-week course of oral prednisolone.[33] There was no significant difference in the proportion of patients with a significant improvement. The authors state that there was slightly more improvement in the IVIg group, although this did not reach significance.[33] Also, this trial had the following shortcomings: (i) the trial was prematurely ended due to reaching the expiration date of the trial medication; (ii) the trial was not powered to detect equivalence; (iii) and the regimen of prednisolone was relatively short; and (iiii) the reduction in dosage was different from what is standard in general practice.[33, 42]

In a cost-utility analysis, IVIg was far more expensive than prednisolone, but IVIg treatment resulted in greater improvements in health-related quality of life and associated utility.[43]

All three treatments are likely to be similar in efficacy, although they differ considerably in availability, cost and adverse effect profiles. Since they show about similar efficacy, it is difficult to suggest a first choice. The pros and cons should be compared on an individual basis. A consensus guideline recommends starting treatment of CIDP with IVIg or corticosteroids.[1] If both these treatments are ineffective, PE is recommended.[1]

Combining IVIg, PE and corticosteroids

Combination therapy may increase the duration of response, increase efficacy or reduce the need for standard therapy.[36] One CIDP patient who did not respond satisfactory to IVIg or PE, and who could not tolerate high-dose prednisolone, responded to a synchronised combination of all three treatments.[44] A CIDP patient who did not respond to high-dose IVIg responded well to moderate-dose IVIg after a short course of PE.[45] Two CIDP patients, who were unresponsive to the conventional treatments, improved immediately after a repeated combination of PE and IVIg.[46]

POTENTIAL TREATMENTS

Subcutaneous immunoglobulin

In patients with a primary immunodeficiency syndrome, immunoglobulins have been given via a subcutaneous portable pump. It seems that subcutaneous immunoglobulin (SCIg) treatment leads to more stable plasma levels and reduced adverse effects.[47] Furthermore, it can reduce the costs significantly and it is easy to handle since no venous access is needed, thus improving autonomy. Two CIDP patients, responsive to IVIg, have been described in whom SCIg led to a stabilisation of the disease course.[48] In both these patients, it was well tolerated and costs were reduced by 50%.[48] Preliminary results of an open label prospective study by Magy[49] of SCIg in CIDP patients are positive.[49]

A disadvantage of SCIg can be the restricted volume per infusion, which may result in the need for regular infusions.[48]

Intravenous Methylprednisolone

An open-label, retrospective study of intravenous methylprednisolone (IVMP) reported improved muscle strength comparable with that of IVIg and oral prednisone.[50] In this study, 16 patients were treated with long-term intermittent IVMP, although not in accordance with a standardised treatment regimen or evaluation regimen. Weight gain and Cushingoid features were reported to occur less often after IVMP than oral pred-

nisolone.[50] Currently, a randomised controlled trial comparing IVIg and IVMP is being conducted by Nobile-Orazio in CIDP patients.[51]

Azathioprine

Azathioprine is an anti-inflammatory drug that causes inhibition of proliferating immunocompetent cells.[22] Although reliable data on its efficacy in CIDP are lacking, azathioprine is often prescribed because it can reduce the dosage of corticosteroids required.[9, 23]

An open-label, randomised controlled trial of 27 patients that compared azathioprine in combination with prednisone with prednisone alone showed no significant difference between treatments.[52] Criticisms of this trial are its small size, lack of power to detect any but large treatment effects and the use of a low dosage. Furthermore, the treatment period of 9 months may have been too short to draw conclusions about its efficacy.[23] Four of five CIDP patients showed a sustained improvement after azathioprine and in the fifth patient it replaced corticosteroid therapy.[53] Other case series have reported positive effects of azathioprine.[54-57] In addition to there being case series describing positive effects, patients have also been described showing no response to azathioprine.[58]

It can take up to several months before azathioprine reaches maximal effect. The most reported adverse effects are leucopenia, thrombocytopenia, anaemia, myelosuppression and pancreatitis.[28]

Cyclosporin

Cyclosporin is a calcineurin inhibitor that inhibits the production of cytokines and is mainly used in organ transplant patients. The most serious adverse effects of cyclosporin are dose-dependant nephrotoxicity and hypertension; therefore, renal impairment is a contraindication.

In a retrospective study, 19 CIDP patients, non-responsive to other treatments, were treated with cyclosporin.[59] The mean disability status (measured on a 5-point scale) declined from 3.8±0.7 to 1.8± 1.1 ($p < 0.001$) in the progressive group, and in the relapsing group the mean annual incidence of relapse declined from 1.0± 0.5 to 0.2± 0.4 ($p < 0.05$) after treatment with cyclosporin. In two patients, cessation of therapy was necessary because of reversible nephrotoxicity.[59] Another case study reported an improvement in clinical symptoms in seven patients.[60]

In eight CIDP patients who were treated with cyclosporin, three improved or were able to stop prednisone; for the other five, it had no effect.[61] In eight other patients with CIDP, of whom five had associated paraproteinaemia, three patients were reported to have an excellent response, two with complete remission.[62] In the other patients, it was possible to reduce the corticosteroid dose and frequency of PE.[62]

Various other small case series have described the treatment of CIDP with cyclosporin.[63, 64] Cyclosporin is more toxic, but it may have a more rapid mode of action and is less allergenic than azathioprine.[61] One organ-transplant patient has been described who developed CIDP while on prednisolone and cyclosporin.[27]

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a fast acting immunosuppressive agent that has been widely and successfully used in preventing the rejection of organ transplants. Furthermore, it is used in immune-mediated diseases such as rheumatoid arthritis and Crohn's disease.[65]

MMF inhibits the proliferation of T and B lymphocytes. In general, MMF is well tolerated and relatively safe to use, causing only mild bone marrow suppression. It can be effective alone or act as an adjuvant by reducing the dosage of corticosteroids required and/or the frequency of IVIg infusions.[66] A small study that retrospectively reviewed the efficacy of MMF in CIDP patients concluded only a modest benefit in 20% of patients, allowing reduction of corticosteroid or IVIg therapy.[67] In two CIDP patients treated with MMF, IVIg dosage could be reduced by 50%.[68] Three other CIDP patients are described, of whom one responded to MMF treatment; no details are given about the response of the other two.[65] Another case series showed an improvement in strength and sensation in two CIDP patients.[69] In four patients with treatment-resistant CIDP, there was no clinical significant benefit and in none of the patients the dosage of other immunosuppressive drugs could be reduced.[70] In one of these patients, adverse effects were severe enough to stop the medication.[70]

The most reported adverse effects are diarrhoea, leucopenia, thrombocytopenia, neutropenia, lymphoma, gastrointestinal bleeding and headache.[28, 65, 67]

Cyclophosphamide

Cyclophosphamide eradicates T and B lymphocytes.[71] The largest series described 15 CIDP patients treated with intravenous pulse cyclophosphamide.[72] Twelve of these showed marked improvement and 11 had a complete response. Three patients showed no improvement and three worsened. Six had minor adverse effects and none showed serious adverse effects.[72] Another study described four CIDP patients having incomplete responses to immunotherapy, but improvement in functional status and muscle strength after high-dose cyclophosphamide (200 mg/kg over 4 days).[71] Neutropenic infections and transient renal insufficiency as well as other mild adverse effects were reported.[71]

Another report described continuous positive effects of cyclophosphamide in four CIDP patients during the follow-up time, as well as positive effects in another patient and an improvement in quality of life in all five.[73] Three of five other CIDP patients improved in muscle strength after high-dose cyclophosphamide.[74] Two of these also

improved in nerve conduction and were able to reduce their immunomodulatory treatment.[74] Another CIDP patient showed a good response to treatment with PE and cyclophosphamide.[75]

The most reported adverse effects are haemorrhagic cystitis, stomatitis, leucopenia, thrombocytopenia, malignancy and cardiomyopathy. [28] Therefore, cyclophosphamide should only be tried in patients with severe disease who are unresponsive to other less toxic drugs.

Methotrexate

Methotrexate is a well known effective treatment for various autoimmune disorders. It is a folate-inhibiting drug and, in general, is an immunosuppressive agent with relatively low toxicity.

Retrospectively, the efficacy of methotrexate was evaluated in ten patients with CIDP who were unresponsive to conventional treatments.[76] Seven patients showed an improvement in strength, measured as increasing at least two points in the Medical Research Council (MRC) sum score, whereas three patients worsened. Only two patients showed an improvement in disability and both of these were also being treated with corticosteroids.[76]

Very recently, the results have been published of a randomised controlled trial showing no significant benefit of methotrexate in CIDP, although a treatment effect could not be excluded because of limitations in the trial design and a high response rate in the placebo group.[77]

Interferons

Interferon (IFN) reduces relapse frequency in multiple sclerosis, a demyelinating disease of the central nervous system. Interferons are immunomodulatory drugs that influence cytokine expression.

Nine of 15 CIDP patients that were treated with IFNα-2a, improved in mean MRC and sensory scores.[78] In five of these, the clinical response was sustained without any further progression or relapse.[78] One patient, unresponsive to corticosteroids and IVIg, and partially responsive to PE, improved substantially after treatment with interferonα-2a.[79] A deterioration occurred after treatment was stopped followed by an improvement after reintroduction.[79] A dramatic long-term response to interferonα in a bedridden CIDP patient, unresponsive to conventional treatments, has also been described.[80] Other case reports described a positive effect of IFNα in CIDP.[81]

In a double-blind, randomised, controlled, cross-over trial that prospectively followed ten CIDP patients, no significant difference was found between IFNβ-1a and placebo.[82] In a prospective, open-label study, 7 of 20 CIDP patients showed a significant improvement from baseline.[83] Other case reports have described positive effects of IFNβ in refractory

CIDP patients.[84-86] An open-label study in therapy-resistant CIDP patients could not demonstrate a beneficial effect of IFNβ-1a, but did show a statistically significant effect when IVIg was combined with IFNβ-1a.[87] Recently, the results of a randomised controlled trial have been presented showing that IFNβ-1a does not result in any significant IVIg dose reduction in IVIg-dependant CIDP patients.[88]

Further complicating the decision of whether to treat some CIDP patients with these agents are reports of patients who have developed CIDP while being treated with interferons for other disorders such as multiple sclerosis and chronic hepatitis C.[89-91] In contrast, a CIDP patient with hepatitis C showed improvement after treatment with IFNα.[92] It is unknown which patients may improve and which ones may deteriorate during these treatments. The most reported adverse effects are flu-like symptoms, leucopenia, thrombocytopenia and psychiatric disturbances. [23, 28, 78]

Rituximab

Rituximab is a monoclonal antibody directed against CD20. Several reports indicated a positive response to rituximab in patients with IgM antibody-associated polyneuropathy or CIDP.[93-96]

A CIDP patient who developed Evans syndrome (haemolytic anaemia/thrombocytopenia) was unresponsive to corticosteroids, IVIg, azathioprine and cyclophosphamide; this patient was reported to respond well to rituximab.[97] Another CIDP patient, unresponsive to conventional treatments with high titers of anti-sulfated glucoronyl paragloboside IgM antibody without M-protein in serum, responded to rituximab.[98] A prospective pilot study investigated rituximab in six patients with IVIg-dependant relapsing immune polyneuropathy.[99] Rituximab did not result in a reduction in the IVIg dosage in the majority of these patients. Of these six patients, two had a CIDP; in both these patients IVIg dosage could not be reduced.[99] Another two CIDP patients with IgM monoclonal gammopathy without myelin associated glycoprotein antibodies showed a good response to rituximab.[100] Rituximab is an expensive treatment. The most reported adverse effects of rituximab are hypotension, leucopenia, neutropenia, thrombocytopenia, bronchospasm and renal failure.[28, 93]

Tacrolimus

Tacrolimus is a well-known immunosuppressant that is often used in organ transplantation and for the treatment of autoimmune disorders. It has been described that 5% of patients who receive tacrolimus develop central nervous system toxicity.[101]

One CIDP patient treated with tacrolimus concurrently with prednisolone and PE improved in muscle strength, although this might have been due to the concurrent treatments.[102]

Of approximately 1000 patients who received an organ transplant, three patients developed a severe sensorimotor neuropathy shortly after initiation of tacrolimus.[101] Neuropathies in these patients responded to IVIg or PE suggesting an immune-mediated cause.[101]

Patients who developed CIDP while being treated with tacrolimus have been reported.[27, 103]

Etanercept

Etanercept is a tumour necrosis factor-α antagonist that has been successfully used in rheumatoid arthritis. In ten patients with CIDP resistant to other treatments, the efficacy of etanercept was retrospectively evaluated.[104] Three of these patients showed improvement and three possibly improved.[104] When prescribing etanercept, it should be noted that in some patients it might possibly induce demyelinative diseases such as multiple sclerosis, optic neuritis and myelitis.[105]

Alemtuzumab

Alemtuzumab is a monoclonal antibody that has been used in leukaemia and multiple sclerosis. It is a monoclonal antibody directed against the CD52 antigen, resulting in the prevention of complement-mediated lysis. Infusion-related adverse effects such as hypotension, fever, shortness of breath and rash are common.[30] Other important adverse effects are autoimmune thyreoditis and idiopathic thrombocytopenic purpura.[30] A CIDP patient, unresponsive to conventional treatments, was reported to respond well to alemtuzumab.[30]

Eculizumab

Complement plays an important role in many inflammatory and autoimmune diseases.[106] Complement is important in recognising and eliminating apoptotic and necrotic cells, and facilitates the elimination of circulating immuuncomplexes.[106] In patients with demyelinating polyneuropathy, the complement pathway may be activated.

Since IVIg inhibits complement binding and has been shown to be effective in CIDP, other complement inhibitors might also effective in CIDP.[18] In 2007, the first complement-specific drug, namely eculizumab, was approved.[106] Eculizumab is a humanised monoclonal antibody that blocks the formation of complement protein (C5) and membrane attack complex. In a murine model, it prevented anti-ganglioside antibody-mediated neuropathy resembling GBS.[106] The recommended intravenous dosage of eculizumab in paroxysmal nocturnal hemoglobinuria is 600 mg/week for 4 weeks, followed by a 900 mg once at week 5, followed by 900 mg every 2 weeks as a maintenance dose.[107]

Sirolimus

Sirolimus is used in organ transplantation and has a different mode of action than tacrolimus.[108] Sirolimus does not inhibit calcineurin and is not associated with nephrotoxicity. In 202 organ-transplant patients who were treated with sirolimus from 2001 to 2004, no evidence of neurotoxicity was found.[108] Therefore, it was postulated that sirolimus could be considered as a substitute immunosuppressant in patients with cyclosporine or tacrolimus neurotoxicity.[108] We could not find any reports from CIDP patients being treated with sirolimus. Liver or kidney transplant patients are treated with an initial loading dose of sirolimus 6 mg and thereafter with doses ranging from 1-10 mg/day, with target serum levels of 8-15 ng/mL.[108] This drug needs to be administered with caution because a patient has been described who developed a posterior reversible encephalopathy after sirolimus treatment.[109] Very recently, a case has been reported of a patient who developed CIDP after treatment with sirolimus.[110]

Stem cell transplantation

Stem cell transplantation is the most extreme form of immunosuppression.

A CIDP patient who improved after autologous stem cell transplantation has been described.[111] In the 10 years before the stem cell transplantation, he had no spontaneous remissions and he developed serious adverse effects to immunosuppressive drugs. After the autologous stem cell transplantation, he was free of relapses needing only prednisone 5 mg/day.[111] Unfortunately, 5 years after the stem cell transplantation, he developed a relapse, but was successfully treated with IVIg.[112] He needed lower doses of IVIg and prednisone than before the stem cell transplantation and the drugs were better tolerated.[112]

Another therapy-resistant CIDP patient was treated with non-myeloablative autologous stem cell transplantation.[113] This patient had no exacerbations during the follow-up time of 22 months.[113] A CIDP patient, unresponsive to therapy, has been described who developed aplastic anaemia after azathioprine therapy.[114] This patient received allogeneic haematopoietic stem cell transplantation and showed a full recovery, without any relapse for at least 6.5 years of follow-up.[114]

Controversially, some patients have developed CIDP as part of a graft-versus-host disease following bone marrow transplantation.[115, 116] Other patients have been described who had exacerbations of CIDP after bone marrow transplantation.[117] The course was progressive despite therapy and both patients died.[117] CIDP has been reported to occur 3-4 weeks after autologous peripheral blood stem-cell transplantation in multiple myeloma.[118]

Stem cell transplantation should be only considered as a last treatment option in patients who are unresponsive to various other treatments or who develop severe adverse effects.

CONCLUSION

IVIg, PE and prednisolone are all treatments proven to be beneficial in the treatment of CIDP in randomised controlled trials. Although their efficacy seems to be similar, they differ considerably in cost, availability and adverse effects. In individual patients, these factors should be taken into account when deciding which drug to initiate treatment with. If the first treatment has no effect, one of the other conventional treatments should be tried. Various other immunosuppressive drugs have potential positive effects in CIDP; however, none have been proven to be beneficial in randomised controlled trials. When prescribing one of these immunosuppressive drugs, it is important to realise that these agents may cause serious adverse effects, and some might even worsen or cause a polyneuropathy. These drugs should only be administered to patients who do not respond, become refractory or intolerant of any of the three conventional treatments for CIDP.

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Chapter 3.2

Randomised controlled trial comparing two different intravenous immunoglobulins in chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

Background: Different preparations of intravenous immunoglobulin (IVIg) are considered to have comparable clinical efficacy, but this has never been formally investigated. Some patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) report that some IVIg brands are more effective than others. A liquid IVIg preparation is more user friendly, and potentially can be infused at a faster rate.

Objectives: The primary objective was to compare the efficacy of two different IVIg brands in CIDP. The secondary objective was to compare their safety.

Methods: This was an investigator-initiated multi-centre randomised controlled double-blind trial. Twenty-seven patients with active but stable CIDP treated with their individual stable IVIg (Gammagard S/D) maintenance dose and interval were randomised to receive four infusions of freeze-dried 5% IVIg (Gammagard S/D) or the new liquid 10% IVIg (Kiovig). The overall disability sum score (ODSS) was used as the primary outcome-scale. The equivalence margin was defined as a difference of ≤1 point in mean ΔODSS between treatment groups. Main secondary outcome scales were the MRC sum score and the Vigorimeter.

Results: Repeated measurements analysis of variance, adjusted for baseline ODSS, showed a clinically insignificant treatment difference of 0.004 (95% CI –0.4 to 0.4). We also found no significant differences in any of the other outcome measures. Besides a lower occurrence of cold shivers in patients randomised to Kiovig (p=0.03) no significant differences were found in the occurrence of adverse events.

Conclusions: This trial demonstrated equal clinical efficacy between a freeze-dried and a liquid IVIg preparation for maintenance treatment of CIDP.

INTRODUCTION

Clinical trials have proven the efficacy of intravenous immunoglobulin (IVIg) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).[1-4] The efficacy of intermittent IVIg in CIDP has been shown to last for a period of at least 24 weeks.[4] However, most patients need IVIg treatment for several years.[5] In many CIDP patients, various brands of IVIg are used over the years, often depending on what is available in the hospital pharmacy.[6] Although some authors recommend that switching between IVIg brands should only occur under careful professional supervision, in practice this is usually done without any specific safety measures.[7] IVIg is increasingly being used for various neurological conditions.[7] Various IVIg brands are generally assumed to be equivalent,[8, 9] but some patients report some brands as more efficacious than others.[7, 10] When CIDP patients show no favourable response to IVIg it is not known whether treatment with an alternative brand might be beneficial. IVIg brands differ in their composition and production processes which might affect their efficacy and tolerability.[8, 10-11] Whether this reflects differences in efficacy or safety in immune-mediated neuropathies has never been investigated and, therefore, trials comparing different preparations are recommended.[12] The freeze-dried lyophilised brand Gammagard S/D has been used in randomised controlled trials in autoimmune polyneuropathies.[13, 14] The manufacturing process of the new liquid IVIg preparation Kiovig employs a Cohn-Oncley cold alcohol fractionation procedure to isolate the IgG fraction which is further purified using chromatography to yield a solution containing ≥ 98% IgG instead of ≥ 90% IgG in Gammagard S/D.[15] Kiovig contains a different distribution of IgG subclasses and no added glucose, sodium or preservatives. It is more concentrated and can be infused at a faster rate with a reduced volume load.[11]

We compared the efficacy and safety of these two products in a controlled double-blind trial. A group of active but stable CIDP patients treated with a stable maintenance dosage of the 5% freeze-dried IVIg preparation were randomised to the same product or to an equivalent dosage of a more concentrated 10% liquid IVIg preparation.

METHODS

This investigator-initiated trial was conducted at three university-affiliated neuromuscular disease centres in the Netherlands and was approved by the Medical Ethical Committees of these centres and the competent authority. This study was conducted in compliance with the E6 International Conference on Harmonization (ICH) guideline for Good Clinical Practice[16] and following local regulations. Monitoring was conducted by an *Association of Clinical Research Professionals* (ACRP) accredited monitor. A data

monitoring committee regularly assessed the progress of the trial and the safety data. Written informed consent was obtained from all patients. This CIC trial (comparing IVIg in CIDP) is registered in the International Standard Randomised Controlled Trial number register as ISRCTN52121370.

Subjects

Inclusion criteria were:

1. Diagnosis of CIDP made by a consultant neurologist and fulfilling the American Academy of Neurology clinical research criteria.[17]
2. Age ≥ 18 years.
3. Initial chronically progressive, stepwise progressive or recurrent weakness of all extremities, developing over at least 2 months, with reduced or absent tendon reflexes.
4. Observed and documented clear improvement of muscle function after the first use of Gammagard S/D.
5. Active CIDP defined by an overall disability sum score (ODSS)[18] grade ≥ 2 and a Medical Research Council (MRC) grade ≤ 4 in at least one of the muscles assessed in the MRC sum score[19] before start of the trial or following a reduction of IVIg dose at some time within the last 12 months before start of the trial.
6. Ongoing intermittent treatment with IVIg (Gammagard S/D) leading to a stable condition. The individual dose must have been stable (within a 25% range of the total dose) for at least 8 weeks and unchanged within the last 4 weeks before start of the trial.
7. Electromyography findings compatible with CIDP at least once during their illness.[20, 21]

Exclusion criteria were:

1. Known hereditary neuropathy or severe concomitant diseases such as HIV infection, Lyme disease, chronic active hepatitis, congestive heart failure, systemic lupus erythematosus, drug or toxin induced neuropathy, vasculitis, and malignancies.
2. IgM paraprotein with anti-myelin-associated glycoprotein (MAG) antibodies.
3. Multifocal motor neuropathy (MMN), fulfilling the European Federation of Neurological Societies /Peripheral Nerve Society criteria.[22]
4. Atypical CIDP with pure sensory or persistent unifocal impairment or significant central nervous system involvement.
5. Treatment with another IVIg brand than Gammagard S/D during the previous 8 weeks.
6. Participation in a controlled trial of a medicinal product within the last 12 weeks.

Study design

The trial consisted of 10 infusions in three phases. First, an open label phase with one Gammagard S/D infusion, second a double-blind phase with four blinded infusions and third an open-label phase with five Kiovig infusions (Figure 1). Patients were treated in the hospital day-care centre or at home according to where they were treated prior to trial entry. Immediately before infusions 1 and 2 (baseline), 4 and 6 (blind phase), 8 and 10 (open label phase) a neurological examination, including the MRC sum score (6 muscles) and INCAT sensory sum score (ISS), was carried out by the assessor (KK). Before every infusion, the ODSS as well as the muscle grip strength (vigorimeter) were recorded (Figure 1). [23] During every infusion and 1 week thereafter the patient was asked to record adverse events (AEs). One week after each infusion the patient completed the following questionnaires: Fatigue severity scale (FSS[24]), Short Form (36) Health Survey, Dutch language acute version 1 (SF-36[25]), and the Rotterdam handicap scale (RHS[26]).

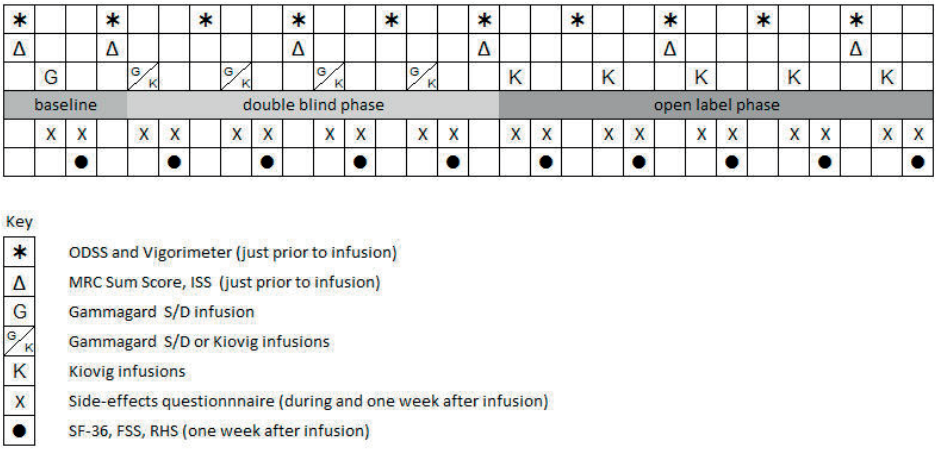

Figure 1. Trial outline
ODSS = overall disability sum score; MRC = medical research council; ISS = INCAT sensory sum score; FSS = fatigue severity scale; RHS = Rotterdam handicap scale; SF-36 = Short Form (36) health survey.

Study drug

Patients were randomised to receive four infusions of 5% (50 g/l) freeze-dried IVIg (Gammagard S/D, Baxter AG, Vienna, Austria) or the new 10% (100 g/l) liquid IVIg (Kiovig, Baxter AG, Vienna, Austria). All included patients had been treated successfully with maintenance IVIg before start of the trial (mean 5 yrs, range 5 months to 13 yrs). For both brands, the IVIg dosage and frequency for each patient was kept the same as their treatment regimen prior to trial entry and remained constant throughout the whole trial. One central trial pharmacist was responsible for the reconstitution (if necessary), packaging, labelling and distribution of the trial medication during the double-blind phase.

Randomisation and blinding

We used a computer-generated randomisation list produced by a statistician (WH). A block randomisation was made for each centre. Patients were checked for eligibility and enrolled by the principal investigator (PD) in agreement with the main investigators of the three centres. The assessor allocated the next available number on entry after consent was given. Allocation concealment was ensured via sequentially numbered, opaque sealed envelopes distributed by the statistician to the principal investigator. After randomisation, the prescription was faxed by the principal investigator to the pharmacy. Patients, the assessor (KK) and the blinded neurologist who assessed the SAEs were all blind to the drug allocations. We did not dilute the 10% (Kiovig) solution to a 5% solution, as we had no data regarding its stability. Due to the different volumes of the preparations, the nurses who were experienced in administering the IVIg could not be blinded for the drug assignment as they had to adjust the infusion speed to ensure the integrity of the blinding for patients. All patients were treated according to their individual established IVIg dosage prior to study entry. The infusion bag and the drip chamber were enclosed in a covering bag and a coloured infusion line was used so neither the assessor nor the patient was able to discern which brand was infused. The IVIg was infused at a standard safe infusion rate. To check whether blinding was maintained, both patients and the assessor were asked after the blind phase and at the end of the trial to guess which drug they thought had been administered in the blind phase.

Allocation was revealed after all patients had completed the study and data entry had been declared complete.

Efficacy

The primary objective was to study the efficacy of Kiovig compared to Gammagard S/D in the treatment of CIDP; the ODSS was used as the primary outcome measure. Before the trial started, we predefined in the protocol that a difference in the mean ODSS change from baseline between the two groups of ≤ 1 point was considered as equivalence. The two ODSS measurements, assessed immediately before infusion one (Gammagard) and two (first blinded infusion), were averaged and the mean value was taken as a baseline measurement. Changes in the vigorimeter values and the MRC sum score were used as secondary outcome measures as were all other measures.

Safety

The secondary objective was to compare the safety of both products. A questionnaire regarding AEs was completed by the patients during every infusion and again 1 week later. A neurologist blinded to the allocation of trial medication (EB, EC, AK) evaluated AEs by telephone at regular intervals.

Statistical analysis

The sample size calculation based on historical data showed a SD of 0.84 for ΔODSS (over a stable period of 2 months).[18] To exclude differences of > 1 point in ΔODSS, 11 patients were required in each treatment group (α =0.05, power 80%). The mean of ODSS changes from baseline for each of the four blinded infusions (infusions 3, 4, 5, 6) was compared using repeated measurements analysis of variance (ANOVA). As an operational criterion for equivalence, the 95% CI for the difference in the mean ODSS should not cross the values -1 and +1.

For all other outcome measures, the change from baseline was calculated by taking the mean of the scores during the double-blind phase and comparison was done with analysis of covariance (ANCOVA) with baseline value as covariate. Data were analysed according to the intention-to-treat principle.

All AEs were recorded. The statistical analysis for the objectives of the study was based upon data from the double-blind phase. The open-label Kiovig phase was primarily used to gain more safety information. The occurrences of AEs were compared using $\chi 2$ or Fisher exact test. Analysis was performed using SPSS V.15.0 and SAS V.8.1.

RESULTS

From December 2007 to September 2008, 75 CIDP patients were screened for eligibility; 48 were excluded mainly because they were not treated with IVIg on a regular basis or had no signs of active disease (Figure 2). Other reasons for non-eligibility were treatment in a different hospital than the neuromuscular centre where the diagnosis was established or treatment with another brand of IVIg (two patients). In total, 27 patients were randomised; 25 completed the full trial period, including the open label phase. The first patient was included in December 2007 and the last patient follow-up was in April 2009. All patients had at least moderate disability in arms or legs at baseline or following IVIg reduction during the 12 months before the start of the trial. To further substantiate that the patients enrolled in this trial had active disease still requiring intermittent IVIg treatment, we determined the occurrence of recent worsening in more detail. Twenty-three of the patients had had at the minimum a worsening of symptoms in the 6 months before the start of the trial. Two patients had a deterioration 8 months before start of the trial. Another patient had a documented deterioration 11 months before entry and one patient had end-of-dose complaints before and during the trial.

All but one patient received the total amount of four blinded infusions. This patient decided to stop the blind treatment after one infusion due to an AE (fatigue). This patient was observed while being treated unblinded with Gammagard S/D during the rest of the double-blind phase and included in the analysis according to the intention-to-treat

principle. One patient decided not to continue with the open-label phase, regardless of what was given in the double-blind phase. Baseline and demographic characteristics were similar in the two groups (Table 1).

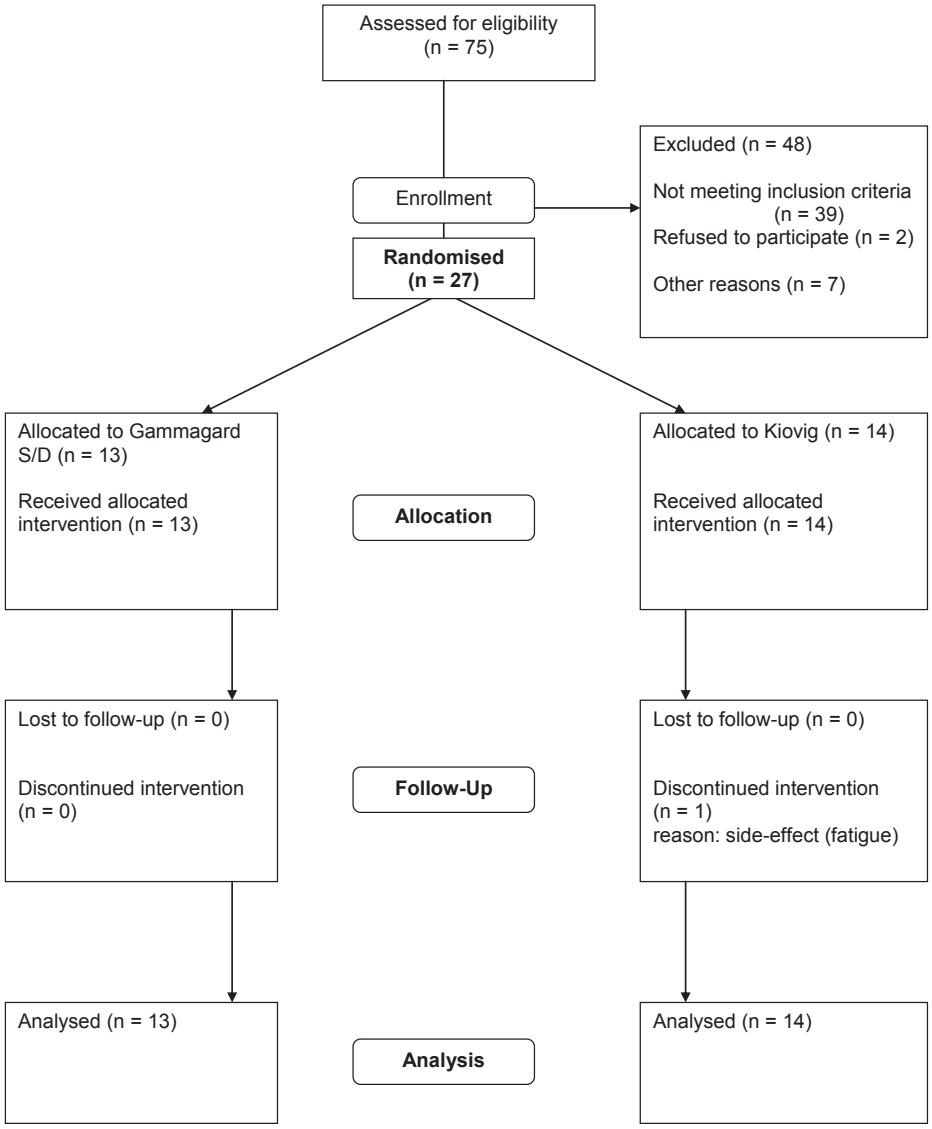

Figure 2. The CONSORT Flowchart

Table 1. Baseline demographic and clinical characteristics

Characteristic	Gammagard S/D (n = 13)	Kiovig (n = 14)
Age (y)	54.0 (12.0)	54.6 (13.8)
Men	8 (62%)	12 (86%)
IVIg dosage (g/week)	12.5 (8-30)	14.6 (10-38)
IVIg interval (days)	18.8 (5.3)	15.5 (4.1)
Body weight (kg)	78.5 (13.2)	85.6 (12.5)
ODSS score* (range 0-12)	3.0 (0-7)	3.7 (1-5)
MRC sum score* (range 0-60)	53.6 (4.4)	54.6 (3.4)
Vigorimeter* (range 0-160 kpa)	89.3 (46.2)	86.8 (31.0)

Data are number (%), mean (SD), or median (range). Higher overall disability sum score (ODSS) values indicate more limitations. Higher Medical Research Council (MRC) sum score values and vigorimeter scores indicate greater strength.

* Mean value of the two measurements before randomisation at baseline.

Treatment efficacy

The treatments were not significantly different in efficacy in the primary outcome measure (difference 0.004 (Gammagard minus Kiovig), 95% CI –0.4 to 0.4), using repeated measurements ANOVA, and this effect did not differ significantly between the four measurements in the blinded phase (p = 0.19). The ODSS showed a similar distribution between both groups (Figure 3). Using ANCOVA, there were no clinically relevant differences between the two treatments in all outcome measures (Table 2). In the patient who received trial medication only once during the blinded phase, the ODSS score after this treatment was exactly the same as after the non-trial medication. One patient required another IVIg dosage in the open label phase due to a minor deterioration.

Treatment tolerance

Both IVIg brands were well tolerated. There were no significant differences between the two treatments in the number of commonly reported AEs except for the lower occurrence of cold shivers in patients randomised to Kiovig (Table 3). Altogether, 4 out of 14 patients in the Kiovig treatment group versus 1 out of 13 patients in the Gammagard S/D group (p=0.33) reported their AEs to be 'severe' in the questionnaires. The number of patients who reported AEs to the blinded neurologist was similar in the two groups (8/14 in the Kiovig vs. 7/13 in the Gammagard S/D group, p=0.86). Two patients, one in each treatment group, had a serious AE (requiring inpatient hospital stay), which was unrelated to the trial drug (elective surgery unrelated to CIDP). One patient had a mild allergic reaction to one of the blinded Kiovig infusions only needing treatment with an oral antihistamine. In the open label Kiovig phase 14/27 patients reported AEs to the blinded neurologist. Half of these patients were treated in the blinded phase with Gammagard S/D, the other half with Kiovig. No serious adverse events occurred in this open-label phase.

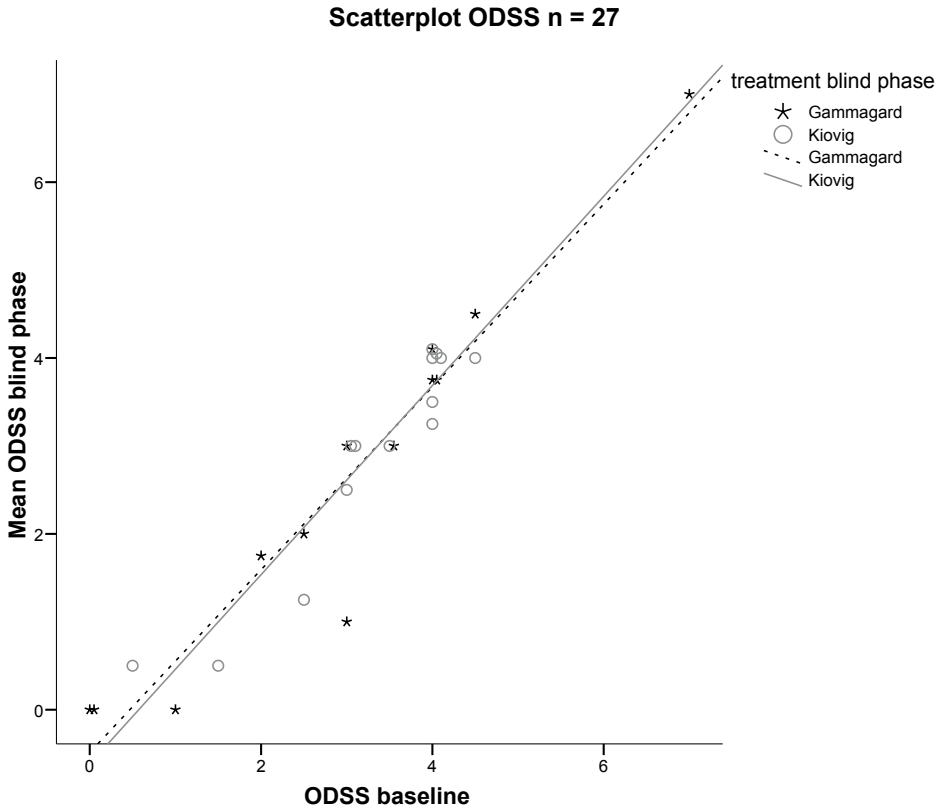

Figure 3. Scatterplot overall disability sum score

Blinding

After the blinded and open label phase, both patients and the assessor were asked which treatment they thought had been administered during the blind phase to check if blinding had been successful. In 25 cases (93%) the assessor had no idea about the treatment that was given. In two cases the assessor thought correctly that the 10% preparation was given; once because the infusion speed was accidentally somewhat faster than regular, and in another case because the patient felt severely fatigued after the infusion. Thirteen patients had no idea what treatment they received in the blinded phase. Seven patients answered the treatment allocation question correctly and seven patients were incorrect.

Table 2. Primary and secondary efficacy outcomes

	Difference (Gammagard minus Kiovig)	95% CI	p Value
Primary outcome			
ODSS	0.004	-0.4 to 0.4	0.98
Secondary outcomes			
MRC sum score	-0.58	-1.9 to 0.7	0.37
Vigorimeter	0.54	-4.0 to 5.0	0.81
ISS	0.59	-0.7 to 1.8	0.33
FSS	0.18	-1.9 to 0.6	0.33
RHS	0.74	-0.2 to 1.6	0.12
SF-36			
Physical functioning	-2.1	-4.5 to 0.28	0.08
Role-physical	1.8	-3.6 to 7.2	0.50
Bodily pain	-2.8	-6.6 to 6.1	0.93
General health	-1.9	-4.8 to 1.0	0.19
Mental component summary	1.5	-2.4 to 5.4	0.43

Data shown are differences from analysis of covariance with adjustment for baseline values with 95% CI and p value.
ODSS = overall disability sum score (range 0-12); a higher value indicates more limitations;
MRC = medical research council (range 0-60); a higher value indicates better muscle strength; Vigorimeter (range 0-160); a higher value indicates better muscle strength;
ISS = INCAT sensory sum score (range 0-20); a higher score indicates more sensory deficits;
FSS = fatigue severity scale (range 0-7); a higher score indicates more fatigue;
RHS = Rotterdam handicap scale (range 9-36); a higher score indicates less handicap;
SF-36 = Short Form (36) health survey (all separate items range 0-100); a higher scores indicate better health or less bodily pain.

Table 3. Number of patients who reported common adverse events during the blinded phase

Adverse events (blinded phase)	Gammagard S/D (n = 13)	Kiovig (n = 14)	p Value
Fatigue	10 (77%)	10 (71%)	1.0
Muscle and joint ache	8 (62%)	9 (64%)	1.0
Headache	8 (62%)	6 (43%)	0.33
Itching	5 (38%)	6 (43%)	0.82
Backache	3 (23%)	6 (43%)	0.42
Dizziness	5 (38%)	4 (29%)	0.70
Warm feeling	3 (23%)	5 (36%)	0.68
Skin rash	3 (23%)	5 (36%)	0.68
Pain at infusion area	3 (23%)	4 (29%)	1.0
Cold shivers	6 (46%)	1 (7%)	0.03

Data are number (%) and compared using $\chi 2$ test or Fisher exact test.

DISCUSSSION

In this study we compared the efficacy of a freeze-dried IVIg (Gammagard S/D) with a liquid preparation (Kiovig) for the treatment of CIDP. We found no significant difference in clinical efficacy as the 95% CI for the difference of mean ODSS was within the interval -1 to +1. Equivalence in this study was primarily based on the ability to carry out everyday functions measured using a disability scale (ODSS) validated in Guillain-Barré syndrome (GBS) and CIDP.[18] No significant differences were found between the two preparations for all other outcome measures, including impairment scales regarding muscle strength and sensory symptoms, and scales measuring handicap, fatigue and quality of life.

An in vitro model of immune neuropathy found a comparable efficacy of eight different IVIg products.[6] A different response to various IVIg brands has been described in a randomised trial in primary immune deficiency.[27] In Kawasaki disease, retrospective studies reported similar as well as different responses to various brands.[28, 29] An open study reported no clinical differences between Gammagard and Kiovig in MMN.[30] As far as we know, no RCT has been published that evaluated differences between IVIg brands in neurological disorders.

The two preparations had similar AEs and there were no problems with the transition from one preparation to the other. Cold shivers were less common in patients treated with the liquid brand, which might be caused by less aggregates and excipients in Kiovig.[15] Aseptic meningitis or neutropenia as AEs after IVIg are reported to be unrelated to the proprietary formulation.[9, 31] A group of 30 healthy subjects showed no difference in tolerance to two different IVIg preparations including one liquid form.[32] A retrospective study in Kawasaki disease reported more infusion-related rigors in one IVIg brand than in another.[29]

Since one IVIg preparation was more concentrated (10%), it was not possible to blind the nurses who administered the trial drug because the IVIg dosage as well as the duration of administering had to be equal for both preparations. Therefore, the nurses were trained thoroughly in maintaining the blind. By asking the patients to report which drug they thought they had received we could show that blinding had been successful. Randomisation was successful as clinical characteristics were well-balanced between the treatment groups.

To ensure that the CIDP patients were still IVIg dependant they had to have had at least moderate disability in arms or legs at baseline or following IVIg reduction during the previous 12 months. Most patients additionally had had at least some documented worsening of their CIDP within the 3-6 months before start of the study and some also had minor fluctuations in their clinical course after they had completed the trial. To make sure no IVIg refractory patients were included, only patients who initially improved after

IVIg, being in a stable condition using a stable maintenance dose of IVIg and who were considered to need IVIg treatment were included.

Previous international trials regarding the efficacy of IVIg in CIDP used treatment periods of ≤6 weeks.[2, 20] Therefore, the double blind treatment period of four infusions, administered over a time period of 6-16 weeks (mean 10 weeks) due to the different inter-individual intervals, seems reasonable as the half-life time of IVIg is about 3 weeks. Since we only compared two different IVIg brands manufactured by the same pharmaceutical company with each other, we can only draw conclusions about the equivalence of these two products. Logistically, it was not feasible to compare more available brands. However, our results suggest that the clinical effects of a new liquid IVIg product are similar to a non-liquid product that has been used for several decades.[13, 14]

In specific situations certain brands are recommended, such as IVIg preparations that contain less IgA in patients with a low IgA level and preparations containing less sucrose in patients with kidney disease. Liquid IVIg preparations do not need reconstitution prior to use and can potentially reduce the infusion time, but this was not investigated in this study.

Although some patients may prefer certain IVIg brands, this trial suggests that this is unlikely to be caused by differences in clinical efficacy or tolerance between a freeze-dried and a liquid product. As we showed no significant clinical differences between these two IVIg brands in their efficacy to treat CIDP it seems reasonable to assume that this will also apply for other diseases treated with IVIg.

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Chapter 3.3

Intravenous immunoglobulin response in treatment-naïve chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

Objective: There is no consensus which treatment should be used preferentially in individual patients with chronic inflammatory demyelinating polyneuropathy (CIDP). Patients unlikely to respond to IV immunoglobulin (IVIg) could be prescribed corticosteroids first to avoid high cost and a delayed treatment response. We investigated which factors determined a response to IVIg.

Methods: Treatment-naïve patients with CIDP initially treated with at least one full course of IVIg (2 g/kg) at one of two neuromuscular disease centers were included. Patients fulfilled the European Federation of Neurological Societies/Peripheral Nerve Society clinical criteria for CIDP. Significant improvement following IVIg was defined as an improvement (≥1 grade) on the modified Rankin scale. Difference in weakness between arms and legs was defined as ≥ 2 grades on the Medical Research Council scale between ankle dorsiflexion and wrist extension. Clinical predictors with a p-value <0.15 in univariate analysis were analysed in multivariate logistic regression.

Results: Of a total of 281 patients, 214 patients (76%) improved. In univariate analysis, the presence of pain, other autoimmune disease, difference in weakness between arms and legs, and a myelin-associated glycoprotein negative IgM monoclonal gammopathy of undetermined significance were associated with no response to IVIg. In multivariate analysis no pain ($p = 0.018$) and no difference in weakness between arms and legs ($p = 0.048$) were independently associated with IVIg response. Of IVIg non-responders, 66% improved with plasma exchange and 58% with corticosteroids.

Conclusion: IVIg is a very effective first-line treatment. Patients with CIDP presenting with pain or a difference in weakness between arms and legs are less likely to respond to IVIg.

INTRODUCTION

In randomised controlled trials, intravenous immunoglobulin (IVIg), plasma exchange (PE) and corticosteroids have been shown to be beneficial in the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).[1-7] The long-term benefits and safety of IVIg in CIDP has been demonstrated in a large randomised placebo-controlled trial in CIDP.[4] Some patients improve more after one of the effective treatments than after another and some can even fail to show a response to one or more of these proven effective treatments.[8-11]

There is no consensus on which is the best treatment for individual cases of CIDP.[12] In order to give the most appropriate treatment in the earliest phase of the disease it would be helpful to identify patients who are more likely to respond to one particular treatment.[8,10] Corticosteroids and IVIg differ in terms of cost, speed of action and adverse events.[13,14] Although expensive, IVIg is often considered a treatment of first choice because of its rapid onset of action compared to the usually slower response to steroids, and because it has a better long-term adverse event profile.[9,15-18] Sometimes only one course of IVIg is sufficient to induce a sustained remission.[12] Corticosteroids are usually prescribed for a lengthy period and require a slow tapering over several months, and thus may be accompanied by serious side effects.[15,19] During that extended period it is likely that some patients may still be treated with corticosteroids although they may already have reached remission.[17] For a yet unknown reason, not all patients improve after IVIg and a delay in starting effective treatment could result in secondary axonal damage that is potentially resistant to treatment.[9] To avoid high cost and to minimise the probability of secondary axonal damage due to the prescription of an ineffective treatment, standard dose steroids or high-dose pulse corticosteroids could be given as a first-line treatment to patients unlikely to respond to IVIg if it can be proven that they are better off with corticosteroids.[19-20] PE is generally considered after the patients fail to respond to IVIg and steroid treatment. PE is relatively inconvenient as special equipment is needed, good venous access is required and there is a risk of adverse events. We have investigated which clinical as well as neurophysiological factors might be associated with a good response to IVIg in a previous single-centre cohort of 52 patients with CIDP.[1]

The aim of this study was to investigate in a larger group of treatment-naïve patients with CIDP which clinical factors are associated with a good response to IVIg, to be able to optimise and personalise treatment at onset.

METHODS

Patients

In this retrospective study we combined data from medical records of patients with CIDP from two large university hospitals (Erasmus MC, University Medical Centre Rotterdam, the Netherlands and London Health Sciences Centre London Ontario, Canada). Patients were diagnosed as CIDP and followed over time by a consultant neurologist (AFH, PAvD, MV, SLV) experienced in neuromuscular diseases, and treated with IVIg between 1980 and 2011 (N = 152 Erasmus MC; N = 129 London Health Sciences Centre). All patients fulfilled the European Federation of Neurological Societies/Peripheral Nerve Society clinical diagnostic criteria for typical or atypical (still considered CIDP but with different features) CIDP.[15] Twenty-five of these patients have been described previously.[1] Not all these patients were included in the current study mainly because they were not all treatment-naïve or they were diagnosed differently over time. Patients with recurrent Guillain-Barré syndrome (GBS) or GBS patients with treatment-related fluctuations were excluded.[21] Patients with multifocal motor neuropathy (MMN) as well as patients with any other chronic acquired or hereditary neuropathy were excluded. Patients with an IgG or IgM monoclonal gammopathy of undetermined significance (MGUS) were only included when they had a clinical course fully consistent with CIDP. Patients with an IgM MGUS who had antibodies against myelin-associated glycoprotein were excluded.

Treatment and response

All patients were treated with IVIg as a first treatment modality and completed at least one full course of IVIg (2 g/kg over 2-5 days). Before IVIg was available some of the patients initially received fresh frozen plasma (FFP).[1,22] Because these patients (N = 15) were treated with IVIg thereafter and showed the same response to FFP as to IVIg it was unlikely that this would have any effect on the results, therefore, they were included in the current study. The 281 patients were followed with a mean duration of 5.2 years (median 3.8 years, range 20 days-28 years).

Clinically important improvement following treatment was defined as an improvement (decrease) of ≥ 1 grade on the modified Rankin scale (range 0-5).[23] When it was unclear whether a patient responded significantly, a second course of IVIg was given. When patients required maintenance IVIg treatment, regular attempts to reduce the dosage were performed to check whether patients were in remission or were still IVIg dependent.

To investigate the response rate to corticosteroids or PE in patients who failed to respond to IVIg, we only analysed data from patients treated with sufficiently large dosages of steroids as monotherapy (e.g. prednisolone ≥ 60 grams a day for at least 6 weeks) or patients who received at least five PE sessions as monotherapy.

Definitions of patient characteristics

Subacute CIDP was defined as an onset phase of 4-8 weeks. All patients with a subacute onset included in this study subsequently had a chronic progressive or relapsing course requiring long-term (IVIg) treatment. Asymmetrical weakness was defined as a difference ≥ 2 grades on the Medical Research Council (MRC) scale in at least one muscle pair (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsiflexion). A difference in weakness between arms and legs was defined as a difference of ≥ 2 grades on the MRC scale between ankle dorsiflexion and wrist extension. The level of the modified Rankin scale at nadir was defined as the worst score prior to or after start of treatment. Pure motor CIDP was defined as CIDP without sensory signs and abnormalities in sensory nerve conduction studies. Pure sensory CIDP was defined as pure sensory symptoms and signs at presentation, nerve conduction studies in these patients, however, could show some minor abnormalities in motor nerve studies and muscle weakness could appear subsequently during follow-up. A clinical remission was defined as a modified Rankin score 0-1 after discontinuation of treatment. Children were defined as <18 years old when IVIg was started. Medical records and letters were reviewed for the occurrence of (other) autoimmune disorders. Since patients were treated by the same consultant neurologist (AFH, PAvD, MV, SLV) from one of the two university hospitals, we could screen the medical records for the occurrence of pain and whether patients were treated with analgaesics. When the presence of pain was not reported and when analgaesics were not used we assumed that pain was not present. We did not analyse EMG findings because these examinations were not always performed in a standardised fashion in this two-centre study.[12, 24-25]

Statistical analysis

The literature was screened for important known factors that might be associated with a response to IVIg. These factors that were present in our data as well as other variables that in our opinion seemed relevant to IVIg response were analysed. To compare relative differences between IVIg responders and non-responders χ^2 test, Fisher's exact test, or Mann-Whitney *U* test were used. For the categorical variables polyneuropathy type and weakness distribution the χ^2 test for trend was used, which gives the overall p value. Predictors that had a p value of < 0.15 in univariate analysis were selected to be analysed in multivariate logistic regression. This level of 0.15 was chosen to improve the power to identify important predictors.[26] Multivariate logistic regression was used to identify which factors were associated with a good response to IVIg. Analysis was performed using SPSS V.20.0. A two-sided p value < 0.05 was regarded significant. The Hosmer-Lemeshow test was used to check for goodness-of-fit.

RESULTS

Patient characteristics

A total of 281 treatment-naïve patients with CIDP initially treated with at least one full course of IVIg (2 g/kg) were included. Main clinical characteristics of these patients are shown in Table 1. Thirty-five patients (13%) were known to have a concurrent autoimmune or immune-mediated disorder (Table 2).

Table 1. Clinical characteristics of IVIg responders and non-responders

		Responsive to IVIg		
	Total (n = 281)	Yes (n = 214)	No (n = 67)	**p Value**
Patient characteristics				
Male	179 (64%)	133 (62%)	46 (69%)	0.33
Children	13 (5%)	10 (5%)	3 (5%)	0.95
Progression of weakness*	267 (95%)	205 (96%)	62 (93%)	0.33
Other autoimmune disease^	35 (13%)	22 (10%)	13 (19%)	**0.048**
Pain^	77 (27%)	50 (23%)	27 (40%)	**0.007**
Subacute onset	29 (10%)	25 (12%)	4 (6%)	0.18
Polyneuropathy type				
Pure motor	37 (13%)	28 (13%)	9 (13%)	
Pure sensory	29 (10%)	22 (10%)	7 (10%)	
Sensory-motor	215 (77%)	164 (77%)	51 (76%)	0.93[#]
Areflexia legs	235 (84%)	175 (83%)	66 (90%)	0.17
Areflexia arms	209 (75%)	155 (73%)	54 (81%)	0.22
Weakness symmetrical	251 (94%)	190 (94%)	61 (94%)	0.94
Weakness distribution				
Legs = arms	170 (62%)	140 (68%)	30 (46%)	
Legs > arms	89 (33%)	56 (27%)	33 (50%)	**0.002**[#]
Legs < arms	14 (5%)	11 (5%)	3 (5%)	
IVIg treatment				
Time symptoms to first treatment, mo	4 (1-11)	3 (1-10)	4 (2-13)	0.75
Age start treatment, y	52 (39-62)	49 (39-61)	53 (42-65)	0.66
Laboratory				
IgG MGUS	14 (5%)	13 (7%)	1 (2%)	0.131
IgM MGUS (anti-MAG negative)	7 (3%)	3 (2%)	4 (6%)	**0.036**

Data are numbers (%) and compared using $\chi 2$ test, Fisher's exact test or $\chi 2$ test for trend, or median (IQR) and compared using Mann-Whitney *U* test.
* In the months prior to IVIg start.
^ These variables were assumed to be absent when they were not reported in medical files.
[#] Overall p-value.
IVIg = intravenous immunoglobulin;
MGUS = monoclonal gammopathy of undetermined significance;
MAG = myelin-associated glycoprotein.

Table 2. Presence of other autoimmune disease (N = 35)

Autoimmune disease	Number of patients
Rheumatoid arthritis	6
Thyroid gland disorder	5
Insulin-dependent diabetes mellitus (IDDM)	5
Inflammatory bowel disease	3
Interstitial nephritis	4
Systemic lupus erythematosus	2
Sjögren's syndrome	1
Systemic sclerosis	1
Psoriasis	1
Asthma	1
Immune thrombocytopenic purpura	1
Crohn's disease + IDDM + thyroid gland disorder	1
Multiple sclerosis + thyroid gland disorder	1
IDDM + thyroid gland disorder	1
Ulcerative colitis + thyroid gland disorder	1
Bechterew + psoriasis	1

Treatment response

The response rate to IVIg was 76% (214/281). The response to IVIg was not significantly different in children than in adults (76% vs. 77%, p = 0.95). Most patients who failed to improve with IVIg received subsequent treatment: 66% improved with PE and 58% with corticosteroids (Figure 1). Of the IVIg non-responders who were treated with at least one other treatment modality, 79% responded either after PE, corticosteroids or both. Only three patients did not respond to any of the three treatments. In 11 out of 37 pure motor CIDP patients, steroids were given with a response rate of 46% (5/11). From 86 treatment-naïve patients who were IVIg responsive and reached a documented clinical remission, 14 (16%) needed only one IVIg course.

Clinical characteristics associated with IVIg response

The age of the patients when IVIg was started, or the time from symptom onset to IVIg start, were not associated with treatment response (Table 1). Furthermore, the presence of a pure motor or sensory CIDP subtype was also unrelated to the response to IVIg. In univariate analysis no difference in weakness between arms and legs, no other autoimmune disease, no MGUS and the absence of pain were all positively associated with IVIg response. In multivariate analysis, no difference in weakness between arms and legs, and the absence of pain were both independently associated with IVIg response (Table 3). In multivariate analysis, the presence of another autoimmune disease or MGUS were not statistically significant associated with IVIg response when adjusted for the other

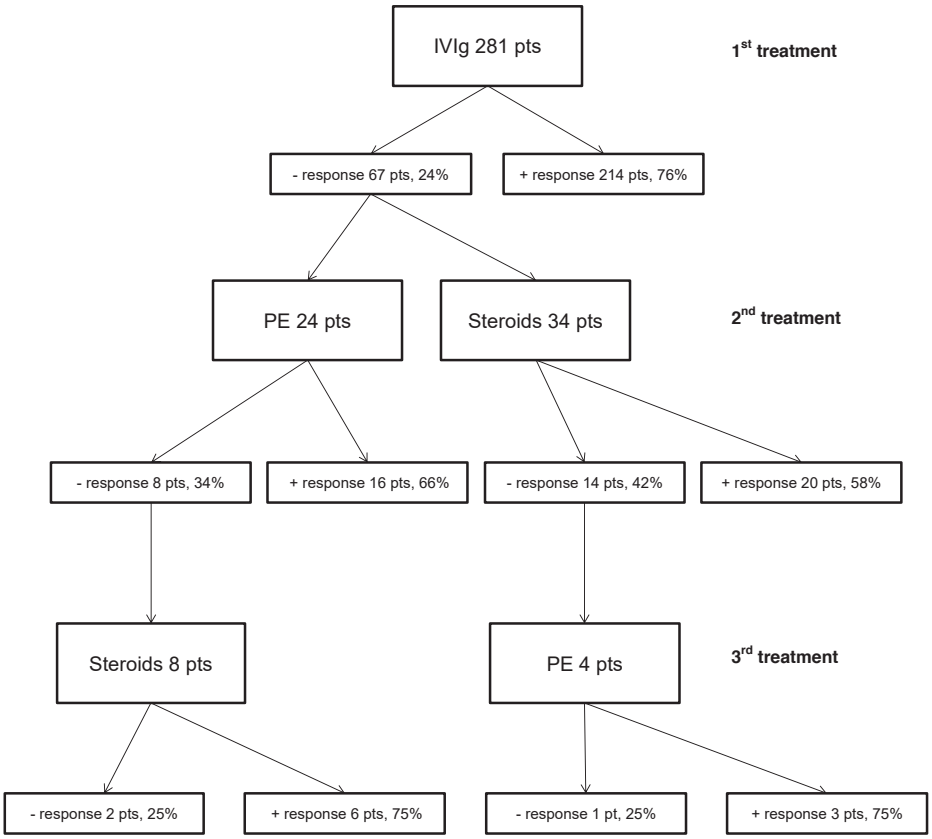

Figure 1. Treatment response in chronic inflammatory demyelinating polyradiculoneuropathy patients initially treated with intravenous immunoglobulin

variables. This model fitted the data well based on the Hosmer-Lemeshow statistic (p = 0.68). The presence of pain or a difference in weakness between arms and legs were not statistically significant associated with a treatment response to corticosteroids. An overview of factors that have been reported to be associated with a response to IVIg in CIDP in the literature is given in Table 4.

Adverse events

In 10 patients IVIg was discontinued due to adverse events. Although these were reasons to stop treatment, most were relatively minor, such as headache. Three of these patients had severe adverse events; one developed a Stevens-Johnson syndrome and two acquired haemolytic anaemia. None developed severe life-threatening adverse events such as an anaphylactic shock.

Table 3. Multivariate logistic regression of a good response to IVIg (N = 256)

	OR	95% CI	p Value
Pain			
No (ref.)	1.0		**0.018**
Yes	0.46	0.24 to 0.88	
Weakness distribution			
Arms = legs (ref.)	1.0		**0.048**[#]
Legs > arms	0.46	0.24 to 0.85	
Legs < arms	0.72	0.18 to 2.93	
Other autoimmune disease			
No (ref.)	1.0		0.10
Yes	0.50	0.23 to 1.13	
IgG MGUS			
No (ref.)	1.0		0.22
Yes	3.73	0.46 to 30.09	
IgM MGUS (anti-MAG negative)			
No (ref.)	1.0		0.06
Yes	0.21	0.04 to 1.04	

[#] Overall p value.

IVIg = intravenous immunoglobulin; MGUS = monoclonal gammopathy of undetermined significance.; MAG = myelin-associated glycoprotein.

Table 4. Factors associated with a response to IVIg in CIDP: a review of the literature

Author	Year	Number of patients	Number of treatment-naïve patients	Response rate to IVIg (%)	Associated with a good response to IVIg
van Doorn, et al. [1]	1991	52	not stated	62	Disease duration < 1 y Progression of weakness Absence of discrepancy between weakness of arms and legs Areflexia arms Slowed NCV of the motor median nerve
Choudhary, et al. [11]	1995	22	not stated	64	Female gender
Hahn, et al.[2]	1996	30	not stated	63	Acute relapse Disease duration < 1 y
Iijima, et al. [9]	2005	312	283	64	Female gender Shorter disease duration Fast progression of symptoms No axonal dysfunction
Tackenberg, et al. [18]	2007	76	76	82	Monophasic or relapsing-remitting form > twofold CSF protein increase
Iijima, et al. [42]	2009	100	100	72	TAG-1 gene polymorphism
Querol, et al. [43]	2014	53	not stated	74	No anti-NF155 antibodies

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CSF = cerebrospinal fluid; IVIg = intravenous immunoglobulin; NCV = nerve conduction velocity; TAG-1 = transient axonal glycoprotein-1.

DISCUSSION

The high response rate to IVIg of 76% in our large cohort was similar to what has been reported before.[3,27-28] We used the modified Rankin scale to assess treatment response. This scale is easy to use and the cut-off point of ≥ 1 point has often been used for clinically relevant improvement in CIDP.[9-11,18,24,29] A disadvantage of this scale is, however, that it is probably too insensitive to show small but clinically meaningful functional improvements. Nonetheless, the percentage of patients who improved is still high and exceeds the improvement rate found in the largest RCT conducted in patients with CIDP.[4] The Peripheral Neuropathy outcome measures Standardisation (PeriNomS) study recently investigated which assessment scale is the most appropriate to use in future studies in inflammatory neuropathies.[30] Because we were mainly interested in large clinical meaningful differences in this retrospective study, we still consider that using the modified Rankin scale gives relevant information.

Clinical characteristics associated with IVIg responsiveness have been investigated in a larger group (N = 312) of IVIg treated patients with CIDP with a 64% response-rate.[9] However, only 283 of these patients were treatment-naïve (a similar number as our cohort), which may explain the somewhat lower response-rate.[9] Our current study showed that the absence of a discrepancy in upper and lower limb weakness is associated with IVIg responsiveness, which has been found previously in a small cohort of patients.[1] Pain has been reported to be prominent in 42% of CIDP patients, but has not been described as a risk factor for IVIg non-responsiveness before and should receive more attention in future studies.[29]

Thirteen per cent of the patients in our study were known to have a concurrent autoimmune disorder in addition to CIDP, a similar percentage has recently been reported in the literature in patients with MMN and in a survey on GBS and CIDP.[31,32] The overall prevalence of autoimmune disorders reported in the general population is 5%, suggesting that patients with CIDP have an increased risk of autoimmune disease and CIDP might be the result of an aberrant immune response.[31]

A higher response rate in children compared to adults, as has been suggested previously, was not found in our cohort.[33] Furthermore, age, sex and disease duration were not associated with IVIg responsiveness in our cohort.[1,9,11] Axonal dysfunction of peripheral nerves has been reported to be associated with a failure of IVIg response.[9] Whether nerve conduction studies are useful in the prediction of treatment response in CIDP remains unclear.[27,34-35]

In a recent study of 86 non-treatment-naïve patients with CIDP treated with IVIg, the only variable that was associated with reaching remission (asymptomatic without treatment) at long term was a better response during the first 6 months.[36] Unfortunately,

some patients in this study had been treated simultaneously with other immunosuppressive agents besides IVIg.[36]

Our study confirms that the (long term) adverse events of IVIg are minor and rarely a reason to discontinue treatment.[9,37] A recent trial over a treatment period of 6 months found that IVIg treatment was less frequently discontinued than intravenous methylprednisolone for reasons such as inefficacy, adverse events or intolerance.[20]

Our study indicates a higher response rate to steroids or PE prescribed as a second or even third treatment modality in patients unresponsive to IVIg than reported previously.[29] Therefore, treatment with corticosteroids or PE should be offered to patients with CIDP who do not respond satisfactorily to IVIg, knowing that there is still a good chance of improvement even with a third treatment modality.[15] Why some patients only respond to a particular treatment remains unknown and requires further investigation. Although 15% of patients with CIDP are reported to be unresponsive to all three treatment modalities, we could only identify three patients (1%) who were unresponsive to all three treatments in our study.[15] It has been reported that patients with CIDP who were unresponsive to steroid treatment often appeared to have been given an alternate diagnosis during follow-up.[38] Clinical data from the three patients in our cohort that were unresponsive to all three treatments were reviewed thoroughly in order to check whether we could find any evidence for an alternative diagnosis during the long-term follow-up. However, no diagnosis other than CIDP could be established. All had clinical features of CIDP and a raised CSF protein level, and either clear demyelinating abnormalities on EMG, sural nerve biopsy findings compatible with CIDP, or a spontaneous remission during follow-up that strongly indicates CIDP.

We investigated a large group of patients with CIDP who were treated with IVIg as a first treatment modality and were followed for a long period of time. It is possible that some patients with CIDP who were thought to have had a therapeutically induced remission had, in fact, a spontaneous remission, making it more difficult to judge treatment efficacy and to identify predictors associated with an IVIg response. Therefore, a large patient cohort, such as ours, is needed to identify important variables associated with treatment effect.[28,39] An important limitation of this study is its retrospective and open nature. Thereby, some items were not assessed systematically, such as the presence or absence of other autoimmune diseases or pain, and this could have lowered our chance of finding factors that are associated with a treatment response. A major limitation is the fact that the presence, severity and type of pain was not investigated in a standardised manner using existing scales. Sixteen per cent of our patients needed only one IVIg course to reach a clinical remission which is in line with the 15-30% reported in the literature.[15] Although no significant difference in remission rate was found in patients with CIDP treated with pulsed high-dose dexamethasone compared to prednisolone, intravenous methylprednisolone seemed to induce more long-term remissions than

IVIg.[19-20] Most of the IVIg non-responders from our cohort received more than one IVIg course. A study suggested that at least two IVIg courses over a period of 6 weeks may sometimes be required to identify an initial improvement.[39] Many patients from that cohort were different from ours as there was often a long delay between onset of symptoms and initiation of IVIg treatment, all patients received a second IVIg dosage after 3 weeks, and many already had fixed axonal deficits.[39] In our cohort, the diagnosis of CIDP was always established by a senior neurologist experienced in neuromuscular diseases possibly explaining the shorter treatment delay and the higher response rate to IVIg.[39] Since we already observed a relatively high treatment response it is unlikely that we missed a substantial number of patients who would have only responded after two or more IVIg courses. Recent data suggest considering an even longer treatment period with IVIg of more than 6 weeks before declaring a patient non-responsive.[40] Yet if one observes only a limited improvement with IVIg, one needs to explore the possibility of fixed neurological deficits caused by axonal degeneration as these in general do not improve with any treatment.

The ability to predict which patients are more likely to respond to IVIg will help physicians to choose the optimal initial treatment. This may prevent unnecessary delay of effective therapy, reduce cost and limit or avoid side effects. Early optimal and personalised treatment is not only needed to improve disability but is important to prevent permanent disability from on-going demyelination and secondary axonal loss.[39,41] As we showed, IVIg is a very effective treatment for CIDP and the short-term and long-term side effects are generally minor; but it is expensive and unfortunately most patients need long-term IVIg treatment. For patients with CIDP who do not suffer from pain or show a clear difference in weakness between arms and legs, IVIg is a good first treatment choice given its efficacy, fast speed of action and low side effect profile. By contrast, patients with CIDP with prominent pain or a clear difference in weakness between arms and legs are less likely to respond to IVIg. In view of the high cost of IVIg, to prevent unnecessary delay in improvement and because high-dose pulse steroid treatment might induce remission more often,[20] it should be further investigated whether these patients are better off being initially treated with corticosteroids.

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Chapter 3.4

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 schedule[4], 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

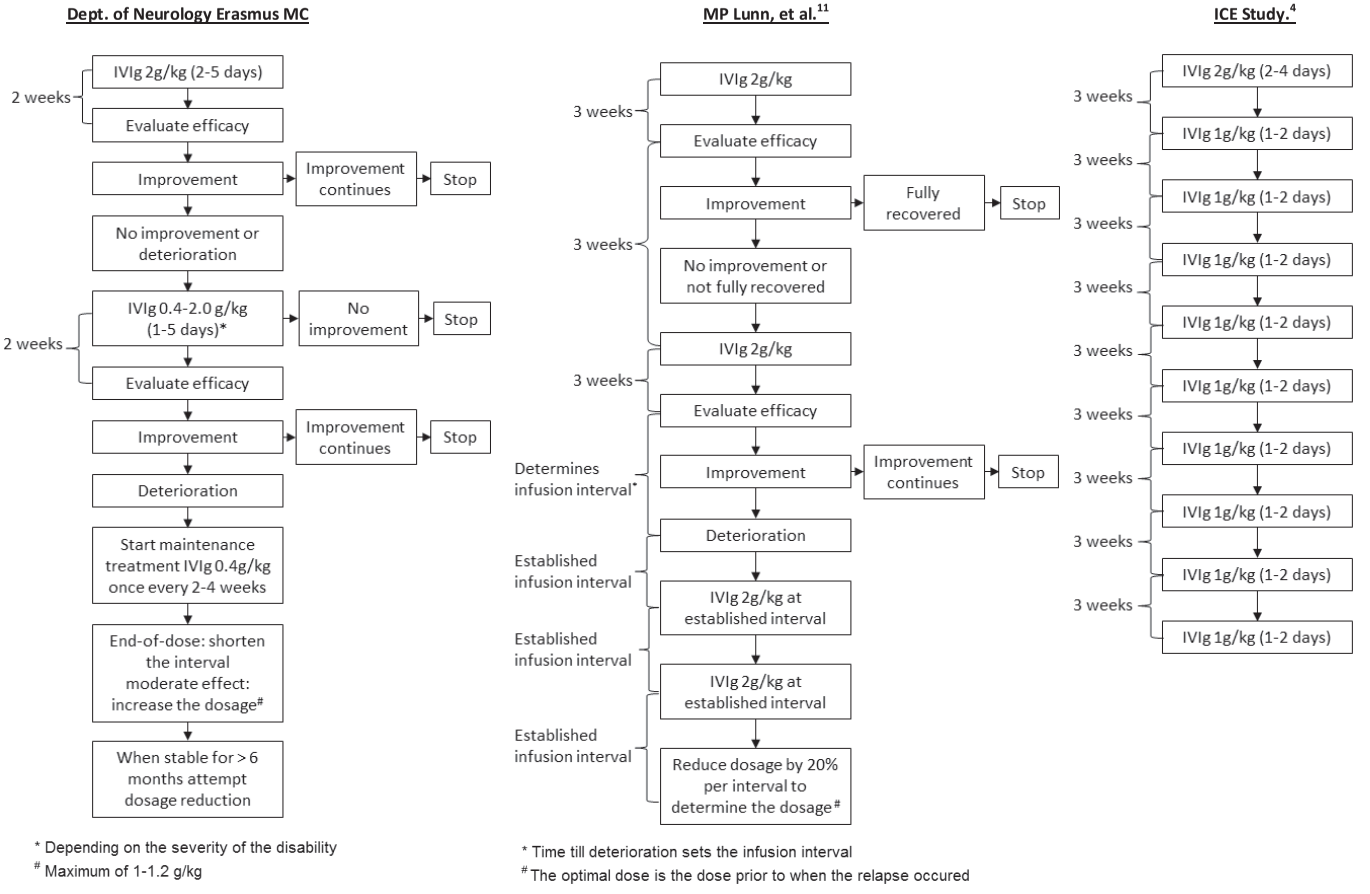

Figure 1. Alternative maintenance regimens of intravenous immunoglobulin (IVIg) treatment in chronic inflammatory demyelinating polyradiculoneuropathy

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 SCIg 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 SCIg to IVIg in CIDP or MMN suggested a somewhat better effect of SCIg 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 SCIg 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 SCIg 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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Chapter 3.5

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.

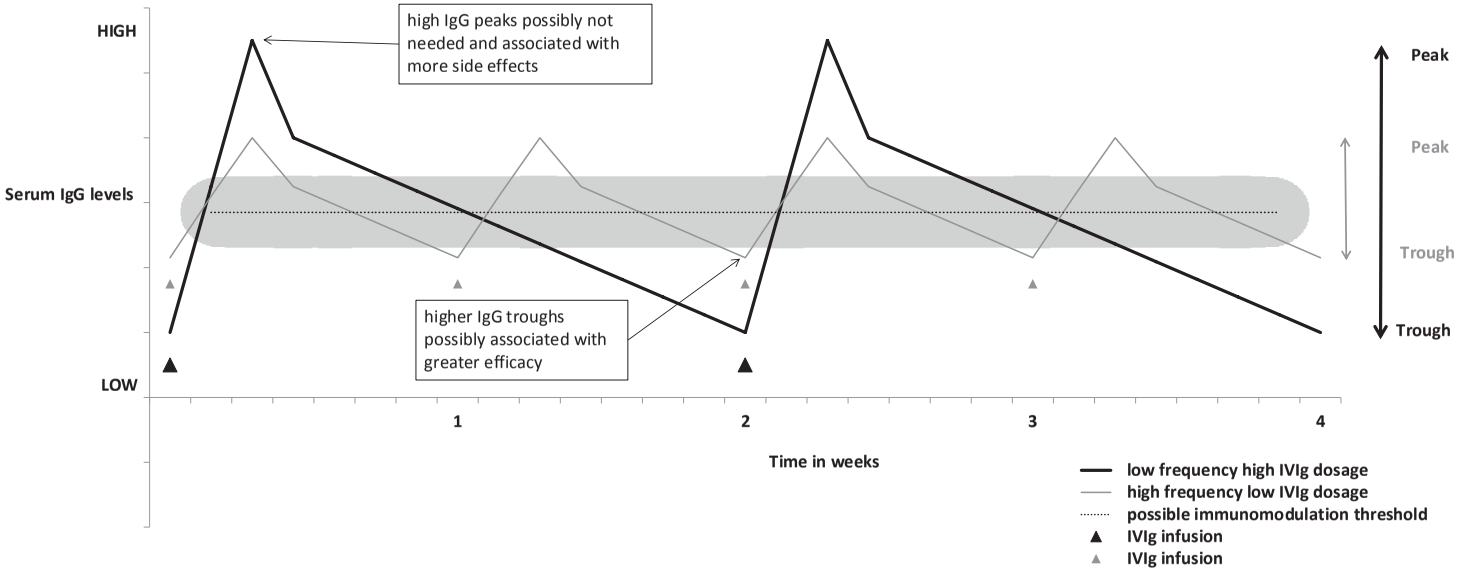


Figure 1. Serum IgG levels in high versus low frequency of IVIg maintenance treatment

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 ≥ 18 years.	2. Hand grip strength (Martin- Vigorimeter [11]) ≥ the median value (kPa) for an age and sex matched healthy control. [11]
3. Significant improvement following the first use of IVIg. (decrease ≥ 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 ≤ 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 Vigorimeter [11] or MRC sum score [28]

[#] Preferentially fulfilling the electro diagnostic criteria proposed by the INCAT [29] or EFNS/PNS.[9]

Treatment allocation and randomisation

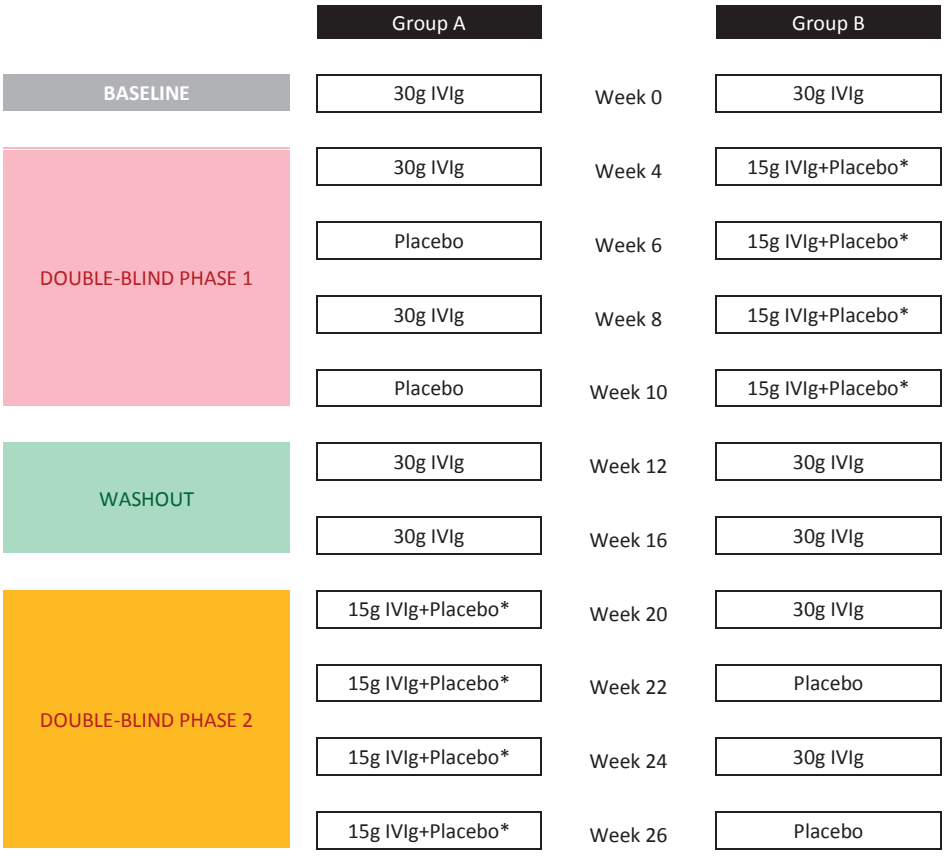
Random assignments will be provided via a computer-generated list produced by the study statistician. A block randomisation will be made for each centre. The pharmacist will hold treatment codes for all the participants in the study. One investigator (KK) will allocate the next available number on entry 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 administrated 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.



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 (ΔVigorimeter).[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 ≥ 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 ½ 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.

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CHAPTER 4

Serum IgG levels in IVIg-treated GBS and CIDP

Chapter 4.1

Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barré syndrome

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ABSTRACT

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

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

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

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

INTRODUCTION

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

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

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

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

PATIENTS AND METHODS

Patients

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

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

Data collection

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

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

Statistical analysis

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

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

RESULTS

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

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

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

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

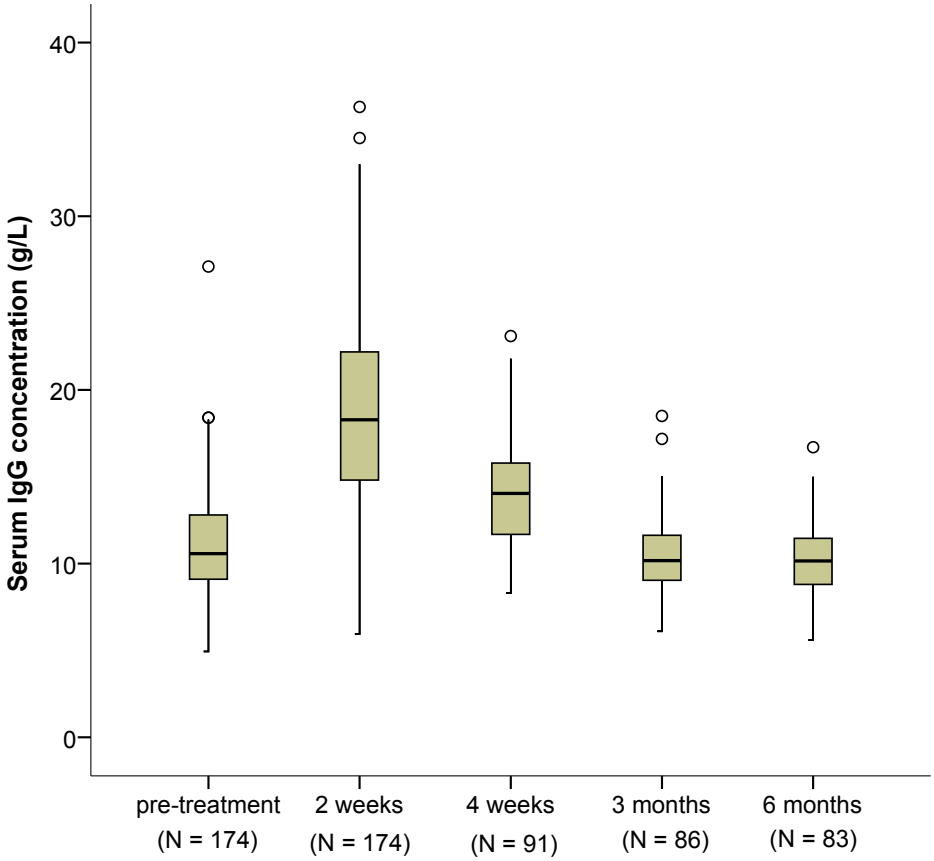

Figure 1. Variability of serum immunoglobulin (Ig)G levels in Guillain-Barré syndrome patients before and at 4 time points after treatment with a standard high dose of intravenous immunoglobulin (2g per kg body weight)

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

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

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

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

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

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

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

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

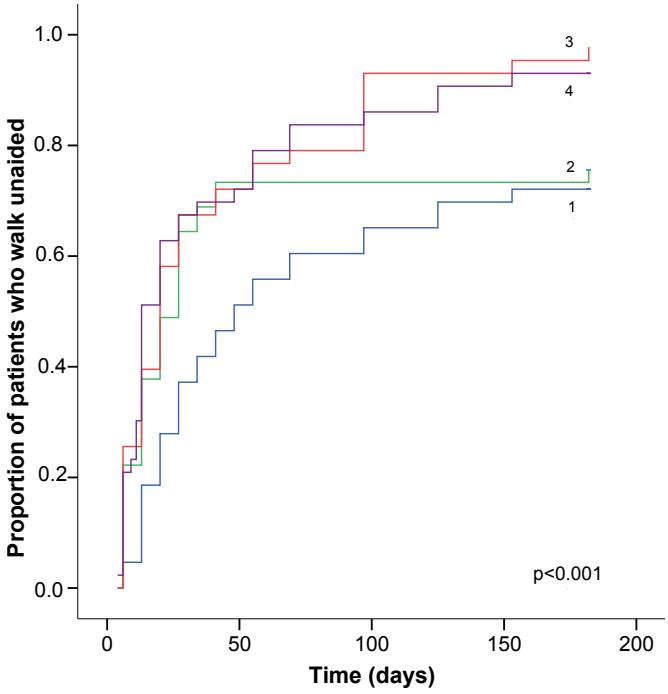

Figure 2. Proportion of patients who regained the ability to walk unaided in quartiles based on increase in serum immunoglobulin (Ig)G 2 weeks after treatment with a standard high dose of intravenous immunoglobulin

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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Chapter 4.2

Serum IgG levels in IV immunoglobulin treated chronic inflammatory demyelinating polyneuropathy

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ABSTRACT

Objective: To determine the variability of serum IgG in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods: All 25 CIDP patients had active but stable disease and were treated with individually optimised fixed dose IVIg regimens. IgG was measured by turbidimetry and variability was defined as coefficient of variation (CV).

Results: The intra-patient variability of the pre-treatment IgG levels, post-treatment levels and increase in serum IgG shortly after IVIg (ΔIgG) was low (mean CV = 3%, 4%, 10%). The inter-patient variability between patients treated with the same dose and interval was low in pre-treatment, post-treatment and ΔIgG level (mean CV = 13%, 11%, 20%). The ΔIgG levels were associated with IVIg dosage ($r_s = 0.78$, $p<0.001$).

Conclusion: Clinically stable CIDP patients show a steady-state in serum IgG after serial IVIg infusions. The low intra- and inter-patient variability in IgG may indicate that constant levels are required to reach this stability.

INTRODUCTION

Intravenous immunoglobulin (IVIg) has been proven effective for Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The precise mechanisms of action are unknown, but the pleiotropic immune-modulating effects of IgG are assumed to be responsible for the therapeutic effect.[1] The optimum dosage and frequency of IVIg to reach a clinically stable situation in CIDP during maintenance treatment differs between patients and varies between 0.4-1.2 g/kg body weight every 2-6 weeks.[2] Currently, the optimum regimen has not been defined and cannot be predicted and needs to be established empirically in clinical practice.[2, 3] The variation in the required dosage and frequency of administration might be partially explained by individual differences in catabolism of IVIg. The aim of this study was to determine the intra-patient and inter-patient variability of serum IgG levels in clinically stable but IVIg-dependent CIDP patients receiving fixed dose maintenance treatment of IVIg.

METHODS

All patients fulfilled the American Academy of Neurology criteria for CIDP and participated in a randomised controlled trial comparing freeze-dried IVIg (Gammagard S/D) with a liquid preparation (Kiovig).[4, 5] All were treated in neuromuscular centers and the dosage and frequency of IVIg was determined by neurologists experienced in treating CIDP. Muscle weakness was defined by the Medical Research Council (MRC) sum score (range 0-60) and Vigorimeter, disability by the overall disability sum score (ODSS) and sensory dysfunction by the INCAT sensory sum score (ISS).[5] Medical ethical approval and informed consent was obtained.[5]

Patients had active CIDP and worsening of symptoms following IVIg reduction within the year before the start of the trial, confirming IVIg dependency.[5] All were treated according to their own individually optimised IVIg dosage and frequency prior to trial entry and these regimens remained constant throughout the trial. To establish the optimal regimen of IVIg, the dosage was increased to achieve the maximal clinical response and the infusion frequency was shortened when patients were experiencing end-of-dose symptoms and signs.[6] Regular attempts to decrease the dose were made as recommended.[6]

Serum IgG concentration (g/L) was determined by turbidimetry. At total IgG levels of 9.0 g/L and 21.5 g/L, the between-run coefficients of variation were respectively 1.6% and 2.6% and the within-run coefficient of variation was <1%.[7] Prior to this study, we had established that peak serum IgG levels were reached 1 minute after infusion, and

remained stable for at least 30 minutes after infusion. In this study, IgG levels were determined in serum samples obtained immediately before and 5 minutes after every infusion. The peak increase in serum IgG after IVIg (ΔIgG) was defined as the IgG level after treatment minus the level just before treatment. The coefficient of variation (CV) was calculated as the ratio of the standard deviation to the mean multiplied by 100 (%). High variability in drugs is generally defined as a CV ≥ 30%.[8]

The ΔIgG of both preparations was compared using Wilcoxon matched-pairs signed-rank test. Correlation was tested with Spearman correlation coefficient (r_s). Analysis was performed using SPSS V.17.0. Two-sided p values <0.05 were regarded significant.

RESULTS

Twenty-seven patients were originally included in the trial. One patient was excluded from this study because of an unusual treatment regimen potentially influencing IgG levels (every other infusion a double dosage) and another because of premature termination of participation. All had been treated successfully with maintenance IVIg before starting the trial (mean 5 years, range 5 months to 13 years).

The ΔIgG after Gammagard infusion was smaller than after Kiovig (median 6.1 g/L (IQR 5-9) vs. 6.8 g/L (6-9), p<0.001), which may in part be attributed to the lower IgG content in Gammagard (95%) compared to Kiovig (~100%). Because of these differences in IgG content and the higher number of Kiovig infusions throughout the trial we focused on the analysis of the IgG values after Kiovig infusions, although a similar low variability in IgG levels was observed after Gammagard. The lowest serum IgG level reached prior to infusion was 9.70 g/L (mean 15.0 g/L; median 15 g/L IQR 13-17) and the minimum ΔIgG level was 3.7 g/L (mean ΔIgG 7.8 g/L; median 7 g/L IQR 6-9). After serial infusions, intra-patient variability was low in pretreatment IgG levels (mean CV 3%, median 4 IQR 3-5), post-treatment levels (mean CV 4%, median 4 IQR 3-4) and ΔIgG levels (mean CV 10%, median 8 IQR 6-12) (Figure 1). Although somewhat larger than the intra-patient variability, the inter-patient variability was small in pre-treatment IgG levels (mean CV 13%, median 8 IQR 4-28), post-treatment IgG levels (mean CV 11%, median 5 IQR 3-20) as well as ΔIgG levels (mean CV 20%, median 14 IQR 9-28) between those patients receiving the same dose and frequency of Kiovig (N = 17, Figure 1, Supplementary Table 1). When we calculated the increase in serum IgG 2 weeks after IVIg in the 13 patients with a frequency of one infusion every 2 weeks the delta IgG was very low and close to zero (mean 0.09 g/L, median 0.07 g/L, range -0.61 till 0.7 g/L), whereas it was much larger in GBS (mean 7.8 g/L) due to the use of a larger dosage in GBS than used in the maintenance IVIg treatment in our CIDP cohort. The 2 week level was unsuitable for this cohort, and therefore, the peak IgG levels were determined shortly after infusion.

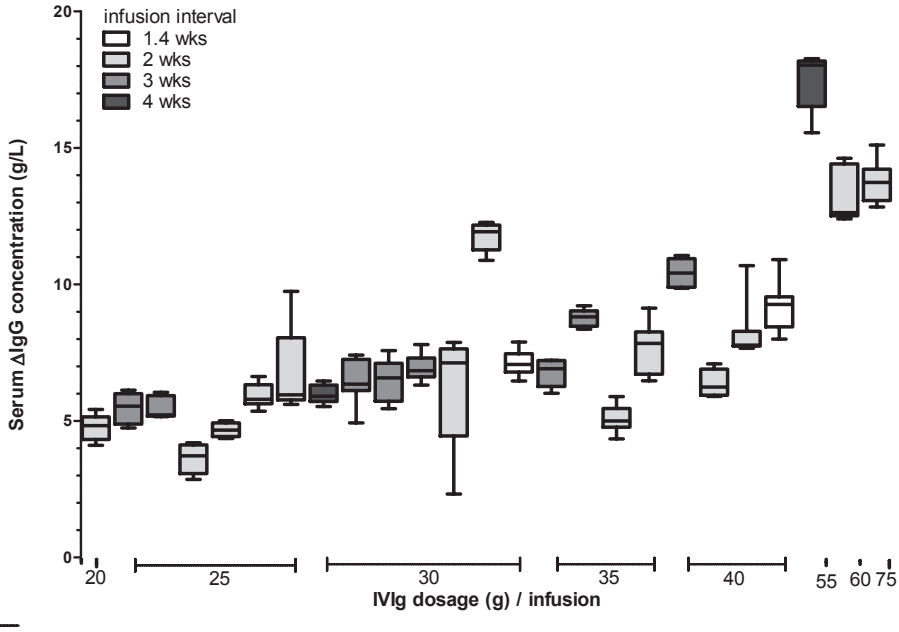

Figure 1. Serum ΔIgG levels in patients receiving maintenance intravenous immunoglobulin (IVIg) treatment (Kiovig, N=25)

ΔIgG = peak increase in serum IgG 5 min after IVIg infusion compared to pretreatment. Box and whisker plots show ΔIgG in 25 different patients, the box indicates 25th-75th percentiles; horizontal line indicates median value and the whiskers indicate minimum and maximum values. Patients are grouped by dosage. The colours of the boxes represent the infusion interval; patients receiving the same dosage and interval are displayed next to each other.

The post-treatment IgG levels and ΔIgG levels were related to the IVIg dosage administered per infusion (r_s = 0.405, p<0.05; r_s = 0.78, p<0.001), but not to the infusion frequency. The total dosage per infusion required to reach a stable clinical state and ΔIgG did not correlate with age, sex, body weight, lean body mass, muscle strength, disability or sensory dysfunction (Supplementary Table 2).[5, 7]

DISCUSSION

We showed that the serum IgG levels before and shortly after serial IVIg infusions were remarkably constant over time in patients with active but stable CIDP on constant maintenance treatment. This indicates that these patients have reached a steady state with a constant distribution rate and turnover of IgG without accumulation over time.

The dosage and frequency of IVIg required to maintain a clinically stable condition differs between CIDP patients, which might be due to interindividual differences in IVIg metabolism. Although there is some inter-patient variability between CIDP patients treated with the same IVIg dose and frequency, the mean CV can still be considered low from a pharmacological perspective which leads us to a different conclusion than previously reported.[9] A higher inter-patient variability in serum IgG levels 2 weeks after a standard course of IVIg has been observed in GBS (CV 31%) and primary immunodeficiency patients.[7, 10] This variation may depend on the activity of the disease, immunological host factors, baseline IgG levels, IgG glycosylation and Fc-receptor polymorphisms.[3, 11, 12] The low inter-patient variability in serum IgG levels we found in CIDP may be explained by the different study design in which none of the CIDP patients were treatment naïve, and all were already known to be IVIg responsive and clinically stable after a previous adjusted regimen of maintenance IVIg treatment. Variation in half-life of IgG is greater among patients with abnormal baseline IgG levels due to its concentration-dependent catabolism. [13, 14] The mean CV in baseline serum IgG level was somewhat lower in the CIDP patients treated with the same dose and interval (CV 13% N = 17) than in GBS (mean CV 28% N=174) (Kuitwaard K, 2009, unpublished data) which might have contributed to the low variability seen in CIDP.[7] Furthermore, the CIDP patients were treated with a lower IVIg dosage than the 2 g/kg used in GBS patients.

In patients with primary immunodeficiency, a minimum level of serum IgG may be required to prevent infections.[10] In GBS, an increase of serum IgG level (about 7.30 g/L) 2 weeks after 2 g/kg IVIg may be required for a better recovery since the increase in the IgG level was independently associated with the ability to walk unaided at 6 months.[7] The results of the current study suggest that a minimum serum IgG level and a minimum increase in serum IgG may be required to induce a clinical response and to reach a stable clinical condition in CIDP. This laboratory finding may be in line with the clinical observation that more than one IVIg course may be required to show improvement in CIDP.[15] We did not include non-responsive or clinically unstable patients in this study; these patients may not have reached this minimum serum IgG level and may benefit from a higher IVIg dosage. Research in these patients is required to define if serum IgG levels can be used as a biomarker to monitor the effect of IVIg treatment.

No factors have been identified so far to predict the optimum regimen for maintenance IVIg treatment in CIDP. [2, 3] Body weight and the degree of disability were not related to the required dose of IVIg, confirming previous reports.[2] Factors other than body weight might determine the optimum dosage, and maintenance IVIg treatment can probably be started at a low dose and should only be increased if required by the clinical situation.[2]

The dose administered was the only factor related to the ΔIgG. The IVIg dosages or ΔIgG levels were not associated with body weight, lean body mass, or severity of disease.

In GBS, we demonstrated an association between disease severity and the increase in serum IgG level at 2 weeks after standard IVIg treatment.[7] This difference may be explained by the fact that in the current study, all patients were in a stable and good neurological condition being treated with optimised regimens.

We have shown that in active but stable CIDP, the inter-patient variability was larger than the intra-patient variability but still considered small. More studies are needed to determine whether unselected treatment-naïve CIDP patients do show a large variability in serum IgG levels after IVIg and if monitoring of serum IgG levels can be used to optimise IVIg treatment regimens in CIDP. Until such time, the reason why CIDP patients require different dosages in their IVIg maintenance treatment remains uncertain.

Supplementary Table 1. Intra- and inter-patient variability in IgG level per subgroup of patients treated with the same dose and interval of IVIg (Kiovig)

	Patient 1	**Patient 2**			**CV of IIV**
Dose/interval (g/wks)	25/3	25/3			
Pre-treatment IgG (g/L)	16.3 (16-17)	15.4 (15-16)			
CV of IOV	3%	2%			4%
Post-treatment IgG (g/L)	22.0 (21-22)	21.1 (20-21)			
CV of IOV	2%	3%			3%
ΔIgG (g/L)	5.5 (5-6)	5.2 (5-6)			
CV of IOV	11%	8%			0.3%
	Patient 3	**Patient 4**	**Patient 5**	**Patient 6**	**CV of IIV**
Dose/interval (g/wks)	25/2	25/2	25/2	25/2	
Pre-treatment IgG (g/L)	15.2 (15-16)	13.6 (13-14)	15.7 (14-16)	16.8 (16-17)	
CV of IOV	5%	7%	6%	3%	9%
Post-treatment IgG (g/L)	21.6 (21-24)	19.3 (19-20)	20.2 (19-21)	20.8 (20-21)	
CV of IOV	7%	4%	4%	3%	6%
ΔIgG (g/L)	6.0 (6-8)	5.8 (6-6)	4.7 (4-5)	3.7 (3-4)	
CV of IOV	25%	7%	6%	15%	26%
	Patient 7	**Patient 8**	**Patient 9**		**CV of IIV**
Dose/interval (g/wks)	30/3	30/3	30/3		
Pre-treatment IgG (g/L)	17.5 (17-18)	12.1 (12-13)	14.3 (14-15)		
CV of IOV	4%	3%	2%		28%
Post-treatment IgG (g/L)	24.1 (24-24)	19.4 (19-20)	20.8 (20-21)		
CV of IOV	2%	3%	6%		20%
ΔIgG (g/L)	6.6 (6-7)	6.8 (7-7)	6.4 (6-7)		
CV of IOV	12%	7%	15%		9%
	Patient 10	**Patient 11**			**CV of IIV**
Dose/interval (g/wks)	30/2	30/2			
Pre-treatment IgG (g/L)	11.1 (11-12)	18.5 (18-19)			
CV of IOV	5%	3%			35%
Post-treatment IgG (g/L)	17.4 (16-19)	30 (30-31)			
CV of IOV	13%	2%			38%
ΔIgG (g/L)	6.3 (5-7)	11.8 (11-12)			
CV of IOV	35%	5%			43%
	Patient 12	**Patient 13**			**CV of IIV**
Dose/interval (g/wks)	35/3	35/3			
Pre-treatment IgG (g/L)	13.5 (13-14)	13.0 (13-13)			
CV of IOV	6%	3%			3%
Post-treatment IgG (g/L)	20.3 (20-21)	21.8 (21-22)			
CV of IOV	4%	2%			5%
ΔIgG (g/L)	6.8 (6-7)	8.8 (8-9)			
CV of IOV	8%	4%			18%

Supplementary Table 1. Intra- and inter-patient variability in IgG level per subgroup of patients treated with the same dose and interval of IVIg (Kiovig) (continued)

	Patient 14	**Patient 15**	**CV of IIV**
Dose/interval (g/wks)	35/2	35/2	
Pre-treatment IgG (g/L)	16.3 (16-17)	14.6 (14-15)	
CV of IOV	2%	3%	8%
Post-treatment IgG (g/L)	21.4 (21-22)	22.2 (22-23)	
CV of IOV	3%	4%	3%
ΔIgG (g/L)	5.1 (5-6)	7.6 (7-8)	
CV of IOV	9%	12%	28%
	Patient 16	**Patient 17**	**CV of IIV**
Dose/interval (g/wks)	40/2	40/2	
Pre-treatment IgG (g/L)	14.4 (14-15)	13.2 (13-14)	
CV of IOV	4%	3%	7%
Post-treatment IgG (g/L)	20.8 (20-21)	21.4 (21-22)	
CV of IOV	4%	4%	2%
ΔIgG (g/L)	6.4 (6-7)	8.2 (8-8)	
CV of IOV	8%	12%	18%

ΔIgG = peak increase in serum IgG 5 minutes after IVIg infusion compared to pre-treatment. Data are presented as medians (IQR). CV = coefficient of variation (mean, %); IIV = inter-individual patient variability; IOV = inter-occasion or intra-patient variability.

Supplementary Table 2. Correlations of IVIg dose and ΔIgG and various patient characteristics

	IVIg dosage (g)	ΔIgG (g/L)
age	r_s = 0.054, p = 0.80	r_s = 0.004 p = 0.98
sex	r_s = -0.120 p = 0.57	r_s = 0.253, p = 0.22
Body weight	r_s = 0.248, p = 0.23	r_s = -0.099, p = 0.64
Lean body mass	r_s = 0.093, p = 0.66	r_s = -0.297, p = 0.15
MRC sum score	r_s = 0.090, p = 0.67	r_s = -0.128 p = 0.54
Vigorimeter	r_s = -0.026, p = 0.90	r_s = -0.18 p = 0.93
ISS	r_s = 0.222, p = 0.29	r_s = 0.336 p = 0.10
ODSS	r_s = 0.101, p = 0.63	r_s = 0.260 p = 0.21
Infusion frequency (days)	r_s = -0.006, p = 0.98	r_s = 0.019, p = 0.93

r_s = Spearman correlation coefficient; MRC = Medical Research Council; ISS = INCAT sensory sum score; ODSS = overall disability sum score

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CHAPTER 5

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] [59] 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 β2-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 labels 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 model[90] 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.

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CHAPTER 6

Summary - Samenvatting

SUMMARY

Both Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are immune-mediated polyradiculoneuropathies.

In **Chapter 1**, the introduction, an overview is given of the diagnostic criteria for both GBS and CIDP including the differential diagnosis and treatment options.

Although GBS and CIDP have been considered as separate entities, there is some evidence that gives weight to the argument that they are part of a spectrum of inflammatory demyelinating polyneuropathies. Some CIDP patients have an acute onset, resembling GBS, and some patients diagnosed with GBS may relapse or experience treatment-related fluctuations 4-8 weeks after onset of GBS. The spectrum of GBS, CIDP and its subforms is investigated in the first part of this thesis (**Chapter 2)**.

Although GBS generally is a monophasic disorder, recurrences do occur in an undefined subgroup of patients. In **Chapter 2.1** we report whether we could identify which subgroup of patients is more likely to develop a recurrence of GBS, and whether preceding infections and neurological symptoms are similar in subsequent episodes. In this study we identified 32 patients with recurrent GBS, who had a total of 81 episodes, and then compared their clinical characteristics with 476 non-recurrent GBS patients. Recurrences occurred more frequently in younger patients (under the age of 30), in patients with milder symptoms (able to walk with or without support) and in patients with Miller Fisher syndrome. While neurological symptoms and signs were often similar, the nature of the preceding infection often varied which may indicate that genetic and immunologic host factors might play an important role in patients with recurrent GBS. In **Chapter 2.2**, four patients are described who all had separate episodes of both GBS and CIDP. These rare cases show that both GBS and CIDP can co-occur in a single patient in different episodes and should be diagnosed and treated accordingly. These case descriptions illustrate that GBS and CIDP probably could be seen as part of a continuum instead of separate entities. In **Chapter 2.3** we describe the whole spectrum of GBS and CIDP and its subforms which were investigated via a survey among members of the Dutch society of neuromuscular disorders (Spierziekten Nederland) known with the diagnosis GBS or CIDP. Two hundred and forty-five GBS and seventy-six CIDP patients were included (response-rate of 70%). in nine patients we could confirm they had a recurrent GBS (4%), and two patients had experienced both GBS and CIDP. We also studied whether autoimmune diseases were more frequently reported in GBS or CIDP. We found that the GBS and CIDP patients included in our study had a slightly higher prevalence of other autoimmune diseases compared to the general population. We studied a large number of patients who may have had multiple vaccinations over time, in order to answer the question whether ex-GBS and CIDP patients can receive vaccinations safely or not. Since none of the 106 GBS patients who received a flu vaccination (range 1-37

times, total 775 vaccinations) reported a recurrence thereafter, seasonal flu vaccinations seem relatively safe in patients who have had GBS. Additionally we investigated the presence of residual symptoms such as pain, severe fatigue, and a reduced quality of life. It appeared that years after the diagnosis of GBS or CIDP, a large number of patients suffer from these sequellae.

The second part of this thesis (**Chapter 3**) is focused on the treatment of CIDP.

Chapter 3.1 contains a review paper on treatment options in CIDP. Intravenous immunoglobulin (IVIg), plasma exchange (PE) and corticosteroids have all been proven to be beneficial in randomised controlled trials (RCTs), albeit the proof for corticosteroids is less clear. Although these treatments are more or less similar in clinical efficacy, they differ in terms of cost, availability and adverse effects. These characteristics should be taken into account when deciding which treatment should be offered to a patient. If the first treatment has no effect, one of the other proven effective treatments should be tried before moving towards other immunosuppressive drugs that are not proven yet to be beneficial. An overview of these treatments, their mode of action, adverse effects and potential place in the spectrum of treatments for CIDP based on their level of evidence is given. Various IVIg preparations are generally assumed to be equivalent, although this has not been investigated. Some patients report that some IVIg brands seem more efficacious than others. In **Chapter 3.2** the results of a RCT comparing two different immunoglobulins in the treatment of CIDP are described. No significant differences were found in clinical efficacy or the occurrence of adverse events between the two IVIg preparations. Although some patients might prefer a certain IVIg brand, the results of this trial suggest that the perceived difference in clinical efficacy is unlikely to be due to differences in the IVIg preparation used. For unknown reasons not all CIDP patients improve after IVIg. In **Chapter 3.3** the results of a retrospective study are presented in which we investigated factors that may determine a clinical response to IVIg. IVIg seemed to be highly effective as a first-line treatment in CIDP, since 76% of patients improved significantly after treatment. The (long term) adverse events were minor and hardly ever a reason to discontinue treatment. Of the IVIg non-responders three quarters of patients still responded to PE, corticosteroids or both. Thirteen percent of the CIDP patients were known to have a concurrent autoimmune disorder which is higher than in the general population. It was shown that pure motor CIDP patients can improve after corticosteroids. Therefore corticosteroid treatment should not be omitted in pure motor CIDP patients who are unresponsive to IVIg. CIDP patients with pronounced pain or a difference in weakness between arms and legs seem less likely to be IVIg responsive. Although most patients need IVIg for a long period of time, 16% only needs one IVIg course to reach clinical remission. The optimal treatment regimen of IVIg maintenance treatment in CIDP is currently unknown. There are large differences in IVIg dosage and interval requirements between individual CIDP patients. **Chapter 3.4** provides an

overview of the different IVIg maintenance schedules currently used in the treatment of CIDP. Randomised trials comparing different dosage schedules of IVIg are needed. In **Chapter 3.5** the protocol of a dose response trial of IVIg in CIDP is presented. This trial investigates whether high frequent low dosage IVIg treatment is more effective than low frequent high dosage IVIg treatment. This dose response trial is currently including patients and is expected to be finished by the end of 2018.

IgG is the main component of IVIg, and probably responsible for most of its immunomodulatory effect.

In **Chapter 4** the focus is on serum IgG levels in IVIg treated GBS and CIDP patients. GBS patients all receive the same arbitrary dose of 2 g IVIg per kg body weight. However, not all patients show a good recovery after this standard dose. In **Chapter 4.1** we describe a study in which we determined whether the pharmacokinetics of IVIg were related to outcome in GBS. Patients showed considerable variability in the increase in serum IgG level two weeks after start of a standard IVIg course (2 g/kg). Patients with a low increase in serum IgG had a more severe disease course, recovered slower and were less likely to reach the ability to walk unaided after 6 months. Even after adjustment for other known prognostic factors, a low increase in serum IgG was independently associated with a worse outcome. These results indicate that patients with a small increase in serum IgG level may benefit from a higher dosage or second course of IVIg. CIDP patients are often treated with IVIg, and receive the same arbitrary initial dose of 2 g/kg of IVIg as GBS patients. Most CIDP patients need long-term treatment and the optimum dosage and frequency of IVIg maintenance treatment varies largely between individual patients and might be partly explained by individual differences in IVIg catabolism. In **Chapter 4.2** the results of a study are presented in which we investigated serum IgG levels in clinically stable but IVIg dependent CIDP patients. All patients received an individually optimised fixed dosage IVIg maintenance treatment. The dosage of IVIg required to reach a stable clinical situation did not correlate with body weight. Clinically stable CIDP patients showed a steady-state in serum IgG after serial IVIg infusions. The low intra- and inter-patient variability in serum IgG may indicate that constant IgG levels are required to reach stability. More studies are required to further optimise the dosage and interval of IVIg maintenance treatment in CIDP.

Given that GBS can reoccur showing similar symptoms after different infections, and that GBS and CIDP can co-occur in a single patient indicates that host-specific immune responses are important in the spectrum of GBS and CIDP. Furthermore autoimmune diseases seem to be more prevalent in both GBS and CIDP. Patients are often treated with the same standard dose of IVIg, but some patients are less likely to respond due to differences in their clinical characteristics or IVIg catabolism. Whether these patients are better off if IVIg is given in a modified dosage or when they receive an alternative treatment needs to be investigated in clinical trials.

SAMENVATTING

Zowel het Guillain-Barré-syndroom (GBS) als de chronische inflammatoire demyeliniserende polyneuropathie (CIDP) zijn immuun-gemedieerde polyradiculoneuropathieën.

In **Hoofdstuk 1**, de inleiding, wordt een overzicht gegeven van de diagnostische criteria voor zowel GBS als CIDP, inclusief de differentiële diagnose en behandelingsopties.

Hoewel GBS en CIDP als afzonderlijke entiteiten worden beschouwd, zijn er aanwijzingen dat zij deel uitmaken van een spectrum van inflammatoire demyeliniserende polyneuropathieën. Sommige CIDP-patiënten hebben een acuut begin, dat lijkt op GBS, en sommige patiënten gediagnostiseerd met GBS kunnen 4-8 weken na aanvang van het GBS een terugval vertonen of behandeling gerelateerde fluctuaties ervaren. Het spectrum van GBS, CIDP en zijn varianten wordt onderzocht in het eerste deel van dit proefschrift (**Hoofdstuk 2**).

Hoewel GBS in het algemeen een monofasische aandoening is, komen recidieven voor in een ongedefinieerde subgroep van patiënten. In **Hoofdstuk 2.1** rapporteren we of we kunnen vaststellen welke subgroep van patiënten een grotere kans heeft op een recidief van het GBS en of neurologische symptomen en voorafgaande infecties vergelijkbaar zijn in opeenvolgende episodes. In deze studie identificeerden we 32 recidiverende GBS-patiënten, die in totaal 81 episoden doormaakten, en vergeleken hun klinische kenmerken met 476 niet-recidiverende GBS-patiënten. Recidieven kwamen vaker voor bij jongere patiënten (jonger dan 30 jaar), bij patiënten met mildere symptomen (in staat om met of zonder ondersteuning te lopen) en bij patiënten met het Miller Fisher-syndroom. Hoewel neurologische symptomen en verschijnselen vaak vergelijkbaar waren, varieerde de aard van de voorgaande infectie regelmatig, wat erop kan duiden dat genetische en immunologische gastheerfactoren een belangrijke rol zouden kunnen spelen in recidiverend GBS. In **Hoofdstuk 2.2** worden vier patiënten beschreven die allemaal afzonderlijke episodes van zowel GBS als CIDP doormaakte. Deze zeldzame gevallen laten zien dat zowel GBS als CIDP samen kunnen voorkomen in een enkele patiënt gedurende verschillende episodes en dienovereenkomstig moeten worden gediagnosticeerd en behandeld. Deze casusbeschrijvingen illustreren dat GBS en CIDP waarschijnlijk kunnen worden gezien als onderdeel van een continuüm in plaats van afzonderlijke entiteiten. In **Hoofdstuk 2.3** beschrijven we het hele spectrum van GBS en CIDP en de varianten die zijn onderzocht via een enquête onder leden van de Nederlandse vereniging van neuromusculaire aandoeningen (Spierziekten Nederland) met de diagnose GBS of CIDP. In totaal werden 245 GBS en 76 CIDP-patiënten geïncludeerd (respons van 70%). In negen patiënten (4%) konden we een recidiverend GBS aantonen en twee patiënten hadden zowel GBS als CIDP doorgemaakt. We hebben tevens onderzocht of auto-immuunziekten vaker voorkomen in GBS of CIDP. We ontdekten een iets hogere prevalentie van andere auto-immuunziekten onder de GBS- en CIDP-patiënten

van ons onderzoek in vergelijking met de algemene bevolking. Om de vraag te beantwoorden of ex-GBS en CIDP-patiënten veilig gevaccineerd kunnen worden of niet hebben we een groot aantal patiënten bestudeerd die mogelijk meerdere vaccinaties hebben gehad in de tijd. Omdat geen van de 106 GBS-patiënten die een griepvaccinatie kregen (variërend 1-37 keer, totaal 775 vaccinaties) daarna een recidief meldden, lijken seizoensgebonden griepvaccinaties relatief veilig bij patiënten die GBS hebben gehad. Daarnaast hebben we de aanwezigheid van restverschijnselen onderzocht, zoals pijn, ernstige vermoeidheid en een verminderde kwaliteit van leven. Het bleek dat jaren na de diagnose van GBS of CIDP een groot aantal patiënten restverschijnselen vertoont.

Het tweede deel van dit proefschrift (**Hoofdstuk 3**) is gericht op de behandeling van CIDP.

Hoofdstuk 3.1 bevat een overzichtsartikel over behandelingsopties in CIDP. Intraveneuze immunoglobuline (IVIg), plasmaferese (PE) en corticosteroïden zijn allemaal bewezen effectief in gerandomiseerde gecontroleerde onderzoeken (RCT's), hoewel het bewijs voor corticosteroïden minder duidelijk is. Hoewel deze behandelingen min of meer vergelijkbaar zijn in klinische werkzaamheid, verschillen ze in kosten, beschikbaarheid en bijwerkingen. Met deze kenmerken moet rekening worden gehouden bij de beslissing welke behandeling men aan een patiënt aanbiedt. Indien de eerste behandeling geen effect heeft, moet een van de andere bewezen effectieve behandelingen worden geprobeerd alvorens over te gaan naar andere immunosuppressiva waarvan nog niet is bewezen dat ze werkzaam zijn. Een overzicht van deze behandelingen, hun werkingswijze, bijwerkingen en mogelijke plaats in het spectrum van behandelingen voor CIDP op basis van hun bewijskracht wordt gegeven. Verschillende IVIg-preparaten worden in het algemeen als gelijkwaardig beschouwd, hoewel dit niet goed is onderzocht. Sommige patiënten geven aan dat sommige IVIg-preparaten beter lijken te werken dan andere. In **Hoofdstuk 3.2** worden de resultaten beschreven van een RCT die twee verschillende immunoglobulinen vergelijkt in de behandeling van CIDP. Er werden geen significante verschillen gevonden in klinische werkzaamheid of het optreden van bijwerkingen tussen de twee IVIg-preparaten. Hoewel sommige patiënten misschien een bepaald IVIg-merk prefereren, suggereren de resultaten van deze studie dat het waargenomen verschil in klinische werkzaamheid waarschijnlijk niet te wijten is aan verschillen in de gebruikte IVIg-preparaten. Om onbekende redenen verbeteren niet alle CIDP-patiënten na behandeling met IVIg. In **Hoofdstuk 3.3** worden de resultaten van een retrospectief onderzoek gepresenteerd waarin we factoren hebben onderzocht die mogelijk de respons op IVIg bepalen. IVIg leek een zeer effectieve eerstelijnsbehandeling te zijn bij CIDP, aangezien 76% van de patiënten na de behandeling aanzienlijk verbeterde. De (lange termijn) bijwerkingen waren minimaal en zelden een reden om de behandeling te staken. Van de patiënten die niet op IVIg reageerden, vertoonden driekwart van de patiënten alsnog een reactie op PE, corticosteroïden of beide. Dertien procent van de

CIDP-patiënten had naast de CIDP een auto-immuunziekte, dit percentage is hoger dan dat in de algemene bevolking. Er werd aangetoond dat puur motore CIDP-patiënten kunnen verbeteren na corticosteroïden. Daarom moet behandeling met corticosteroïden niet worden overgeslagen in puur motore CIDP-patiënten die niet reageren op IVIg. CIDP-patiënten met uitgesproken pijn of een verschil in zwakte tussen armen en benen reageren minder goed op IVIg. Hoewel de meeste patiënten langere tijd IVIg behandeling nodig hebben, heeft 16% slechts één IVIg-kuur nodig om een klinische remissie te bereiken. Het optimale behandelingsregime van IVIg onderhoudsbehandeling in CIDP is momenteel onbekend. Er zijn grote verschillen in benodigde IVIg-dosering en interval tussen individuele CIDP-patiënten. **Hoofdstuk 3.4** geeft een overzicht van de verschillende IVIg-onderhoudsschema's die momenteel worden gebruikt bij de behandeling van CIDP. Gerandomiseerde studies zijn nodig die verschillende doseringsschema's van IVIg met elkaar vergelijken. In **Hoofdstuk 3.5** wordt het protocol van een dosis-respons-trial van IVIg in CIDP gepresenteerd. Deze studie onderzoekt of hoog frequent lage dosering IVIg-behandeling effectiever is dan laagfrequente IVIg-behandeling met hoge dosering. Deze dosis respons studie includeert momenteel patiënten en zal naar verwachting eind 2018 voltooid zijn.

IgG is de belangrijkste component van IVIg en waarschijnlijk verantwoordelijk voor het grootste deel van het immuun modulerende effect.

In **Hoofdstuk 4** ligt de nadruk op serum IgG waardes bij IVIg-behandelde GBS- en CIDP-patiënten. GBS-patiënten ontvangen allemaal dezelfde willekeurige dosis van 2 g IVIg per kg lichaamsgewicht. Niet alle patiënten vertonen echter een goed herstel na deze standaarddosis. In **Hoofdstuk 4.1** beschrijven we een onderzoek waarin we bepaalden of de farmacokinetiek van IVIg gerelateerd was aan de uitkomst in GBS. Patiënten vertoonden aanzienlijke variabiliteit in de toename van serum IgG waarde twee weken na start van een standaard IVIg-kuur (2 g/kg). Patiënten met een geringe stijging van IgG in het serum hadden een ernstiger ziektebeloop, herstelden langzamer en hadden minder kans om na 6 maanden zelfstandig te kunnen lopen. Zelfs na correctie voor andere bekende prognostische factoren, was een lage toename van serum IgG onafhankelijk geassocieerd met een slechtere uitkomst. Deze resultaten geven aan dat patiënten met een geringe stijging van het serum IgG mogelijk gebaat zijn met een hogere dosering of een tweede kuur met IVIg. CIDP-patiënten worden vaak behandeld met IVIg en krijgen dezelfde willekeurige aanvangsdosis van 2 g/kg als GBS patiënten. De meeste CIDP-patiënten hebben langdurige behandeling nodig en de optimale dosering en frequentie van IVIg-onderhoudsbehandeling varieert sterk tussen individuele patiënten en kan waarschijnlijk deels worden verklaard door individuele verschillen in IVIg-katabolisme. In **Hoofdstuk 4.2** worden de resultaten gepresenteerd van een onderzoek waarin we serum IgG waardes hebben onderzocht in klinisch stabiele maar IVIg-afhankelijke CIDP-patiënten. Alle patiënten kregen een individueel geoptimali-

seerde IVIg-onderhoudsbehandeling volgens een stabiele dosering. De dosering van IVIg die nodig is om een stabiele klinische situatie te bereiken, correleerde niet met het lichaamsgewicht. Klinisch stabiele CIDP-patiënten vertoonden stabiele serum IgG waardes na opeenvolgende IVIg-infusies. De lage intra- en interpatiënt variabiliteit in serum IgG kan erop wijzen dat constante waardes nodig zijn om een stabiele klinische situatie te bereiken. Meer studies zijn nodig om de dosering en het interval van IVIg-onderhoudsbehandeling in CIDP verder te optimaliseren.

Aangezien GBS kan recidiveren en vergelijkbare symptomen kan vertonen na het doormaken van verschillende infecties, en GBS en CIDP samen kunnen voorkomen in één enkele patiënt geeft aan dat gastheer specifieke immuunreacties belangrijk zijn in het spectrum van GBS en CIDP. Tevens blijken auto-immuunziekten meer voor te komen in GBS en CIDP. Patiënten worden vaak behandeld met dezelfde standaarddosis IVIg, maar sommige patiënten reageren minder goed vanwege verschillen in hun klinische kenmerken of IVIg-katabolisme. Of deze patiënten gebaat zijn met IVIg in een aangepaste dosering of een alternatieve behandeling, dient in klinische trials te worden onderzocht.

CHAPTER 7

Epilogue

DANKWOORD

Dit is misschien nog het moeilijkste gedeelte van dit proefschrift, aangezien dit het meest (en vaak het enige) gelezen gedeelte is…

Dit proefschrift is enkel mogelijk door de lange geschiedenis van onderzoek naar en behandeling van GBS en CIDP door de GBS- en CIDP-onderzoeksgroep van het Erasmus MC. Allereerst wil ik alle patiënten bedanken voor hun continue inspanning en bereidheid tot deelname aan vaak meerdere onderzoeken en hun gastvrijheid bij de huisbezoeken waarbij ik bij velen een hapje mocht mee-eten. Tevens wil ik alle verpleegkundigen van de dagbehandeling en van Eurocept Homecare bedanken voor hun inzet.

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ABOUT THE AUTHOR

Krista Kuitwaard was born on September 30th 1978 in Alkmaar, the Netherlands. She studied medicine at the Free University in Amsterdam. After obtaining her medical degree in 2003 she worked for a year at the Department of Neurology of the Medical Centre in Alkmaar (Noordwest Ziekenhuisgroep). Here, her interest in the Guillain-Barré syndrome (GBS) started which resulted in the publication of a case report of a GBS patient. Thereafter she worked as a resident in neurology at the Erasmus Medical Centre in Rotterdam and started her neurology training in 2005 (head: Prof. Dr. P.A.E. Sillevis Smitt). Parallel to this residency she started her PhD research under supervision of Prof. Dr. P.A. van Doorn and Prof. Dr. B.C. Jacobs. In 2009 she received the C.U. Ariëns Kappers prize from the Dutch Neurological Society (NVvN) for the best neurology-related publication: "Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barré syndrome". After completing her neurology residency in 2013 she worked for 10 months as a neurologist and clinical neurophysiologist in the Erasmus Medical Centre. Since 2014 she works as a neurologist in the Albert Schweitzer hospital in Dordrecht. Currently she is continuing CIDP research in the Erasmus Medical Centre for one day a week, by conducting an IVIg dose finding trial in CIDP patients (DRIP study) and investigating genetic polymorphisms in CIDP patients treated with IVIg, for which she received the SPIN award for innovative ideas in the field of immunoglobulin research in neurology. She lives with her partner James Winter and their two children; Hinke and Taeke in Rotterdam.

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PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: K. Kuitwaard Erasmus MC Department: Neurology	PhD period: 2007-2018 Promotor(s): Prof. P.A. van Doorn & Prof. B.C. Jacobs	
1. PhD training		
	Year	**Workload (ECTS)**
General courses		
- Principles of research in Medicine	2007	0.7
- Introduction to data analysis	2007	0.7
- Regression analysis	2007	1.4
- Clinical trials	2007	0.7
- Pharmaco-epidemiology	2007	0.7
- Classical methods of data analysis	2007	5.7
- Repeated measurements	2007	1.4
- Good Clinical Practice	2007	0.7
- Biomedical English and writing	2008	4.0
- Recertification BROK	2014	
Specific courses (e.g. Research school, Medical Training)		
- Molmed introductory course statistics and survival analysis	2010	0.4
Seminars and workshops		
- Department Journal club and seminars	2007-2013	2.0
- Boerhaave neuromuscular course, Leiden/Amsterdam (9X)	2008-2018	4.5
Oral presentations (& conference attendance)		
- American Academy of Neurology (AAN) Toronto	2010	1.0
- Peripheral Nerve Society (PNS) Rotterdam	2012	1.0
- Peripheral Nerve Society (PNS) Sitges	2017	1.0
Poster presentations (& conference attendance)		
- INC meeting Paris (2 posters)	2008	1.0
- PNS meeting Würzburg (3 posters)	2009	1.5
- PNS/INC meeting Sydney (2 posters)	2010	1.0
- PNS/INC meeting Rotterdam (2 posters)	2012	1.0
- INC meeting Düsseldorf (1 poster)	2014	1.0
- INC meeting Glasgow (1 poster)	2016	1.0
(Inter)national conferences		
- Scientific meeting NVvN Garderen (Ariëns kappers prize)	2009	0.5
- PNS meeting Quebec (SPIN award)	2015	0.5
Other		
- AANEM podcast interview	2010	0.5

2. Teaching	Year	Workload (ECTS)
Lecturing		
- Muscle disease congress Zoetermeer (oral presentation)	2008	1.0
- Muscle disease congress Lunteren (oral presentation)	2009	1.0
- Neuromuscular Study Group, Utrecht (2 oral presentations)	2009	2.0
- Muscle disease congress Veldhoven (poster presentation)	2014	0.5
- Muscle disease congress Veldhoven (oral presentation)	2015	1.0
- Neuromuscular Study Group, Utrecht (oral presentation)	2015	1.0
- Anniversary congress GBS/CIDP Zoetermeer	2016	1.0
Continuous activities		
- Teaching nurses	2006-2016	0.5
- Reviewing papers for international peer-reviewed journals	2010-2017	1.0
Total		42.9