Pathogenesis and treatment of immune-mediated neuropathies

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***Abstract*:** Immune-mediated neuropathies represent a heterogeneous spectrum of peripheral nerve disorders that can be classified according to time course, predominant involvement of motor/sensory fibers, distribution of deficits and paraclinical parameters such as electrophysiology and serum antibodies. In the last few years, significant advances have been achieved in elucidating underlying pathomechanisms, which made it possible to identify potential therapeutic targets. In this review, we discuss the latest development in pathogenesis and treatment of immune-mediated neuropathies.

***Keywords*:** immune neuropathies, Guíllan-Barré syndrome, cidp, paraproteinemic neuropathies, treatments

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Introduction

Immune-mediated neuropathies represent a heterogeneous group of peripheral nerve disorders, which can be classified according to clinical symptoms and signs, time course and paraclinical parameters. Over the last few years, significant advances in the development of preclinical models for these diseases have allowed us to gain a deeper insight into the molecular and cellular mechanisms resulting in immune-mediated injury of the peripheral nervous system. This progress went along with the discovery of new promising therapeutic targets, which may have the potential to be further evaluated in future clinical trials. In this review we summarize current knowledge of pathogenesis, clinical course and treatment of the most frequent forms of immune-mediated neuropathies. These include the Guillain–Barré syndrome (GBS), as a prototype of an acute, immune-mediated peripheral neuropathy, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) and the paraproteinaemic polyneuropathies.

Guillain–Barré syndrome

The Guillain–Barré syndrome (GBS) is the prototype of an immune-mediated, monophasic inflammatory polyneuropathy with acute disease onset [Kieseier *et al.* 2006; Hughes and Cornblath, 2005; Kieseier and Hartung, 2003]. Several subtypes of GBS exist, which can be differentiated on the basis of their clinical course, electrophysiological criteria and underlying pathology. The reported incidence rates (1–2 per 100 000) of GBS are comparable in different geographical regions of the world [Lehmann *et al.* 2007a; Govoni and Granieri, 2001; Cheng *et al.* 2000; van Koningsveld *et al.* 2000; Rees *et al.* 1998; Hughes and Rees, 1997; Sedano *et al.* 1994]; however, the distribution of GBS subtypes differs markedly between different regions. By far the most frequent form (90–95%) in Europe and North America is the acute inflammatory demyelinating polyneuropathy (AIDP), whereas the axonal GBS forms (acute motor axonal neuropathy [AMAN] and acute motor sensory axonal neuropathy [AMSAN]) are rare in these regions but can reach 30–40% in China, Japan and South America [Yuki, 2005; Ho *et al.* 1995a; Ramos-Alvarez *et al.* 1969]. Apart from these subtypes, there are atypical variants such as the Miller–Fisher syndrome and the cervico-brachial-oropharyngeal weakness [Halstead *et al.* 2005; Overell and Willison, 2005; Willison, 2005; O'Leary *et al.* 1996].

Pathogenesis

Several lines of evidence suggest that in GBS, triggers such as an infection of the respiratory or gastrointestinal tract generate an aberrant immune response, which subsequently leads to a breakdown of the blood–nerve barrier and to a

destruction of myelin sheaths and/or axons [Meyer zu Horste *et al.* 2007; Kieseier *et al.* 2004]. Apart from bacterial and viral infections, several other triggers have been reported for example vaccinations (including influenza) [Haber *et al.* 2004; Lasky *et al.* 1998] and events such as surgery, which may lead to an activation of the immune system [van Doorn *et al.* 2008]. Pathologically, AIDP is characterized by multifocal segmental demyelination and the presence of inflammatory infiltrates. Demyelinated axons can be found within the spinal roots and the peripheral nerves and often, signs of secondary axonal degeneration accompany the severe demyelinative process. Inflammatory infiltrates contain T cells and macrophages [Prineas, 1981; Asbury *et al.* 1969]. CD3+T cells are the dominating lymphocyte population, whereas B cells are less frequently detected. Apart from cellular infiltrates, deposition of activated complement and the membrane attack complex on Schwann cells have been reported [Hafer-Macko *et al.* 1996], which supports the notion that both the cellular and the humoral immune system contribute to the pathogenesis in GBS. A recently published study suggests that complement deposition on demyelinated fibers is mainly found during the acute stage of GBS, whereas CD8+ cells and granzyme B-positive lymphocytes predominate the subacute stage of the disease [Wanschitz *et al.* 2003]. In AIDP, the autoantigens targeted by T cells and/or autoantibodies are largely unknown. A GBS-like disease can be induced by immunization of rodents with different myelin preparations, the so-called experimental allergic neuritis (EAN) [Lonigro and Devaux, 2009; Bechtold *et al.* 2005; Kieseier *et al.* 2004; Felts *et al.* 2002; Hadden *et al.* 2002; Gold *et al.* 2000; Kieseier *et al.* 2000]. The observation that EAN can be induced with the myelin proteins P0, P2 and PMP22, and by passive transfer of P0 or P2 specific CD4+ T cells points to a role of these proteins as potential autoantigens in GBS. However, only a small proportion of patients with AIDP elicit immune reactivity against those myelin proteins [Makowska *et al.* 2008]. More recently it has been suggested that neurofascin and gliomedin, two cell adhesion molecules, which are involved in clustering of voltage-gated sodium channels at the nodes of Ranvier may be targeted in EAN [Lonigro and Devaux, 2009]. The occurrence of IgG autoantibodies directed against these nodal proteins was associated with a more severe disease course and demyelinating neurophysiology in one EAN model.

In contrast to the demyelinating forms of GBS, the presumed targets of a pathologic autoantibody response in the axonal GBS variants and in the Miller–Fisher syndrome are much better defined [Willison and Yuki, 2002]. Clinical studies over the last two decades have shown that antibodies against several gangliosides can be detected in serum of patients with AMAN [Willison, 2002; Khalili-Shirazi *et al.* 1999; Ho *et al.* 1995b; Illa *et al.* 1995; Yuki *et al.* 1990]. These include antibodies against the major gangliosides GM1 and GD1a, and against GalNAc-GD1a and GD1b. The best correlation between antiganglioside antibodies and a clinical syndrome, however, can be found in patients with Miller–Fisher syndrome. In up to 90% of cases, antibodies against GQ1b can be detected [Overell and Willison, 2005; Willison, 2005, 2002]. Antiganglioside antibodies have shown to exert a variety of different pathogenic effects in various *in vivo* and *in vitro* models [Buchwald *et al.* 2007; Lehmann *et al.* 2007c; Susuki *et al.* 2007; Goodfellow *et al.* 2005; Halstead *et al.* 2004; Zhang *et al.* 2004; Buchwald *et al.* 2002]. Based on these studies it has been suggested that the nodes of Ranvier and the motor nerve terminals are the preferential targets of antiganglioside antibodies, due to high concentrations of complex gangliosides located there and the easy accessibility of 'axonal' targets within the myelinated fibers. It has been demonstrated that antiganglioside antibodies which bind to gangliosides at the nodes or at the level of the neuromuscular junction are able to induce conduction block and lead to injury to perisynaptic Schwann cells [Goodfellow *et al.* 2005; Halstead *et al.* 2004; O'Hanlon *et al.* 2003]. These effects are dependent on the activation of complement. Further complement-independent effects include an inhibition of the evoked quantal release at motor nerve terminals and an inhibition of axonal regeneration by passive transfer of anti-GD1a antibodies [Lehmann *et al.* 2007c; Buchwald *et al.* 1998].

It is believed that in these GBS variants, the mechanism of so-called molecular mimicry essentially contributes to the induction of an autoimmune response against peripheral nerve tissue [Yuki and Odaka, 2005]. The observation that microbes express carbohydrate epitopes that resemble glycolipid antigens on the surface of peripheral nerves is the basis for the hypothesis of postinfectious molecular mimicry in GBS. This is best documented for the gram-negative

rod *Campylobacter jejuni*, which can be identified as cause of a preceding infection in up to 60% of all GBS cases. This enteropathogen contains several ganglioside-like moieties on the outer leaflet of its lipooligosaccarides [Yuki, 1997; Yuki *et al.* 1994, 1993].

Clinical course

Early symptoms of GBS are pain, limb paresthesia and weakness. These symptoms progress typically within several days from distal to proximal and reach a nadir within 2–4 weeks. Cranial nerve involvement is common; the facial nerves in particular are often affected (bilateral facial paresis). In up to two-thirds of the patients autonomic dysfunction occurs which may present as bradycardia, arrhythmia, arterial hypertension, blood pressure fluctuation, sweating abnormalities and bowel/bladder disturbances [Flachenecker *et al.* 1997a, 1997b]. Pain is another frequent symptom, which can occur at early stages in sensory and motor forms of GBS and may present as backache or interscapular pain [Ruts *et al.* 2008, 2007]. Functional recovery in GBS is usually much slower than the initial clinical deterioration and may be complicated by relapses. Although GBS has an overall good prognosis, around 5–10% of patients die due to complications and around 20–30% of the patients remain disabled after 1 year [Hughes and Cornblath, 2005]. Currently no treatment is known to enhance the recovery of GBS patients.

Treatment

Generally the two mainstays of treatment in GBS are (1) supportive care and (2) immunomodulatory treatment. Supportive care is crucial to prevent complications that may occur due to the immobilization, such as thrombembolism and infections. Pneumonia is common, especially in patients that have significant bulbar weakness. Prophylactic anticoagulation, together with careful monitoring and early antibiotic treatment may help to reduce the risk for such complications. Whenever possible, GBS patients should be admitted to an ICU which is experienced in the management of GBS. Approximately one-third of patients need ventilatory assistance. Monitoring of vital capacity and respiration frequency can identify impending respiratory failure. When autonomic fibers are involved and brady-arrhythmia is observed the temporary use of pacemakers might be required. Further measures of supportive care include physiotherapy and early rehabilitation.

Currently there are two 'causal' treatments available for GBS (Table 1). Plasma exchange and intravenous immunoglobulins (IVIg) have shown beneficial effects in large randomized GBS trials. Although both treatments are considered equal in terms of efficacy, IVIg is currently favored in most centers due to its easier availability, handling and more favorable side-effect profile.

Several randomized trials have demonstrated the efficacy of plasma exchange in comparison with supportive care. In the first North American trial 245 patients were randomized to receive plasma exchange or conventional supportive therapy. The PE group showed an improvement on the disability scale at 4 weeks, time to improve one clinical grade and outcome at 6 months [Guillain–Barré Syndrome Study Group, 1985]. In the study by the French Cooperative Group on Plasma Exchange in Guillain–Barré Syndrome [1987] 220 patients were randomized to plasma exchange or supportive care alone. The PE group showed a statistically significant faster time to recover the ability to ambulate with assistance, which served as primary endpoint. Secondary parameters also favored PE treatment (reduction of patients needing assisted ventilation, time to walk with and without assistance). Further benefit of plasma exchange compared with supportive care alone was also documented after 1 year as the percentage of patients with a recovery of full muscle strength in a follow-up study [French Cooperative Group on Plasma Exchange in Guillain–Barré Syndrome, 1992]. Based on the results from another large GBS plasma exchange trial from France, the number of plasma exchanges can be adjusted to the disease severity of the patient. In this trial 556 GBS patients were included and randomized according to their disease severity [French Cooperative Group on Plasma Exchange in Guillain–Barré Syndrome, 1997]. Mildly affected patients received either no or two plasma exchange sessions, whereas patients who were unable to walk but did not require assisted ventilation received either two or four sessions. GBS patients who required assisted ventilation received either four or six plasma exchange sessions. Mildly affected patients had more benefit from treatment with two plasma exchange sessions than supportive care alone. Four plasma exchange sessions were more beneficial than two in the group of the moderately affected patients. However, more than four treatments did not yield any additional benefit in severely affected patients who required

Table 1. Treatment of adult Guillain–Barré syndrome based on evidence of clinical trials.

Treatment	Trial	Year	Trial design	Patients (n)	Outcome
Effective treatment					
Plasma exchange	The Guillain–Barré syndrome Study Group	1985	PE *versus* supportive care, single-blind	245	Improvement at 4 weeks, time to improve one clinical grade, time to independent walking, and outcome at 6 months in the PE-group.
	French Cooperative Group on Plasma Exchange in Guillain–Barré syndrome	1987	PE (4×) with albumin ($n=57$) *versus* PE (4×) with fresh frozen plasma ($n=52$) *versus* no PE ($n=111$), non-blind	220	Shorter time to recover walking with assistance (30 d *versus* 44 d, $p<0.01$) in PE group. Reduced number of patients requiring assisted ventilation, shorter time to onset of motor recovery. No differences between PE groups.
	The French Cooperative Group on Plasma Exchange in Guillain–Barré Syndrome	1997	3 groups: 'mild' affected: 0 *versus* 2 PE treatments; 'moderate' affected: 2 *versus* 4 PEs; 'severe' affected: 4 *versus* 6 PEs. non-blind	556	2 PEs more effective than 0 for time to onset of motor recovery (4 d *versus* 8 d, $p=0.0002$) in mild group. 4 PEs superior as 2 PEs for time to walk with assistance (20 *versus* 24 d; $p=0.04$) in moderate group. No difference between 4 and 6 PEs in the severe group.
IVIg	The Dutch Guillain–Barré Study Group	1992	IVIG (0.4 g/kg × d, 5×), *versus* PE (5×) non-blind, bias-controlled	150	Improvement one or more points on functional score 34% in PE-group *versus* 53% in IVIG-group ($p=0.024$). Time to improvement by one grade 41 d *versus* 27 d ($p=0.05$). Both treatments are of equal efficacy.
	Plasma Exchange/ Sandog lobulin Guillain–Barré Syndrome Trial Group	1997	PE 5 × ($n=121$) *versus* IVIG (0.4 g/kg, 5 d) ($n=130$) *versus* PE (5×) + IVIG (0.4 g/kg, 5 d), single-blind	383	No significant difference in major outcome measure (improvement on disability scale after 4 weeks and in secondary outcome measures (time to recovery of unaided walking, time to discontinuation of ventilation)
Uncertain benefit or resumably ineffective treatment (compared to PE or IVIg)					
Combination of PE and IVIg	Plasma Exchange/ Sandog lobulin Guillain–Barré Syndrome Trial Group	1997	PE 5 × ($n=121$) *versus* IVIG (0.4 g/kg, 5 d) ($n=130$) *versus* PE (5×) + IVIG (0.4 g/kg, 5 d), single-blind	383	No significant difference in major outcome measure (improvement on disability scale after 4 weeks and in secondary outcome measures (time to recovery of unaided walking, time to discontinuation of ventilation)
Combination of IVIg and Methylpredn-isolone (intravenously)	Konigsveld et al., Dutch GBS trial group	2004	IVIg (0.4 g/kg, 5 d) + methylprednisolone ($n=112$) *versus* IVIg (0.4 g/kg, 5 d) + placebo ($n=113$), double-blind, randomized-controlled	225	No significant difference between number of patients improved by 1 disability grade after 4 weeks. No significant differences in secondary outcome measures (ability to walk unaided after 8 weeks or time to walk independently)
Combination of IVIg, methyl-prednisolone and mycophe-nolate mofetil	Garssen *et al.*	2007	IVIg (0.4 g/kg/5 d + 500 mg methylprednisolone i.v. 5 d + mycophenolate mofetil (2000 mg/d 6 weeks) ($n=26$) compared to historical control (Koningsveld *et al.*) IVIg (0.4 g/kg, 5 d) + methylprednisolone ($n=112$), open-labeled pilot study	26	No statistical differences in primary endpoint (improvement by at least one grade on the GBS disability score after 4 weeks)
Combination of IVIg, and inter-feron beta 1a	Pritchard *et al.*	2003	IVIg + interferon beta 1a (22 µg 1 week then 44 µg up to 24 weeks) ($n=13$) *versus* IVIg + placebo ($n=6$)	19	No statistical differences between the two groups

PE, plasma exchange; IVIg, intravenous immunoglobulins; NDS, neurological disability score; i.v., intravenously.

assisted ventilation. In this regard, it is important to consider autoantibody kinetics during plasma exchange. It has been demonstrated that at least two plasma exchange sessions are required to significantly reduce the amount of circulating immunoglobulins in GBS [Yuki *et al.* 1998].

Besides plasma exchange, IVIg is currently the only proven immunomodulatory treatment in GBS [Hughes *et al.* 2006]. To date, both treatments are considered to be comparable in terms of outcome and efficacy, whereas side effects tend to be lower in those patients who receive IVIg [Lehmann *et al.* 2006]. Evidence for the efficacy of IVIg in adult GBS patients stems from several multicenter trials that compared IVIg with plasma exchange [Diener *et al.* 2001; Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group, 1997; Bril *et al.* 1996; van der Meche and Schmitz, 1992]. The combination of IVIg treatment followed by plasma exchange does not yield any additional benefit for GBS patients, therefore this strategy is not generally recommended [Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group, 1997]. In childhood GBS, at least two trials have shown some beneficial effects (faster recovery) of IVIg compared with no treatment [Hughes *et al.* 2007; Korinthenberg *et al.* 2005; Gürses *et al.* 1995]. However, the primary study endpoint (disease severity) in the trial by Korinthenberg *et al.* [2005] did not show a difference between the treatment groups.

The standard dose of IVIg (0.4 g/kg/day over 5 days) used is empirically based on experience from the treatment of other autoimmune diseases [Imbach *et al.* 1981]. Alternative treatment regimens of IVIg delivering the drug over a shorter period of days have been tested in smaller trials, without showing a clear benefit for the shorter treatment interval [Korinthenberg *et al.* 2005].

Corticosteroids given either orally or intravenously are ineffective in GBS. This is based on the results of several smaller trials that found no differences when corticosteroids were compared with placebo or supportive care alone [Singh and Gupta, 1996; Goodall *et al.* 1974]. One trial compared intravenous methylprednisolone with placebo, but also failed to demonstrate any beneficial effects of corticosteroid treatment [Guillain–Barré Syndrome Steroid Trial Group, 1993]. In 2004 van Koningsveld and colleagues published a double-blind, randomized controlled trial in which 225 GBS patients received either methylprednisolone (500 mg/day for 5 days) or placebo in addition to standard IVIg treatment [van Koningsveld *et al.* 2004]. However no significant differences were observed in the primary outcome (improvement in GBS disability score of at least one grade) after 4 weeks.

More recently, Garssen *et al.* [2007] reported the results of an open-label pilot study of mycophenolate mofetil in addition to a combination of IVIg and methylprednisolone in GBS. Mycophenolate mofetil is an immunosuppressive agent acting on B- and T-lymphocytes, which has been shown to be beneficial as add-on therapy in other diseases of autoimmune etiology [Moore and Derry, 2006]. Twenty-six GBS patients received IVIg (0.4 g/kg/day) and 500 mg methylprednisolone (MP) intravenously on 5 consecutive days. In addition patients received mycophenolate mofetil at a dose of 2000 mg/day for 6 weeks. This group was compared to a historical control group treated with IVIg and MP in the Dutch IVIg-MP trial [van Koningsveld *et al.* 2004]. There were no statistically significant differences regarding the primary endpoint, improvement by at least one grade on the GBS disability score after 4 weeks. The authors concluded that mycophenolate mofetil is probably of limited value in the treatment of GBS. Similarly, interferons are ineffective in GBS based on a randomized controlled study that failed to demonstrate a beneficial effect of interferon beta as add-on therapy to IVIg in GBS [Pritchard *et al.* 2003].

Future directions in the treatment of GBS

Despite treatment with plasma exchange or IVIg during the acute phase of GBS, a proportion of patients show a poor recovery with significant disability, which emphasizes the need for more effective therapies. Over the past years, new therapeutic approaches have been explored mainly in preclinical studies. These include the selective depletion of pathogenic autoantibodies, and the use of agents that prevents complement-dependent nerve injury [Halstead *et al.* 2008; Bullens *et al.* 2005; Andersen *et al.* 2004]. Antiganglioside antibodies can be selectively removed by synthetic molecules, which bear the terminal trisaccharide structure of gangliosides [Willison *et al.* 2004]. More recently, it has been shown that eculizumab, a humanized monoclonal antibody preventing formation of the terminal membrane attack complex C5b-9, can protect neuromuscular junctions from antiganglioside

antibody mediated, complement dependent injury in an *in vivo* model of Miller–Fisher syndrome [Halstead *et al.* 2008; Lehmann and Hartung, 2008]. These findings may provide a rationale for future clinical trials with eculizumab in MFS and perhaps GBS.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated polyradiculoneuropathy, clinically characterized by proximal and distal motor/sensory deficits and a relapsing or progressive disease course [Köller *et al.* 2005]. Reported prevalence rates of CIDP are similar in different geographical regions and range 1–3/100 000. The disease may affect children and elderly individuals [Iijima *et al.* 2008; Chiò *et al.* 2007; Lunn *et al.* 1999; McLeod *et al.* 1999].

Pathogenesis

Similar to GBS, it is believed that CIDP is caused by an aberrant immune response which is mediated by autoantibodies, complement, lymphocytes and macrophages [Köller *et al.* 2005]. Current concepts assume that the upregulation of cellular adhesion molecules allow autoreactive T cells and B cells to transmigrate through the blood–nerve barrier. Within the endoneurium, T cells can activate residing macrophages, which lead to enhanced phagocytosis and production of proinflammatory noxious molecules, such as nitric oxide, reactive oxygen species, proteases and proinflammatory cytokines [Lehmann *et al.* 2007b; Kieseier *et al.* 2004]. This view is supported by numerous studies demonstrating the presence of inflammatory infiltrates consisting of T cells and macrophages [Illés *et al.* 2004; Winer *et al.* 2002; Illés *et al.* 2000; Schmidt *et al.* 1996] in nerve biopsies from CIDP patients. In addition, the observation of immunoglobulin and complement deposits on myelinated nerve fibers strongly suggests that autoantibodies contribute to the process of demyelination and axonal injury by complement activation or antibody-dependent cellular cytotoxicity [Dalakas and Engel, 1980]. This is further supported by passive transfer experiments in which serum or purified IgG from CIDP patients was able to induce a conduction block and demyelination [Yan *et al.* 2000]. Despite intensive research, the target antigens of the aberrant immune responses in CIDP are still unknown. Experimental studies suggested that glycolipids and myelin proteins may be potential candidates; however, autoantibodies against those myelin components are detectable in a minority of CIDP patients only [Sanvito *et al.* 2009, Yan *et al.*, 2001].

Clinical course

Clinical symptoms of CIDP include symmetrical proximal and distal muscle weakness and diminished tendon reflexes which progress over a period of more than 8 weeks, as well as sensory deficits in a similar distribution and diminished tendon reflexes. Cranial nerve involvement is only rarely seen. Further features that support the diagnosis are elevated cerebrospinal fluid protein levels (~90% of patients) and signs of demyelination in nerve conduction studies [Köller *et al.* 2005]. Magnetic resonance imaging can show increased gadolinium enhancement and/or enlargement of nerve roots, cauda equina or the plexuses [Duggins *et al.* 1999; Midroni *et al.* 1999]. A sural nerve biopsy can provide further diagnostic support especially if features are present such as endoneurial edema, mononuclear cell infiltrates and signs of demyelination [Köller *et al.* 2005]. In general, CIDP has a variable time course and can present with a relapsing or progressive disease course.

Treatment

Current treatment concepts in CIDP are aimed to modulate and/or suppress inflammation so as to prevent injury of nerve fibers and subsequent axonal degeneration. Generally there is consensus that due to the heterogeneity of the disease course, treatment of CIDP has to be customized to the special needs of the individual patient. Low disease incidence explains the relatively small patient numbers in the currently available trials. Corticosteroids, IVIg and plasma exchange are the mainstays of CIDP treatment [Köller *et al.* 2005]. Their benefit has been documented in randomized controlled trials (Table 2). In circa 80–90% of patients, a satisfactory initial treatment response can be achieved by one of those three treatment options [Tackenberg *et al.* 2007 Chan *et al.* 2006; Köller *et al.* 2005].

Clinical presentation, predominant affection of motor or sensory fibers, side effects and concomitant diseases are parameters, which can influence the decision about the first choice treatment for each individual patient. A positive response can be monitored as increase in muscle strength either clinically or by isokinetic dynamometry

Table 2. Treatment of chronic inflammatory demyelinating polyradiculoneuropathy based on evidence of clinical trials.

Treatment	Trial	Year	Trial design	Patients (*n*)	Outcome
Effective treatment compared to supportive care or placebo alone					
Corticosteroids	Dyck *et al.*	1982	Prednisone (120 mg/2 d tapered to 0 mg 12 weeks) ($n=14$) *versus* supportive care. Randomized controlled trial, no blinding	28	Significant better outcome in changes in NDS and nerve conduction studies after 12 weeks.
Plasma exchange	Dyck *et al.*	1986	PE (6×) *versus* sham-treatment, double-blind	29	Significant better outcome in measurements of nerve conduction (total, motor, proximal, velocity, and amplitude) in the PE-group.
	Hahn *et al.*	1996	PE (10×) *versus* sham-treatment, double-blind, crossover	18	Significant improvement in PE group in clinical outcome measures (NDS) and in most electrophysiological measurements.
IVIg, plasma exchange	Dyck *et al.*	1994	PE (7×) *versus* IVIG (0.4 g/kg, 1 per 3 weeks then 0.2 g/kg, 1 per 3 weeks) crossover in case of no improvement or worsening, single-blind	20	No significant differences between the two groups in clinical outcome (NDS) and electrophysiological parameter.
IVIg	Van Doorn *et al.*	1990	IVIg (0.4 g/kg, 5 d) *versus* placebo, randomized, double-blind, crossover trial	7	Clinical response in 7 of 7 patients after IVIg treatment.
IVIg	Vermeulen *et al.*	1993	IVIg 0·4 g/kg, 5 d ($n=15$) *versus* placebo ($n=13$), double-blind, parallel group randomized, controlled trial	28	No differences in clinical improvement defined as decrease on Rankin scale.
IVIg	Hahn et al. 1996	1996	IVIg (0.4 g/kg, 5 d) *versus* placebo, randomized, double-blind, crossover trial	25	Improvement in neurological scores (NDS); clinical grade (CG), grip strength (GS) after IVIg treatment.
IVIg	Mendell et al. 2001	2001	IVIg (1 g/kg on d 1, 2, 21) ($n=30$) *versus* placebo ($n=23$), randomized, controlled, double-blind	53	Improvement in primary outcome measure (change in muscle strength from baseline to day 42) and secondary outcome measures (vital capacity, nerve conduction studies)
IVIg, corticosteroids	Hughes et al.	2001	IVIg (2.0 g/kg) ($n=12$) *versus* prednisolone (60 mg/d 2 weeks, 40 mg/d, 1 week, 30 mg/d 1 week, 20 mg/d 1 week, 10 mg/d 1 week) ($n=12$), randomized, double-blind, crossover trial	24	Significant improvement in changes in an 11-point disability scale after 2 weeks in both treatment arms.
IVIg	The ICE Trial	2008	IVIg (2 g/kg, 2–4 days then 1 g/kg every 3 weeks for up to 24 weeks) *versus* placebo, randomized, double-blind, placebo-controlled, response-conditional crossover trial. Two periods (response-conditional crossover (rescue) period, extension phase)	117	54% participants treated with IVIg improved in adjusted INCAT disability score that was maintained through to week 24 compared to 21% of patients who received placebo ($p=0.0002$). Longer time to relapse during the extension phase in IVIg treated patients ($p=0.011$).
Treatments with uncertain or no benefit					
Azathioprine	Dyck *et al.*	1985	Azathioprine 2 mg/kg + prednisone ($n=14$) *versus* prednisone ($n=13$). Randomized trial, parallel group design, not blind.	27	No significant differences between the two groups after 9 months.
Interferon-beta 1a	Hadden *et al.*	1999	IFN-ß (3 MIU for 2 weeks then 6 MIU for 10 weeks) s.c. 3 × weekly *versus* placebo, controlled double-blind, crossover trial.	10	No significant difference between the treatment arms in any of clinical or neurophysiological measures.

PE, plasma exchange; IVIg, intravenous immunoglobulins; NDS, neurological disability score.

[Harbo *et al*. 2009]. In case of insufficient or lack of response, treatment needs to be readjusted, whereas an effective initial treatment should be continued to achieve a maximum improvement. For maintenance therapy the dose of corticosteroids can be subsequently reduced to minimize side effects. Should a dose increase be required, addition of a further immunosuppressant needs to be considered. Several other immunosuppressants (azathioprine, cyclophosphamide) have been used as maintenance therapy for CIDP; however, none of those has been tested in larger controlled trials.

A beneficial effect of oral daily prednisone has been documented in a smaller trial with 28 CIDP patients, in which prednisone was given (120 mg every other day) over 12 weeks [Dyck *et al*. 1982]. More recently, the efficiency of pulsed oral methylprednisolone has been explored in an open-labeled prospective study [Muley *et al*. 2008]. In ten CIDP patients, who were followed up for at least 22 months, this steroid regimen was found to significantly improve the weakness in all patients, while treatment was well tolerated. Similarly, also the treatment regimen of high-dose intermittent methylprednisolone is often used as initial therapy for CIDP and its efficacy seems comparable to that of IVIg and oral prednisone, according to a recently published retrospective study [Lopate *et al*. 2005].

Two randomized controlled double-blind studies have demonstrated beneficial effects of plasma exchange in CIDP [Mehndiratta and Singh, 2007; Hahn *et al*. 1996b; Dyck *et al*. 1986]. In the first study, 29 patients with CIDP were randomized to receive six cycles of plasma exchange or sham exchange over three weeks [Dyck *et al*. 1986]. In the study by Hahn and co-workers, 18 CIDP patients were randomized to plasma exchange or sham treatment for 4 weeks before they were assigned to receive the alternate treatment in a crossover design [Hahn *et al*. 1996b].

One controlled, observer-blind study compared IVIg to plasma exchange in CIDP. In this study 20 patients with CIDP were randomized to receive either of the two treatments for 6 weeks, before they received the other treatment in a crossover design after a washout period. Both treatments improved the primary outcome measures consisting of a clinical score and summed compound muscle action potentials of motor nerves [Dyck *et al*. 1994].

Pooled data from four double-blind randomized controlled trials with totally 113 patients provided evidence for a short-term benefit effect of IVIg over placebo in CIDP [Mendell *et al*. 2001; Hahn *et al*. 1996a; Vermeulen *et al*. 1993; van Doorn *et al*. 1990]. A meta-analysis of these studies concluded that a significantly higher proportion of patients improved after IVIg treatment [Van Schaik *et al*. 2002]. Compared to oral prednisolone, IVIg has a comparable short-term efficacy according to a randomized, crossover trial that compared these two treatments in 24 patients [Hughes *et al*. 2001].

More recently, the ICE (Intravenous Immune Globulin for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy) study was published which investigated the long-term efficacy of IVIg in CIDP [Hughes *et al*. 2008]. This randomized, double-blind, placebo-controlled, response-conditional crossover trial was designed to explore the short- and long-term benefits of 10% caprylate chromatography-purified IVIg in patients with CIDP. The percentage of patients who maintained an improvement from baseline in adjusted INCAT disability score of at least one point over 24 weeks served as primary outcome measure.

A total of 117 CIDP patients were randomized to receive either placebo (0.1% albumin; $n = 58$) or IVIg ($n = 59$) at a baseline dose of 2 g/kg over 2–4 days followed by a 1 g/kg over 1–2 days every 3 weeks for up to 24 weeks. Patients were considered as nonresponders and were assigned to the alternate treatment arm if the adjusted INCAT disability score worsened by at least one point relative to baseline or remained unchanged during the first 6 weeks, or if the score improved but returned to baseline or lower during week 6 to week 24. Treatment responders during this first period as assessed by the adjusted INCAT disability score were eligible to be randomly reassigned to IVIg or placebo in a double-blind extension phase for an additional 24 weeks. Seventy-four patients were re-randomized for the trial's extension phase, of which 43 received IVIg and 31 patients received placebo. In the first phase of the trial 32 patients (54%) who received IVIg were adjusted-INCAT responders compared with 12 patients (21%) who received placebo ($p = 0.0002$). Although there was only a nonsignificant trend in the extension phase in several efficacy outcome measures that favor IVIg treatment, patients who continued to receive IVIg had a significantly

longer time to relapse as compared to placebo treated patients ($p = 0.011$). This demonstrated that patients who improved under IVIg treatment were able to maintain this benefit under ongoing IVIg treatment, whereas the withdrawal of IVIg resulted in an increased risk of relapse.

This trial provided evidence that IVIg treatment has significant short-term and long-term benefits in CIDP patients. Furthermore, this study showed that patients benefit from IVIg maintenance therapy if they responded during an initial treatment with IVIg [Nobile-Orazio, 2008; Vermeulen, 2008]. The same group also reports improvement and maintenance of outcome measures regarding the health-related quality of life during the trial's treatment period [Merkies *et al.* 2008].

Immunosuppressive treatments that are widely used in CIDP include cyclophosphamide, azathioprine and cyclosporine. Azathioprine has been tested in a small, randomized controlled trial, but did not yield any additional benefit when added to prednisone [Dyck *et al.* 1985]. Cyclophosphamide has never been evaluated in randomized controlled trials, but beneficial effects have been reported in CIDP with an intravenous pulse therapy (1 g/m^2 a month for up to six months) [Good *et al.* 1998]. According to one case series, high dose cyclophosphamide treatment can also be beneficial in CIDP patients, but there are obviously increased risks related to this treatment, such as neutropenic infections, transient renal insufficiency and alopecia [Brannagan *et al.* 2002]. The same group also reported a long-term benefit after a median of 2.9 years in clinical and electrophysiological parameters [Gladstone *et al.* 2005]. Further positive effects have been reported in case studies and smaller series for mycophenolate mofetil [Gorson *et al.* 2004], cyclosporine [Odaka *et al.* 2005; Ryan *et al.* 2000], alemtuzumab [Hirst *et al.* 2006], methotrexate [Fialho *et al.* 2006], autologous hematopoietic stem-cell transplantation [Reményi *et al.* 2007] and a combination of high dose cyclophosphamide and autologous hematopoietic stem cell transplantation [Axelson *et al.* 2008b]. In contrast, Interferon-beta fails to generate clinical improvement, according to a randomized controlled trial in ten CIDP patients [Hadden *et al.* 1999]. Similarly, intramuscular interferon beta-1a failed to significantly reduce IVIg maintenance therapy in patients with IVIg-dependent CIDP, according to the results of a randomized double-blind, placebo-controlled study [Gorson *et al.* 2008].

Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) is an immune-mediated neuropathy characterized by a slowly progressive, mainly distal muscle weakness without sensory deficits [European Federation of Neurological Societies, 2006; Van Asseldonk *et al.* 2005; Nobile-Orazio, 2001]. Clinically it may resemble a motor neuron disease, which is the most important differential diagnosis. The exact incidence and prevalence rates of MMN are unknown, but it is believed to be a rare disease with estimated prevalence rates of 1–2/100 000 [Nobile-Orazio *et al.* 2005].

Pathogenesis

Observations that patients with MMN can improve by treatment with immunomodulatory agents, especially IVIg [Léger *et al.* 2001], and the frequent occurrence of serum IgM antiganglioside antibodies [Willison and Yuki, 2002] suggest an immune-mediated pathogenesis of the disease. Pathological studies of motor nerves have reported loss of axons and signs of axonal degeneration at sites where a conduction block was present [Taylor *et al.* 2004]. In contrast, prominent changes in myelin morphology were not observed in this study, suggesting a primarily axonal pathology as underlying cause of the disease. Others have reported signs of demyelination with abnormally thin myelin and small onion-bulb formations [Kaji *et al.* 1993; Auer *et al.* 1989].

Detection of antibodies against various gangliosides (GM1, GD1a, GD1b) in up to 60% of all patients with MMN [Slee *et al.* 2007; Van Asseldonk *et al.* 2006, 2005; Willison and Yuki, 2002; Pestronk *et al.* 1988] provides hints for a role of these antibodies in the pathogenesis of MMN. Gangliosides, which are sialic acid containing glycolipids, can be found in most mammalian tissues, but are enriched in the nervous system. The gangliosides mentioned above belong to the most abundant types in the nervous system. It is noteworthy that the ganglioside content of motor and sensory nerves is similar [Gong *et al.* 2002; Ogawa-Goto and Abe, 1998; Svennerholm *et al.* 1994, 1992; Ogawa-Goto *et al.* 1990], which argues against the hypothesis that differences in ganglioside distribution are mainly responsible for the selective motor nerve damage in MMN and other antiganglioside

antibody associated neuropathies. Rather, other factors, such as antibody affinity and antigen accessibility probably play an important role. GM1 and GD1a are localized at the nodes of Ranvier and in motor nerve terminals [Gong *et al*. 2002; Sheikh *et al*. 1999]. There is evidence that under certain circumstances antiganglioside antibodies may exert various pathogenic effects. This has been shown in different experimental paradigms, which demonstrated that antiganglioside antibodies can induce conduction block, evoke demyelination, and inhibit axon regeneration [Buchwald *et al*. 2007; Lehmann *et al*. 2007c; Goodfellow *et al*. 2005; Halstead *et al*. 2004]. However, other factors are likely to contribute to the pathogenesis of MMN, since almost half of the MMN patients do not have circulating antibodies against GM1 and passive transfer studies have failed to replicate the disease in rodents [Harvey *et al*. 1995].

Clinical course

Clinically, MMN is characterized by a slowly progressive weakness with an asymmetrical distribution of motor nerve involvement. It is usually more pronounced distally than proximally, and often starts in the upper limbs. Apart from muscle weakness, progressive muscle atrophy, fasciculations and muscle cramps can occur. The age of onset is between 20 and 65 years and men tend to be more frequently affected than women [Van Asseldonk *et al*. 2005]. Although MMN is a slowly progressive disease, it can be associated with substantial disability in the later stages of the disease. The involvement of the upper limbs often affects manual tasks, which are important for daily living (use of keys, turn on switches, etc.) [Lange *et al*. 2006; Van Asseldonk *et al*. 2005]. A hallmark of the disease is the presence of proximal partial motor conduction block, defined as reduction in proximally stimulated muscle evoked response compared with the distally stimulated response. This can be found in 70% of patients. However, although conduction block is an electrophysiological hallmark of the disease, it remains controversial if it is essential for the diagnosis of MMN to be established [Chaudhry and Swash, 2006]. This is supported by the notion that cases of MMN without conduction block may be otherwise undistinguishable in terms of clinical course and response to IVIg [Delmont *et al*. 2006]. A further characteristic feature is the presence of progressive axonal degeneration, which may account for the disability in the later stages of the disease.

Treatment

In contrast to motor neuron diseases, MMN is a treatable disorder. It has been reported that patients with MMN improve by treatment with several immunomodulatory agents; however, the best evidence is available for IVIg [Léger *et al*. 2001; Federico *et al*. 2000] (Table 3). The efficacy of IVIg has been demonstrated in four randomized trials [Léger *et al*. 2001; Federico *et al*. 2000; Van den Berg *et al*. 1997; Azulay *et al*. 1994]. Despite clinical improvement observed in all, the data are somewhat conflicting with regard to reversibility of conduction block by IVIg treatment [Kieseier *et al*. 2008]. GM1 antibody titers do not correlate with treatment response [Léger *et al*. 2001], whereas younger patients and those with conduction blocks may benefit more from IVIg treatment. Maintenance therapy is usually required, and if it is stopped, the weakness may progress. Long-term follow-up studies revealed that the effectiveness of IVIg tends to decrease over time [Kieseier *et al*. 2008; Léger *et al*. 2008; Terenghi *et al*. 2004; Taylor *et al*. 2000]. In contrast to other chronic immune-mediated neuropathies, corticosteroids and plasma exchange are considered ineffective, and may even worsen the clinical course [Nobile-Orazio *et al*. 2005; Specht *et al*. 2000].

In a recent retrospective case series the effects of plasma exchange in MMN were studied [Lehmann *et al*. 2008]. Two out of seven patients responded to plasma exchange in the early phase of the disease, whereas the majority of patients did not show any clinical response and electrophysiological follow-up examinations demonstrated further worsening. This suggests that the therapeutic value of plasma exchange in MMN is limited. However, it is possible that carefully selected patients may benefit from plasma exchange treatment; for example, those with high titers of antiganglioside antibodies. Since antiganglioside antibodies are only transiently reduced, plasma exchange is probably only useful as an adjunctive treatment in combination with long-term immunosuppression.

Other agents that have been proposed as treatment for MMN include cyclophosphamide [Chaudhry *et al*. 1993; Feldman *et al*. 1991; Pestronk *et al*. 1988] and azathioprine [Hausmanowa-Petrusewicz *et al*. 1991]. According to one case report cyclophosphamide and autologous stem cell transplantation are ineffective in MMN [Axelson *et al*. 2008a]. Beneficial effects have

Table 3. Treatment of multifocal motor neuropathy based on evidence of clinical trials.

Treatment	Trial	Year	Trial design	Patients (n)	Outcome
Effective treatment					
IVIg	Léger *et al.*	2001	IVIg (500 mg/kg/day, 5 d 1 × month for 3 months *versus* placebo, double-blind, randomized, controlled crossover trial	18	7/9 patients who received IVIg responded compared with 2/9 patients who received placebo ($p = 0.03$). No differences in MRC score, electrophysiological studies and changes in anti-GM1 antibody titers.
IVIg	Federico et al.	2000	IVIg (0.4 g/kg/day, 5 d) *versus* placebo, double-blind, randomized, controlled crossover trial	16	Improvement in NDS with IVIg treatment compared to placebo ($p = 0.038$) after 28 d. Improvement in grip strength ($p = 0.0021$) and conduction block ($p = 0.037$) with IVIg treatment.
IVIg	Azulay et al.	1994	IVIg (0.4 g/kg/day, 5 d) *versus* placebo, double-blind, randomized, controlled crossover trial	12	Improvement in muscle strength after IVIg treatment.
IVIg	Van den Bergh et al.	1997	IVIg (2 × 0.4 g/kg/day, 5 d) ($n = 4$) and placebo; IVIg (1 × 0.4 g/kg/day, 5 d) and placebo ($n = 2$), double-blind, randomized, controlled crossover trial	6	Clinical improvement in 5/6 patients with IVIg but not placebo.
Presumably ineffective treatment					
Combination of IVIg and mycophenolate mofetil	Pieper *et al.*	2007	Standard dose IVIg every 2–5 weeks + 1000 mg/d mycophenolate mofetil first week then 2000 mg/d *versus* placebo for 12 months, randomized, double-blind, placebo-controlled study	28	No statistical differences in primary endpoint (IVIg dose reduction of 50% during adjunctive treatment).

PE, plasma exchange; IVIg, intravenous immunoglobulins; NDS, neurological disability score; MIU, million international units, s.c., subcutaneously.

been observed in patients treated with the monoclonal anti-CD20 antibody rituximab, [Ruegg *et al.* 2004]; however, other groups were unable to confirm this [Gorson *et al.* 2007; Rojas-García *et al.* 2003]. More recently, a randomized controlled trial evaluated the efficacy of mycophenolate mofetil as adjunctive therapy for MMN [Piepers *et al.* 2007]. Twenty-eight patients who received IVIg were randomized to receive in addition to IVIg either mycophenolate mofetil or placebo for a period of 12 months. A reduction of the IVIg dose to 50% served as the primary endpoint. After 1 year, there was no significant difference between the two groups, suggesting that mycophenolate mofetil is probably ineffective in MMN.

Polyneuropathy associated with monoclonal gammopathy

In approximately 10% of patients with idiopathic polyneuropathies a monoclonal immunoglobulin can be detected in serum or urine [Kelly *et al.* 1981]. Of those, monoclonal gammopathy of undetermined significance (MGUS) is the most frequent form, whereas lymphoproliferative disorders such as Waldenström's macroglobulinemia represent rare causes of monoclonal gammopathies [Ropper and Gorson, 1998]. Occasionally, a paraprotein occurs as part of the POEMS syndrome (peripheral neuropathy – organomegaly – endocrinopathy – myeloma – skin disease) [Dispenzieri *et al.* 2003]. Polyneuropathies associated with monoclonal gammopathy can be very heterogeneous in terms of clinical course, electrophysiology and response to treatment. The best-defined paraprotein- associated neuropathic condition is the IgM paraprotein associated demyelinating polyneuropathy in which the IgM reacts with myelin-associated glycoprotein (MAG) [Nobile-Orazio, 2004; Vital, 2001]. Whether axonal changes noticed in the context of a monoclonal

gammopathy are a coincidental finding or part of the disease spectrum [Allen *et al.* 2007; Lunn and Nobile-Orazio, 2006] remains a matter of debate, since both polyneuropathy and monoclonal gammopathy are common in the elderly.

Pathogenesis

Due to the heterogeneous disease spectrum of IgA and IgG paraprotein associated polyneuropathies, no consistent pathogenesis has been established for these neuropathic conditions. In contrast, the finding that up to 50% of IgM paraproteins react with MAG suggests a role of these antibodies in the pathogenesis of this subgroup. Pathologic studies have demonstrated segmental demyelination and signs of secondary axonal degeneration in sural nerve biopsies [Willison and Yuki, 2002]. By immunohistochemistry deposits of IgM and complement can be found on dermal myelinated fibers [Lombardi *et al.* 2005]. Another pathological feature is abnormally spaced myelin, which can be detected by electron microscopy [Ritz *et al.* 1999; Jacobs and Scadding 1990]. Lunn and colleagues reported in an electron microscopic study an altered distance of neighboring neurofilaments in axons of sural nerves from patients with anti-MAG paraproteinaemic neuropathies [Lunn *et al.* 2002]. These findings implicate a pathogenic effect of the anti-MAG antibody by alteration of MAG dependent control of neurofilament spacing in peripheral nerves.

Clinical course

Anti-MAG paraproteinaemic neuropathy is clinically characterized by a predominantly sensory demyelinating neuropathy [Nobile-Orazio, 2004]. It is slowly progressive and has an overall better prognosis than other chronic immune-mediated neuropathies. Sometimes an upper limb postural neuropathic tremor may occur.

Treatment

Treatment in patients with paraproteinaemic neuropathy is aimed at targeting the presumably pathogenic paraprotein or abnormal B-cell clone. An adequate hematological treatment is the mainstay in cases in which a lymphoproliferative disorder can be identified as cause for the gammopathy [Nobile-Orazio, 2004]. In those cases patients can be referred to a specialized hematology service, which establish the primary treatment strategy in cooperation with the treating neurologist, who can be consulted in case of any questions that relates to the accompanying neuropathy. For example in POEMS syndrome, high-dose chemotherapy with autologous hematopoietic stem-cell transplantation is a treatment strategy, which can result in remission of hematological manifestations and marked improvement of the neuropathy [Créange *et al.* 2008].

Generally, controlled trials are rare for paraproteinaemic neuropathies, which makes it difficult to recommend any particular evidence-based immunotherapy [Lunn and Nobile-Orazio, 2003] (Table 4). In a randomized double-blind placebo-controlled crossover trial IVIg was not effective in the majority of 11 patients with IgM paraproteinemic demyelinating neuropathy [Dalakas *et al.* 1996]. Another double-blind crossover trial of 22 patients with IgM paraproteinemic demyelinating neuropathy demonstrated a clinical benefit at 4 weeks [Comi *et al.* 2002]. These results indicate that IVIg may only have a short-term benefit in the treatment of IgM paraproteinemic neuropathy [Lunn and Nobile-Orazio, 2003].

According to one randomized, controlled, double-blind trial, patients with MGUS associated polyneuropathy can benefit from plasma exchange [Dyck *et al.* 1991]. In this study, 39 patients received either plasma exchange twice weekly for 3 weeks or sham treatment. The primary outcome measures, the neuropathy disability score and summed compound muscle action potentials of motor nerves showed a beneficial effect in the plasma exchange group. A subgroup analysis further demonstrated that patients with IgM gammopathy are less responsive to plasma exchange than those with IgG or IgA gammopathy.

A recent study evaluated the effects of rituximab in 26 patients with anti-MAG-antibody positive polyneuropathy. The patients were randomized to receive either four weekly infusions of 375 mg/m^2 rituximab or placebo. As primary outcome served a change of 1 or more on the INCAT leg disability scores after 8 months. In the rituximab group 4 out of 13 patients improved, whereas none of the patients in the placebo group showed an improvement [Dalakas *et al.* 2007]. This study was preceded by several case series and open trials that evaluated the therapeutic potential of rituximab on IgM paraproteinaemic neuropathies with and without anti-MAG reactivity [Benedetti *et al.* 2008, 2007; Gorson *et al.* 2007; Renaud *et al.* 2006, 2003;

Table 4. Treatment of paraproteinemic neuropathies (with and without anti-MAG antibodies) based on evidence of clinical trials.

Treatment	Trial	Year	Characteristics: design	Patients (*n*)	Outcome
Effective treatment					
IVIg	Comi *et al.*	2002	IVIg (2 g/kg) ($n=12$) *versus* placebo, double-blind, randomized, controlled crossover trial	22	Decrease in overall disability during IVIg treatment ($p=0.001$). Improvement in secondary outcome measures (Rankin scale, time to walk 10 meters, grip strength) during IVIg treatment.
IVIg	Dalakas et al.	1996	IVIg (2 g/kg 1 × /month for 3 months) *versus* placebo, double-blind, randomized, controlled crossover trial	11	Improvement only in 2/11 patients during IVIg treatment. No significant benefit of IVIg treatment
Plasma exchange	Dyck *et al.*	1991	PE (6×) *versus* sham-treatment, double-blind	39	Marked improvement in disability score. More benefit in the IgG and IgA gammopathy subgroup as compared with IgM gammopathy population.
Presumably ineffective treatment					
Cyclophosphamide with prednisone	Niermeijer *et al.*	2007	Oral cyclophosphamide (500 mg/d, 4 d + oral prednisone 60 mg/d 5 d *versus* placebo every 28 d (6×)	35	No difference in functional scale after 6 months. Improvement in several secondary outcomes.
Interferon-alpha	Mariette *et al.*	2000	Interferon-α (4.5 MIU 3 × week for 6 months) *versus* placebo, randomized, double blind trial	24	No clinical improvement compared to placebo.

PE, plasma exchange; IVIg, intravenous immunoglobulins; NDS, neurological disability score; MIU, million international units, s.c., subcutaneously.

Levine and Pestronk, 1999]. In a mixed cohort of 21 patients with different forms of polyneuropathies associated with antiganglioside or anti-MAG antibodies the majority showed an improvement in muscle strength after one and two years of treatment, IgM levels and antibody titers decreased [Pestronk *et al.* 2003]. In a case series by Rojas-Garcia *et al.* [2003] rituximab had no favorable effect on two patients (one with chronic motor neuropathy and antiganglioside IgM antibodies, one with an IgM monoclonal gammopathy). In contrast Renaud and colleagues reported a salutary effect of rituximab (dose 375 mg/m^2) in nine patients with anti-MAG associated polyneuropathy. Clinical improvement was correlated with diminished IgM levels and antibody titers [Renaud *et al.* 2003]. The same group also reported a follow-up study in which eight patients were treated with a higher dose (750 mg/m^2). The higher dosage was well tolerated and four patients experienced marked clinical improvement, which went in parallel with a decrease in anti-MAG antibody titers and serum IgM levels.

One randomized, double-blind trial investigated the effect of interferon-alpha in 24 patients with polyneuropathy with monoclonal IgM but could not demonstrate any benefit [Mariette *et al.* 2000]. Likewise, oral cyclophosphamide combined with prednisone did not show a benefit in primary outcome measures compared with placebo treatment in a double-blind, randomized study in 35 patients with IgM MGUS polyneuropathy [Niermeijer *et al.* 2007].

Conflict of interest statement

None declared

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