An update on the management of chronic inflammatory demyelinating polyneuropathy

Kenneth C. Gorson

Abstract: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune mediated disorder of the peripheral nervous system with clinical features that include weakness, sensory loss, imbalance, pain and impaired ambulation which may lead to substantial disability. This review highlights current treatment strategies for CIDP, how best to utilize proven therapies such as intravenous immunoglobulin, oral prednisone, pulse dexamethasone, and plasma exchange, and when and how to use alternative immunosuppressive agents when first-line therapies are ineffective or poorly tolerated.

Keywords: CIDP, demyelinating neuropathy, immune neuropathy, inflammatory polyneuropathy, IVIg, treatment

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic, acquired, immune-mediated condition affecting the peripheral nervous system [Köller *et al.* 2005; Dalakas, 2011]. The pathogenesis of CIDP is incompletely understood and includes several humoral and cell-mediated mechanisms [Köller *et al.* 2005; Dalakas, 2011]. The classic form of the disorder is characterized by: (1) progressive limb weakness, usually with a predilection for proximal muscles, sensory loss, and areflexia with a relapsing or progressive course; (2) electrophysiological features of demyelination, including prolonged distal motor and F-wave latencies, reduced conduction velocities, and conduction block and temporal dispersion; (3) laboratory features of albumino-cytological dissociation in the cerebrospinal fluid; and (4) inflammation, demyelination, and remyelination on nerve biopsy [Dyck *et al.* 1993; Joint Task Force of the EFNS and PNS, 2010]. In most cases the diagnosis can be confidently established by clinical and electromyography (EMG) criteria, and nerve biopsy is less often required but can be helpful in selected cases. Numerous clinical trials have established the short-term efficacy of immune therapies such as corticosteroids, plasma exchange (PE), and intravenous immune globulin (IVIg) as the mainstay of treatment for CIDP, with several reports indicating the promise of novel immune therapies [Dalakas, 2011].

Although guidelines for the diagnosis and treatment of CIDP have been developed, the large variety of clinical and electrophysiological variants, associated systemic conditions, and lack of sustained improvement with standard treatments in up to one third of cases provide challenges to the clinician in practice. This review highlights the currently accepted therapies for CIDP and the role of potentially effective but unproven novel therapies.

Clinical features

CIDP is one in a spectrum of acquired immune-mediated demyelinating neuropathies that differ from each other mainly in their time course and clinical features. The two traditional categories of acute inflammatory demyelinating neuropathy (AIDP; Guillain–Barré syndrome) and CIDP have similar presentations except that the symptoms peak in less than 4 weeks in AIDP and are monophasic, and progress for 8 weeks or more in CIDP. For an illness that reaches its nadir between 4 and 8 weeks, the term subacute demyelinating neuropathy has been used [Oh *et al.* 2003]. The natural history of the latter group can follow the pattern of either AIDP (monophasic course with a plateau and then recovery) or CIDP (progressive or relapsing). In large series, CIDP represents approximately 20% of initially undiagnosed neuropathies and accounts for approximately

Correspondence to:
Kenneth C. Gorson, MD
Department of Neurology,
St. Elizabeth's Medical
Center, 736 Cambridge
Street, Boston, MA 02135,
USA
kengorson@comcast.net

Table 1. Clinical features of chronic inflammatory demyelinating polyneuropathy [Joint Task Force of the EFNS and PNS, 2010].

Progressive symmetrical or asymmetrical polyradiculoneuropathy
Relapsing or progressive course >2 months
Proximal weakness usually prominent
Large fiber sensory loss in the distal limbs (vibration and joint position sense)
Generalized hyporeflexia or areflexia

10% of all patients referred to neuromuscular clinics. The disorder most commonly occurs in adults between 40 and 60 years, but can affect the elderly and children. There is a slight predilection for men. The prevalence of CIDP is approximately two to five cases per 100,000 individuals, comparable to the frequency of AIDP [Rajabally *et al.* 2009]. Two-thirds of cases are progressive and the remainder relapsing, although in the modern era 'relapses' often reflect treatment withdrawal (e.g. IVIg, or rapid tapering of prednisone), but also may be triggered by infections or other systemic illnesses. Spontaneous relapses tend to affect younger individuals.

In its classic form, the initial symptoms of CIDP are progressive, symmetric limb weakness and sensory loss that usually begin in the legs (Table 1). Patients report difficulty walking, climbing stairs, arising from a chair, and may fall, or they may complain of reduced manual dexterity (trouble buttoning shirts, pulling up zippers, etc.) if hand weakness is present. A core clinical feature is proximal limb weakness, indicating a non-length-dependent neuropathy that implies proximal

nerve demyelination and distinguishes such cases from the far more commonly encountered distal axonal polyneuropathies. The majority of patients also have sensory features, with complaints of numbness, tingling or buzzing of the acral extremities (paresthesias), and gait unsteadiness reflecting a sensory ataxia. Neuropathic pain is less common. The examination shows symmetric proximal and distal limb weakness, generalized hyporeflexia or areflexia, and distal sensory loss with large fiber modalities (joint position, vibration) disproportionately affected [Gorson *et al.* 1997; Köller *et al.* 2005; Dalakas, 2011].

Electrodiagnostic criteria
Nerve conduction studies establish the diagnosis of CIDP with confidence in the majority of cases. Several electrodiagnostic criteria have been proposed, all requiring some combination of:

(1) reduced conduction velocities (CVs; e.g. <80% of the lower limit of normal [LLN] if the distal motor amplitude is normal, and <70% of LLN if the amplitude is substantially reduced);
(2) prolonged distal motor latencies (DMLs);
(3) prolonged F-wave latencies (FLs; e.g. >125% of the upper limit of normal [ULN] if the distal motor amplitude is normal, and >150% of ULN if the amplitude is reduced for distal latencies and F-waves); and
(4) conduction block/temporal dispersion (CB/TD; e.g. conduction block is >50% reduction of proximal/distal [p/d] amplitude and abnormal temporal dispersion is >130% increase of p/d duration);

Table 2. American Academy of Neurology Ad Hoc Subcommittee Electrodiagnostic Criteria for chronic inflammatory demyelinating polyneuropathy [Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. (1991).].

Three of four criteria must be fulfilled
1. Reduction in conduction velocity (MNCV) in two or motor nerves:
a. <80% of lower limit of normal (LLN) if amplitude >80% of LLN
b. <70% of LLN if amplitude is <80% of LLN
2. Partial conduction block (CB) in one or more motor nerves defined as <15% change in duration between proximal and distal sites and >20% drop in negative peak (−p) are or peak-to-peak (p–p) area or peak-to-peak (p–p) amplitude between proximal and distal sites.
3. Prolonged distal latencies (DML) in two or more nerves:
a. >125% of upper limit or normal (ULN) if amplitude is >80% of LLN
b. >150% of ULN if amplitude is <80% of LLN
4. Absent F-waves or prolonged minimum F-wave latencies in two or more motor nerves:
a. >120% of ULN if amplitude >80% of LLN
b. >150% of ULN if amplitude <80% of LLN

these criteria were initially established by expert consensus for research purposes through the American Academy of Neurology (AAN) [Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. (1991).] (Table 2).

According to these AAN criteria, the presence of three of the four criteria, in two or more nerves, establishes the electrophysiological diagnosis of CIDP for research purposes. For the practicing clinician, these various schemes are contrived since only 50–60% of patients with typical clinical features of CIDP fulfill these strict electrodiagnostic criteria. Accordingly, over the last 20 years at least 15 alternative EMG criteria have been proposed with varying degrees of sensitivity and specificity [Bromberg, 2011], thus contributing to further controversy and confusion. Unfortunately, many of these criteria were established by way of circular reasoning or self-referential analysis (for example, investigators used certain EMG criteria to select CIDP cases to study, and then 'validated' the very same EMG criteria). Both the Koski and colleagues and EFNS diagnostic criteria (Tables 3 and 4) have high sensitivity (>80%) and specificity (>95%), and thus either can be recommended for use in clinical practice and for research purposes [Koski et al. 2009; Joint Task Force of the EFNS and PNS, 2010].

Electrodiagnostic studies have several important shortcomings in establishing the diagnosis of CIDP: (1) patients may accrue substantial axonal loss with absent or greatly reduced motor potentials, and therefore nerve conduction abnormalities may not fulfill criteria for demyelination; (2) those with a pure sensory variant may have absent sensory nerve action potential (SNAPs) and relatively normal motor potentials; (3) a few patients have electrodiagnostic abnormalities limited to proximal motor nerve segments that are detected only with motor root or Erb's point stimulation [Menkes et al. 1998]; and (4) in clinical practice, there is a large group of patients, without axon loss, who do not fulfill any of the proposed EMG criteria and yet may still benefit from treatment [Magda et al. 2003]. In these patients, spinal fluid analysis and nerve biopsy may be especially helpful to confirm the diagnosis, and a therapeutic trial may be warranted in patients who do not fulfill strict electrodiagnostic criteria [Magda et al. 2003].

Treatment

The primary goals of treatment for CIDP are to reduce symptoms (weakness, sensory loss, imbalance, and pain), improve functional status (reduce disability and handicap), and if possible, maintain long-term remission. Conventional therapy for CIDP has included corticosteroids, PE, and IVIg (Table 5). Improvement can be expected in 50–80% of patients with one of the standard treatments (steroids, IVIg, PE) [Gorson et al. 1997; Köller et al. 2005; Dalakas, 2011]. Each of these treatments has been demonstrated to be superior to placebo in randomized, double-blind, placebo-controlled studies, and accordingly, insurance reimbursement in the United States should no

Table 3. Koski and colleagues criteria for the classification of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) [Koski et al. 2009].

Patients with a chronic polyneuropathy, progressive for at least 8 weeks, would be classified as having CIDP if:
• No serum paraprotein and
• No documented genetic abnormality
AND EITHER
a) At least 75% of motor nerves tested had recordable response AND one of the following conditions is satisfied:
i) more than 50% of the motor nerves tested had abnormal distal latency[1], or
ii) more than 50% of the motor nerves tested had abnormal conduction velocity[1], or
iii) more than 50% of the motor nerves tested had abnormal F-latency.[1]
OR
b) i) Symmetric onset or symmetric exam, and
ii) Weakness in all four limbs, and
iii) At least one limb with proximal weakness
[1]According to American Academy of Neurology criteria

Table 4. European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) Guideline Electrodiagnostic Criteria [Joint Task Force of the EFNS and PNS, 2010].

I. Definite: at least one of the following :

   A. At least 50% prolongation of motor distal latency above the upper limit of normal values in two nerves, or

   B. At least 30% reduction of motor conduction velocity below the lower limit of normal values in two nerves, or

   C. At least 20% prolongation of F-wave latency above the upper limit of normal values in two nerves (>50% if amplitude of distal negative peak compound muscle action potential [CMAP] ←80% of lower limit of normal values), or

   D. Absence of F-waves in two nerves if these nerves have amplitudes of distal negative peak CMAPs at least 20% of lower limit of normal values + at least one other demyelinating parameter in at least one other nerve, or

   E. Partial motor conduction block: at least 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter in at least one other nerve, or

   F. Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in at least two nerves, or

   G. Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) of at least 9 ms in at least one nerve + at least one other demyelinating parameter in at least one other nerve

II. Probable

   At least 30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP at least 20% of lower

     limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter in at least one other nerve

III. Possible

   As in 'I' but in only one nerve

longer be a problem. Furthermore, randomized, prospective clinical trials have shown that PE and IVIg, and IVIg and prednisolone, have similar short-term efficacy [Dyck *et al.* 1994; Hughes *et al.* 2002]. The practical issues associated with these agents are the lack of a durable response in many patients and the difficulties of using these therapies, ideally suited for short-term administration, for long-term management of a chronic disease. IVIg is expensive, time-consuming, and may have limited availability in some circumstances, PE can be invasive for those who require central venous catheters, and the therapy requires well-trained personnel at specialized centers. Corticosteroids have a large number of potentially serious side effects and often are tolerated poorly when used as a long-term therapy.

Prednisone
Prednisone was first established as an effective therapy and superior to placebo in a 3-month, randomized, placebo-controlled trial of alternate-day, high-dose prednisone (120 mg) in 28 patients

[Dyck *et al.* 1982]. The effect was similar between patients with a progressive and relapsing course. The average time to induce a response with prednisone (60 mg/day) has been reported to be approximately 2 months with maximal improvement not observed until after 6 months [Barohn *et al.* 1989]. One study showed improvement in disability scores within 2 weeks of starting 60 mg of daily prednisolone [Hughes *et al.* 2002]. A minority of patients remained in remission after tapering steroids, but most (up to 70%) have relapsed after discontinuing treatment and have required repeated courses of prednisone or alternative immunotherapy [Wertman *et al.* 1988]. In some patients the addition of azathioprine, or other so-called 'steroid-sparing' agents, may sustain a remission and reduce or eliminate the requirement for high-dose prednisone [Barohn *et al.* 1989; Dalakas, 2011], but this benefit has not been confirmed in a randomized, controlled trial [Dyck *et al.* 1985]. However, it should be noted that this study was limited in trial design due to the short duration of exposure to azathioprine, as the benefits of the drug typically require

Table 5. Therapy for chronic inflammatory demyelinating polyneuropathy.

Proven therapies from randomized controlled trials: Level I evidence [Ashman and Gronseth, 2012]
IVIg
Prednisone
Plasma exchange
Pulse oral dexamethasone

Therapies ineffective based upon randomized controlled trials: Level I evidence; These studies all had difficulties in trial design:
Azathioprine
Interferon B1a (Level II evidence)
Methotrexate

Therapies of unproven benefit but probably helpful as steroid sparing agents, based upon clinical experience, and > 1 case series: Level IV evidence

Cyclosporine A
Cyclophosphamide
Azathioprine

Other therapies of unproven benefit: Level IV evidence

Mycophenolate mofetil
Pulse weekly oral prednisolone
Pulse weekly oral dexamethasone
Pulse weekly intravenous methylprednisolone
Rituximab
Interferon alpha 2a
Etanercept
Tacrolimus
Alemtuzumab
Natalizumab
Hematopoietic stem cell transplantation

up to 12–18 months of therapy (see below). Young age at onset, duration of symptoms less than 6 months, slight neurologic impairment, and mild slowing of nerve conduction velocities have been associated with a favorable response to corticosteroids [Wertman *et al.* 1988]. Rapid tapering of prednisone also may increase the risk of relapse.

Owing to concern regarding long-term daily prednisone exposure, several alternative corticosteroid treatment regimens have been proposed. In a double-blind, placebo-controlled, randomized trial, high-dose oral dexamethasone (40 mg) was administered daily for 4 days sequentially, every month for 6 months, and was shown to be as effective as 60 mg of daily oral prednisone for 4 weeks followed by a tapering schedule over 6 months (approximately 40% response rate for both drugs) [van Schaik *et al.* 2010]. Adverse effects were similar between the groups, but one wonders whether side effects may have increased in the prednisone group with longer exposure [Gorson, 2010].

A retrospective study has suggested that intravenous, high-dose (1 g) methylprednisolone, administered daily for 3–5 days followed by a weekly regimen for 4–8 weeks, and then monthly as dictated by clinical course, was effective in 13 of 16 patients at 6-month follow up [Lopate *et al.* 2005]. If confirmed in larger, randomized, controlled trials, this approach may provide an effective alternative to daily oral prednisone with fewer adverse effects. In another retrospective study, 10 patients improved when treated in an open-label fashion with 500 mg of oral methylprednisolone weekly for 3 months, followed by a tapering dose that was dependent upon the patient's clinical status. There was a sustained remission in six patients off therapy at last follow up [Muley *et al.* 2008].

Most patients observe improvement in strength and sensory symptoms after several weeks of steroid treatment. Maximal improvement occurs after 3–6 months of therapy, and only a minority of patients experience further recovery after 6 months [Wertman *et al.* 1988; Barohn *et al.* 1989]. The standard dosage of prednisone is 1.0–1.5 mg/kg/day, administered as a single morning dosage. Those who experience substantial clinical improvement with daily prednisone may reduce the dosage by switching to an alternate day regimen after 2 or 3 months and tapering by 5–10 mg on the alternate day, every 2–4 weeks, as gauged by the patient's clinical state. If the patient deteriorates, the dosage should be increased to the minimum dose that induces sustained improvement. Anecdotal experience suggests that adding an alternative treatment (PE, IVIg, azathioprine, cyclophosphamide, or cyclosporine A) should be considered in patients who develop adverse effects, relapse repeatedly following reduction of the prednisone dosage, or require more than 35 mg of prednisone every other day.

Prednisone is best suited for younger patients with CIDP who have few other medical illnesses. Long-term prednisone therapy is generally poorly tolerated in the elderly and those who have concurrent medical conditions (e.g. hypertension, diabetes mellitus, obesity, peptic ulcer disease, and osteoporosis). Weight, blood pressure, blood glucose, electrolytes, ophthalmological evaluation, and stool guaiac require regular monitoring. In addition, periodic bone density measurements and a regimen to prevent steroid-induced osteoporosis should be instituted. This may include calcium and vitamin D, and biphosphonates. Contraindications to prednisone therapy include active peptic ulcer disease, poorly controlled diabetes mellitus or hypertension, severe osteoporosis, and systemic fungal infections. The major limitation of prednisone therapy is the large number of potentially serious adverse effects that develop after chronic (usually > 2 months) exposure. Some of the potential complications include: fluid retention, weight gain, insomnia, mood lability, psychosis, hyperglycemia, gastritis, osteoporosis, aseptic necrosis of the femoral or humeral heads, vertebral fractures, steroid myopathy, impaired wound healing, increased susceptibility to infections (herpes zoster, cutaneous fungal infection, reactivation of tuberculosis, recurrent pneumonia), cataracts, glaucoma, hirsutism, cushingoid state, and pseudotumor cerebri.

Plasma exchange

Two short-term randomized, placebo-controlled trials have demonstrated that PE is superior to placebo, with response rates ranging between 33% and 80% [Dyck *et al.* 1986; Hahn *et al.* 1996a]. The beneficial effects of plasma exchange in CIDP also have been supported by a Cochrane review [Mehndiratta *et al.* 2004]. Improvement was observed in the mean Neurologic Disability Score, grip strength, clinical disability grade, and summated mean motor potential amplitudes and conduction velocities that increased after treatment. Patients improved within 4 weeks after initiating therapy, and those with a chronic progressive course responded as well as patients with relapsing disease. Although the short-term efficacy of PE has been convincingly demonstrated, 50–67% of patients have deteriorated weeks to months after treatment and have required repeated exchanges or an alternative therapy to maintain improvement [Choudhary and Hughes, 1995]. Long-term outpatient plasma exchange can be used successfully in selected patients if peripheral access can be maintained or after placement of an arteriovenous fistula. Alternatively, combining prednisone or other immunosuppressive agents with PE may induce a prolonged remission [Hahn *et al.* 1996a]. Those with a short duration of disease and EMG or pathological features of a primary demyelinating neuropathy (without axonal loss) are more likely to respond to PE [Pollard *et al.* 1983; Hahn *et al.* 1996a]. Dyck and coworkers have established that the short-term (6 weeks) efficacy of plasma exchange is similar to IVIg [Dyck *et al.* 1994]. The beneficial effect of PE presumably results from the removal of pathogenic humoral factors, such as circulating immunoglobulins, auto-antibodies, pro-inflammatory cytokines or complement. A single exchange removes 3–5 liters of plasma and reduces intravascular IgG by approximately 45%, such that three to five exchanges are required to remove approximately 90% of circulating IgG. The exchanged plasma is replaced with 5% albumin and saline, sometimes supplemented with calcium, and with acid-citrate dextrose or heparin.

Although no specific guidelines have been established for the frequency or schedule of treatment, the frequency of PE can be guided by the duration of a clinical response. For example, those with severe disability (e.g. nonambulatory) generally are treated with five exchanges (each exchange 250 ml/kg) performed over a period of 7–10 days. Improvement usually occurs within

several weeks followed by a stable phase of weeks to months; exchanges may be repeated periodically in a similar fashion as necessary to maintain improvement. The addition of prednisone or other immunosuppressive agents (azathioprine or cyclosporine A) may sustain longer periods of remission and reduce the frequency of exchanges. Those who have mild or moderate disability and remain ambulatory may benefit from two or three exchanges/week over a period of 2–3 weeks, followed by once or twice weekly exchanges for an additional 3 weeks. PE may be used safely as a long-term therapy (years) in patients with a chronic relapsing course who do not respond or develop adverse effects with other treatment modalities [Choudhary and Hughes, 1995]. PE may be an especially appealing therapy for patients who have contraindications to other treatments, such as prednisone for patients with diabetes mellitus and IVIg for those with pre-existing renal insufficiency.

Patients with poor peripheral venous access may require placement of a central venous catheter with the associated risk of pneumothorax, catheter site infection, and venous thrombosis. The placement of a permanent central venous catheter facilitates frequent exchanges in those patients who have poor peripheral venous access. Intravenous saline (0.5–1.0 liter) administered several hours before an exchange reduces the risk of hypotension and vasovagal symptoms. PE is generally well tolerated and safe, but it is invasive and time consuming and requires special equipment and well-trained personnel in medical facilities familiar with the procedure. There are relatively few contraindications to PE, and include coagulopathy, thrombocytopenia, and hypotension. Complications of PE are: hypotension, cardiac arrhythmia, vasovagal reaction, citrate toxicity with nausea and vomiting, electrolyte imbalance (citrate-induced hypocalcemia), allergic reactions to infused plasma or plasma substitutes, anemia, thrombocytopenia, muscle cramps, paresthesias, and infection, bleeding, venous thrombosis and pneumothorax as a complication of central catheters for venous access.

Intravenous IVIg

IVIg has been introduced as the main therapy for CIDP over the last two decades. Multiple well-controlled studies have demonstrated that approximately 50–70% of patients respond to IVIg [Hahn *et al.* 1996b; Mendell *et al.* 2001; Hughes *et al.* 2008]. Improvement occurs within a few weeks, and rarely recovery may be dramatic, appearing 1 or 2 days after completing the infusion. Usually the benefit is transient (1–6 weeks) with 50% of patients relapsing within weeks to months and subsequently requiring regular infusions to maintain maximum improvement. Patients with a progressive course or predominantly sensory deficits with tremor may be less likely to improve. Mendell and coworkers showed that 11 of 29 treatment-naïve patients with CIDP improved by one or more disability grades after receiving IVIg, 1.0 g/kg/day at baseline and after 3 weeks, compared with two of 21 patients who received placebo; 76% of IVIg-treated patients had improved strength [Mendell *et al.* 2001]. Improvement was noted as early as 10 days after therapy.

The recently published IVIg in CIDP Efficacy (ICE) trial was the largest and longest randomized, double-blind placebo-controlled trial demonstrating sustained efficacy of IVIg in CIDP utilizing a loading dose of 2 g/kg administered over 2–5 days, followed by repeated infusions of 1 g/kg administered every 3 weeks for 6 months [Hughes *et al.* 2008]. There were 117 CIDP patients enrolled in the trial who were randomized to IVIg or placebo and treated for 6 months, followed by re-randomization to an open phase of treatment for an additional 6 months follow up. This study showed 54% of treated patients responded with substantial improvement in measures of strength, functional disability, and quality of life compared with placebo-treated patients. Importantly, approximately half of those randomized to placebo in the open phase after having received IVIg in the blinded phase maintained their clinical response (i.e. approximately 50% of patients maintained their improvement off IVIg for 6 months), suggesting that some IVIg responders may be over treated with continued long-term therapy. IVIg responders were defined as having a two or more point improvement in the INCAT disability score, and the majority of such patients could be identified after 2 cycles of treatment [Latov *et al.* 2010]. Therefore, it seems reasonable to offer patients with CIDP three cycles of IVIg every 3 weeks, and if there is no meaningful clinical response, consider an alternative first line treatment (corticosteroids or plasma exchange). With the data from the ICE trial and other positive IVIg treatment trials, there is Level I evidence for the efficacy of IVIg in CIDP. Because it has a low frequency of adverse effects and is easy to

administer, most experts believe IVIg has been established as the standard of care and should be the initial treatment of choice for patients with CIDP [Joint Task Force of the EFNS and PNS, 2010]. IVIg (Gamunex) has an FDA indication for this condition.

As with PE, anecdotal reports suggest that combining IVIg with prednisone or other immunosuppressive medications may further augment the duration of remission and reduce the frequency of IVIg infusions [Hahn *et al.* 1996b]. Most treatment trials in CIDP now incorporate IVIg therapy as standard of care treatment in the trial design when assessing the efficacy of other agents [RMC Trial Group 2009; Hughes *et al.* 2010].

The standard IVIg dosage is a loading dose of 2.0 gm/kg administered intravenously over 2–5 days, followed by 1 g/kg over 1 day every 3 weeks. Those who initially respond and then relapse after discontinuation of treatment likely will require long-term IVIg therapy. In practice, the addition of an oral immunosuppressant can be offered in an attempt to decrease the frequency of IVIg administration. Once the patient has stabilized, most tolerate IVIg dosage reduction or an increase of the treatment interval and still maintain clinical stability. Not surprisingly, the presence of axon loss (demonstrated clinically by prominent muscle atrophy or electrophysiologically by low or absent motor amplitudes) is the major prognostic factor for lack of response to IVIg therapy [Iijima *et al.* 2005].

A single infusion of IVIg is derived from plasma from approximately 5000 human blood donors. The mechanism of the beneficial effects of IVIg is not precisely known but is thought to be related to modulation of pathogenic autoantibodies [Dalakas, 2011]. Other considerations include suppression of pathogenic cytokines, Fc receptor blockade, reduced complement deposition, increased levels of macrophage stimulating factor and monocyte chemoattractant protein-1, and alteration in pathogenic T-cell function [Creange *et al.* 2003; Köller *et al.* 2005; Dalakas, 2011].

IVIg may be administered by rapid infusion (1.0 g/kg/day over 4–6 hours, for 2 days) in younger patients and is generally well tolerated [Grillo *et al.* 2001]. The drug should be given at a slower rate to the elderly or those with vascular disease, cardiac or renal insufficiency. Headache, fluid overload and flu-like symptoms are more likely to occur at higher infusion rates. Pretreatment with 60 mg of intravenous methylprednisolone may reduce the severity of headaches in headache-prone patients. The first treatment should be monitored in a supervised setting (hospital, office, or outpatient clinic), and if well tolerated, subsequent infusions may be provided safely in the home. An IgA level and renal function studies should be checked before the first IVIg administration. Elderly patients with borderline renal function are at especially high risk for renal failure.

There does not appear to be a significant difference regarding the efficacy of various brands of IVIg [Kuitwaard *et al.* 2010], however, in practice side effects may be more problematic with a particular brand of immunoglobulin in some patients; if a patient develops intolerable side effects from a specific formulation of IVIg (e.g. severe headache, rash, serum sickness reaction), it is advisable to change to an alternative brand and observe if efficacy can be maintained without adverse effects. For those patients who develop intolerable side effects to several brands of IVIg (usually headache), immunoglobulin may be administered subcutaneously (SCIg). Data are limited to open-label case reports but suggest this is a viable option to administer the drug with similar efficacy to IVIg and allowing greater patient autonomy with self-administered home infusion therapy [Cocito *et al.* 2011b]. A randomized, placebo-controlled trial to assess the efficacy of SCIg has been initiated in patients with CIDP who are dependent upon IVIg.

IVIg is contraindicated in patients with absolute IgA deficiency or a history of a previous allergic reaction following exposure to human immune globulin. Minor side effects are common and include headache, malaise, fatigue, and fever. Other adverse effects include: aseptic meningitis, rigors, myalgias, flushing, fluid overload with edema or congestive heart failure, renal insufficiency (presumably due to hyperosmolarity), hemolysis, transient neutropenia, back, chest, leg or abdominal pain, and eczematous rash. Rarely, IVIg induces a hyperviscosity syndrome with increased risk for deep venous thrombosis, myocardial ischemia, or stroke. Anaphylactic reactions may occur in IgA-deficient patients due to anti-IgA antibodies. Revised manufacturing processes have largely eliminated the risk of viral transmission.

Alternative immunosuppressive regimens

The indications for considering alternative immunosuppressive agents for patients with CIDP are: (1) the patient has not improved with sequential or combined trials of the above outlined conventional therapies that have demonstrated efficacy in randomized, controlled trials; (2) the patient has improved with these treatments but has frequent relapses, usually with attempts at weaning the medication, making continued therapy cumbersome, time-consuming, and costly; or (3) the patient has developed intolerable adverse effects with the proven therapies. The usual approach to using these medications would be in a situation where the patient has failed to remain in remission after discontinuing the proven therapies, and the goal is to stabilize the patient with an 'add-on' immunosuppressant, maximizing the appropriate dosage and duration of therapy before another attempt at weaning the first-line therapy; this has been classically used as a 'steroid-sparing' strategy but also can be used with attempts to wean IVIg or plasma exchange. It is critical to use these alternative drugs for long enough (for example, azathioprine for at least 12–18 months) before concluding the second-line drug has been ineffective and moving on to alternative second-line medication trials. Most of the agents reviewed below have been reported to be effective in some patients with CIDP in single case reports, open-label case series, and retrospective reviews, but few have been submitted to rigorous clinical trials that establish efficacy. In other cases, some of these agents (e.g. azathioprine, methotrexate, interferon B1a) have been carefully studied in larger controlled trials and were proven ineffective. There are several explanations why these drug trials were negative, including lack of appropriate duration of treatment (e.g. for azathioprine, the endpoint of the trial was only 9 months); complex trial design (e.g. in the methotrexate trial, patients were on varying tapering doses of IVIg or prednisone); lack of adequate power due to small sample size (azathioprine, interferon B1a trials) to detect a significant response; and a surprisingly high placebo response in patients assigned to the placebo arm of several studies (up to 44% in the methotrexate and interferon B1a trials), suggesting many patients randomized to placebo may have had inactive disease and therefore did not relapse as anticipated when IVIg was discontinued. The last, and perhaps most important conclusion, is that these agents simply may not be effective treatments for CIDP. Accordingly, it is prudent to advise the patient that these agents are not likely to be more effective than proven treatments and to maintain realistic expectations about recovery; this is particularly relevant for patients with a prolonged disease course and concomitant severe axon loss in whom the neurological deficit may be irreversible. In those individuals, a reasonable expectation would be to stabilize the condition and halt further progression.

Azathioprine

Although anecdotal reports have indicated that azathioprine is an effective therapy for CIDP [McCombe *et al.* 1987; Barohn *et al.* 1989], one randomized study of only 9 months duration showed that the degree of improvement with azathioprine combined with prednisone was similar to prednisone alone [Dyck *et al.* 1985]. However, the immunosuppressive effects of this agent may not occur for over 1 year, as previously noted, and therefore the duration of this trial was too short to exclude benefit. Others have found that azathioprine is helpful in some patients not only for stabilizing the disease course but, more importantly, for allowing reduction of prednisone dosage. Therefore, azathioprine is used ideally as adjunctive therapy for CIDP as a steroid-sparing agent. The usual dosage is 2.0–3.0 mg/kg/day administered orally as a single daily dose. A test dose of 50 mg/day may be given for the first week. If this is tolerated, the dose is gradually increased by 50 mg every few days. A compete blood count and liver enzymes should be monitored monthly for 6 months, and then every 3 months thereafter. An acute hypersensitivity reaction may occur in the first several days to weeks of therapy characterized by severe nausea and vomiting, diarrhea, fever, malaise and myalgias, rash, elevation in liver enzymes, and pancreatitis; these adverse effects are reversible upon discontinuation of the drug.

Cyclosporine A

Patients with treatment refractory CIDP may improve with cyclosporine A. Although published experience with cyclosporine A is restricted to several small case series, response rates ranged from 40–90%. Patients improved within 2–3 months of initiating treatment, and several discontinued prednisone without clinical deterioration [Barnett *et al.* 1998; Odaka *et al.* 2005]. The starting dosage is 5.0 mg/kg/day orally, in two divided dosages 12 hours apart; dose adjustments are made by following target

blood levels. Once the patient has stabilized, the dosage should be titrated to the lowest dose required to maintain improvement. Cyclosporine A is contraindicated in patients with systemic infection, history of previous hypersensitivity reaction, abnormal renal function, uncontrolled hypertension, and malignancy. Blood pressure, renal and liver function (including creatinine clearance), serum lipids, magnesium and potassium require regular monitoring. Checking trough serum cyclosporine levels may minimize toxicity. A trough level should be maintained between 100 and 400 ng/ml. The main side effects of cyclosporine A are renal insufficiency, hypertension, hirsutism, tremor, gingival hyperplasia, increased risk of opportunistic infection, sepsis, nausea, vomiting, hepatotoxicity, seizures (possibly related to hypomagnesemia), headache, and cramps.

Cyclophosphamide

Oral cyclophosphamide also has been reported to be beneficial when administered for several months as monotherapy or in combination with prednisone [Good *et al*. 1998] Uncontrolled case series suggest monthly, pulse intravenous cyclophosphamide is effective when combined with prednisone or administered after cycles of PE [Fowler *et al*. 1979; Good *et al*. 1998; Dalakas, 2011]. Good and coworkers reported that 12 of 15 CIDP patients who were refractory to plasma exchange, IVIg or steroids improved with monthly intravenous pulse cyclophosphamide (1 g/m²); the average time to sustained improvement was 8.5 months [Good *et al*. 1998]. Complications included nausea, headache, rash, and anticipated leukopenia. No patient developed severe bone marrow suppression or malignancy with an average follow up of 3 years. Other reports have highlighted a treatment response following high-dose cyclophosphamide (200 mg/kg daily for 4 days) as myelo-ablative chemotherapy with or without autologous stem cell rescue [Brannagan *et al*. 2002]. The toxicity of these latter approaches requires that they be offered only within experimental study protocols.

Cyclophosphamide generally is reserved for patients with CIDP who fail conventional immunotherapy and is most often administered in conjunction with prednisone, IVIg or PE. The drug may be given orally as a single daily dose or as pulse intravenous therapy on a monthly basis. The response rate has been reported to be as high as 80%, however experience is restricted to retrospective case series. Leukopenia is a common adverse effect and a complete blood count with differential count, platelet count, and urinalysis should be checked 2 weeks after intravenous administration and every 2–4 weeks in patients taking oral cyclophosphamide. With intravenous therapy, the dosage should be adjusted by 25% increments to produce a transient reduction of the white blood cell count to 2.0–3.0 K/μl. Significant nausea can be avoided by administering ondansetron hydrochloride (8 mg p.o., b.i.d.) or other anti-emetics, and at least 3 liters of intravenous fluid should be given to reduce the risk or hemorrhagic cystitis. The standard oral dosage is 2.0 mg/kg/day; when administered intravenously, the typical dose is 1.0 g/m² administered monthly for 6–12 months. The main side effects are dose-dependent bone marrow suppression, reduced resistance to infection, hemorrhagic cystitis, infertility, teratogenic effects, amenorrhea, nausea, vomiting, anorexia, alopecia, and malaise. Clinicians should be aware of the increased risk of malignancies, especially lymphoma and leukemia, in patients exposed to long-term or high-dose cyclophosphamide therapy. A history of previous bone marrow suppression or myelodysplastic syndrome is a contraindication to treatment with cyclophosphamide.

Interferons

Interferons have complex immunomodulating effects and may influence the levels of pro-inflammatory cytokines, especially tumor necrosis factor (TNF) alpha, interleukin-2, and interferon gamma, which have been demonstrated to have a role in the development of inflammatory demyelination. Several case reports and one prospective, pilot study indicated that interferon alpha 2a was effective in patients with CIDP who were refractory to conventional immunomodulating agents [Gorson *et al*. 1998]. No randomized, controlled trials with this agent have been conducted. Similarly, initial reports indicated that interferon beta-1a was effective in several patients with CIDP who did not improve after trials of prednisone, plasma exchange, cyclosporine A, IVIg, and azathioprine [Choudhary *et al*. 1995]. A prospective, multicenter, open-label trial of interferon B1a (30 μg IM weekly) for 6 months in 20 patients with CIDP showed significant improvement in the neurological disability score and clinical grading scale compared with baseline measures [Vallat *et al*. 2003]. However, a prospective, randomized,

double-blind, placebo-controlled trial of interferon B1a (30 or 60 μg twice weekly for 4 months) in 67 IVIg-dependent CIDP patients did not show clinical improvement or reduced IVIg dosing in treated patients compared with placebo. *Post hoc* analysis indicated that a subset of more severely affected patients who required higher doses of IVIg at baseline did improve. Furthermore, the conclusions regarding lack of efficacy of interferon B1a cannot be considered definitive as the study was underpowered due to poor patient recruitment, and there was a surprisingly high rate (40%) of placebo responders [Hughes *et al.* 2010]. The usual dosage of interferon alpha 2a is 3 million IU, subcutaneously 3 times/week, and for interferon-beta 1a, 30 μg intramuscularly once per week. Common side effects include influenza-like symptoms (fever, chills, sweating, and myalgias), headache, fatigue, dizziness, nausea and vomiting, diarrhea, anorexia, abdominal pain, depression, irritability, and injection site reaction.

Mycophenolate mofetil

Mycophenolate mofetil (MM) is an immunosuppressant that has been used successfully for treatment of acute rejection after renal transplantation, and holds promise for the treatment of immune-mediated neuromuscular diseases [Sievers *et al.* 1997]. MM is an inhibitor of the *de novo* pathway of purine nucleotide synthesis, thereby blocking the proliferation of B- and T-cell lymphocytes [Sievers *et al.* 1997]. MM produces immunosuppression that is comparable to azathioprine without causing major bone marrow suppression. Several groups have reported improved strength and successful corticosteroid dosage reduction following therapy with MM [Gorson *et al.* 2004; Bedi *et al.* 2010]. The onset of improvement occurred within 3–4 months. Larger, randomized, controlled trials may further clarify the role of this agent in CIDP. The drug is appealing because it is easy to use, well tolerated, and has few long-term adverse effects.

MM has been administered in combination with cyclosporine A and prednisone. The efficacy and safety of MM in combination with other immunosuppressants has not been determined. This agent should not be used in pregnant women because of its teratogenic effect in animals. The standard dosage is 1.0 g administered twice per day, similar to the dosage that is recommended for renal transplant patients. Patients should be monitored for neutropenia with complete blood counts monthly for 6 months, then every 3 months thereafter. There are no contraindications to the use of MM. Potential side effects include nausea, headache, tremor, susceptibility to infection, leukopenia, and possibly an increased risk of developing lymphoma and other malignancies.

Methotrexate

Methotrexate has been a safe and effective agent for patients with inflammatory myopathies and other connective tissue disorders and has been used as a steroid-sparing drug for decades. Open label series have suggested a beneficial role in CIDP [Díaz-Manera *et al.* 2009]. However, a randomized, double-blind, placebo-controlled trial of escalating doses of methotrexate in steroid- or IVIg-treated CIDP patients showed no benefit over placebo [RMC Trial Group 2009]. However, the trial design was complicated, the placebo response was 44%, and the maximum dose of methotrexate (15 mg/week) was low. Therefore, the role of this agent as a steroid- or IVIg-sparing agent in patients with CIDP still remains uncertain.

Etanercept

Etanercept is a TNF alpha inhibitor approved for use in patients with rheumatoid arthritis. There is one report of three of 10 patients with CIDP who improved after 4–6 months of therapy [Chin *et al.* 2003]. The treatment was administered as a subcutaneous injection of 25 mg twice per week and was well tolerated. The authors suggested this novel therapy for CIDP warrants further study in a randomized, controlled trial. Conversely, several patients have been reported to develop a condition indistinguishable from CIDP after treatment with similar TNF inhibitors [Alshekhlee *et al.* 2010], and thus the role of this class of drugs in the treatment of CIDP remains unclear.

Rituximab

Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen on B-lymphocytes. Depletion of B-lymphocytes may interfere with antibody-dependent, cell-mediated cytotoxicity involving peripheral nerve [Perosa *et al.* 2005]. Investigators reported that six of 13 treatment-refractory patients with CIDP responded to ritxuximab in an open-label, unblinded fashion [Benedetti *et al.* 2011]. Another retrospective

open-label review from a nationwide CIDP patient registry suggested rituximab was beneficial in some patients [Cocito *et al.* 2011a]. The drug has also been reported to be effective in single cases of patients with CIDP and coexistent autoimmune diseases such as myasthenia gravis with Morvan syndrome [Sadnicka *et al.* 2011], CIDP with diabetes [Münch *et al.* 2007], Evans syndrome [Knecht *et al.* 2004], and idiopathic thrombocytopenic purpura [Benedetti *et al.* 2008]. Other investigators found rituximab was not helpful in weaning patients from IVIg in an open-label pilot study [Gorson *et al.* 2007]. The drug is generally well tolerated but currently is considered experimental pending confirmatory trials.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen, an epitope located on the surface membrane of all lymphocytes and monocytes. The drug causes significant, rapid and prolonged depletion of CD4 and CD8 T-cells and B-cells after a single infusion and has been shown to be effective in multiple sclerosis [Minagar *et al.* 2010]. There is one case series of seven treatment refractory, IVIg-dependent, CIDP patients treated with one or two infusions of alemtuzumab; two had a prolonged remission and two had a partial response allowing for reduction of IVIg dose and frequency of infusions [Marsh *et al.* 2010]. Three developed complications from acquired autoimmune diseases, one of whom died. Another prospective open-label pilot study is planned, but the use of the drug is limited by a higher risk of side effects, specifically autoimmune thyroiditis and idiopathic thrombocytopenic purpura. The drug should be considered an experimental therapy for CIDP.

Other immunosuppressant approaches

There was one report of efficacy of total lymphoid irradiation (TLI) in treatment refractory CIDP dating back over 25 years [Rosenberg *et al.* 1985]. This study has never been replicated and because of the potential toxicity and availability of safer and effective therapies, TLI has been discarded as a therapy by most experts in the field. There has been one case report of efficacy with tacrolimus [Ahlmen *et al.* 1998], and one case of clinical worsening after treatment with natalizumab [Wolf *et al.* 2010].

Hematopoietic stem cell transplantation, with or without pretreatment with cyclophosphamide, has been reported to induce sustained remission or even 'cure' in patients with treatment refractory CIDP [Axelson *et al.* 2008; Mahdi-Rogers *et al.* 2009]. This very aggressive intervention has been associated with significant complications related to immunosuppression, such as pneumonia and sepsis [Mahdi-Rogers *et al.* 2009]. Owing to the associated risks, this treatment only should be considered in patients who have severe disabling CIDP refractory to sequential trials of multiple less-toxic therapies listed above, performed at medical centers skilled in the procedure and management of potential complications, and ideally under the auspices of an institution approved study protocol.

Supportive therapies

Patients certainly may benefit from walking sticks, walkers, ankle–foot orthotics and other rehabilitation devices and strategies to assist ambulation and other activities of daily living. Physical and occupational therapy may be helpful to maintain range of motion, prevent joint contractures in paretic limbs, and assist in gait retraining. A moderate exercise regimen may help reduce physical fatigue and increase endurance. Psychological counseling can be helpful to manage symptoms of depression, anxiety, anger, and frustration associated with chronic disability. Symptomatic medications are available to offer relief of neuropathic and mechanical pain, fatigue, and alleviate depression and anxiety, but none have been studied in a rigorous fashion in patients with CIDP.

Funding

Conflict of interest statement

The author has received financial compensation for speaking engagements from Grifols Pharmaceuticals.

References

Ahlmen, J., Andersen, G., Hallgren, G. and Peilot, B. (1998) Positive effects of tacrolimus in a case of CIDP. *Transplant Proc* 30: 4194.

Alshekhlee, A., Basiri, K., Miles, J., Ahmad, S. and Katirji, B. (2010) Chronic inflammatory demyelinating polyneuropathy associated with tumor necrosis factor alpha antagonists. *Muscle Nerve* 41: 723–727.

Ashman, E. and Gronseth, G. (2012) Level of evidence reviews. Three years of progress. *Neurology* 79: 13–14.

Axelson, H., Oberg, G. and Askmark, H. (2008) Successful repeated treatment with high dose cyclophosphamide and autologous blood stem cell transplantation in CIDP. *J Neurol Neurosurg Psychiatry* 79: 612–614.

Barnett, M., Pollard, J., Davies, L. and McLeod, J. (1998) Cyclosporine A in resistant chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve* 21: 454–460.

Barohn, R., Kissel, J., Warmolts, J. and Mendell, J. (1989) Chronic inflammatory demyelinating polyneuropathy. Clinical characteristics, course, and recommendations for diagnostic criteria. *Arch Neurol* 46: 878–884.

Bedi, G., Brown, A., Tong, T. and Sharma, K. (2010) Chronic inflammatory demyelinating polyneuropathy responsive to mycophenolate mofetil. *J Neurol Neurosurg Psychiatry* 81: 634–636.

Benedetti, L., Briani, C., Franciotta, D., Fazio, R., Paolasso, I., Comi, C. *et al.* (2011) Rituximab in patients with chronic inflammatory demyelinating polyradiculoneuropathy: a report of 13 cases and review of the literature. *J Neurol Neurosurg Psychiatry* 82: 306–308.

Benedetti, L., Franciotta, D., Beronio, A., Cadenotti, L., Gobbi, M., Mancardi, G. *et al.* (2008) Rituximab efficacy in CIDP associated with idiopathic thrombocytopenic purpura. *Muscle Nerve* 38: 1076–1077.

Brannagan, T., III, Pradhan, A., Heiman-Patterson, T., Winkelman, A., Styler, M., Topolsky, D. *et al.* (2002) High-dose cyclophosphamide without stem-cell rescue for refractory CIDP. *Neurology* 58: 1856–1858.

Bromberg, M. (2011) Review of the evolution of electrodiagnostic criteria for chronic inflammatory demyelinating polyradiculopathy. *Muscle Nerve* 43: 780–794.

Chin, R., Sherman, W., Sander, H., Hays, A. and Latov, N. (2003) Etanercept (Enbrel) therapy for chronic inflammatory demyelinating polyneuropathy. *J Neurol Sci* 210: 19–21.

Choudhary, P. and Hughes, R. (1995) Long-term treatment of chronic inflammatory demyelinating polyradiculoneuropathy with plasma exchange or intravenous gammaglobulin. *Q J Med* 88: 493–502.

Choudhary, P., Thompson, N. and Hughes, R. (1995) Improvement following interferon beta in chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol* 242: 252–253.

Cocito, D., Grimaldi, S., Paolasso, I., Falcone, Y., Antonini, G., Benedetti, L. *et al.* (2011a) Immunosuppressive treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy. A nationwide retrospective analysis. *Eur J Neurol* 18: 1417–1421.

Cocito, D., Serra, G., Falcone, Y. and Paolasso, I. (2011b) The efficacy of subcutaneous immunoglobulin administration in chronic inflammatory demyelinating polyneuropathy responders to intravenous immunoglobulin. *J Peripher Nerv Syst* 16: 150–152.

Creange, A., Gregson, N. and Hughes, R. (2003) Intravenous immunoglobulin modulates lymphocyte CD54 and monocytes FcgammaRII expression in patients with chronic inflammatory neuropathies. *J Neuroimmunol* 135: 91–95.

Dalakas, M. (2011) Advances in the diagnosis, pathogenesis and treatment of CIDP. *Nat Rev Neurol* 7: 507–517.

Díaz-Manera, J., Rojas-García, R., Gallardo, E. and Illa, I. (2009) Response to methotrexate in a chronic inflammatory demyelinating polyradiculoneuropathy patient. *Muscle Nerve* 39: 386–388.

Dyck, P., Daube, J., O'Brien, P., Pineda, A., Low, P., Windebank, A. *et al.* (1986) Plasma exchange in chronic inflammatory demyelinating polyneuropathy. *N Engl J Med* 314: 461–465.

Dyck, P., Litchy, W., Kratz, K., Suarez, G., Low, P., Pineda, A. *et al.* (1994) A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 36: 838–845.

Dyck, P., O'Brien, P., Oviatt, K., Dinapoli, R., Daube, J., Bartleson, J. *et al.* (1982) Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. *Ann Neurol* 11: 136–141.

Dyck, P., O'Brien, P., Swanson, C., Low, P. and Daube, J. (1985) Combined azathioprine and prednisone in chronic inflammatory demyelinating polyneuropathy. *Neurology* 35: 1173–1176.

Dyck, P., Prineas, J. and Pollard, J. (1993) Chronic inflammatory demyelinating polyneuropathy. In: Dyck, P., Thomas, P., Griffin, J., Low, P. and Podulos, J. (eds), *Peripheral Neuropathy*. Philadelphia, PA: Saunders.

Fowler, H., Vulpe, M., Marks, G., Egolg, C. and Dau, P. (1979) Recovery from chronic progressive

polyneuropathy after treatment with plasma exchange and cyclophosphamide. *Lancet* 2: 1193.

Good, J., Chehrenama, M., Mayer, R. and Koski, C. (1998) Pulse cyclophosphamide therapy in chronic inflammatory demyelinating polyneuropathy. *Neurology* 51: 1735–1738.

Gorson, K. (2010) A new trick for an old dog: pulsed dexamethasone treatment for chronic inflammatory demyelinating polyneuropathy. *Lancet Neurol* 9: 228–229.

Gorson, K., Allam, G. and Ropper, A. (1997) Chronic inflammatory demyelinating polyneuropathy: Clinical features and response to treatment in 67 consecutive patients with and without monoclonal gammopathy. *Neurology* 48: 321–328.

Gorson, K., Amato, A. and Ropper, A. (2004) Efficacy of mycophenolate mofetil in patients with chronic immune demyelinating polyneuropathy. *Neurology* 63: 715–717.

Gorson, K., Natarajan, N., Ropper, A. and Weinstein, R. (2007) Rituximab treatment in patients with IVIg-dependent immune polyneuropathy: a prospective pilot trial. *Muscle Nerve* 35: 66–69.

Gorson, K., Ropper, A., Clark, B., Dew, R., Simovic, D. and Allam, G. (1998) Treatment of chronic inflammatory demyelinating polyneuropathy with interferon alpha 2a. *Neurology* 50: 84–87.

Grillo, J., Gorson, K., Lewis, J., Ropper, A. and Weinstein, R. (2001) Complications of rapid infusion intravenous immune globulin (IVIG) in neuromuscular disorders. *Neurology* 57: 1699–1701.

Hahn, A., Bolton, C., Pillay, N., Chalk, C., Benstead, T., Bril, V. *et al.* (1996a) Plasma exchange therapy in chronic inflammatory demyelinating polyneuropathy. A double-blind sham-controlled, cross-over study. *Brain* 119: 1055–1066.

Hahn, A., Bolton, C., Zochodne, D. and Feasby, T. (1996b) Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled cross-over study. *Brain* 119: 1067–1077.

Hughes, R., Bensa, S., Willison, H., Van den Bergh, P., Comi, G., Illa, I. *et al.* (2002) Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 50: 195–201.

Hughes, R., Donofrio, P., Bril, V., Dalakas, M., Deng, C., Hanna, K. *et al.* for the ICE Study Group (2008) Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol* 7: 136–44.

Hughes, R., Gorson, K., Cros, D., Griffin, J., Pollard, J., Vallat, J. *et al.* for the Avonex CIDP Study Group (2010) Imtramuscular interferon beta 1a in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 74: 651–657.

Iijima, M., Yamamoto, M., Hirayama, M., Tanaka, F., Katsuno, M., Mori, K. *et al.* (2005) Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP. *Neurology* 64: 1471–1475.

Joint Task Force of the EFNS and PNS (2010) Guideline on the management of chronic inflammatory demyelinating polyradiculopathy: Report of a joint task force of the European Federation of Neurological Societies and Peripheral Nerve Society – First Revision. *J Peripher Nerv Syst* 15: 1–9.

Knecht, H., Baumberger, M., Tobòn, A. and Steck, A. (2004) Sustained remission of CIDP associated with Evans syndrome. *Neurology* 63: 730–732.

Köller, H., Kieseier, B., Jander, S. and Hartung, H. (2005) Chronic inflammatory demyelinating polyneuropathy. *N Engl J Med* 352: 1343–1356.

Koski, C., Baumgarten, M., Magder, L., Barohn, R., Goldstein, J., Gorson, K. *et al.* (2009) Derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy. *J Neurol Sci* 277: 1–8.

Kuitwaard, K., van den Berg, L., Vermeulen, M., Brusse, E., Cats, E., van der Kooi, A. *et al.* (2010) Randomised controlled trial comparing two different intravenous immunoglobulins in chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry* 81: 1374–1379.

Latov, N., Deng, C., Dalakas, M., Bril, V., Donofrio, P., Hanna, K. *et al.* (2010) Timing and course of clinical response to intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *Arch Neurol* 67: 802–807.

Lopate, G., Pestronk, A. and Al-Lozi, M. (2005) Treatment of chronic inflammatory demyelinating polyneuropathy with high-dose intermittent intravenous methylprednisolone. *Arch Neurol* 62: 249–254.

Magda, P., Latov, N., Brannagan, T., III,, Weimer, L., Chin, R. and Sander, H. (2003) Comparison of electrodiagnostic abnormalities and criteria in a cohort of patients with chronic inflammatory demyelinating polyneuropathy. *Arch Neurol* 60: 1755–1759.

Mahdi-Rogers, M., Kazmi, M., Ferner, R., Hughes, R., Renaud, S., Steck, A. *et al.* (2009) Autologous peripheral blood stem cell transplantation for chronic inflammatory demyelinating neuropathy. *J Peripher Nerv Syst* 14: 118–124.

Marsh, E., Hirst, C., Llewelyn, J., Cossburn, M., Reilly, M., Krishnan, A. *et al.* (2010) Alemtuzumab in the treatment of IVIG-dependent chronic inflammatory demyelinating polyneuropathy. *J Neurol* 257: 913–919.

McCombe, P., Pollard, J. and McLeod, J. (1987) Chronic inflammatory polyradiculoneuropathy: A clinical and electrophysiological study of 92 cases. *Brain* 110: 1617–1630.

Mehndiratta, M., Hughes, R. and Agarwal, P. (2004) Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 3: CD003906.

Mendell, J., Barohn, R., Freimer, M., Kissel, J., King, W., Nagaraja, H. *et al.* (2001) Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculopathy. *Neurology* 56: 445–449.

Menkes, D., Hood, D., Ballesteros, R. and Williams, D. (1998) Root stimulation improves the detection of acquired demyelinating polyneuropathies. *Muscle Nerve* 21: 298–308.

Minagar, A., Alexander, J., Sahraian, M. and Zivadinov, R. (2010) Alemtuzumab and multiple sclerosis: therapeutic application. *Expert Opin Biol Ther* 10: 421–429.

Muley, S., Kelkar, P. and Parry, G. (2008) Treatment of chronic inflammatory demyelinating polyneuropathy with pulsed oral steroids. *Arch Neurol* 65: 1460–1464.

Münch, C., Anagnostou, P., Meyer, R. and Haas, J. (2007) Rituximab in chronic inflammatory demyelinating polyneuropathy associated with diabetes mellitus. *J Neurol Sci* 256: 100–102.

Odaka, M., Tatsumoto, M., Susuki, K., Hirata, K. and Yuki, N. (2005) Intractable chronic inflammatory demyelinating polyneuropathy treated successfully with ciclosporin. *J Neurol Neurosurg Psychiatry* 76: 1115–1120.

Oh, S., Kurokawa, K., de Almeida, D., Ryan, H., Jr, and Claussen, G. (2003) Subacute inflammatory demyelinating polyneuropathy. *Neurology* 61: 1507–1512.

Perosa, F., Favoino, E., Caragnano, M., Prete, M. and Dammacco, F. (2005) CD20: a target antigen for immunotherapy of autoimmune diseases. *Autoimmun Rev* 4: 526–531.

Pollard, J., McLeod, J., Gatenby, P. and Kronenberg, H. (1983) Prediction of response to plasma exchange in chronic relapsing polyneuropathy: a clinical-pathological correlation. *J Neurol Sci* 58: 269–287.

Rajabally, Y., Simpson, B., Beri, S., Bankart, J. and Gosalakkal, J. (2009) Epidemiologic variability of chronic inflammatory demyelinating polyneuropathy with different diagnostic criteria: study of a UK population. *Muscle Nerve* 39: 432–438.

Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. (1991). Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). *Neurology* 41(5): 617–618.

RMC Trial Group (2009) Randomised controlled trial of methotrexate for chronic inflammatory demyelinating polyradiculoneuropathy (RMC trial): a pilot, multicentre study. *Lancet Neurol* 8: 158–164.

Rosenberg, N., Lacy, J., Kennaugh, R., Holers, V., Neville, H. and Kotzin, B. (1985) Treatment of refractory chronic demyelinating polyneuropathy with lymphoid irradiation. *Muscle Nerve* 8: 32.

Sadnicka, A., Reilly, M., Mummery, C., Brandner, S., Hirsch, N. and Lunn, M. (2011) Rituximab in the treatment of three coexistent neurological autoimmune diseases: chronic inflammatory demyelinating polyradiculoneuropathy, Morvan syndrome and myasthenia gravis. *J Neurol Neurosurg Psychiatry* 82: 230–232.

Sievers, T., Rossi, S., Ghobrial, R., Arriola, E., Nishimura, P., Kawano, M. *et al.* (1997) Mycophenolate mofetil. *Pharmacotherapy* 17: 1178–1197.

Vallat, J., Hahn, A., Léger, J., Cros, D., Magy, L., Tabaraud, F. *et al.* (2003) Interferon beta 1a as an investigational treatment for CIDP. *Neurology* 60(Suppl. 3): S23–S28.

van Schaik, I., Eftimov, F., van Doorn, P., Brusse, E., van den Berg, L., van der Pol, W. *et al.* (2010) Pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind, randomised, controlled trial. *Lancet Neurol* 9: 245–253.

Wertman, E., Argov, Z. and Abrmasky, O. (1988) Chronic inflammatory demyelinating polyradiculoneuropathy: features and prognostic factors with glucocorticoid therapy. *Eur Neurol* 28: 199–204.

Wolf, C., Menge, T., Stenner, M., Meyer zu Hörste, G., Saleh, A., Hartung, H. *et al.* (2010) Natalizumab treatment in a patient with chronic inflammatory demyelinating polyneuropathy. *Arch Neurol* 67: 881–883.

Visit SAGE journals online
http://tan.sagepub.com

SAGE journals