Chronic Inflammatory Demyelinating Polyradiculoneuropathy – An Overview of Existing Treatment Options and Prospects for the Future

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Abstract

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated polyneuropathy. CIDP can cause prolonged periods of disability with many patients becoming severely debilitated at some time during their illness. Several open, uncontrolled studies and blinded, randomised clinical trials have shown that immunomodulatory therapy has a beneficial effect in CIDP. This paper reviews existing treatment options, provides a treatment algorithm and discusses prospects for the future. Corticosteroids, intravenous immunoglobulin, plasma exchange, immunosuppressive agents such as azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, cyclosporine A, rituximab, alemtuzumab, etanercept, tacrolimus, interferon beta and alpha and autologous stem cell transplantation have been used in CIDP. Only corticosteroids, intravenous immunoglobulin and plasmapheresis have been proven to be effective in randomised controlled trials, however. As non-responsiveness to treatment seems to be associated with a greater degree of axonal dysfunction, finding therapies aimed at protecting the axon and restoring axonal damage are needed.

Keywords

Chronic inflammatory demyelinating polyradiculoneuropathy, CIDP, polyneuropathy, immunotherapy, treatment

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a relatively rare immune-mediated polyneuropathy with an overall prevalence of one to three per 100,000 adults.[1–3] The clinical diagnosis of CIDP is based on clinical, electrophysiological and cerebrospinal fluid features. A typical CIDP patient has chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least two months with absent or reduced tendon reflexes in all extremities.[4,5] Various other clinical phenotypes have emerged over the years, including: distal acquired demyelinating symmetric neuropathy (DADS); multifocal acquired demyelinating sensory and motor neuropathy (MADSAM or Lewis-Sumner syndrome); focal involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb; and a pure motor and pure sensory form (including chronic immune sensory polyradiculopathy).[6–14] Although the majority of patients will develop the disease slowly over more than two months, approximately 5% will have an acute Guillain–Barré syndrome-type onset.[15,16] Electrophysiologically, reduced nerve conduction velocities, abnormal temporal dispersion and conduction blocks are important disease features.[4,17,18] Cerebrospinal fluid protein levels are often elevated without cellular reaction.[5] Many sets of diagnostic criteria for CIDP have been published. Recently, the European Federation of Neurological Societies and the Peripheral Nerve Society published revised criteria,[19] which are designed for clinical practice and are easy to use.

Treatments for Chronic Inflammatory Demyelinating Polyneuropathy

CIDP can cause prolonged periods of disability, with many patients becoming severely disabled (modified Rankin score of 4 or 5) at some time during their illness. More than 10% remain severely disabled despite treatment.[20] Several open, uncontrolled studies and blinded, randomised clinical trials have shown that immunomodulatory therapy has a beneficial effect in CIDP. Corticosteroids, intravenous immunoglobulin (IVIg), plasma exchange (PE), immunosuppressive agents (such as azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, cyclosporine A, rituximab, alemtuzumab, etanercept, tacrolimus, interferon beta and alpha) and autologous stem cell transplantation have been used in CIDP. Of these, only corticosteroids, IVIg and plasmapheresis have been shown to be effective in randomised controlled trials (RCTs). This paper reviews existing treatment options, provides a treatment algorithm and discusses prospects for the future.

Corticosteroids

Corticosteroids have been considered an effective treatment for CIDP since the report in 1958 of a corticosteroid responsive neuropathy.[21] Several open, uncontrolled series have suggested that corticosteroid treatment induces improvement in 65–75% of patients with CIDP.[4,22–25] The efficacy of corticosteroids in patients with CIDP has been investigated in three randomised trials.[26–28] The first showed that

improvements in disability scores for patients started on prednisone 120mg every other day, subsequently tapered and stopped at 12 weeks were significantly greater than for patients who received placebo.[26] The second trial had a cross-over design and compared six weeks oral prednisolone starting with 60mg daily and tapering to 10mg with a single course of IVIg at 2.0g/kg.[27] Sixty-two per cent of prednisolone-treated patients had improved disability scores. There was no significant difference in the proportion of responders in the two treatment groups. The third, double-blind study compared pulsed high dose dexamethasone with standard prednisolone for 32 weeks.[28] Forty per cent of patients in both treatment arms achieved and remained in remission at 12 months and both treatments were generally well tolerated. Dexamethasone had a faster onset of action than prednisolone. Surprisingly, 38% of patients deteriorated after start of corticosteroid therapy and this was more frequent in prednisolone-treated patients that in those treated with dexamethasone.

In open-label studies, pulsed high-dose corticosteroids not only appeared to be effective, but a considerable number of patients went into a long-term remission and did not need additional treatment.[29–31]

The serious long-term side effects – such as diabetes, hypertension, cataract, osteoporosis, peptic ulcer disease and aseptic necrosis of the joints – seen with prolonged treatment with corticosteroids are a major concern in patients with CIDP. Pulsed oral and intravenous corticosteroid treatment seems to reduce the incidence of these long-term adverse events.[28–32]

Intravenous Immunoglobulin

Several uncontrolled studies have suggested short-term beneficial effects with IVIg administration.[17,18,33–37] The mode (or modes) by which IVIg exerts this effect in CIDP is unknown, but several mechanisms have been suggested and are reviewed elsewhere.[38–42]

The evidence from RCTs showing that IVIg reduces disability in patients with CIDP has been summarised in a Cochrane systematic review.[43] Five randomised trials have compared IVIg (2g/kg bodyweight administered over two to five days) treatment with placebo.[44–48] A pooled analysis of these five trials showed that a significantly higher proportion of patients treated with IVIg had improved disability scores within six weeks of onset of treatment than patients who received placebo – relative risk (RR) 2.40 (95% confidence interval [CI] 1.72–3.36); number needed to treat (NNT) 3.03 (95% CI 2.33–4.55).

One RCT compared IVIg with plasma exchange in a cross-over design.[49] A total of 1.8g/kg bodyweight IVIg was administered over the course of six weeks and the results compared with plasma exchange twice weekly for three weeks followed by once weekly for a further three weeks. There were no significant differences in outcome between the two treatments. A trial comparing IVIg to prednisolone treatment was discussed above.[27]

While a minority of patients who respond to initial IVIg treatment do not need further treatment, others often need repeated courses of IVIg over a prolonged period of time. To date, only the Immune Globulin Intravenous CIDP Efficacy (ICE) trial has investigated long-term management with IVIg.[48] This trial investigated IVIg used for up to 48 weeks. The initial loading dose was replaced by a maintenance dose of 1g/kg every three weeks. After 24 weeks of treatment, 54% of patients in the IVIg group had a favourable response, whereas only 21% of patients in the placebo group had improved (NNT 3; 95% CI 2.00–5.85). In a 24 week extension phase, most patients were re-randomised to IVIg or placebo. The majority of patients (86%) treated with IVIg had no relapse and remained clinically stable or improved, whereas 52% patients in the placebo group had no relapse (NNT 2.9; 95% CI 1.82–7.13). Approximately 40% of participants who had been treated with IVIg in the first 24 weeks and were re-randomised to placebo remained clinically stable in the extension phase of the study. This finding may indicate that a considerable number of patients treated with IVIg for six months can achieve remission for at least another 24 weeks. In a long-term follow-up study in 84 patients with CIDP who responded to IVIg treatment, remission was reported in most patients.[50] Seventy-three patients (87%) needed at least two courses of treatment. Ten per cent of patients needed IVIg for more than 8.7 years. Median time to remission was 2.1 years.

IVIg has an excellent safety profile. In one series, the incidence of headache was reported to be 54%,[51] but in a large long-term observational study adverse reactions were reported in 7% of 1,093 patients with autoimmune diseases treated with IVIg;[52] 90% of these were mild-to-moderate and transient, however. The most common adverse events were headache, myalgia, fatigue, fever, nausea, rigors, chest discomfort and high blood pressure. Aseptic meningitis, haemolysis and skin reactions were less frequent.[53,54] Serious adverse reactions occur in less than 0.5% of patients and include thromboembolic events such as stroke and myocardial infarction due to increased serum viscosity, renal tubule necrosis and anaphylactic reactions.[55,56]

Plasma Exchange

Several uncontrolled studies have been published that show a beneficial effect from PE in patients with CIDP.[57–60] Two double-blind, randomised, sham-controlled trials have been summarised in a Cochrane systematic review, which concluded that PE provides significant short-term benefit in about two-thirds of patients with CIDP (although rapid deterioration may occur subsequently).[59,61,62] Recently, a small case series reported stable and long-lasting clinical remission in five patients with CIDP receiving long-term PE.[63]

As described above, PE and IVIg treatments have been shown to be equivalent.[49] More recently, protein immunoadsorption has been compared to IVIg in a small pilot study in patients with CIDP.[64] The rationale behind protein immunoadsorption involves the selective removal of immunoglobulins leaving non-specific protein untouched. At two months, four of five patients had a favourable response to immunoadsorption compared with four of eight patients treated with IVIg. Although immunoadsorption appeared to be safe and efficacious in this study, the small number of patients, large drop-out rate, lack of intention-to-treat analysis and the fact that patients in the IVIg arm had more severe disease severely limits the interpretation of the results.

There is a requirement for PE to be administered by trained staff in a hospital setting. Difficulties with venous access occur in approximately 1% of patients.[65,66] Adverse events – such as paraesthesia, mild hypotension, urticaria and mild nausea – occur in approximately 4% of PE treatments. Severe side effects – such as severe hypotension, arrhythmia, dyspnoea and severe nausea necessitating interruption or termination of treatment – occur in approximately 1%.

Immunosuppressive and Immunomodulating Agents

Immunosuppressive and immunomodulating agents are used as a substitute or add-on therapy for corticosteroids and IVIg.[67] Case studies and small case series report benefits from treating with azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, cyclophosphamide, cyclosporine A, rituximab, alemtuzumab, etanercept, tacrolimus, interferon beta and interferon alpha. Azathioprine, methotrexate and interferon beta have been investigated in a RCT.

Azathioprine

Azathioprine is probably the most commonly-used immunosuppressive drug in CIDP, although its use is not supported by clinical evidence. Azathioprine was found not to be effective in a small trial, but this lacked power to detect or exclude any but very large treatment effects, had a too short duration and used a lower dose of azathioprine than has been used in other autoimmune diseases.[68] There is much clinical experience with azathioprine and it seems to be relatively safe to use, although it can give bone marrow toxicity, acute pancreatitis and liver toxicity. Screening for low thyopurine methyltransferase activity has been promulgated, as this is associated with increased risk of myelotoxicity.

Methotrexate

There is one retrospective, consecutive, open-label study in which seven of 10 patients with treatment resistant CIDP improved in strength when treated with oral methotrexate 10–15mg dosed weekly.[69] This result led to a multicentre, double-blind RCT comparing oral methotrexate with placebo for 32 weeks in 60 patients with CIDP treated with IVIg or corticosteroids.[70] Fifty-two per cent of patients in the methotrexate group and 44% in the placebo group were able to reduce their dose of corticosteroid or IVIg by more than 20%, suggesting that oral methotrexate does not have a significant beneficial effect over placebo. Most interesting was the high rate of response in the placebo group, which meant that a considerable number of patients did not need IVIg or could have been treated with a lower dose when entering the trial.

After this trial, a case report was published that described a patient who had CIDP and progressive resistance to standard treatment who showed a striking response to a higher dose of methotrexate (20mg/week). The improvement started 5 months after initiation of therapy and was consistent and permanent. This case suggests that there may be a role for higher doses of methotrexate in the treatment of patients with CIPD.[71] Common serious side effects associated with methotrexate are gastrointestinal symptoms, myelotoxicity and liver toxicity. Ten per cent of patients with rheumatoid arthritis treated with low dose methotrexate and followed for five years discontinued treatment due to adverse effects.[72] Methotrexate is considered to be a relatively safe and well-tolerated immunosuppressant.

Mycophenolate Mofetil

A number of small, open series studies in patients with CIDP have provided conflicting results for mycophenolate mofetil (MMF).[73–78] In a recent survey of a database of 184 CIDP patients,[79] eight patients received MMF and subsequently had improved Neuropathy Impairment Scores. Six patients were either able to stop corticosteroid or IVIg treatment or to reduce the dose and/or frequency of their medication.

Gastrointestinal side effects are common with MMF. Myelotoxicity and liver toxicity are thought to be less frequent than with other immunosuppressive agents, however.

Cyclophosphamide

Several small case reports and case series have reported beneficial effects with oral and intravenous cyclophosphamide in CIDP.[22,80–82] In the largest series, 11 of 15 patients achieved complete remission with pulsed monthly intravenous cyclophosphamide for a maximum of six months.[82] Cyclophosphamide in conjunction with autologous blood stem cell transplantation has been reported to have induced remission in a patient with CIDP who was refractory to other treatments.[83]

Common adverse events with cyclophosphamide are gastrointestinal symptoms and alopecia. Prolonged bone marrow suppression, haemorrhagic cystitis and neoplasia are relatively frequently encountered serious adverse events, and discourage many neurologists from using this agent first line.

Cyclosporine A

Beneficial effects with cyclosporine A have been reported in five case series in patients refractory to other treatments.[84–88] In two series, involving a total of 21 patients, oral cyclosporine improved symptoms in all patients.[84,85] No differences were found between various dosing schedules, although fewer adverse events were seen at lower doses. In the other series, response rates of 35–80% have been reported. The most common adverse events are nephrotoxicity and hypertension.

Rituximab

Controversial results have been published in the four case reports and one small case series on the efficacy of rituximab in CIDP.[89–93] Recently, a retrospective, observational, multicentre study reported a favourable response in nine of 13 patients with CIDP. Seven of the responders had a concurrent haematological disease.[94] Rituximab seems to be a promising therapeutic choice for CIDP, but a RCT is necessary to confirm this.

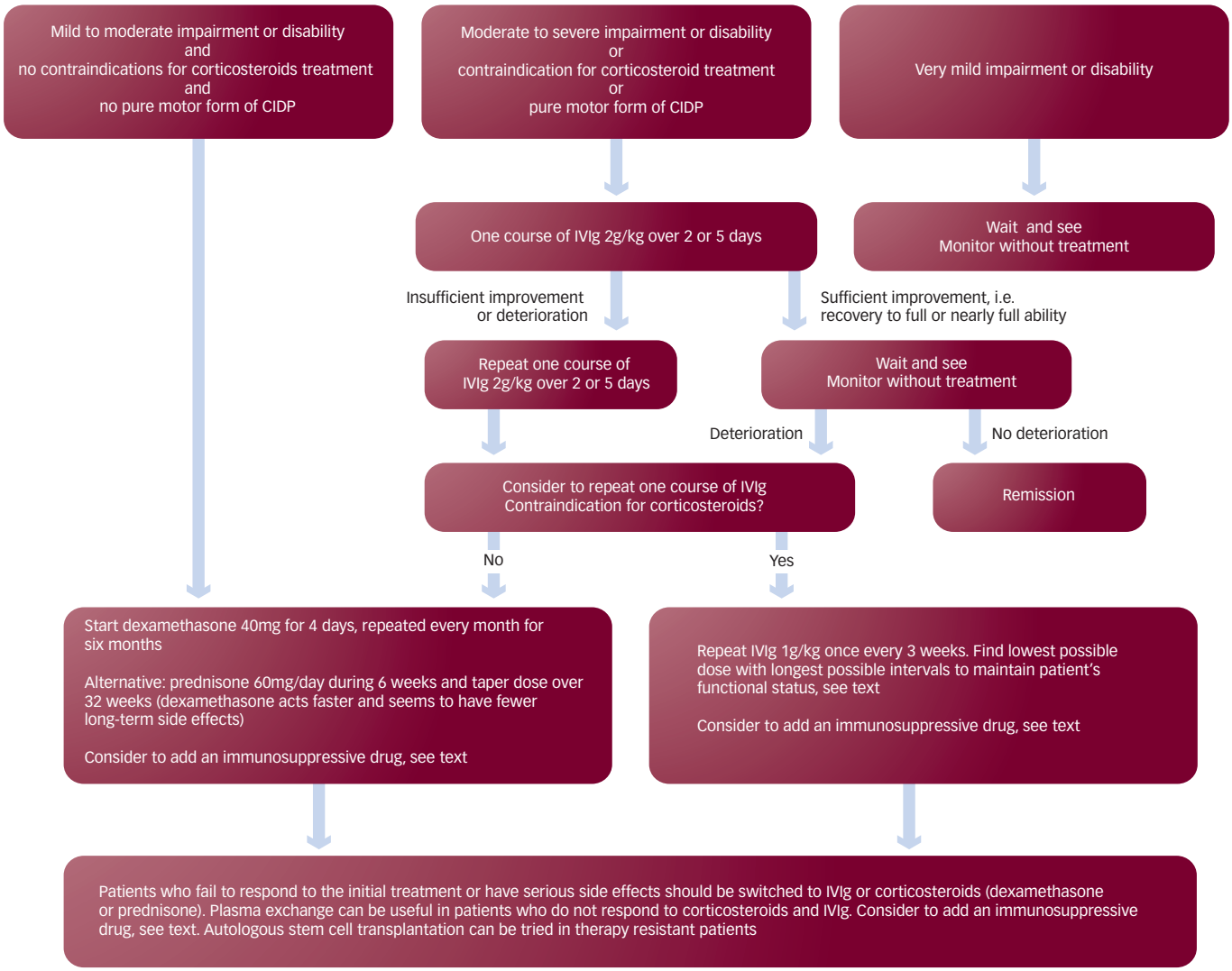
Alemtuzumab

Alemtuzumab targets human CD52, an antigen expressed on the surface of lymphocytes and monocytes. A single intravenous infusion results in rapid and profound lymphopenia lasting for more than 12 months. There is one case report describing remission following treatment.[95] In a small series of seven patients who had failed to respond to conventional immunosuppression, two had prolonged remission, two had a partial response and three had no clear benefit after treatment with nine courses of alemtuzumab.[96] Three patients developed autoimmune disease following treatment with alemtuzumab. This also has been encountered in MS patients treated with alemtuzumab, and will limit the drug's use to seriously disabled patients who are refractory to all known other treatments.

Etanercept

Etanercept acts as a inhibitor of tumor necrosis factor-alpha, the major regulator of the inflammatory response. In one series, three of 10 patients with CIDP improved significantly after treatment;[97] however, two more recent reports described four patients with rheumatoid arthritis who developed neuropathy resembling CIDP following treatment with etanercept.[98,99]

Figure 1: Treatment Algorithm for Chronic Inflammatory Demyelinating Polyradiculoneuropathy



CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; IVIg = intravenous immunoglobulin.

Tacrolimus

Tacrolimus is an immunosuppressant that inhibits both T-lymphocyte signal transduction and interleukin (IL)-2 transcription. One case report notes that tacrolimus had a positive effect in a patient with CIDP.[100] Nephrotoxicity is the most important, although reversible, side effect. Many case reports and cases series have reported tacrolimus-related polyneuropathies often resembling CIDP, however.[101–104]

Interferon Beta

Three case reports showed improvement after treatment with different brands of interferon beta.[105–107] In two series, including a total of 24 CIDP patients, nine patients improved significantly;[108,109] however, a randomised controlled trial including 10 treatment refractory CIDP patients did not show a significant effect on predetermined impairment and disability scales. Recently, these results were confirmed in a RCT with intramuscular interferon beta-1a, which, when added to IVIg, had no effect in CIDP.[110]

The most commonly seen adverse events are flu-like symptoms, mild leucocytopenia and alteration of liver function. Two case reports of patients with multiple sclerosis developing CIDP after interferon beta-1b treatment have been published.[111,112] These adverse events, together with its doubtful efficacy and high costs, must lead to the conclusion that there is no place for interferon beta treatment in CIDP.

Interferon Alpha

Nine of 14 patients with CIDP treated with subcutaneous interferon alpha-2a three times a week for six weeks had a favourable response, although three patients later had a relapse.[113] There are a few case reports confirming these beneficial results.[114–116] Adverse events are similar to those seen with interferon beta, but costs are lower. Development of CIDP upon treatment with interferon alpha has also been reported, however.[117,118]

Haematopoietic Autologous Stem Cell Transplantation

Autologous stem cell transplantation was used successfully in CIDP for the first time in 2001.[119] Since this first case report, successful treatment with autologous stem cell transplantation has been reported in several patients with CIDP refractory to other treatments.[83,120–122] In an open label non-randomised study, two of three patients with CIDP improved.[123] One patient relapsed five years after transplantation. This patient was no longer refractory to treatment and responded well to normal doses of IVIg.[124] One case report describes a patient who developed CIDP after autologous stem

cell transplantation for multiple myeloma.[125] The potential for serious adverse events with this treatment, treatment-related mortality rates of 3–14% and lack of sustained response in some patients, means that this treatment is likely only to be suitable for refractory CIDP patients with sufficiently severe disability.[126]

Treatment Algorithm

Patients with very mild and stable symptoms and disease which does not (or only slightly) interfere with the activities of daily living may be monitored without treatment (see *Figure 1*). Treatment should be initiated if symptoms or signs progress or are moderate-to-severe from the onset. For first line treatment a choice has to be made between corticosteroids and IVIg. This choice will depend on possible contraindications for either treatment, local availability, cost and patient preference. Patients with a pure motor CIDP should be treated with IVIg rather than corticosteroids, as several patients have been reported to deteriorate following steroid treatment. In the case of corticosteroids, these authors recommend pulsed high-dose dexamethasone as initial treatment (i.e. 40mg for four days) repeated every month for six months. After this, a 'wait and see' policy should be implemented as almost 40% of patients will not require further treatment. At least three cycles of dexamethasone should be given before deciding there is no treatment response. In the event that dexamethasone is insufficiently effective, regular daily prednisolone, IVIg or PE should be tried in preference to other treatments. Depending on the degree of disease activity, an immunosuppressive drug can be added to corticosteroid treatment, as these medications may have a steroid-sparing effect (see *Table 1*).

The starting dose of IVIg is usually 2g/kg bodyweight given over two to five consecutive days. After the first loading dose of IVIg patients should be observed closely, as some will not need further treatment. Patients responding to the loading dose but who subsequently deteriorate should be treated with maintenance IVIg therapy. Apart from the ICE trial – in which all patients got a maintenance dose of 1g/kg every three weeks – there is no evidence on the interval and dosage needed to achieve a stable condition. The dose and frequency of administration need to be titrated according to individual need and regular attempts should be undertaken to decrease the dose to make sure a patient is still IVIg-dependent. When doing this, the dose should be reduced first, and then the frequency of administration. It is important to avoid deterioration (wearing-off) which may be seen just before the next IVIg course is due. Treatment intervals should be such that this deterioration does not happen. If a patient becomes stable on intermittent IVIg, the dose should be reduced after approximately six months in order to test the continued need for IVIg. If high doses of IVIg are needed to maintain good functional status in a patient, the addition of corticosteroids or an immunosuppressive agent should be considered (see *Table 1*).

Plasma exchange has no advantages over immunoglobulin treatment, but can be used depending on local availability and may be useful in patients who do not respond to corticosteroids or IVIg.

The most important lesson from the Randomised Trial of Methotrexate in CIDP (RMC), Prednisolone Versus Dexamethasone In CIPD Trial (PREDICT) and ICE studies is that patients often are treated for too long. These observations have important practical implications for the treatment of patients with CIDP and mean that regular attempts should be made to taper and to stop therapy. An estimated 15% of patients fail to respond to any treatment. In these patients, the diagnosis should be reconsidered. Some of them probably will not respond to any therapy because of severe secondary axonal involvement which may be irreversible.[127]

Table 1: Treatments in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

First-line Treatment*	Second-line Treatment**	Third-line Treatment**
Corticosteroids	Azathioprine***	Autologous stem cell transplantation
Intravenous immunoglobin	Methotrexate***	
Plasma exchange	Mycophenolate mofetil	
	Cyclophosphamide	
	Cyclosporine A	
	Rituximab	
	Etanarcept	
	Intramuscular interferon beta-1a****	
	Interferon alpha-2a	
	Alemtuzumab	
	Tacrolimus	
	Subcutaneous immunoglobulin	

**Shown to be effective in randomised controlled trials; **Efficacy based on case reports and/or case series; ***Efficacy uncertain because only one randomised controlled trial available, which shows no effect in chronic inflammatory demyelinating polyradiculoneuropathy; ****Proven not to be effective.*

Prospects for the Future

Several immunosuppressive agents are being used, although none has been proven to be effective in a RCT. A full trial with azathioprine is required and treatment with higher doses of methotrexate in patients with CIDP should also be explored. A trial with MMF in CIDP is currently being designed. Based on the pathophysiological assumption that CIDP is an antibody-mediated disease, a trial with rituximab also should be conducted. Recently, there has been a renewed interest for subcutaneous immunoglobulin infusion (SCIg) as an alternative route of immunoglobulin administration. The advantages of weekly subcutaneous self-infusion are a greater level of independency, lower incidence of systemic adverse events and reduction of treatment costs.[128] There are two small case series describing three patients with CIDP maintaining functional status after switching from IV to subcutaneous (SC) immunoglobulin.[129,130] SCIg has been shown to be effective in patients with multifocal motor neuropathy.[131,132]

Current treatments are aimed at modulating the immune response, but as yet there is no clear evidence that these treatments also induce axonal regeneration. As non-responsiveness to treatment seems to be associated with a greater degree of axonal dysfunction, finding therapies aimed at protecting the axon and restoring axonal damage are needed. Complement activation plays a major role in secondary axonal damage and poor regeneration and recovery of damaged axons.[133–138] The membrane attack complex – the complement's final pathway – damages axonal membranes and recruits and activates macrophages. Macrophages produce matrix metalloproteases, and breakdown and penetrate the Schwann cell's basal lamina. Complement inhibition has been shown to ameliorate the clinical, electrophysiological and morphological symptoms and signs in a mouse model of Miller Fisher syndrome.[139,140] As complement plays a role in CIDP,[141–143] well designed, proof-of-principle studies in patients with CIDP are warranted. ■

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