Newer therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

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

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

INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

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

CURRENT PROVEN EFFECTIVE TREATMENTS

Intravenous immunoglobulin (IVIg)

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

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

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

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

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

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

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

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

Plasma exchange (PE)

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

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

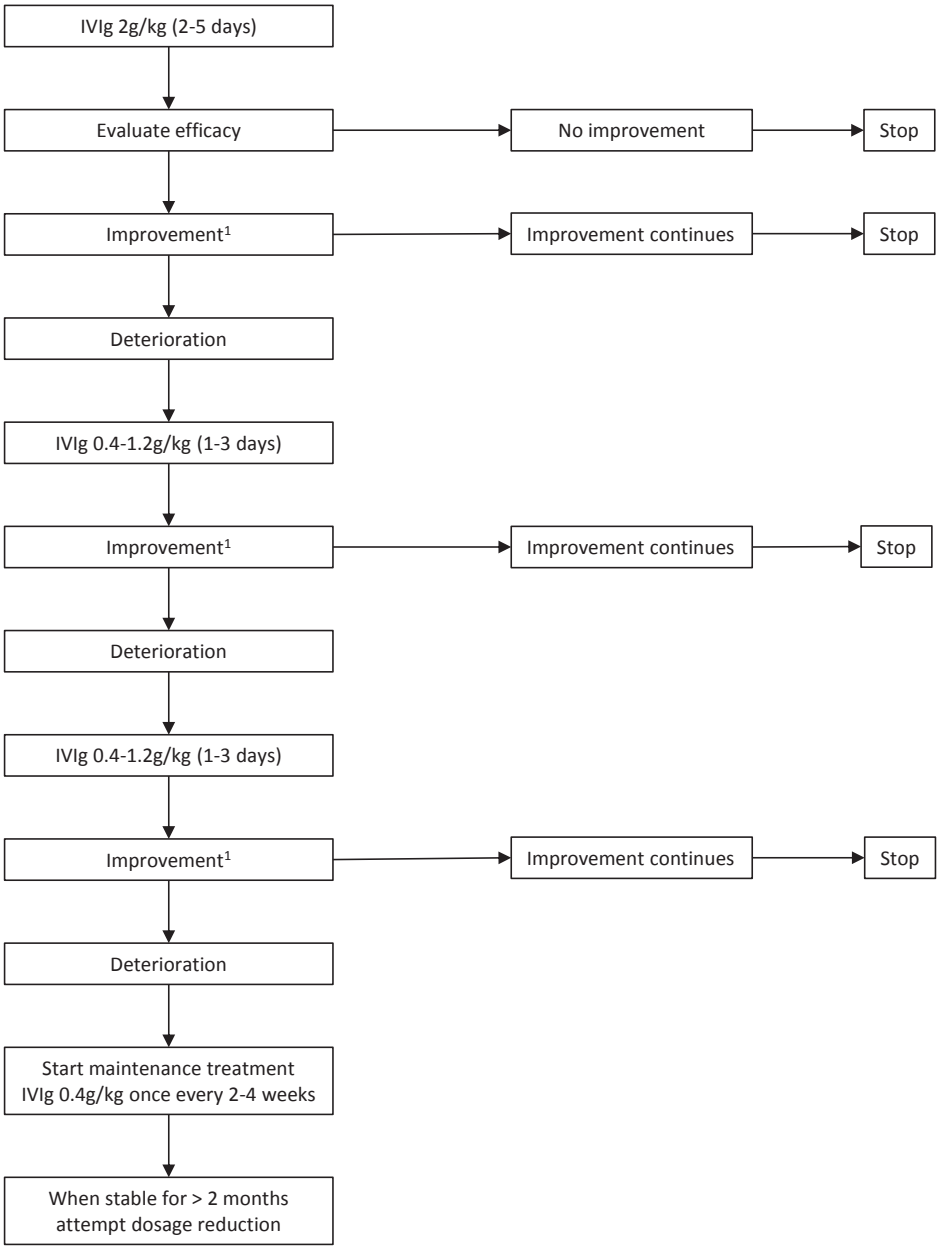

Figure 1. Intravenous immunoglobulin (IVIg) treatment in chronic inflammatory demyelinating polyradiculoneuropathy

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

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

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

Prednisolone

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

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

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

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

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

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

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

Comparing IVIg, PE and steroids

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

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

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

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

Combining IVIg, PE and corticosteroids

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

POTENTIAL TREATMENTS

Subcutaneous immunoglobulin

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

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

Intravenous Methylprednisolone

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

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

Azathioprine

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

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

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

Cyclosporin

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

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

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

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

Mycophenolate Mofetil

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

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

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

Cyclophosphamide

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

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

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

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

Methotrexate

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

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

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

Interferons

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

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

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

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

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

Rituximab

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

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

Tacrolimus

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

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

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

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

Etanercept

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

Alemtuzumab

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

Eculizumab

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

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

Sirolimus

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

Stem cell transplantation

Stem cell transplantation is the most extreme form of immunosuppression.

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

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

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

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

CONCLUSION

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

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