

Immune Therapy in Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronically progressive or relapsing and remitting, symmetrical, sensory and motor polyradiculopathy. It typically causes weakness of proximal and distal limb muscles and sensory loss in a stocking-and-glove distribution. Cytoalbuminologic dissociation is a characteristic finding in the cerebrospinal fluid (CSF). The peripheral nerve shows evidence of demyelination and remyelination, particularly in relapsing and remitting cases. However, in the long-term, axonal loss tends to occur, leading to irreversible damage.

The pathophysiology of CIDP is thought to be due to an autoimmune process involving both antibodies and T lymphocytes. There are several lines of evidence for this: (a) sera and CSF of patients with CIDP show markers of T cell activation and migration, and (b) active lesions in nerve biopsies contain endoneurial infiltrates of T lymphocytes and macrophages.¹ Several rabbit and rodent models of experimental autoimmune neuritis with CIDP-like features have been developed with immunisation of peripheral nerve components such as myelin,² although the exact antigens in human CIDP remain undiscovered.

In addition to the core clinical picture of the symmetrical sensory and motor syndrome, several other subgroups of CIDP have been described (Table 1).^{1,3,4} Whether these variants need specific treatment is as yet largely unknown, with the exception of pure motor neuropathy and multifocal motor neuropathy where intravenous immunoglobulin (IVIG), but not corticosteroids, are effective.^{3,4}

Table 1: Variants of CIDP

<i>Classical symmetrical sensorimotor CIDP</i>
<i>Pure motor demyelinating neuropathy</i>
<i>Sensory ataxic neuropathy</i>
<i>Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) or Lewis-Sumner syndrome</i>
<i>Distal acquired demyelinating symmetric neuropathy (DADS)</i>
<i>Subacute sensorimotor demyelinating neuropathy</i>
<i>Multifocal motor neuropathy (MMN)</i>

This review will concentrate on the short- and long-term therapeutic options for CIDP, the most common of which is the classical symmetrical sensorimotor subtype. The primary goals for current treatments are to control symptoms, improve functional ability and maintain long-term remission. Recommendations on treatment options in this paper take into consideration recent consensus guidelines established by the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society.^{5,6} A detailed discussion of the adverse events associated with each treatment is beyond the scope of this article, but we will provide an overview of common and serious adverse events for the main treatment options.

Corticosteroids

In an unblinded randomised controlled trial with 28 patients, prednisolone was superior to no treatment as it improved neurological disability at three months.⁷ Long-term efficacy of corticosteroids in CIDP is more difficult to assess as treatment regimens often include combinations of treatment modalities such as IVIG, plasma exchange (PE) and other immunosuppressive agents. Patient series have reported that around 90% of

patients were doing well two or more years after the initial treatment.^{8,9}

Recommendations

Corticosteroids should be used first-line for short-term therapy as there is evidence of efficacy from a small randomised controlled trial (class II evidence). However, there is no clear evidence on whether prednisolone should be used daily or on alternate days, or whether intermittent high-dose intravenous regimens are better than oral regimens.¹⁰ The long-term use of corticosteroids is associated with many adverse events, including cushingoid features, infections, hypertension, diabetes, osteoporosis, psychiatric disorders, insomnia and white blood cell count elevation. Therefore, the dose of corticosteroids is usually tapered down slowly to the lowest possible that allows sustained clinical improvement. In addition, other immunosuppressive and immunomodulatory treatments may be added to achieve the lowest maintenance dose.

Intravenous immunoglobulin

Meta-analysis of four double-blind, placebo-controlled, cross-over trials of intravenous immunoglobulin (IVIG) versus placebo with a total of 113 CIDP patients have shown significant improvement in disability lasting two to six weeks.¹¹⁻¹⁵ More recently, a randomised, double-blind, placebo-controlled, response-conditional crossover trial of IVIG in 117 patients with CIDP showed both significant short-term (first 24 weeks) and long-term (extension phase of 24 weeks) benefit of IVIG over placebo.¹⁶

A randomised, double-blind crossover trial of IVIG versus corticosteroids of 32 patients did not show any short-term difference in improvement of neurological disability at two weeks.¹⁷

Recommendations

There is evidence from relatively large randomised controlled trials (class I evidence) for the efficacy of IVIG as first-line therapy for both short- and long-term use. The usual initiating dose of IVIG is 2g/kg/course and treatment usually needs to be repeated at intervals of several weeks to maintain improvement. However, doses of IVIG may be individually titrated to the lowest possible level for maintenance without altering treatment frequency.¹⁸ If frequent high-dose IVIG is needed, the addition of corticosteroids or another immunosuppressive/immunomodulatory agent should be considered. Common adverse events associated with IVIG such as headache, nausea, diarrhoea, flushing, fever, shortness of breath, hypertension and rashes are usually transitory and related to the initial infusion. IVIG is generally well tolerated and easy to administer except in cases of immunoglobulin A deficiency, renal failure, vascular disease and cardiac insufficiency. Serious adverse events include acute renal failure, thrombogenesis and anaphylactic shock.

Plasma exchange (PE)

Two randomised double-blind sham-controlled trials in a total of 47 patients showed that PE provided short-term benefit in approximately two-thirds of patients.^{19,20,21} However, a randomised crossover study that compared PE to IVIG demonstrated that they were equally effective in CIDP.²²



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Recommendations

There is good randomised controlled trial evidence for the efficacy of PE as first-line short-term therapy in CIDP (class I evidence). Common and relatively minor adverse events include nausea, fever, urticaria, mild hypotension and hypocalcaemia. However, the difficulties associated with the use of PE, such as poor venous access and haemodynamic instability, make this a less attractive option than either corticosteroids or IVIG, especially in the long-term. Therefore, corticosteroids or another immunosuppressive / immunomodulatory agent should be started in conjunction with PE for maintenance therapy.

Interferons

Two small open labelled studies in CIDP, one of interferon- α 2a in 16 patients for six weeks,²³ and the other of interferon- β 1a in 20 patients for six months,²⁴ revealed benefit in 56% and 85% of cases respectively. However, the only randomised double-blind placebo-controlled crossover trial of interferon- β 1a for 12 weeks in 10 CIDP patients failed to detect any significant benefit.²⁵

Recommendations

The very small number of patients in the only randomised controlled trial of interferon in CIDP makes the interpretation of the data very difficult. At best, there is class II evidence that interferons are not effective for short-term use in CIDP. However, interferons should be considered for short- or long-term use when the response to corticosteroids, IVIG or PE is inadequate. Common adverse events include fatigue, flu-like reaction, injection site reaction, headache, nausea, diarrhoea and depression. More serious adverse events include tremor and asthenia.

Other immunosuppressive and immunomodulatory drugs

A randomised parallel group open trial of azathioprine plus prednisolone versus prednisolone monotherapy with 27 patients for nine months showed no significant difference in disability scores.²⁶ There are no other published randomised controlled trials of other immunosuppressive drugs in CIDP, although results of a recently completed randomised placebo-controlled trial of methotrexate in CIDP is expected soon.²⁷

There are several small case series or reports of the use of methotrexate, ciclosporin, cyclophosphamide, mycophenolate mofetil, etanercept and rituximab in CIDP.²⁸ More recently, alemtuzumab has also been reported to be effective in CIDP.²⁹

Recommendations

A relatively small trial has not demonstrated efficacy of azathioprine in CIDP (class II evidence). However, as azathioprine is generally well tolerated, it should be considered as a long-term immunosuppressant in CIDP when the response to corticosteroids, IVIG or PE is inadequate, as it can take several months for the drug to be effective. Common adverse events of azathioprine include hepatotoxicity,

Table 2: Use of main immunosuppressant/immunomodulatory treatments in CIDP

Drug	Evidence class ^a	Recommendation
Corticosteroids	Class II	First-line therapy, best for short-term use
Intravenous immunoglobulin	Class I	First-line therapy for short- and long-term use
Plasma exchange	Class I	First-line therapy, best for short-term use
Interferons	Class II	To be considered for short- or long-term use in patients with inadequate response to corticosteroids, IVIG or PE
Azathioprine	Class II	To be considered for long-term use in patients with inadequate response to corticosteroids, IVIG or PE
Methotrexate, ciclosporin, cyclophosphamide, mycophenolate mofetil, etanercept, rituximab, alemtuzumab	Class IV	More data needed before any recommendations can be made
^a Evidence: Class I, controlled randomised trials available; class II, controlled trial without randomisation or randomised trial with small patient number; class III, uncontrolled trials; class IV, case series.		

nausea, vomiting, rash, cytopenia and pancreatitis. In the long-term, malignancy is a potential complication, although the absolute risk is difficult to evaluate because it is hard to separate the effects of the drug from age-related increases in the background incidence of cancer.

More data from proper randomised controlled trials are needed for the other drugs which currently have class IV evidence before recommendations can be made on their use in CIDP.

Conclusions

There are huge gaps in our knowledge of immune therapy in CIDP. While there is reasonably good evidence for the short-term treatment of CIDP, long-term management is more difficult as a large amount of the evidence that we use in determining the choice of immunosuppressant or immunomodulatory treatment comes from clinical experience, observational studies and expert opinion (see Table 2 for a summary of recommendations). Treatment regimens among physicians from different parts of the world differ. The main reason for this is each physician's experience and familiarity with a particular treatment regimen. In addition, patients with different personal circumstances (e.g. pregnancy), disease subtypes and treatment responses warrant individualisation of treatment regimens.

There are many challenges to carrying out treatment trials in CIDP. One of the main problems is the number of different disease subtypes that exist. Indeed, most trials do not provide a breakdown of the subtypes of patients in a particular study. In addition, it can be difficult to design an immunosuppressant or immunomodulatory treatment trial in CIDP. Some treatments may take several months to be effective, making it expensive to conduct the studies and difficult to predict when these treatments reach their maximum

effectiveness. Different study designs and the lack of long-term head-to-head treatment studies make it difficult to quantify the relative efficacies of different treatments in the condition.

It is important that in the future, better designed randomised controlled trials, especially for long-term treatments, be performed to inform us on best practice in CIDP.

Competing interests

Dr B Lecky and Dr S Sathasivam were involved in the recently completed randomised placebo-controlled trial of methotrexate in CIDP, which is yet to be published.²⁷

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The primary goals for current treatments are to control symptoms, improve functional ability and maintain long-term remission

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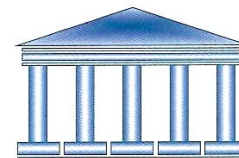
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