



# Acquired Demyelinating Neuropathy – Is There an Optimal Treatment Strategy?

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## INTRODUCTION

Despite extensive clinical investigations there remains doubt as to the optimal approach to the treatment of patients with acquired demyelinating neuropathy from an immunomodulatory perspective. This paper attempts to bring together some of the evidence which is available in this difficult area of neurological practice based on the outcome of Cochrane systematic reviews.

## CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a peripheral neuropathy caused by peripheral nerve inflammation probably due to autoimmunity and as such might be expected to benefit from corticosteroids. It is characterised by progressive or relapsing symmetrical motor or sensory symptoms and signs in more than one limb, developing over at least two months. It may cause prolonged periods of disability and even death. Non-randomised studies suggest that corticosteroids are often beneficial. A Cochrane review has been undertaken to evaluate the efficacy of corticosteroids for treating CIDP.

Only a single randomised controlled trial was found. This was an open study in which 19 patients treated with corticosteroids showed more improvement than 16 untreated controls after 12 weeks. Experience from large non-randomised studies also suggests that steroids are beneficial. The single randomised controlled trial with 35 participants thus provided weak evidence to support the conclusion from non-randomised studies that oral corticosteroids reduce impairment in CIDP. Corticosteroids are known to have serious long-term side effects however. The issue of a long term risk/benefit analysis has not been adequately addressed.<sup>1</sup>

While corticosteroids have clearly been widely used as a potential disease modifying therapy for CIDP, clinical observation and some formal studies have also suggested a beneficial effect of intravenous immunoglobulin. A Cochrane review has been undertaken to systematically review the evidence from randomised controlled trials concerning the efficacy and safety of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy.

Six randomised controlled trials were eligible for inclusion including 170 patients. Four studies on 113 patients compared intravenous immunoglobulin against placebo. One trial with 17 patients compared intravenous immunoglobulin with plasma exchange in a cross-over design and one trial compared intravenous immunoglobulin with prednisolone in 32 patients. The evidence from these randomised controlled trials showed that intravenous immunoglobulin improves disability for at least two to six weeks compared with placebo, with a number needed to treat of three. During this period it has similar efficacy to plasma exchange and oral prednisolone. Since intravenous immunoglobulin, plasma exchange and prednisolone seem to be equally effective, it is currently uncertain which of these treatments should be the first choice. Cost, side effects, duration of treatment, dependency on regular hospital visits and ease of administration all have to be considered before such a decision can be made.<sup>2</sup>

Sometimes patients with CIDP seem not to respond to corticosteroids, immunoglobulins or plasma exchange. In view of their immunomodulatory effects the potential use of cytotoxic drugs or even interferons is often considered in these patients. The use of such interventions has also been addressed in a further Cochrane review. A search was made for randomised and quasi-randomised trials of immunosuppressive agents including azathioprine, cyclophosphamide, methotrexate, cyclosporin A, mycophenolate mofetil, and rituximab and all immunomodulatory agents such as alpha-interferon and beta-interferon in participants fulfilling standard diagnostic criteria for CIDP.

One parallel group open trial of azathioprine for nine months involving 27 participants and another of interferon beta involving 10 participants in a double blind crossover trial with each treatment period lasting 12 weeks were found. Neither trial provided the declared primary outcome measure and neither also showed a significant beneficial effect on any of the outcome measures selected by the authors in the protocol for this review. It was thus concluded that the evidence was inadequate to decide whether azathioprine, interferon-beta or any other immunosuppressive drug or interferon is beneficial in CIDP.<sup>3</sup>

## GUILLAIN BARRÉ SYNDROME

Guillain Barré syndrome (GBS) is an acute peripheral neuropathy which often develops following an intercurrent infection.

While usually self-limiting, paralysis can be severe and involve respiratory muscles such that ventilatory support may be needed. In some cases the disorder can thus be life-threatening. GBS is thought to be an immunologically mediated inflammation of the peripheral nerves which might be expected to benefit from corticosteroids. A Cochrane review was done to examine the efficacy of corticosteroids in hastening recovery and reducing the long-term morbidity from GBS.

Quasi-randomised or randomised controlled trials of corticosteroid or adrenocorticotrophic hormone in GBS were sought. Six randomised trials were identified. These six trials included a total of 195 corticosteroid treated patients and 187 controls. One study of intravenous methylprednisolone accounted for 243 of the total 382 subjects studied (63%). This trial did not show a significant difference in any disability-related outcome between the corticosteroid and placebo groups. All in all there was no significant difference between the corticosteroid and control groups for the primary outcome measure, improvement in disability grade four weeks after randomisation. There were also no significant differences between the groups for most of the secondary outcome measures. It was concluded that it was inappropriate to use corticosteroids in the treatment of GBS. If a patient with GBS needed corticosteroid treatment for some other reason its use was thought likely to be harmful. It was noted that the effect of intravenous methylprednisolone combined with intravenous immunoglobulin in GBS is being tested with a randomised trial.<sup>4</sup>

An impression has however been gained that intravenous immunoglobulin and plasma exchange might be useful in GBS. Cochrane reviews have therefore been undertaken to try and determine the efficacy of intravenous immunoglobulin and plasma exchange in GBS.

Two trials comparing intravenous immunoglobulin with supportive treatment were inadequate to establish its value. Six randomised trials were found comparing intravenous immunoglobulin with plasma exchange. In a meta-analysis of five trials involving 536, mostly adult, participants who were unable to walk unaided and had been ill for less than two weeks. There were no statistically significant differences in time to walk unaided, mortality, and proportion of participants unable to walk without aid after a year.

Sequential treatment was addressed in one trial involving 249 participants comparing plasma exchange followed by intravenous immunoglobulin with plasma exchange alone, and another involving 37 participants compared immunoabsorption followed by intravenous immunoglobulin with immunoabsorption alone. Neither revealed significant extra benefit from intravenous immunoglobulin.

One study of only 39 participants showed a trend towards more improvement with high-dose compared with low-dose intravenous immunoglobulin.

Although there are no adequate comparisons with placebo, intravenous immunoglobulin seems to hasten recovery from GBS to a similar extent to plasma exchange. Giving intravenous immunoglobulin after plasma exchange is not significantly better than plasma exchange alone.<sup>5</sup>

A further Cochrane review more specifically addressed the place of plasma exchange as a potential disease modifying treatment in GBS. Plasma exchange removes antibodies and other potentially injurious factors from the plasma. It involves connecting the patient's blood circulation to a machine which exchanges the plasma for a substitute solution, usually albumin. Several studies have evaluated plasma exchange in GBS. The review sought to systematically review the evidence concerning the efficacy of plasma exchange for treating GBS.

Six trials were identified including 649 patients. All of these compared plasma exchange with supportive treatment alone. In the two trials in which time to recover walking with aid was reported, the median time to recover this ability was faster in the plasma exchange than the control group. In the one trial in which time to onset of motor recovery in mildly affected patients was recorded, the time was significantly shortened in the plasma exchange group. There were significantly more patients who had improved by one disability grade or more at four weeks in the plasma exchange group as compared to the control group in the five trials where this was assessed. In general terms patients treated with plasma exchange fared significantly better in time to recover walking without aid, percentage of patients requiring artificial ventilation, duration of ventilation, full muscle strength recovery after one year, and severe sequelae after one year. There were fewer patients with infectious events and cardiac arrhythmias in the plasma exchange than the control groups.

Single studies suggested that two plasma exchanges were significantly superior to none for mild GBS and four to two for moderate GBS, but that six were not significantly superior to four for severe GBS requiring ventilation. One study suggested that continuous flow plasma exchange was significantly superior to intermittent flow. Another study found no significant difference between the two techniques. The same study found a significantly higher rate of adverse events with fresh frozen plasma as the replacement fluid than albumin.

A single trial comparing plasma exchange with cerebrospinal fluid filtration did not show any significant difference in outcomes but was too small to demonstrate equivalence.

Plasma exchange is thus the only treatment that has been proven to be superior to supportive treatment alone in GBS. It is therefore suggested that plasma exchange should be the treatment against which new treatments, such as intravenous immunoglobulin, should be judged.<sup>6</sup>

## MULTIFOCAL MOTOR NEUROPATHY

Multifocal motor neuropathy (MMN) is a distinct clinical entity characterised by progressive, predominantly distal, asymmetrical limb weakness and minimal sensory abnormality. It can often occur as an MND mimic syndrome. The differential diagnosis of MND and MMN is thus very important. The pathognomonic feature of MMN is the presence of multiple partial motor nerve conduction blocks. Controlled trials have demonstrated the efficacy of regular intravenous immunoglobulin infusions. Other immunosuppressive agents and measures such as corticosteroids, plasma exchange, azathioprine, cyclophosphamide, cyclosporin, methotrexate, mycophenolate, interferon, total lymphoid irradiation or bone marrow transplantation have also been discussed as possible treatments. A Cochrane review was therefore

undertaken to identify and review systematically randomised controlled trials of these immunosuppressive agents excluding the use of intravenous immunoglobulins.

No trials satisfying the search criteria were found and the discussion was based solely on prospective and retrospective case series. Data from controlled trials, case series and anecdotal experience have established IV immunoglobulin as the first-line treatment of MMN. A non-systematic review of case series can only provide limited support for the beneficial effects of a therapeutic intervention. Furthermore, the wide variability in the clinical course and IV immunoglobulin responsiveness of MMN makes it all the more difficult to interpret uncontrolled data. With these caveats, a few observations can be made on the role of immunosuppressive agents in the treatment of MMN.

There are some reports of benefit but also of serious adverse events from cyclophosphamide either as a primary agent or for patients who do not respond to IV immunoglobulin, lose their responsiveness to IV immunoglobulin or require frequent infusions. The use of corticosteroids has been associated with deterioration. There is little evidence about less toxic immunosuppressive agents such as azathioprine, beta-interferon or about plasma exchange. The value of these agents can only be determined by randomised controlled trials which are urgently needed. Other issues which need to be addressed in further studies include:

1. What is the best option for patients who do not respond to IV immunoglobulins?
2. Less toxic drugs such as azathioprine, mycophenolate and beta-interferon should be studied.
3. For patients who lose their responsiveness or require frequent IV immunoglobulin infusions, the adjunctive therapeutic role of less toxic cytotoxic drugs, beta-interferon and lower doses of cyclophosphamide should be explored. Such treatment regimes may also reduce the slow neurological deterioration that is sometimes seen even in patients treated optimally with regular IV immunoglobulin infusions.
4. In addition, studies that identify factors that predict lack or gradual loss of response to IV immunoglobulins would be useful in selecting patients relatively early for alternative and combination treatment regimes, before axonal damage precludes significant recovery.<sup>7</sup>

### **SERUM MONOCLONAL ANTI-MYELIN ASSOCIATED GLYCOPROTEIN ANTIBODY ASSOCIATED NEUROPATHY**

Serum monoclonal anti-myelin associated glycoprotein (anti-MAG) antibodies may be pathogenic in some patients with IgM paraprotein and demyelinating neuropathy. Immunotherapies aimed at reducing the level of these antibodies might be expected to be of benefit in the treatment of the neuropathy. Many potential therapies have been described in small trials, uncontrolled studies and case reports. A Cochrane review was carried out to

examine the efficacy of immunotherapy in reducing disability and impairment resulting from IgM anti-MAG demyelinating peripheral neuropathy.

Six randomised controlled trials were found of which five were eventually included. There were no significant benefits of the treatments used in the predefined outcomes stated in the review protocol. However intravenous immunoglobulin showed benefits in terms of improved modified Rankin scale at two weeks and 10 metre walk time at four weeks. It was concluded that there was inadequate reliable evidence from trials of immunotherapies in anti-MAG paraproteinaemic neuropathy to recommend any particular immunomodulatory treatment. Intravenous immunoglobulin is relatively safe and may produce some short-term benefit but it was suggested that further large well-designed randomised trials were required to assess the treatment of this disorder.<sup>8</sup>

### **GENERAL COMMENT**

Despite much work it is seen that the literature is still unable to provide clear and unequivocal guidance on the use of immunomodulatory therapy in acquired demyelinating neuropathy. In some areas such as GBS this guidance is stronger than in some others. It is hoped that this paper will have given an impression of how Cochrane principles can be applied in such situations and will give practising physicians an overview of current thoughts in this sometimes confusing area of practice.

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