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# Standard and escalating treatment of chronic inflammatory demyelinating polyradiculoneuropathy

**Min-Suk Yoon, Andrew Chan and Ralf Gold**

***Abstract*:** Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, immune-mediated polyradiculoneuritis that is progressive or relapsing over a period of at least 8 weeks. Although the exact pathogenesis is unclear, it is thought to be mediated by both cellular and humoral immune reactions directed against the peripheral nerve myelin or axon. CIDP also involves spinal nerve roots. Early medical treatment of CIDP is important to prevent axonal loss. Only three treatment regimens for CIDP have demonstrated benefit in randomized, controlled studies: corticosteroids, plasma exchange, and intravenous immunoglobulins (IVIg). Approximately 25% of patients respond inadequately to corticosteroids, plasma exchange or IVIg. Large placebo-controlled trials with alternative immunosuppressive compounds, e.g. mycophenolate mofetil, cyclosporine, cyclophosphamide, or monoclonal antibodies, are lacking.

***Keywords*:** chronic inflammatory demyelinating polyradiculoneuropathy, immunosuppression, monoclonal antibodies

Correspondence to:
**Min-Suk Yoon, MD**
Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital Bochum, Gudrunstrasse 56, 44791 Bochum, Germany
**min-suk.yoon@uni-due.de**

**Andrew Chan, PhD**
**Ralf Gold, Prof.**
Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Gudrunstrasse 56, 44791 Bochum, Germany

## Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP), a chronic inflammatory disease of the peripheral nervous system (PNS), is clinically characterized by hyporeflexia or areflexia and progressive or relapsing motor or sensory dysfunction developing over weeks [Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force, 1991]. The prevalence of CIDP is estimated at between 2 and 7 per 100,000 [Merkies *et al*. 2009] and peaks between 40 and 60 years with a slight predominance amongst males.

Compared with acute inflammatory demyelinating polyneuritis, the most common presentation of Guillain–Barré syndrome (GBS) with an acute onset reaching the nadir of symptomatology by approximately 4 weeks and a monophasic pattern, CIDP shows a slower progression of symptoms followed by a progressive or relapsing course. However, approximately 3% of CIDP patients may present with a peracute onset, so that the diagnosis of CIDP is often made in retrospect [Ruts *et al*. 2010; McCombe *et al*. 1987]. Onset of CIDP is not triggered by infectious agents.

The diagnosis of CIDP is primarily made on the basis of clinical presentation and neurophysiological findings. The presence of proximal weakness in the context of a neuropathy suggests the impairment of nerve roots and is commonly observed in CIDP patients [Dyck *et al*. 1975]. Early evaluation with nerve conduction velocity studies classically shows evidence of demyelination with slowed nerve conduction, temporal dispersion, prolonged distal latencies, and prolonged F-wave latencies speaking for affliction of spinal roots. Neurophysiologic studies performed late during the disease course or in severe cases may show loss of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs). However, these neurophysiologic findings are not mandatory for the diagnosis. Similarly, as cerebrospinal fluid analysis is often performed in patients suspected of having CIDP, cytoalbuminologic dissociation is common but not obligatory for the diagnosis.

For the diagnosis of CIDP the Inflammatory Neuropathy Cause and Treatment (INCAT), the AAN and Saperstein criteria come into operation [Sander and Latov, 2003]. Of these, the INCAT criteria are less invasive and restricted than the AAN or Saperstein criteria. The INCAT criteria require the presence of progressive or relapsing motor or sensory dysfunction of more than one limb resulting from neuropathy developing over at least 2 months, and hyporeflexia or areflexia. If in electrophysiological studies demyelination is present in only two nerves, however, a nerve biopsy with histologic evidence of demyelinated and remyelinated nerve fibers must also be present.

In the last two decades, clinical trials have revealed the therapeutic efficacy of prednisolone, plasma exchange, and, in particular, intravenous immunoglobulins (IVIg) [Hahn, 1998; Hahn *et al.* 1996; Dyck *et al.* 1994, 1982]. Along with corticosteroids, IVIg remain the mainstay of treatment with efficacy in 60–80% of CIDP patients [Kuitwaard and van Doorn, 2009; Mehndiratta and Hughes, 2002]. Patients who are refractory to individual trials with these conventional therapies are typically considered for an alternative immunomodulatory or immunosuppressive treatment. Treatment of CIDP should be initiated early in the course of the disease to avoid permanent axonal injury.

## Corticosteroids

A placebo-controlled study showed a benefit in CIDP patients [Dyck *et al.* 1982]. Despite the lack of randomized, double-blind (Table 1), placebo-controlled studies, treatment of CIDP with steroids is commonly accepted as long-term experience exists [Mehndiratta and Hughes, 2002]. The mean time to improvement was 1.9 months (range: several weeks to 5 months), the time to maximal benefit was $6.6 \pm 5.4$ months [Barohn *et al.* 1989]. The typical starting dose of prednisone is 1–1.5 mg/kg/day for 2–4 weeks [Dyck *et al.* 1982; Dalakas and Engel, 1981; Prineas and McLeod, 1976]. Intravenous steroid pulse therapy is also used in more severe cases [Lopate *et al.* 2005; Molenaar *et al.* 1997].

At lower dosage below 1 mg/kg body weight, glucocorticoids inhibit inflammation by activating the cytosolic glucocorticoid receptor. This complex is transported to the nucleus and regulates gene expression. There are also interactions of the glucocorticoid receptor that inhibit the proinflammatory transcription factor, nuclear factor kappa B (NF-kB). These interactions are important in anti-inflammatory effects of glucocorticoids [Garside *et al.* 2004]. Glucocorticoids also suppress inflammation by decreasing the release of proinflammatory cytokines and vasoactive factors.

## Intravenous immunoglobulins

Several randomized, controlled studies demonstrated the short-term benefit of IVIg in patients with CIDP [Hughes *et al.* 2008, 2001; Hahn *et al.* 1996; Dyck *et al.* 1994]. The usual dose is 2 g/kg as a starting regimen, which can be divided over 2–5 days. IVIg contains >95% IgG and <2.5% IgA and has pleiotropic effects on the human immune system. IVIg modulate antigen recognition, autoantibodies, chemokines and adhesion molecules and their receptors, inhibit complement activity, limit apoptosis by anti-Fas antibodies and modulates phagocytosis by binding on the Fc-receptor on macrophages [Gold *et al.* 2007; Dalakas, 2004]. In a large randomized, double-blind, placebo-controlled, response-conditional, crossover designed study, 117 participants who met the specific neurophysiological inflammatory neuropathy cause and treatment criteria were enrolled. Treatment responders after 24 weeks were re-randomized to an extension phase. During the first 24 weeks patients treated with IVIg showed a significant benefit compared with placebo group. In the extension period participants treated with IVIg had less deterioration compared with the placebo group [Hughes *et al.* 2008]. CIDP patients show a significant improvement in their quality of life [Merkies *et al.* 2009]. This 'ICE' study was the first controlled long-term study of IVIg in CIDP.

An alternative approach due to the high costs of IVIg is the subcutaneous application of immunoglobulins (SCIg) via a small portable pump [Leahy, 1986; Berger *et al.* 1982, 1980]. This regimen is well established and results in well-balanced IgG plasma levels while lowering peak concentrations compared with IVIg [Waniewski *et al.* 1994]. With respect to pharmacoeconomic aspects, the use of SCIg can reduce the therapy costs significantly by up to 50%.

## Plasma exchange

In randomized, placebo-controlled studies plasmapheresis demonstrated its benefit in patients with CIDP [Hahn *et al.* 1996; Dyck *et al.* 1986]. Compared with IVIg,

glucocorticosteroids or chemotherapy plasma exchange has a higher incidence of relapse [Hahn *et al.* 1996]. Patients with a dual treatment (plasmapheresis and cyclophosphamide) also improved [Blume *et al.* 1995].

Humoral factors are removed by separating the plasma by filtration and returning the blood cells in a plasma substitute, e.g. albumin. In addition, plasma exchange may act by removing complement products and cytokines. A course of 4–6 sessions over 10 days can reduce IgG by approximately 70–90% [Brecher, 2002; Weinstein, 2000]. Plasma exchange can be used as a maintenance treatment solely or concomitantly with other immunomodulatory or immunosuppressive medications. As plasma exchange is invasive and fraught with risk, the authors use plasma exchange in the daily routine with 4–5 sessions at 50 mg/kg body weight exchange volume to deescalate a severe deterioration and not for long-term maintenance treatment.

## Alternative options

About 25% of CIDP patients fail to respond or respond incompletely to glucocorticosteroids, IVIg or plasma exchange. In these cases the treatment is switched to immunosuppressive medication or monoclonal antibodies. Available data in the literature are insufficient to give a general recommendation with respect to different immunotherapies (e.g. immunosuppressants such as azathioprine, or immunomodulatory agents such as monoclonal antibodies directed against defined components of the immune system).

Reported cases include patients refractory to the conventional treatment which therefore are using multiple agents in sequence. This makes it difficult to evaluate the superiority of a specific treatment. The choice of an alternative option is highly individualized and dependent on comorbidity, age, potential risk, availability and pricing of the chosen treatment.

## Azathioprine

The effect of azathioprine on CIDP is controversial. A dose of 2 mg/kg over 9 months in combination with glucocorticoids did not show a benefit [Dyck *et al.* 1985]. In this work the study sample was too small to detect all but a large treatment effect, and typically azathioprine needs 3–6 months to achieve full efficacy. In other small case series, glucocorticosteroid unresponsive CIDP patients [Pentland *et al.* 1982; Dalakas and Engel, 1981] or concurrent glucocorticosteroid therapy and higher dose of azathioprine [Pentland *et al.* 1982] led to an improvement. Azathioprine is generally well tolerated. The authors prefer a dose of 2.5–3.0 mg/kg. If patients do not tolerate the standard dose of 2.5–3.0 mg/kg, a lower starting dose can be used twice daily. It is of note that azathioprine is contraindicated in patients simultaneously treated with allopurinol.

## Mycophenolate mofetil

Mycophenolate mofetil is a reversible inhibitor of inosine monophosphate dehydrogenase. It inhibits lymphocyte proliferation and formation of adhesion molecules and migration [Gold and Schneider-Gold, 2008; Gorson *et al.* 2004; Umapathi and Hughes, 2002; Chaudhry *et al.* 2001; Mowzoon *et al.* 2001]. The usual dose is 2000 mg divided into two daily dosages, and the recommended trough level in plasma is 1–2 mg/l. Some treatment refractory patients may respond to mycophenolate mofetil. In small cases series MPA was beneficial in conventional treatment refractory CIDP patients or helped reducing the glucocorticosteroid dose [Gorson *et al.* 2004].

## Cyclosporine

Cyclosporine A was used in patients unresponsive to conventional therapy. Available data are retrospective or based on small study samples [Matsuda *et al.* 2004; Barnett *et al.* 1998; Mahattanakul *et al.* 1996]. In one retrospective study, cyclosporine A exhibits a beneficial effect in patients with progressive and relapsing CIDP [Barnett *et al.* 1998]. In a small study sample of eight treated patients only three of them were felt to be successfully treated [Mahattanakul *et al.* 1996]. In seven patients with refractory CIDP treated with cyclosporine A grip strength was found to be increased, and modified Ranking and INCAT disability scores were decreased significantly [Matsuda *et al.* 2004]. It is of note that cyclosporine A has frequent drug interactions. Medication inducing P450 3A System (CYP3A), e.g. carbamazepine reduce cyclosporine A level and agents inhibiting CYP3A, e.g. contraceptive pills can elevate cyclosporine A to a toxic level. Patients should be screened for renal function prior to cyclosporine A treatment. The authors use 100–150 mg twice daily. The typical trough concentration is 70–120 μg/l.

### High-dose cyclophosphamide

High-dose cyclophosphamide (200 mg/kg) leads usually to neutropenia for approximately 7–14 days post administration. Hence, cyclophosphamide allows a rapid recovery of the white cell lineage. The enzyme deficiency in T- and B-lymphocytes determines the cytotoxicity consecutively leading to a highly immunosuppressive therapy. CIDP patients who had been refractory to conventional treatment achieve a remission and improvement in quality of life [Gladstone *et al.* 2007, 2005; Brannagan *et al.* 2002]. Fifteen patients were reviewed retrospectively who underwent a cyclophosphamide pulse therapy for up to 6 months [Good *et al.* 1998]. They found, that 11 patients had a complete remission and 12 patients were able to return to their routine work. Our preference is an initial pulse of three cycles with 350 mg/m$^2$ body surface followed by single infusions at 600 mg/m$^2$ body surface in 6–8 week intervals. A switch to azathioprine or mycophenolate mofetil is possible after a remission is achieved. The intravenous pulse treatment is better tolerated compared with long-term oral treatment and it takes longer to reach the critical cumulative dose of 50 g bearing an increased risk of developing malignant disease [Pedersen-Bjergaard *et al.* 1985].

### Methotrexate

Sixty patients were enrolled in a multicenter trial either receiving placebo or methotrexate [RMC Trial Group, 2009]. The study dose was equal to those used in trials showing efficacy in autoimmune rheumatologic diseases (7.5 mg weekly for 4 weeks, then 10 mg weekly for 4 weeks, and then 15 mg weekly for 32 weeks). All of them were cotreated with glucocorticoids or IVIg. The primary endpoint was 20% reduction in mean weekly dose of either glucocorticoids or IVIg by the end of the trial. There was no significant difference in primary outcome between the methotrexate and the placebo group.

Methotrexate is given once weekly orally, subcutaneously, or intramuscularly. Renal or hepatic disorder and pulmonary fibrosis are clear contraindications. The typical weekly dose of methotrexate is 10–20 mg. Neurological side effects can be reduced by low-dose supplementation of oral folate (e.g. 5 mg daily).

### Rituximab

Rituximab targeting CD20 on B-lymphocyte is a chimeric monoclonal antibody. It depletes mature B-lymphocytes for approximately 10 months [Dalakas *et al.* 2009; Silverman and Weisman, 2003]. Cells that do not express CD20 antigen are not affected. The usual dose in oncology is 375 mg/m$^2$ given in four weekly intravenous infusions; in autoimmune disorders typically 1000 mg are given twice within 14 days [Hauser *et al.* 2008]. Rituximab has been beneficial for patients with anti-MAG [Pestronk *et al.* 2003; Renaud *et al.* 2003; Levine and Pestronk, 1999] and MMN [Pestronk *et al.* 2003; Levine and Pestronk, 1999]. Benefit is noted starting after 4 weeks and lasting up to 12 months. In a more recent open-label study in 13 refractory CIDP patients, nine patients responded to rituximab at a median time of 2.0 months after the end of rituximab cycle lasting for up to 12 month [Benedetti *et al.* 2011]. Rituximab is usually well tolerated in patients with neurological disorders. Side effects are more common in patients with lymphoma and include mucocutaneous reactions or, more commonly, fever, chills, hypotension, and dyspnea [Grillo-Lopez *et al.* 2002].

### General approach and pragmatic treatment

The optimal treatment of CIDP depends on the early diagnosis before significant axonal degeneration or even axon loss occurs that is associated with an incomplete treatment response. To avoid a cost explosion in health economics it is important to achieve long-term remission in a cost-effective manner.

The first-line treatment for CIDP includes glucocorticoids, IVIg or plasma exchange.

A pragmatic approach is a steroid pulse treatment, which is better tolerated [van Schaik *et al.* 2010; Muley *et al.* 2008] and cost-effective. Yet the costs of long-term steroid-associated side effects also have to be considered for a balanced treatment decision.

The authors start in severely afflicted patients with intravenous glucocorticosteroids for 3–5 days in a dose of 500–1000 mg methylprednisolone, and then switch to an oral steroid agent at a dose of 1 mg/kg. To avoid steroid-related adverse-effects an immunosuppressant can be used as steroid-sparing agent whilst reducing the oral steroid dose by 10 mg per week until a maintenance dosage of 10 mg is achieved. Wide experience exists with azathioprine [Koller *et al.* 2005; Gorson and Ropper, 2003] even though large randomized, controlled trials are lacking.

**Table 1.** Summary of studies.

| Drugs/Intervention | Study/Series | | Number of participants enrolled | Number of participants improved/primary endpoint fulfilled | Notes |
|---|---|---|---|---|---|
| Steroids | Dyck *et al.* [1982] | Prednisone *vs.* no treatment | 40 | 12 | 28 patients completed trial, $n=14$ prednisone treated |
| Plasma exchange | Dyck *et al.* [1986] | Prospective double blinded | 15 | 9 | $n=15$ (PE), $n=14$ (sham) |
| | Hahn *et al.* [1996] | Double blind, sham controlled, crossover | 18 | 12 | 15 participants completed trial |
| IVIg | Hughes *et al.* [2008] | Randomized, placebo-controlled | 117 | 32 | $n=59$ IVIg, $n=58$ placebo |
| Azathioprine | Dalakas and Engel [1981] | Case series | 4 | 3 | Steroid nonresponder |
| | McCombe *et al.* [1987] | Case series | 7 | 4 | |
| Cyclophosphamide | Good *et al.* [1998] | Case series | 15 | 11 | |
| | Gladstone *et al.* [2005] | Case series | 5 | 4 | Severe, refractory patients Long time follow up [range: 1.6–4.8 years] |
| Ciclosporine A | Matsuda *et al.* [2004] | | 7 | 7 | |
| | Barnett *et al.* [1998] | Case series | 19 | 15 | Retrospective, relapsing and progressive course, patients refractory to steroid, IVIg, azathioprine, cyclophosphamide, plasma exchange |
| Mycophenolate Mofetil | Gorson *et al.* [2004] | Case series | 12 | 3 | Retrospective, mean dose: 2.1 g/day |
| | Umapathi and Hughes [2002] | Case series | 4 | 0 | No reduction of steroids or other immunosuppressants |
| Rituximab | Benedetti *et al.* [2011] | Case series | 13 | 9 | Retrospective |
| Methotrexate | RMC Trial Group [2009] | Randomized, double-blind, controlled trial | 60 | 28 | Primary endpoint: 20% reduction of steroids or IVIg; $n=27$ (MTX), $n=32$ (Placebo) |

MTX: methotrexate; PE: plasma exchange; IVIg: Intravenous immunoglobulin.

Mycophenolate mofetil, cyclosporine and methotrexate can be used if adverse effects due to azathioprine become evident.

If contraindications against steroids or immunosuppressants exist, the authors prefer IVIg as first-line treatment. In view of the high costs of IVIg and the need for intravenous administration that requires physician's consultation, considering the possibility of SCIg application is worthwhile [Lee *et al*. 2008].

## Incomplete response and treatment nonresponders

About 60% of the CIDP patients respond to the first-line treatment with steroids, IVIg or plasma exchange [Mehndiratta and Hughes, 2002]. In intractable cases high-dose cyclophosphamide has been shown to be effective [Gladstone *et al*. 2007, 2005; Brannagan *et al*. 2002]. We prefer an initial pulse of three cycles at 350 mg/m$^2$ body surface followed by 600 mg/m$^2$ body surface at an interval of every 6–8 weeks.

The authors use plasma exchange (50 ml/kg) if rapid deterioration of symptoms occurs. If conventional treatment fails, five courses of plasma exchange are realized before establishing an immunosuppressive regimen.

Another promising compound that is well tolerated is rituximab. Even though randomized, controlled trials are lacking there is growing evidence that rituximab is effective in the treatment of CIDP refractory to other approved therapies [Benedetti *et al*. 2011, 2008; Munch *et al*. 2007].

We are aware that existing data are scarce and based on small case series. In daily routine patients complain of lack of remission shortly after the beginning of CIDP treatment. And in some cases a more aggressive immunosuppression or treatment change are discussed although the time course until a remission could be achieved is too short. We would like to draw the attention to this latter case and recommend to be patient shortly after the beginning of treatment. Also physicians should be cautious in handling off-label regulations for the use of the above-described therapies.

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## Conflict of interest statement

None declared.

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