

Cochrane Corner

Are the treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) effective and safe? - A Cochrane Overview summary with commentary

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Abstract.

BACKGROUND: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a potentially disabling health condition.

OBJECTIVE: To assess the effects of different pharmacological interventions used in CIPD.

METHODS: To summarize and to discuss the rehabilitation perspective on the published Cochrane Overview “Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews” by Anne Louise Oaklander, et al., representing the Cochrane Neuromuscular Group.

RESULTS: Five CSRs and 23 RCTs, reporting data on corticosteroids, plasma exchange and intravenous immunoglobulin, were considered in the overview.

CONCLUSIONS: High quality trials investigating the combined effectiveness of drugs and exercise using ICF based outcomes should be encouraged.

The aim of this commentary is to discuss the rehabilitation perspective on the published Cochrane Overview “Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an

overview of systematic reviews” by Anne Louise Oaklander, Michael P.T. Lunn, Richard A.C. Hughes, Ivo N. van Schaik, Chris Frost, Colin H. Chalk¹, representing the Cochrane Neuromuscular Group. This Cochrane Corner is produced in agreement with *NeuroRehabilitation* by Cochrane Rehabilitation.

¹The abstract/plain language summary of this Cochrane Overview is taken from a Cochrane Overview previously published in the Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD010369. Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

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1. Background

Chronic inflammatory demyelinating polyneuropathy (CIDP), which affects 1–9/100.000, is potentially disabling. Although disability measures such as the CIDP-RODS are the preferred out-

come for trials, the effects of disease-modifying and symptomatic pharmacotherapies on rehabilitation and functioning are inadequately studied.

Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): An overview of systematic reviews

(Oaklander, Lunn, Hughes, van Schaik, Frost, & Chalk, 2017)

2. What is the aim of the Cochrane Review?

To summarize the quality of the data and conclusions of Cochrane systematic reviews (CSRs) and non-CSRs regarding treatment trials for CIDP to help guide treatment decisions by rehabilitation clinicians.

3. What was studied and methods

The authors reported primary outcomes, prioritize disability changes after 12 months. Five CSRs and 23 RCTs were considered, among which 15 had been included in CSRs. The authors struggled to compare treatments because outcome measures and intervals differed. Weakness was the primary outcome measure in most studies; no trials using fatigue or pain as primary outcomes were found. Regarding adverse events (AE), not all trials collected these data and when they did so, details and quality of reporting varied. All treatments had potential AE that varied from common post-treatment (for example bruising after intravenous (IV) therapies), to rare potentially life-threatening. Reliable comparable data on the AEs of treatment were not available.

The authors considered all SRs of RCTs of any treatment for any form of CIDP. Two authors independently identified published SRs for inclusion and collected data and reported the quality of evidence using GRADE criteria. Two other authors independently checked review selection, data extraction and quality assessments. On 31 October 2016, the authors searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (in the Cochrane Library), MEDLINE, Embase, and CINAHL Plus for systematic CIDP reviews as well as for RCTs of any CIDP in the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL Plus.

4. Results

4.1. Corticosteroids

It was uncertain whether daily oral prednisone improved impairment in CIDP versus no treatment because of the very low quality of evidence (1 trial, 28 participants). For high-dose monthly oral dexamethasone compared to oral prednisolone, moderate-quality evidence (1 trial, 41 participants) indicated that 6-month use did not improve disability more than daily oral prednisolone. IV methylprednisolone was also no better than oral prednisolone. AEs were poorly reported but clinical use and other research has established multiple serious effects of prolonged corticosteroid use.

4.2. Plasma exchange

Moderate-quality evidence (2 trials; 59 participants) showed that twice-weekly exchanges produced short-term improvement in neurological examination and probably improved disability. Three through 17% of procedures had AEs including difficult venous access and haemodynamic changes (Mahdi-Rogers et al., 2017).

4.3. Intravenous immunoglobulin (IVIg)

High-quality evidence (5 trials, 269 participants) showed more short-term improvement with IVIg than placebo (49% vs. 18%). AE were overall more common, but serious ones were not (moderate-quality evidence, 3 trials, 315 participants). Serious AE related to IVIg included thromboembolism and meningeal inflammation, but these are almost always prevented by slow administration, concurrent hydration, diphenhydramine and anti-inflammatories (Eftimov et al., 2013, Mahdi-Rogers et al., 2017).

4.4. Comparison studies and other treatments

A high-quality study (45 participants) reported similar efficacy of IVIg and IV methylprednisolone, which in another study had similar efficacy to daily oral prednisolone. Moderate-quality evidence supported comparable short-term improvement of disability between IVIg, plasma exchange (1 trial, 19 participants) and oral prednisolone (1 trial, 29 participants). It is uncertain whether adding azathioprine (2 mg/kg) to prednisone improved impairment more than prednisone alone, as trial quality was very low (1

trial, 27 participants). Observational studies showed treatment-ending effects of azathioprine in 10%, although treatment-ending effects were not always reported for other therapies to permit comparison. According to low-quality evidence (1 trial, 60 participants), compared to placebo, methotrexate 15 mg/kg did not allow more participants to reduce corticosteroid or IVIg doses by 20%. Serious AE were no more common with methotrexate than placebo, but observational studies showed that methotrexate can cause teratogenicity, abnormal liver function, and pulmonary fibrosis. According to moderate-quality evidence (2 trials, 77 participants), interferon beta-1a (IFN beta-1a) did not allow more people to withdraw from IVIg than placebo and there were not more serious AE.

5. Conclusions

Daily oral prednisolone and prednisone are used as primary treatments for CIDP based on clinical experience, global availability, and very low cost, although because they are generic, there are no high-quality trials. These are urgently needed to evaluate dosing, efficacy for specific symptoms, and for long-term safety data. IV methylprednisolone and monthly high-dose oral dexamethasone offer no advantages and thus are not primary.

The IV treatments of total plasma exchange and pooled immunoglobulin therapy also conveyed short-term benefit and are primary treatment options. Neither increased serious side effects, but proper administration and equipment are required. IVIg, which competitively inhibits pathogenic immune effectors with healthy replacements, uses standard peripheral IV but it is very expensive and blood supplies are limited. Home IV and subcutaneous administration can reduce costs and other studies (awaiting inclusion in a CSR and not included here) report similar efficacy for subcutaneous administration. Plasma exchange immediately transiently lowers circulating unbound immune effectors. It is sometimes preferred during pregnancy or as immediately treatment for urgent patients, but it requires dialysis equipment and effects are short lived, so it is now usually used along with with more-definitive inhibitors of B-cell antibody production.

Other immunotherapies were inadequately studied in the limited, small and inadequate studies that often did not demonstrate benefit. Thus we need more trials of adequate size, dose and duration—not only on older

agents but on new ones as they become available. Dosing, administration regimens and routes and on non-immunotherapy treatments for symptoms need to be studied (Léger et al., 2016). These studies should prioritize longer-term benefits, wider functional outcomes including pain and fatigue, and predictors of response. Standardizing outcomes, metrics, and AE reporting would add interoperability permitting extraction of more conclusions and cost-effectiveness comparisons (Léger et al., 2016).

6. Implications for practice in neurorehabilitation

There are no CIDP-specific data, but a 2004 CSR investigating the effect of exercise on functioning in people with neuropathy, including CIDP, found moderate quality evidence that strengthening exercises increased muscle strength (White 2004). Thus, integration of individualized rehabilitation treatment with pharmacotherapy appears useful. Ideally, future trials might investigate combined effectiveness of drugs and exercise using ICF based outcomes, including weakness, pain and fatigue, activity limitation and participation restriction.

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Conflict of interest

The authors declare no conflicts of interest.

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