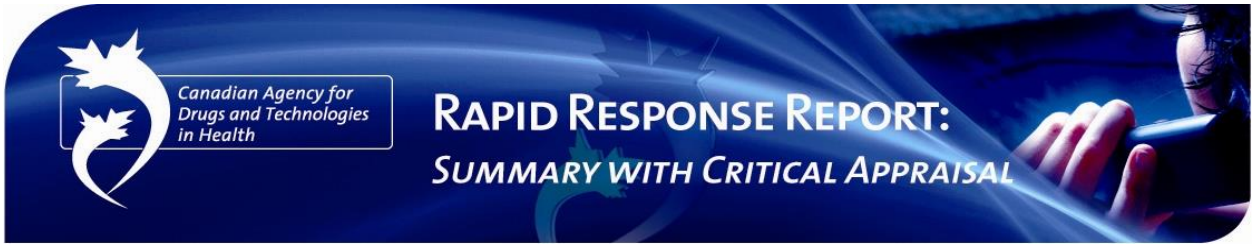


TITLE: **Immunomodulatory Drugs and Intravenous Immunoglobulin (IVIg) for Patients with Chronic Demyelinating Polyneuropathy Who Are in Remission: A Review of Clinical and Cost-effectiveness and Guidelines**

DATE: 13 Mar 2015

CONTEXT AND POLICY ISSUES

Chronic inflammatory demyelinating polyneuropathy (CIDP) encompasses a group of acquired, immune-mediated inflammatory disorders that present chronically and progress for greater than eight weeks.[1,2] CIDP is thought to emerge from a synergistic interaction of cell-mediated and humoral immune responses that are directed against incompletely characterized peripheral nerve antigens; thus, leading to the hallmark characteristic of demyelination of the peripheral nerves.[1] Disease course for CIDP can be classified as chronically progressive, monophasic, or relapsing.[2] Although CIDP can occur at all ages, it is more prevalent in older individuals and in males.[2] Older patients are more likely to present with chronic non-relapsing course whereas younger patients are more likely to experience a relapsing-remitting course of the disease.[1,2] In developed countries, reported prevalence from six studies ranged from 0.46 to 7.7 per 100,000 individuals.[3-8]

Given its immunopathophysiology, typical clinical features of CIDP include symmetrical motor weakness of the proximal and distal muscles, and/or impaired sensory function.[1,2] Patients may experience global muscle weakness and a general reduction or absence of deep tendon reflexes that may be so profound that walking is inhibited. In severe cases where denervation of the respiratory muscles occurs, death may result. Sensory symptoms mainly involve vibration and position (e.g., numbness, paresthesia, gait imbalance) rather than pain and temperature.[2]

Existing therapies for CIDP have been focused on blocking immune processes to arrest inflammation and demyelination.[1] One of the standard first-line treatments has been intravenous immunoglobulin (IVIg), a blood product that contains immunoglobulin G pooled from many thousands of human blood donors.[2,9] A 2009 health technology assessment by CADTH found that, compared to placebo, IVIg led to a statistically significant reduction in impairment and

disability amongst patients with CIDP although the incremental-cost effectiveness ratio of IVIg compared to corticosteroids was $549,449 per quality-adjusted life year (QALY).[10]

In terms of the disease course, patterns of relapses and remissions will vary greatly between individuals. Medical literature presently suggests treatment continuation until maximum improvement or stabilization is observed by responders. Thereafter, maintenance therapy can be tailored to an individual's need, with the goal of preventing or diminishing the frequency of relapses, or hindering the disease's progression.[1,9] In a previous study,[11] up to 55% of responders to IVIg were able to discontinue treatment after 24 weeks without a relapse. This has led to the question of whether tapering and eventual discontinuation of infusions may be possible to avoid overtreatment, to reduce costs and to minimize side-effects.[12] Given the presumed autoimmune basis for CIDP and its suggested pathogenetic similarities to multiple sclerosis, immunomodulatory drugs (including immunosuppresants) have been suggested as a therapeutic option.[1] Specifically, maintenance therapy with immunomodulatory drugs, alone or in combination with a lower dose of IVIg, has been proposed although the clinical and economic evidence supporting such a practice is unclear.

The purpose of this rapid review is therefore to compare the available evidence on immunomodulatory drugs, alone or in combination with a lower concentration of IVIg, in terms of their comparative clinical effectiveness, safety and cost-effectiveness for patients with CIDP under remission. Furthermore, guidelines on maintenance therapy for CIDP patients in periods of remission were identified and assessed.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of using either immunomodulatory drugs alone or as adjunctive treatment to intravenous immunoglobulin (IVIg) therapy in patients with chronic demyelinating polyneuropathy (CIDP) who are in remission?

2. What is the cost-effectiveness of using either immunomodulatory drugs alone or as adjunctive treatment to IVIg therapy in patients with CIDP who are in remission?

3. What are the guidelines associated with the use of either immunomodulatory drugs alone or as adjunctive treatment to IVIg therapy in patients with CIDP who are in remission?

KEY FINDINGS

The efficacy, safety and cost-effectiveness of immunomodulatory drugs remain largely unclear given the limited number of studies that were identified. Two studies met the inclusion criteria for this review. One was a systematic review of randomized and quasi-randomized studies while the other was a European clinical practice guideline that covered the diagnosis and treatment of CIDP. Among the trials identified within the systematic review, no significant benefit from interferon beta-1a or methotrexate was observed in patients receiving these immunomodulators as an adjunctive agent to IVIg. Based on consensus reached by clinical experts, the clinical practice guideline recommended adding an immunosuppressant or immunomodulator only if response to therapy is inadequate or if one desires a lower dose of the maintenance therapy, and the remaining first-line treatments alternatives have been tried without success.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and February 10, 2015.

Selection Criteria and Methods

One reviewer screened the search results to identify relevant publications, including: health technology assessments (HTAs); systematic reviews (SRs) and meta-analyses (MA); randomized controlled trials (RCTs); non-randomized studies; economic evaluations; and clinical practice guidelines (CPGs). The initial screen was based on title and abstract, which was followed by a full-text screen of any potentially relevant articles. Studies considered for inclusion were based on the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with chronic demyelinating polyneuropathy (CIDP) who are in remission
Intervention	Immunomodulatory drugs (e.g., cyclosporine, azathioprine, interferon beta 1a, interferon alpha, tacrolimus, mycophenolate mofetil) alone or in combination with standard practice (i.e. IVIg therapy)
Comparator	Standard practice alone
Outcomes	Clinical effectiveness (e.g., retaining remission, benefits, harms, etc.) cost-effectiveness, guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, nonrandomized studies, economic evaluations, clinical practice guidelines

Exclusion Criteria

Articles were excluded if there were a duplicate report of the same study; if they were already included in a selected SR or HTA; if they were published prior to 2010; or if they did not meet the specified inclusion criteria (Table 1).

Critical Appraisal of Individual Studies

SRs were appraised using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist.[13] Items considered in the AMSTAR checklist include: a priori design of the review; duplicate independent reviewers; a priori defined eligibility criteria; comprehensive search of information sources; transparent reporting of study selection; clear presentation of study characteristics; assessment of studies' quality; scientifically-sound interpretation of the results; appropriate methods to combine data from studies; assessment of publication bias; and reporting of funding sources.[13]

Guidelines were appraised using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[14] The domains included in the AGREE instrument include: scope and purpose of the guideline; stakeholder involvement; rigor of development; clarity and presentation; applicability; and editorial independence.[14]

In conducting the critical appraisal, an overall numeric score was not calculated for each study. Rather, the selected instrument was used as a tool to identify strengths and limitations that were subsequently reviewed narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

231 citations were identified from the literature search and ten potentially relevant reports were selected for full-text review following the initial title and abstract screen. Two publications, a SR[15] and a CPG,[16] were found that satisfied the inclusion criteria (Table 1) and were included in this report. Grey literature search retrieved no additional records and overall, no HTA reports, primary clinical studies or economic evaluations were identified that met the pre-specified selection criteria. The PRISMA flowchart[17] detailing the study selection process is presented in Appendix 1. Additional references of potential interest but not meeting the selection criteria are provided in Appendix 2.

Summary of Study Characteristics

Systematic Review

An updated 2013 Cochrane SR, conducted by authors from the UK, included randomized and quasi-randomized trials on immunosuppressive and immunomodulatory agents for CIDP, from the inception of the electronic databases up to July 2012.[15] It was unclear whether a language restriction was imposed on the literature search or in the selection of studies. The SR addressed both comparative efficacy and safety.

Four clinical studies were identified: one on azathioprine, one on methotrexate, and two on interferon beta 1a (IFNb-1a); involving a total of 151 patients. In relation to the research questions posed within this rapid response, two of the trials did not meet our inclusion/exclusion criteria. In one study, the comparator studied was the corticosteroid, prednisone. In the other study, the patient population was restricted to those who were treatment-resistant.[15]

Of the remaining two studies that met the selection criteria for this review, two different immunomodulators were studied: IFNb-1a and methotrexate, in addition to first-line therapy of IVIg. The trial on IFNb-1a was a dose-ranging study that explored four different doses of IFNb-1a over a 32 week period. Patients remained on IVIg therapy during the first 16 weeks and discontinued in the last 16 weeks unless symptoms worsened whereupon IVIg could be restarted. The trial on methotrexate was based on a treatment schedule that consisted of 7.5 mg weekly of methotrexate for four weeks, followed by 10 mg weekly for 4 weeks and lastly 15 mg weekly for 32 weeks. In both trials, the comparator studied remained standard of care: IVIg. The number of randomized participants in each trial was 67 and 60, respectively. Both trials shared similar patient demographics with only adult CIDP patients studied.[15]

The outcomes of interest within this SR included changes to disability, impairment, maximum motor nerve conduction velocity, compound muscle action potential amplitude and change in the amount of medication taken after randomization. Furthermore, any serious adverse events were also outcomes collected.

No comparative studies were identified in which immunomodulators were given as a stand-alone therapy.

Clinical Practice Guidelines

A revised CPG, published in 2010 by two separate journals,[16,18] was identified. Endorsed jointly by the European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society, this consensus guideline covered the definition, the investigation, and the treatment of CIDP. This guideline was not limited to any specific age subgroup and reviewed both the efficacy and safety of a broad range of interventions for CIDP.[16]

The clinical evidence that informed guideline development was rated according to the EFNS guidelines on evidence classification. This consisted of four hierarchical classes: Class I corresponds to well-conducted (e.g., adequate power, low attrition, masked outcome assessment) prospective RCTs while Class IV corresponds to lower levels of evidence such as uncontrolled studies, case series, case reports or expert opinions.[19] Recommendations were then rated on three levels, ranging from A to C. Level A recommendations were those with at least one convincing Class I study or at least two consistent, convincing Class II studies while Level C required at least two convincing Class III studies. When only the lowest quality of evidence (Class IV) was available but consensus could be reached amongst clinical experts, the recommendation was categorized as good practice points.[16]

Summary of Critical Appraisal

Systematic Review

The Cochrane SR[15] was overall well conducted and followed rigorous methodology: clearly described inclusion criteria were set *a priori*, a comprehensive set of databases were searched, and data selection was done in duplicate. The list of included and excluded studies was however not provided within the report and publication bias was not addressed by the study authors.

The risk of bias assessment, conducted as part of the SR, found that the majority of the selected studies were at low risk of bias (e.g., selection bias, performance bias, detection bias, reporting bias). All studies were randomized and most followed proper methods to ensure allocation concealment and blinding. Overall, there was a low risk of attrition and low risk of selective reporting.[15] However, it was unclear whether the trials had sufficient power to detect meaningful differences between treatments given their small sample size.

Clinical Practice Guideline

The CPG clearly described its scope, purpose and intended target user(s).[16] An updated literature review was conducted as part of this guideline development process although it was difficult to assess the quality of the systematic retrieval of the evidence since a detailed search strategy and the selection criteria were not provided in the update or the original guideline.

Although the development of this CPG involved disease experts with clearly stated potential conflict of interest statements, patients' views and preferences were not considered. No details were provided on whether an external review was conducted nor how the guidelines would be updated.[16]

Only clinical evidence was considered when developing this guideline with no consideration on cost-effectiveness or potential organizational barriers.[16]

Summary of Findings

Clinical outcomes of immunomodulatory drugs for CIDP patients under remission

Clinical outcomes: Immunomodulatory drugs, alone, compared to standard of care

No studies were identified that addressed the clinical effectiveness of immunomodulatory drugs alone compared to IVIg therapy.

Clinical outcomes: Immunomodulatory drugs as adjunct to IVIg therapy

The Cochrane SR[15] identified two studies, that addressed the research question.

In the study on methotrexate, the relative risk (RR) of corticosteroids or IVIg dose reduction was 1.21 (95% confidence interval [CI] 0.4 to 3.7). No significant difference in disability change score, as measured by the Overall Neuropathy Limitation Scale or the Amsterdam Linear Disability Scale, was noted following adjustment for age, baseline score and baseline corticosteroid or IVIg dose. However, more adverse events were reported in patients receiving methotrexate + standard therapy (event rate: 11 per 100) than in patients receiving placebo + standard therapy (event rate: 3 per 100) although this was not statistically significant (RR: 3.56, 95% CI 0.39 to 32.23).[15]

In the study on IFNb-1a, patients were administered either IFNb-1a or placebo alongside their IVIg treatment. IVIg was then discontinued after the 16th week and, upon worsening of symptoms, patients would restart IVIg therapy. No difference was observed between groups with respect to IVIg re-initiation amongst participants who completed the study (RR: 1, 95% CI 0.54 to 1.88). Although 24% (11/45) of patients in the combined IFNb-1a + IVIg discontinued the study drug compared to 14% (3/22) in the placebo + IVIg group, the key reasons for study discontinuation in the treatment group were related to safety and voluntary withdrawal whereas the main reasons for study discontinuation in the placebo group involved safety, voluntary withdrawal and worsening of the disease. No serious adverse events were noted in the placebo-control group while four serious adverse events were observed in the IFNb-1a group. These events included CIDP, leukopenia and urticarial. The most frequently-reported adverse events observed in both treatment groups included flu-like symptom, headache, and fatigue.[15]

Comparative cost-effectiveness of immunomodulatory drugs, alone or as adjunctive treatment to IVIg, during remission in patients with CIDP

No relevant economic evaluation on immunomodulatory drugs, alone or as an adjunct treatment to IVIg, in patients with CIDP under remission was identified.

Evidence-based guidelines for immunomodulatory drugs, alone or as adjunctive treatment to IVIg, for CIDP patients in remission

As first-line therapy, the guideline recommended IVIg (Level A) or corticosteroids (Level C) for patients with disabling sensory and motor CIDP symptoms, and only IVIg in patients presenting pure motor CIDP (good practice point).[16] Although plasma exchange may have a similar efficacy, concerns remained on its safety profile (Level A).[16] In terms of maintenance therapy, the first-line therapy that was demonstrated to be efficacious was recommended to be continued until maximum benefit is achieved (good practice point). In terms of the role of immunomodulatory drugs, low quality evidence was found in support of its use. However, the general consensus amongst the guideline experts was to add an immunosuppressant or immunomodulatory drug if patient's response to therapy was found to be inadequate or if they desired a lower dose, and when other first-line treatments alternatives have been tried without success (good practice point). No particular drug was recommended within the guideline.[16]

Limitations

Overall, a main limitation was the lack of comparative studies as most trials simply prescribed patients with an immunomodulator, separately or as an addition to their first-line therapy. Indeed, this was a finding in the systematic review and despite their focus on randomized and quasi-randomized studies, the SR further described non-comparative case reports and case series on immunomodulators in CIDP patients separately within their report.

Among the randomized and quasi-randomized studies that were identified, the overall sample size was small (< 75 patients randomized in each study). This may have resulted in a lack of statistical power to detect clinically meaningful difference between treatment groups and could have limited the interpretation of the study results. Furthermore, it is not possible to ascertain whether differences exist in the comparative benefit and harm of specific immunomodulators.

In the existing trial designs, it may be difficult to parse out the impact of immunomodulatory agents when administered as an adjunct to IVIg, especially with respect to the clinical performance measures (e.g., disability, maximum motor nerve conduction velocity). Most comparative trials involved a dosing strategy that aimed to reduce IVIg dose depending on a patient's response to the immunomodulatory agent. This practice can introduce confounding. For instance, if no differences were observed in the disability changes for patients receiving immunomodulatory agent + IVIg, it may be uncertain whether a patient's response is a result of ineffectiveness of the added immunomodulatory drug or is a result of the reduction in the IVIg dose. Therefore, an outcome that may be useful to collect under such trial design is the change in the amount of medication taken post-randomization.

The searched literature did not provide any evidence on the cost-effectiveness of immunomodulatory drugs alone, or as an adjunct to standard of care in patients with CIDP.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This review assessed the evidence surrounding the clinical effectiveness and cost-effectiveness of immunomodulatory drugs, alone or as an adjunct to IVIg, in patients with CIDP under remission and the clinical practice guidelines for their use. One SR[15] identified four RCTs that were mostly well-conducted (i.e., low risk of bias) although heterogeneity existed in the patient population, the interventions and the outcomes studied. Furthermore, as each trial involved a

small sample size, studies may have lacked power to detect meaningful changes. Caution is therefore required when interpreting these results.

Many case series and non-comparative studies have described the clinical efficacy of immunomodulators. The included SR[15] identified and described some of these studies separately. Of the case reports and case series identified, the greatest experience appears to have been with azathioprine, cyclophosphamide and ciclosporin (i.e. >50 patients combined across studies). The authors highlight that none of the immunomodulatory agents were found to have produced a consistent improvement and any conclusions drawn from these studies must be interpreted with extreme caution, given the nature of the evidence.

No relevant literature was identified that addressed the cost-effectiveness of immunomodulators for a patient population under remission. One evidence-based guideline was identified.[16] Similar to the SR, the guidelines noted that mainly low quality evidence exists supporting the clinical effectiveness of immunomodulatory drugs. Consensus from experts was that, if response to therapy was inadequate or if one desired to lower the dose for maintenance therapy, and other first-line treatments alternatives have been tried without success, adding an immunosuppressant or immunomodulatory drug could then be considered.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Koller H, Kieseier BC, Jander S, Hartung HP. Chronic inflammatory demyelinating polyneuropathy. N Engl J Med. 2005 Mar 31;352(13):1343-56.

2. Dimachkie MM, Barohn RJ. Chronic inflammatory demyelinating polyneuropathy. Curr Treat Options Neurol. 2013 Jun;15(3):350-66. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3987657

3. Kusumi M, Nakashima K, Nakayama H, Takahashi K. Epidemiology of inflammatory neurological and inflammatory neuromuscular diseases in Tottori Prefecture, Japan. Psychiatry Clin Neurosci. 1995 Jun;49(3):169-74.

4. McLeod JG, Pollard JD, Macaskill P, Mohamed A, Spring P, Khurana V. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. Ann Neurol. 1999 Dec;46(6):910-3.

5. Lunn MP, Manji H, Choudhary PP, Hughes RA, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. J Neurol Neurosurg Psychiatry. 1999 May;66(5):677-80. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1736351

6. Chio A, Cocito D, Bottacchi E, Buffa C, Leone M, Plano F, et al. Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. J Neurol Neurosurg Psychiatry. 2007 Dec;78(12):1349-53. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2095630

7. Mygland A, Monstad P. Chronic polyneuropathies in Vest-Agder, Norway. Eur J Neurol. 2001 Mar;8(2):157-65.

8. Iijima M, Koike H, Hattori N, Tamakoshi A, Katsuno M, Tanaka F, et al. Prevalence and incidence rates of chronic inflammatory demyelinating polyneuropathy in the Japanese population. J Neurol Neurosurg Psychiatry. 2008 Sep;79(9):1040-3.

9. Sederholm BH. Treatment of chronic immune-mediated neuropathies: chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, and the Lewis-Sumner syndrome. Semin Neurol. 2010 Sep;30(4):443-56.

10. Canadian Agency for Drugs and Technologies in Health. Intravenous immunoglobulin for chronic inflammatory demyelinating polyneuropathy: clinical- and cost-effectiveness analyses [Internet]. Ottawa: The Agency; 2009 Mar. (Technology Report Issue 117). [cited 2015 Feb 20]. Available from: http://www.cadth.ca/media/pdf/H0298C_Intravenous_Immunoglobulin_for_CIPD_tr_e.pdf

11. Hughes RA, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol. 2008 Feb;7(2):136-44.

12. Dalakas MC. Clinical trials in CIDP and chronic autoimmune demyelinating polyneuropathies. J Peripher Nerv Syst. 2012 May;17 Suppl 2:34-9.

13. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007;7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

14. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ [Internet]. 2010 Dec [cited 2014 Apr 9];182(18):E839-E842. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf

15. Mahdi-Rogers M, van Doorn PA, Hughes RA. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev. 2013;6:CD003280.

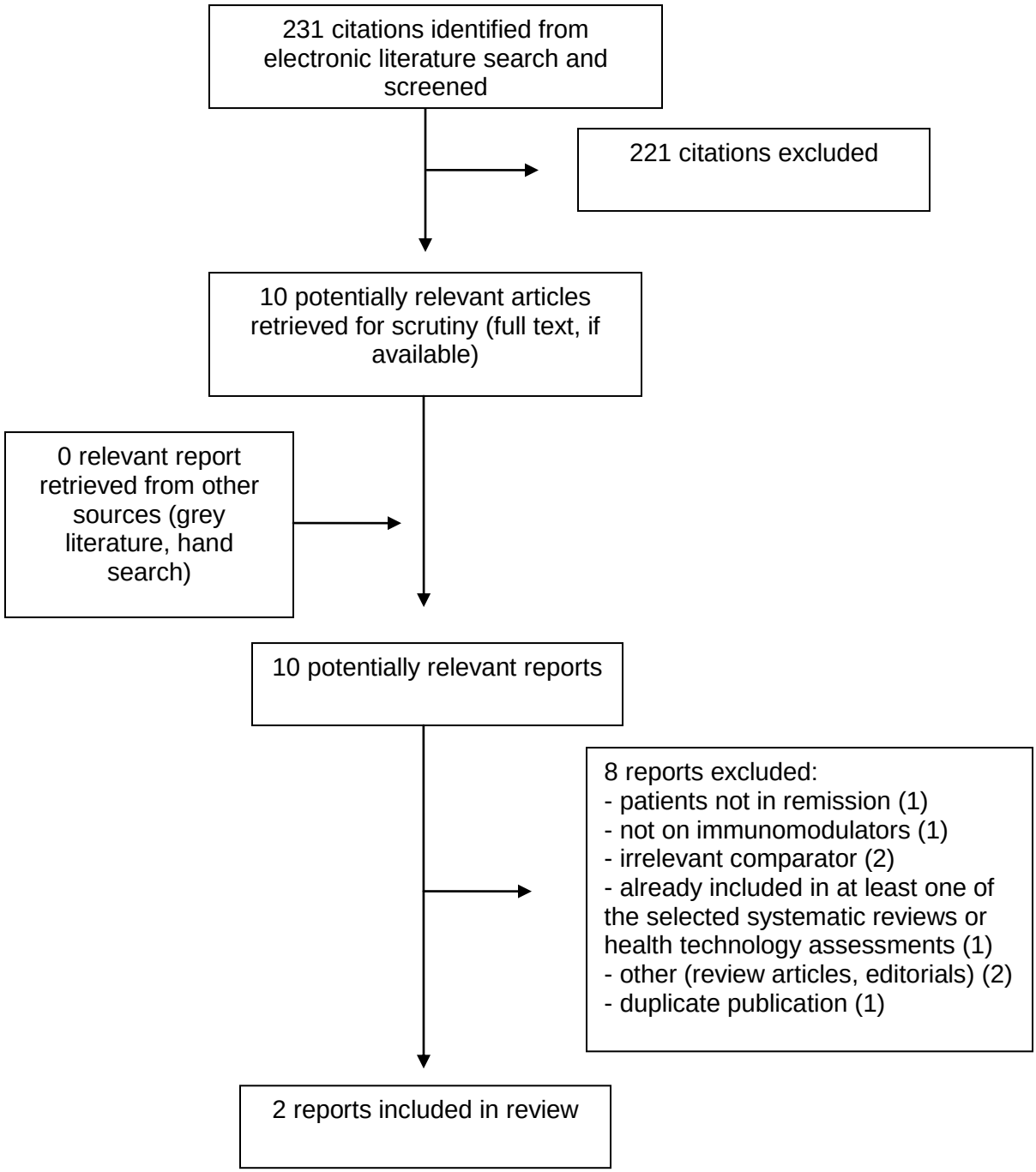
16. Van den Bergh PY, Hadden RD, Bouche P, Cornblath DR, Hahn A, Illa I, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision. Eur J Neurol. 2010 Mar;17(3):356-63.

17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-e34.

18. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--First Revision. J Peripher Nerv Syst. 2010 Mar;15(1):1-9.

19. Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces--revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional References of Potential Interest

Randomized Studies

Alternative Comparator (i.e., corticosteroids)

Eftimov F, Vermeulen M, van Doorn PA, Brusse E, van S, I, PREDICT. Long-term remission of CIDP after pulsed dexamethasone or short-term prednisolone treatment. Neurology. 2012 Apr 3;78(14):1079-84.
PubMed: PM22442436

van S, I, Eftimov F, van Doorn PA, Brusse E, van den Berg LH, van der Pol WL, et al. Pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind, randomised, controlled trial. Lancet Neurol. 2010 Mar;9(3):245-53.
PubMed: PM20133204

Clinical Practice Guidelines – Methodology Uncertain/ Not Provided

Bašić-Kes V, Kes P, Zavoreo I, Lisak M, Zadro L, Ćorić L, et al. Guidelines for the use of intravenous immunoglobulin in the treatment of neurologic diseases. Acta Clin Croat. 2012 Dec;51(4):673-83.
PubMed: PM23540178
See: Chronic Inflammatory Demyelinating Polyradiculoneuropathy, pages 674-75