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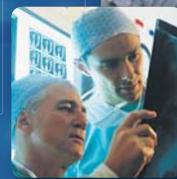
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Intravenous Immunoglobulin for Chronic
Inflammatory Demyelinating Polyneuropathy:
Clinical- and Cost-Effectiveness Analyses



Supporting Informed Decisions

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Canadian Agency for Drugs and Technologies in Health

**Intravenous Immunoglobulin for Chronic Inflammatory
Demyelinating Polyneuropathy: Clinical- and
Cost-Effectiveness Analyses**

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March 2009

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Industry: The following manufacturers were provided with an opportunity to comment on an earlier version of this report: Talecris Biotherapeutics and Baxter Canada. All comments that were received were considered when preparing the final report.

This report is a review of existing public literature, studies, materials, and other information and documentation (collectively the “source documentation”) that are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured, or represented in any way by CADTH, and CADTH does not assume responsibility for the quality, propriety, inaccuracies, or reasonableness of any statements, information, or conclusions contained in the source documentation.

CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of its Panel members or reviewers.

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Kathryn Gaebel, Clinical Lead and Systematic Reviewer, conducted the clinical literature review, data abstraction, and meta-analyses; contributed to the writing of the report; and responded to all review comments for the final report.

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Kaitryn Campbell was responsible for the design and performance of the literature search strategies, for the associated appendix, and for the bibliographies.

Conflicts of Interest

Feng Xie, Nazila Assasi, Kaitryn Campbell, Diana Robertson, and Mita Giacomini disclosed no conflicts of interest. Gord Blackhouse received funding from Eli Lilly Canada Inc. and GlaxoSmithKline Inc. for consulting. Mitch Levine received funding from AstraZeneca Canada Inc., Eli Lilly Canada Inc., Pfizer Canada Inc., and Merck Frosst Canada Ltd., and acted as an expert witness for Novartis Pharmaceuticals Canada Inc. and Wyeth Pharmaceuticals. He was also Chair, Expert Drug Committee for Health Canada. Kathy Gaebel received funding grants from Abbott Laboratories Ltd. for a speaking engagement. Ron Goeree was advisory board member to Janssen-Ortho Inc. and Hoffman-La Roche Ltd. and consultant for Eli Lilly Canada Inc. Colin Chalk received funding from Talecris Biotherapeutics Ltd. and is the primary investigator in a multi-centre study funded by Baxter Canada. No payments were received by him or by patients who were enrolled in the study at the time of completion of the report. Dr. Timothy J. Benstead is a neurology consultant to the Nova Scotia Provincial Blood Coordinating Program.

EXECUTIVE SUMMARY

Issue

There are a few approved indications for intravenous immunoglobulin (IVIg), and there is an increasing number of off-label uses. Until October 2008, chronic inflammatory demyelinating polyneuropathy (CIDP) was an off-label indication in Canada. Escalating cost, increasing demand for more indications, and an IVIg shortage have prompted Canada to adopt new approaches to manage IVIg use. To maintain an adequate supply of IVIg, Canadian Blood Services has begun to diversify the supplier base. One additional IVIg product will be available in 2009. Assessing the impact of IVIg treatments on patients with CIDP has been identified as a priority, given the high utilization rates in Canada, high costs, the potential availability of alternative treatments, and the uncertainty of a therapeutic advantage over alternative therapy.

Objectives

The aim of this health technology assessment is to evaluate the comparative clinical-effectiveness, cost-effectiveness, and health services impact of IVIg in the treatment of CIDP.

Research Questions

- What is the comparative effectiveness of IVIg versus other standard therapies for short- and long-term CIDP management?
- What is the economic impact (trade-off of resources for health)?
- What is the cost-effectiveness of IVIg for short- and long-term CIDP management?
- What is the cost-effectiveness of IVIg among subgroups of patients with CIDP (progressive or relapsing-remitting; pure motor variant, pure sensory variant, or mixed variant)?
- What are the budgetary implications of adopting optimal treatment strategies?

Clinical Review of Efficacy and Effectiveness

Methods: Two systematic searches were undertaken to locate relevant clinical trials, meta-analyses, systematic reviews, or health technology assessments assessing IVIg for CIDP. The search strategy was developed by an information specialist with input from the project team. Eleven articles reporting on nine unique clinical trials were retrieved for this review. Three of the nine trials compared IVIg therapy with an active comparator (plasma exchange, extracorporeal immunoadsorption, or oral prednisolone). The other six trials were placebo-controlled. Six trials were of a two-arm, two-treatment, crossover design. The other three trials were of parallel group designs, with two trials using two treatment arms and the third trial using three treatment arms. The main clinical outcomes were change in disability or impairment (at least two to four weeks after treatment onset), durability of change in disability or impairment, change in electrophysiologic outcomes (for example, maximum motor nerve conduction velocity), change in quality of life, and adverse events (including treatment-related events and withdrawals due to adverse events).

Results: No incremental benefit was seen in the primary outcomes when comparing IVIg therapy and active comparators. A benefit in one secondary outcome measure (grip strength) occurred with IVIg therapy when it was compared with prednisolone therapy. A meta-analysis using the change in disability scores from four placebo-controlled trials resulted in a statistically significant treatment effect of -0.65 (95% CI -1.08 to -0.23) favouring IVIg. The pooled analysis of the proportion of treatment responders, as defined by the investigators in each trial, resulted in a risk ratio (RR) of 2.74 (95% CI 1.80 to 4.16), favouring IVIg.

Among the six trials, three demonstrated a statistically significant improvement in an electrophysiological parameter when IVIg therapy was compared with placebo. One systematic review of IVIg for CIDP stated that one of the six trials that were reviewed showed improvement in an electrophysiological parameter.

Economic Analysis

Methods: A systematic search was undertaken to locate full economic evaluations assessing IVIg for CIDP. The search strategy was developed by an information specialist (KC) with input from the project team. Retrieved articles were reviewed.

A cost-utility primary economic analysis was conducted from a publicly funded health care system perspective using a Markov model that focused on adult patients with CIDP. The treatment comparators were IVIg and oral corticosteroids, and the time horizon was five years.

Results: One paper, which was found during the systematic search, reported results from a patient-level economic evaluation. It was based on patients with CIDP who were participating in an international clinical trial that used a crossover design. Patients were randomized to receive IVIg or oral prednisolone. After adjusting for baseline costs, patients on IVIg incurred €3,439 higher costs than those in the prednisolone group. IVIg was also found to result in greater utility gain over a six-week period compared with prednisolone. This difference was 0.12, which the study authors claimed to be equivalent to 0.014 quality-adjusted life-years (QALYs). Based on the reported incremental costs and effects, the cost per QALY was €245,643 (C\$388,110).

The primary economic evaluation, taking into account the gain in utility from IVIg treatment and the disutility from adverse events, found that the IVIg treatment arm had 0.187 more QALYs than the corticosteroid arm. The resulting incremental cost-utility ratio of IVIg compared with corticosteroids is \$549,449 per QALY gained. The incremental cost-utility ratio varied from \$262,260 to \$694,933 when patient weight was decreased to 35 kg and increased to 95 kg respectively. Assuming that maintenance treatment with IVIg consists of 0.4 mg/kg doses every eight weeks instead of 1.0 mg/kg doses every three weeks resulted in a cost-per-QALY estimate of \$125,241. In the probabilistic sensitivity analysis, it was found that at a willingness to pay for a QALY threshold of \$552,000, the probability that IVIg is cost-effective is 50%.

One published study provided limited efficacy data on the CIDP subgroups. Therefore, we cannot draw any conclusions about the cost-effectiveness of IVIg in these subgroups.

Health Services Impact

Because there are no relevant Canadian prevalence and incidence data, the estimated number of Canadians with CIDP was based on international estimates. The estimated number of prevalent cases varied from 145 to 2,434, and the number of incident cases varied from 47 to 152. With an initial dosing schedule followed by maintenance IVIg therapy, the potential financial impact of IVIg treatment for all patients with CIDP was estimated to be in the range of \$10.6 million to \$43.1 million.

Conclusions

Compared with placebo, IVIg statistically significantly reduces impairment and disability in patients with CIDP. The improvements are similar to those resulting from corticosteroid and plasma exchange therapy. Compared with active comparators, however, it is unclear whether IVIg has therapeutic advantages in the management of CIDP. The cost per QALY of IVIg compared with corticosteroids for CIDP treatment (\$549,449) is higher than what might be viewed as a cost-effective use of health care resources.

ABBREVIATIONS

| | |
|-------|---|
| AAN | American Academy of Neurology |
| AE | adverse event |
| AMS | average muscle score |
| CEAC | cost-effectiveness acceptability curve |
| CI | confidence interval |
| CIDP | chronic inflammatory demyelinating polyneuropathy |
| CMAP | compound muscle action potential |
| GBS | Guillain-Barré syndrome |
| HFDS | Hughes functional disability scale |
| ICE | IGIV-C CIDP efficacy |
| IgA | immunoglobulin A |
| INCAT | inflammatory neuropathy cause and treatment |
| ITP | immune (idiopathic) thrombocytopenic purpura |
| IVIg | intravenous immunoglobulin |
| MCV | motor nerve conduction velocity |
| MRC | Medical Research Council |
| NDS | neurological disability score |
| ODEM | Ontario Diabetes Economic Model |
| QALY | quality-adjusted life-year |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SD | standard deviation |
| SMD | standardized mean difference |
| SNAP | sensory nerve action potential |
| WAE | withdrawal due to adverse event |

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1 INTRODUCTION

1.1 Background and Setting in Canada

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated inflammatory disorder. It targets the myelin sheaths that wrap the nerves of the peripheral nervous system. The motor weakness symptoms of CIDP resemble those of Guillain-Barré syndrome (GBS), and CIDP is sometimes considered to be the chronic GBS counterpart.¹ The course of CIDP may be chronic progressive, stepwise, or monophasic. CIDP can occur at all ages and in both sexes, but it is more common in older individuals and males. It is believed that the older age group is more likely to have a chronic progressive course of CIDP and younger patients a relapsing-remitting course.² Reported mean prevalence estimates from six studies varied from 0.46 to 7.7 per 100,000 people.³⁻⁸ There are reported regional differences; for example 0.46 to 1.24 per 100,000 people in southeast England⁵ and 0.26 to 1.90 per 100,000 people in Japan.³ Reported prevalence rates vary by age and gender, with the highest prevalence rates of 3.12,⁸ 9.47,⁴ and 19.24⁶ reported in men who are 55 years old or older, 70 years to 79 years old, and 80 years old or older respectively. The prevalence and incidence rates for Canada are unavailable. One could assume that Canada's rate falls within the range that is reported in the trials from other countries with similar demographic characteristics such as England and Australia: 1.0 to 1.9 per 100,000 people.

CIDP is usually distinguished from GBS (also called “acute inflammatory demyelinating polyneuropathy” or AIDP) by its time course.² Patients with GBS usually reach maximum clinical deficit within four weeks of onset, whereas patients with CIDP will worsen for eight weeks or more. In addition, GBS is a self-limited, monophasic illness, whereas CIDP has a prolonged course, over months to years, which may be steadily progressive or relapsing-remitting.²

CIDP leads to motor and sensory symptoms, with motor symptoms being predominant. There is symmetrical involvement of arms and legs, and proximal and distal muscles, resulting in global muscle weakness and a general reduction or absence of deep tendon reflexes.² Occasionally, muscle weakness so profound that patients cannot walk.⁹ The sensory symptoms mainly involve vibration and position sense rather than pain and temperature. Sensory involvement follows a distal to proximal gradient, although finger involvement often occurs as early as toe or foot involvement.² The cardinal pathophysiologic feature of CIDP is segmental demyelination and remyelination, and onion bulb formation, which can be demonstrated using nerve biopsy or inferred from electrodiagnostic findings.² Demyelination is the destruction or loss of the myelin sheath that envelopes the axon. When myelin is lost, the conduction of signals along the underlying axon is slowed or fails. In most patients with CIDP, there is also some axonal degeneration, which is considered to be a secondary, bystander product of the inflammatory demyelinating process.² The disconnection of the motor neuron from its target muscle is the result of axonal degeneration.¹⁰ In severe cases where denervation of the respiratory muscles occurs, the result can be death.

Some patients with CIDP have mild disease with a minimal impact on function and quality of life, but most will need treatment to arrest or reverse the progression of the illness. A prevalence

study that was conducted by Lunn et al.⁵ reported that 54% of patients had been severely disabled at a point in the past, and 13% were still severely disabled at the time of the prevalence assessment.

Patients with CIDP show improvement after treatment with corticosteroids or plasma exchange,^{11,12} but both therapies have disadvantages. Because of the chronic nature of the disease, the long-term use of corticosteroids is usually required. This carries the risk of adverse events (AEs) and serious adverse events (SAEs).¹³ The benefit from plasma exchange is usually transient. Therefore, it is usually used concomitantly with other therapy.¹² Also, plasma exchange must be provided in specialized centres, and the repeated procedures require good vascular access.¹⁴ Shumak and Rock¹⁵ report in a review of therapeutic plasma exchange that plasma exchange is associated with complications that include those that are common to all procedures, some that are related to the disease being managed, and some that are related to particular replacement fluids.¹⁵ The more serious complications are related to venous access (infection in indwelling lines), plasma as the replacement fluid (urticarial reactions, anaphylactic reactions, hepatitis C), and electrolyte abnormalities (cardiac arrhythmias). The procedure is also associated with patient death.

1.2 Overview of Technology

Intravenous immunoglobulin (IVIg) is a blood product containing immunoglobulin G (IgG) that has been pooled from many human donors. It is used as a replacement therapy in primary and secondary humoral immunodeficiencies and as an immunomodulatory therapy in autoimmune diseases and transplantation.^{16,17} No single mechanism accounts for all the immunomodulatory effects of IVIg. The blockage of the Fc receptor on macrophages of the reticuloendothelial system accounts for the major immediate effects of IVIg. The blockage is a result of a competitive interaction between IVIg and anti-platelet antibodies for the Fc receptor and between soluble Fc γ receptors and membrane Fc receptors for circulating IVIg-sensitive platelets.¹⁸ The long-term effects can be attributed to the immunomodulatory effects of IVIg on T cells and macrophages. IVIg enhances T cell suppressor function and inhibits B cell function or antigen-processing cells through the Fc receptor.¹⁸ IVIg is available as four products through Canadian Blood Services (Table 1).

| Brand Name | Manufacturer | Sizes Available |
|-----------------------|--|-------------------------------------|
| Gamunex, 10% | Talecris Biotherapeutics | 2.5 g, 5.0 g, 10.0 g, 20.0 g |
| IGIVnex, 10% | Talecris Biotherapeutics / Canadian Blood Services | 10.0 g, 20.0 g |
| Gammagard-SD | Baxter Bioscience | 0.5 g, 2.5 g, 5.0 g, 10.0 g |
| Gammagard Liquid, 10% | Baxter Bioscience | 1.0 g, 2.5 g, 5.0 g, 10.0 g, 20.0 g |

Canadian blood donations are used in the production of IGIVnex, which is available only through Canadian Blood Services. Blood donations from the US are used in the production of Gamunex, which is a commercial product. Gammagard-SD is a freeze-dried product that requires reconstitution. It has the lowest immunoglobulin A (IgA) content of all IVIg available in Canada. This is important for patients with IgA deficiency who develop an immune response against IgA

(anti-IgA antibodies). This can lead to severe reactions including anaphylaxis to blood transfusions or IVIg. Blood donations from the US are used in the production of Gammagard Liquid and Gammagard-SD. Another IVIg product, Privigen, which is manufactured by CSL Behring, will be made available in 2009 in an attempt to maintain a stable inventory of IVIg and reduce the risk of shortages.¹⁹

Most of Canada's plasma supply comes from paid donors in the US, with 25% to 30% from voluntary donation in Canada.¹⁶ The cost of IVIg, which was provided by Canadian Blood Services, is \$59.19/g (Mathias Haun, Director, Plasma Products and Services, Canadian Blood Services, Ottawa, ON: personal communication, 2008 Apr).

IVIg is a blood product. Therefore, there are general safety and specific issues regarding its use listed on the product monographs. Blood products may contain infectious agents, even after the inactivation or removal of certain viruses. Immediate anaphylactic and hypersensitivity reactions are possible, as are hemolysis, transfusion-related acute lung injury, thrombotic events, and aseptic meningitis syndrome.

2 THE ISSUE

There are a few approved indications for IVIg, and there is an increasing number of off-label uses. Until September 2008, CIDP was an off-label indication. In September 2008, the FDA granted Talecris Biotherapeutics supplemental licenses for an IVIg product to include CIDP as an indication.²⁰ The Health Products and Food Branch of Health Canada granted approval for this indication in October 2008.²¹ IVIg treatment of CIDP does not, by itself, usually lead to remission, and it requires repeated treatments every two to six weeks.² Canada has one of the highest per capita rates of consumption of IVIg in the world, and the consumption rate has been increasing annually over the past decade.¹⁶ Escalating cost, increasing demand for a higher number of indications, and an IVIg shortage have prompted Canada to adopt new approaches to manage IVIg use. Assessing the impact of IVIg on patients with CIDP has been identified as a priority, given its high utilization rates in Canada, the potential availability of alternative treatments, and the uncertainty of a therapeutic advantage over alternative therapy.

3 OBJECTIVES

The aim of this health technology assessment is to evaluate the comparative clinical-effectiveness, cost-effectiveness, and health services impact of IVIg in the treatment of CIDP.

3.1 Research Questions

- What is the comparative effectiveness of IVIg versus other standard therapies for short- and long-term CIDP management?
- What is the economic impact (trade-off of resources for health)?
- What is the cost-effectiveness of IVIg for short- and long-term CIDP management?

- What is the cost-effectiveness of IVIg among subgroups of CIDP patients (progressive or relapsing-remitting; pure motor variant, pure sensory variant, or mixed variant)?
- What are the budgetary implications of adopting optimal treatment strategies?

4 CLINICAL REVIEW

4.1 Methods

A protocol for the review was written a priori and followed throughout the review process. The original protocol defined the population as adults 18 years of age or older. Because there was no rationale to limit the search to adults, this age limit was removed.

4.1.1 Literature search strategy

CADTH Technology Report Issue 108, *Polyclonal Intravenous Immunoglobulin in Patients with Immune Thrombocytopenic Purpura: Clinical Systematic Review*, was originally intended to also include a literature review in CIDP and was the starting point for this research. In the original strategy, articles were retrieved up to November 2007, and there was a language limit. The original search strategy included a request for information from the IVIg manufacturers (Talecris Biotherapeutics Inc. and Baxter Bioscience) (Appendix A). A large randomized controlled trial (RCT) of IVIg therapy in patients with CIDP was published after the authors stopped reviewing citations. Therefore, an update of the literature on CIDP was undertaken.

A second systematic search was undertaken to locate relevant clinical trials, meta-analyses, systematic reviews, or health technology assessments assessing IVIg for CIDP to update the first search. The search strategy was developed by an information specialist (KC) with input from the project team. The search strategy underwent peer review by a CADTH information specialist. All search results were imported into a Reference Manager Version 11 database for removal of duplicates and title and abstract screening.

The following bibliographic databases were searched through the Ovid interface: MEDLINE (1996 to present; In-Process & Other Non-Indexed Citations), EMBASE (1996 to present), and CINAHL (1982 to present). Parallel searches were run in PubMed (for non-MEDLINE records only), Wiley's Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Methodology Register and Health Technology Assessment Database), and Thomson's BIOSIS Previews (1995 to present).

The search strategy's controlled vocabulary and keywords focused on "CIDP" and "IVIg."

A methodological filter was applied to limit retrieval to clinical trials, meta-analyses, systematic reviews, or health technology assessments. Retrieval was limited to database entry date December 2007 to the present (when possible) or publication date 2007 to 2008, and the human population (human for clinical trials only). No language restrictions were used. Appendix B shows the detailed strategy.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies and their associated databases, the Talecris Biotherapeutics Inc. and Baxter Bioscience websites, and clinical trial registers. Websites of professional associations such as the American Society of Hematology, the European Hematology Association, the American Academy of Neurology, the American Neurological Association, and the Canadian Neurological Sciences Federation were also searched for relevant evidence (including conference abstracts from 2007 to 2008, if available). Google and AlltheWeb search engines were used to search for additional web-based materials and information. These searches were supplemented by reviewing the bibliographies and abstracts of key papers and conference proceedings.

OVID and PubMed AutoAlerts were set up to send biweekly updates with any new literature, with the last automatic updates received on November 1, 2008. Quarterly updates were performed on The Cochrane Library, with the last update search performed on October 8, 2008 (Issue 4, 2008).

4.1.2 Selection criteria

Criteria that were used to select studies appear in Table 2.

| Study Design | Population | Intervention | Comparators | Outcomes |
|---------------------|--|--|--|---|
| RCTs | Patients of any age with documented and defined diagnosis of probable or definite CIDP, confirmed by electro-physiological findings of demyelinating neuropathy, but not those with other associated conditions* | Any preparation source, dose, and dosing regimen of IVIg | IVIg (alternative dose, dosing regimen, route of administration) <ul style="list-style-type: none"> ▪ Corticosteroids (any dose, dosing regimen, route of administration) ▪ Plasma exchange ▪ Extracorporeal immunoadsorption ▪ Other immunosuppressants ▪ IVIg in combination with other immunomodulators ▪ Placebo | <ul style="list-style-type: none"> ▪ Treatment response as dichotomous measure ▪ Change in disability or impairment (at least 2 to 4 weeks after treatment onset) ▪ Durability of change in disability or impairment ▪ Change in electrophysiologic outcomes (e.g., maximum motor nerve conduction velocity) ▪ Change in quality of life ▪ AEs, SAEs including treatment-related events, WAEs |

AEs = adverse events; CIDP = chronic inflammatory demyelinating polyneuropathy; IVIg = intravenous immunoglobulin; SAEs = serious adverse events; WAEs = withdrawals due to adverse events.

*According to investigator or using published diagnostic criteria such as American Academy of Neurology criteria, modified American Academy of Neurology criteria, or European Federation of Neurological Societies / Peripheral Nerve Society criteria. Patients in studies that reported solely on CIDP in association with other conditions were not included. Studies on mixed populations (with and without associated conditions or other forms of neuropathy) were included only if CIDP patients were reported separately. Patients with multifocal motor neuropathy were not included.

4.1.3 Selection method

Screening was performed in two stages: screening of the retrieved citations based on title and abstract and full-text review of the potentially relevant citations. One reviewer (KG) independently screened titles and abstracts (if available) for relevancy. Exclusions were screened by a second reviewer (GB). If there was uncertainty about relevance or if there was disagreement between reviewers, the citation was passed through to full-text screening. Two reviewers (KG, GB) independently examined the full-text reports of the potentially relevant records, applying more stringent eligibility criteria, which had been developed a priori. Any discrepancies were resolved by discussion and consensus.

4.1.4 Data extraction strategy

One reviewer (KG) independently extracted data from each study. These data were subsequently verified by another reviewer (GB). The information included population characteristics at baseline (for example, mean age) and study characteristics such as drug interventions (including dose and dosing regimen), timing of assessment, and AEs (Appendix C). The reviewers were not blinded to the study authors' names or funding sources. Any discrepancies were resolved by discussion.

4.1.5 Strategy for validity assessment

The validated Jadad scale²² was used in quality assessment. Two reviewers (KG and GB) independently performed quality assessment of the included studies. The Jadad scale is used to assess the methods for the generation of random assignments and double blinding. It is also used to determine whether there is a description of dropouts and withdrawals by intervention group. The scores range from 1 to 5, with higher scores indicating higher quality. Allocation concealment was rated as adequate, inadequate, or unclear using the Schultz treatment allocation concealment questionnaire.²³ Both scales appear in Appendix D.

4.1.6 Data analysis methods

The decision whether to perform a statistical pooling of individual studies was based on clinical and methodological judgment. Studies with Jadad²² scores of 3 or more, that reported the mean change from baseline with standard deviation (SD) for the disability outcomes would be pooled to estimate the effect size of IVIg treatment. The meta-analyses were based on DerSimonian and Laird's²⁴ random-effects model. This model was consistently used, because some clinical and methodological diversity is inevitable, even when tests for statistical heterogeneity cannot be used to detect it. For binary outcomes (for example, the proportion of patients with CIDP who showed a treatment response), risk ratio (RR) and 95% confidence intervals (CIs) were calculated for each study using RevMan Version 5.²⁵ The pooled RR (with 95% CI) was then calculated. A RR greater than 1 indicates that more patients in the IVIg arm relative to the control or comparator arm developed a favourable outcome. For continuous outcomes (for example, mean change in disability scores), the difference between study arms, the SD of the difference, and 95% CIs were calculated using RevMan. Then a standardized mean difference (SMD) was calculated with 95% CIs. A SMD of 0.2 to 0.3 was defined as a small effect, 0.5 a moderate effect, and 0.8 or higher a large effect.²⁶ SMDs are also used when different studies use

a variety of scales to measure the same conceptual outcome. The degree of statistical heterogeneity among studies was assessed using chi-square (χ^2) and I^2 . The I^2 expresses the percentage of between-study variability that is attributable to heterogeneity rather than sampling error. A value greater than 50% is considered to be substantial, whereas an I^2 of 0% indicates that all variability in effect estimates is due to sampling error.²⁷ The interpretation of heterogeneity estimates requires caution, especially when small numbers of trials are included.

A conservative approach was used when combining crossover and parallel trial results. Only the data from the first period of crossover trials were pooled. This decision was based on the methodological shortcomings of the identified crossover trials (for example, crossover based on the response to previous treatment rather than the original randomization).

Sensitivity analyses were planned to examine if the effect of IVIg varied by trial design and trial quality (for example, those with adequate allocation concealment). Subgroup analyses were planned to examine if the effect of IVIg differed depending on the duration and dose of IVIg treatment or the types of CIDP (for example, pure motor variant). Differences in IVIg preparations were not considered. All IVIg products are not identical, because of the manufacturing process. Product features that may affect a patient's tolerance of the IVIg product and of its clinical effect are sodium content, type and concentration of sugar, osmolality and osmolality, pH, IgA content, and volume load.²⁸

A narrative synthesis of each study is provided whether the study data were pooled for meta-analyses.

4.2 Results

4.2.1 Quantity of research available

In the primary and updated searches, 495 citations were identified. Of the 495 citations, 325 were excluded after level-one screening (citation and title and abstract if available). One hundred and eighty-one citations, which included results from the grey literature search, were subjected to full-text screening. Of these, 20 publications were identified as potentially relevant trials.^{12,14,29-46} On further screening, two publications were excluded because they were not RCTs.^{41,42} One RCT was excluded because the study population included patients with multifocal motor neuropathy. Separate data were not reported for patients with CIDP.³⁷ Eight publications were not full-study reports (abstracts or conference proceedings only). Six of these eight abstracts were excluded^{36-38,43,45,46} because the full articles were included for data abstraction.^{14,31,40} Thus, 11 articles reporting on nine unique RCTs,^{12,14,29-35,40,44} including two abstracts reporting outcomes that were not in the original published RCT, were retained.

A modified QUOROM flowchart appears in Figure 1 and an excluded study list in Appendix E.

4.2.2 Study characteristics

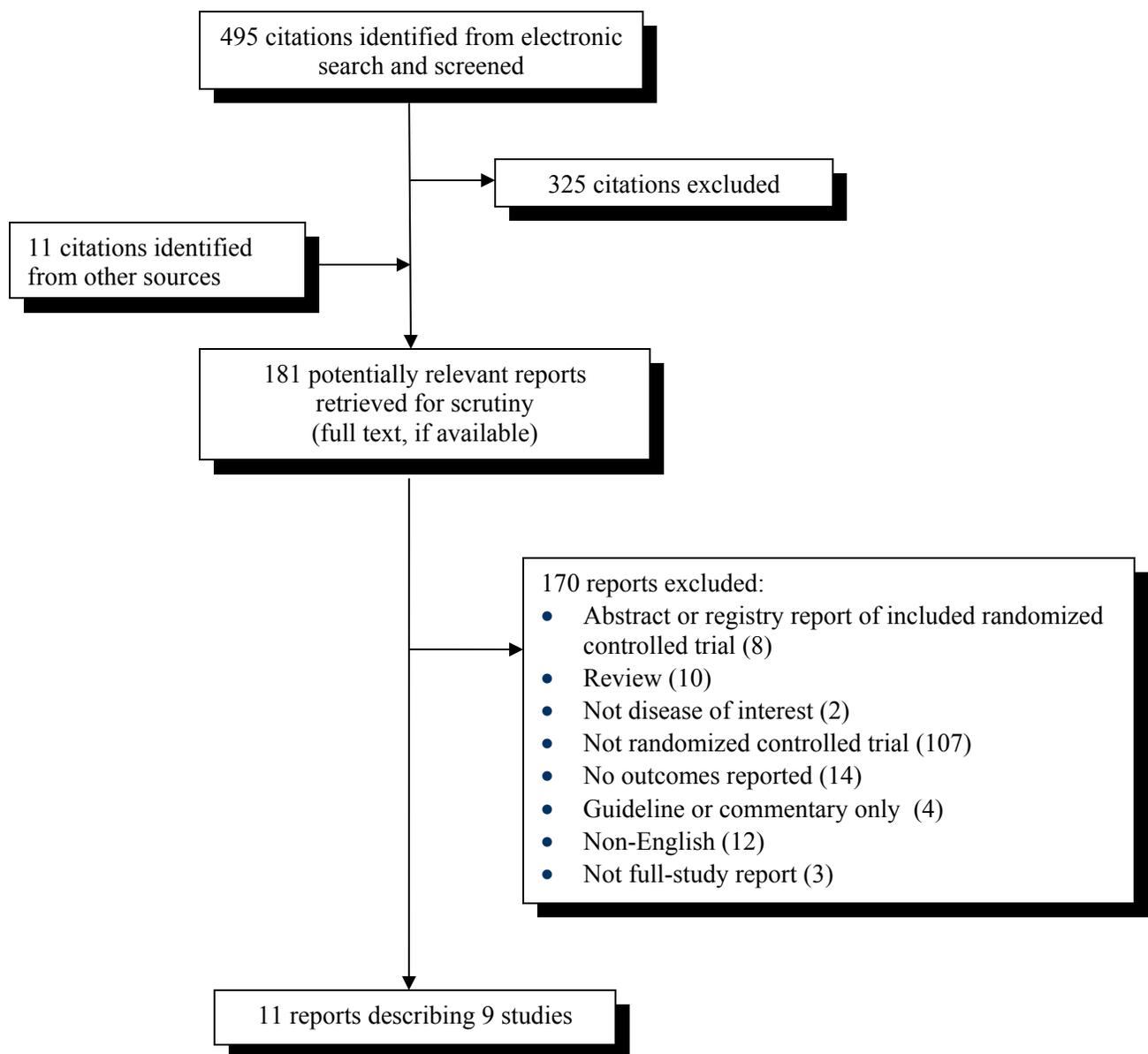
a) **Study design, comparators, and funding**

The nine RCTs were published from 1990³⁵ to 2008.⁴⁰ Trial characteristics appear in Appendix F Table 1, and efficacy and harms outcomes appear in Appendix F Table 2.

Three of the nine trials compared IVIg therapy with an active comparator (plasma exchange,³³ extracorporeal immunoadsorption,²⁹ or oral prednisolone³⁰), and the other six trials were placebo-controlled.^{14,31,32,34,35,40} Six identified trials were of a two-arm, two-treatment crossover design.^{14,30,32,33,35,40} The other three trials used parallel group designs with two treatment arms^{31,34} or three treatment arms.²⁹

Six identified trials obtained financial support from non-pharmaceutical funding sources,^{14,29,31-34} two were sponsored by the pharmaceutical industry,^{30,40} and one trial did not report the funding source.³⁵ Two trials that were sponsored by non-pharmaceutical funding sources obtained the IVIg therapy from the manufacturers.^{33,34}

Figure 1: Selected Reports for Clinical Review



b) Study population

The crossover trials^{14,30,32,33,35,40} randomized 213 patients (mean 36 patients), varying from a sample size of seven^{32,35} patients to 117⁴⁰ patients. The total number and the mean number of patients who were randomized in the parallel group design were 101 and 25 respectively, varying from a sample size of 20²⁹ patients to 53³¹ patients.^{29,31,34}

All trials included adult patients, and three trials also included pediatric patients,^{14,31,35} but the authors did not report results stratified by population age. Patient ages varied from 9 years¹⁴ to 83 years,⁴⁰ with one trial not reporting age.³³ The mean age that was reported in the two largest RCTs was 51.5 years⁴⁰ and 52 years³¹ respectively. The mean duration of disease before treatment randomization varied from 12 months¹⁴ to 28 months.^{29,34,40} One trial reported a range of 66 months to 161 months for duration of disease without reporting the mean,³² and three trials did not report the disease duration.^{30,33,35} One study¹⁴ reported the number of patients by disease course (progressive versus relapsing-remitting).

All studies included patients with a diagnosis (which included electrophysiological data) of probable or definite CIDP. Three^{14,31,32} used American Academy of Neurology (AAN) criteria,⁴⁷ and two studies^{30,40} used the inflammatory neuropathy cause and treatment (INCAT) criteria.³⁰ The AAN proposed diagnostic criteria for CIDP research studies. The criteria require a nerve biopsy for a definite diagnosis of CIDP. The INCAT criteria mandate a nerve biopsy only when the neurophysiological abnormalities occur in two nerves. AAN also require the presence of three of four abnormal physiological features, whereas the INCAT criteria require the presence of two of the four abnormal features. Four studies prespecified a minimum disability score^{14,33,34,40} for inclusion. The disability and impairment scales that were used for inclusion and for outcome measures were heterogeneous among studies (Appendix F Table 1).

Exclusion criteria included comorbidities that were known to cause neuropathy, pregnancy or lactation, and the use of concomitant therapies. Patients using immunosuppressant therapy were excluded in two studies,^{34,35} previous treatment with IVIg was an exclusion criterion in four studies,^{14,29,30,32} and previous treatment with plasma exchange was an exclusion criterion in one study.³⁵ Five studies enrolled patients who had previous treatment with immunomodulation or immunosuppressant therapy, IVIg, plasma exchange, or steroids if these therapies were not used in the six weeks to six months before randomization.^{29-31,33,40} One small trial included patients who had responded to IVIg therapy and had deteriorated once IVIg was discontinued.³⁵ Two studies allowed patients to use a stable dose of corticosteroids,^{14,29} and another allowed a stable dose of azathioprine throughout the intervention period.³⁰

c) Study interventions

A 0.4 g/kg/day dose of IVIg for five consecutive days was used in four studies.^{14,32,34,35} In the fifth study, this dose of IVIg was administered weekly for three weeks, and then the dose was reduced to 0.2 g/kg/day for an additional three weeks.³³ Four studies evaluated a 1.0 g/kg/day IVIg dose that was administered for two consecutive days in two studies^{29,30} and administered for two consecutive days followed by a third dose 20 days later in another study.³¹ In the fourth study, a loading dose of 2.0 g/kg was administered over two to four days followed by a dose of 1 g/kg over two consecutive days every three weeks for 24 weeks.⁴⁰

In the trials with an active comparator, oral prednisone was administered at a dose of 60 mg/day for two weeks followed by tapering (10 mg/week) over the next four weeks starting at 40 mg/day in one study.³⁰ In another study, plasma exchange was administered twice a week for three weeks followed by plasma exchange weekly for three weeks.³³ In another study, three extracorporeal immunoabsorption treatments were administered per week for six months.²⁹

The intervention periods for the three trials with parallel group designs were 16 days,³⁴ six weeks,³¹ and six months.²⁹ The crossover group design intervention periods were eight days,³⁵ four weeks,^{14,32} six weeks,^{30,33} or six months⁴⁰ respectively. Three trials continued open-label IVIg treatments after the blinded intervention and reported follow-up periods of mean \pm SD 29.5 \pm 12.4 months (range 12 months to 52 months)¹⁴ and 57.0 \pm 31 weeks (range 6.1 weeks to 107.7 weeks).³³ The third trial did not report the length of the open-label follow-up period.³⁴

All six trials had a conditional crossover depending on the patient's response to the first treatment (responders were not crossed over to second treatment until the disease had deteriorated).^{14,30,32,33,35,40} Washout periods were fixed in three trials at eight days,³⁵ four weeks,³² and six weeks,³³ with the remaining three trials allowing patients who had deteriorated to crossover to the second treatment early.^{14,30,40} The mean length of the washout periods and the number of patients crossing over early were not reported.

d) Study outcomes

Efficacy outcomes varied among all nine studies (Appendix G). Changes from baseline in the score or parameter were reported for IVIg and the comparator treatments. All nine trials^{14,29-35,40} used a disability or impairment scale as a primary outcome. One trial did not use an electrophysiological parameter as a secondary outcome.³⁵ Three trials used a disability or impairment score and an electrophysiological parameter as the primary outcome.^{32,33,35} One trial also used a quality-of-life score (SF-36)⁴⁸ as an outcome but did not report the change after treatment.³⁰

Six trials^{14,29,32,34,35,40} used a treatment response as an outcome. The criteria that were used to define the improvement varied among trials. Definitions ranged from a one-point improvement using the Rankin scale,^{34,35} to improvement in two of four measures with no deterioration in the other measures,²⁹ to improvement in three of six outcome measures.³²

AEs were not reported in detail by any study, and two trials provided no information about AEs.^{32,34}

4.2.3 Data analyses and synthesis

Because of the different outcome measures and different comparators that were used in the nine trials, each trial was reviewed separately. Meta-analyses were performed for the placebo-controlled trials only.

a) Intravenous immunoglobulin versus active comparator

Prednisolone

One randomized crossover trial³⁰ compared 1.0 g/kg IVIg given on two consecutive days with a six-week course of oral prednisolone, initial dose 60 mg/day for two weeks, then tapered to 10 mg/day over four weeks. The trial had a Jadad score of 5 with adequate concealment. The trial recruited 32 of the expected 40 patients, because study medication would have exceeded the expiry date. Seven patients withdrew before the second treatment period. Further treatment was deemed unnecessary in three patients. Of the remaining four patients, one responded, then worsened and withdrew to receive open-label IVIg. Small cell lung carcinoma was discovered in one patient. One patient developed psychosis, and the final patient did not respond to treatment and preferred not to enter the second treatment period. An additional patient deteriorated within one week of starting the second treatment period and withdrew to begin open-label IVIg therapy. This resulted in data being based on 24 patients for the primary analysis.

The primary outcome was an improvement from baseline in the INCAT disability score³⁰ at two weeks for all patients completing both arms of the trial. Each group showed statistically significant improvement after therapy initiation, with a mean (SD) improvement after IVIg therapy of 0.58 (0.93) grades ($P = 0.005$) and 0.71 (1.27) grades with prednisolone ($P = 0.012$). The authors stated that the scale grades are coarse and that a difference of 0.5 or more would seem worthwhile to patients. An improvement from grade 0 to grade 1 is not clinically important, but all other one-point improvements are clinically important.⁴⁰ No statistically significant differences were seen in the disability scores between treatment arms at two weeks or six weeks. The change from baseline in the secondary outcomes, which included Medical Research Council (MRC) sum scores (muscle strength),⁴⁹ grip strength, 10-metre walk time, nine-hole peg test, modified Rankin scale scores,⁵⁰ and the Rotterdam Handicap Score⁵¹ were not statistically significant, except for grip strength at six weeks in the IVIg group (scores not reported).

The incidence of total AEs was similar between the two treatments. Three SAEs were reported: carcinoma and psychosis with prednisolone treatment, and heart failure with IVIg. Two withdrawals due to AEs (WAEs) were reported: urticaria with IVIg treatment and psychosis with prednisolone.

Plasma exchange

One randomized, crossover trial³³ compared IVIg 0.4 g/kg once a week for three weeks followed by 0.2 g/kg once a week for three weeks with plasma exchange twice a week for three weeks followed by plasma exchange weekly for the remaining three weeks. The trial had a Jadad score of 1 with no allocation concealment. Of the 20 patients who were enrolled, 19 completed the first treatment period, and 13 completed the second treatment period. Two patients withdrew to receive treatment elsewhere. Four patients did not need a second treatment.

The primary outcomes were the changes after six weeks in the neurological disability score (NDS),⁵² NDS weakness subset score, and the summated compound muscle action potential (Σ CMAP) of ulnar, median, and peroneal nerves. There was statistically significant improvement from baseline in the primary outcomes after treatment with plasma exchange: average NDS (SD) 38.3 (34.6) points ($P < 0.001$); weakness score 33.4 (29.5) points ($P < 0.001$); and Σ CMAP 3.7

(3.5) mV ($P < 0.001$). The corresponding changes with IVIg therapy were NDS 36.1 (32) points ($P = 0.006$); weakness score 31.4 (31.5) points ($P < 0.002$); and Σ CMAP 3.3 (2.8) mV ($P < 0.001$). There were no statistically significant differences between the two treatment groups, and both groups were responsive to treatment. The maximum impairment on the NDS scale is 132. Therefore a change of 36 points equates to approximately 25% clinical improvement. Other authors report that a change of at least 20 points would be clinically important.¹⁴ There was also no statistically significant difference between treatments for the secondary outcomes of summated sensory nerve action potential (Σ SNAP) of median and sural nerves and vibratory threshold of the great toe.

Total AEs and SAEs were not reported. There was one WAE reported: an infection occurred with an indwelling catheter that was used in the plasma exchange group. Lightheadedness, rash, and nausea were reported as AEs, but the frequency was not reported.

A randomized, three-arm parallel group trial²⁹ compared IVIg 1g/kg/day for two consecutive days, 0.5 g/kg/day for two consecutive days, and three treatments of plasma exchange using special Excorim staphylococcal protein immunoadsorption columns over seven days. The trial had a Jadad score of 2 with no allocation concealment. Twenty patients were enrolled, and 18 received treatment before the study was halted because of the cessation of funding. Data from the low-dose arm were not compared with the other treatment arms, because of the small number of patients. Therefore, data from nine patients on IVIg and five patients on plasma exchange were used for the analysis.

The primary outcome measure was the determination of clinical responders to treatment. As defined by the authors, a clinical responder showed improvement in two of four measures, (average muscle score,³¹ grip strength, Toronto clinical neurology score,¹⁶ Hughes functional disability scale [HFDS]⁵³) without deterioration in the other measures. The authors did not specify the criteria for improvement in each of the four assessment scales. There was no statistically significant difference in the proportion of responders that was determined at two and six months between the two treatment groups. At two months, 50% of the IVIg group were considered to be clinical responders versus 80% in the plasma exchange group ($P = 0.56$). Results for the secondary outcome measure (determination of electrophysiological responders defined as improvement in two of four parameters, [sensory nerve conduction velocity, motor nerve conduction velocity (MCV), CMAP, F-wave latencies] without deterioration in other measures) was not reported. The authors did report a comparison of the four parameters used for the nerve conduction changes in each treatment group. There were no statistically significant differences between the treatment groups, although the sensory nerve conduction velocity and the F-wave latencies improved numerically with plasma exchange and worsened with IVIg.

There were two SAEs reported (sepsis and pneumonia, and heart failure resulting in death) in patients who were randomized to be in the low-dose IVIg arm. The authors deemed both deaths to be unrelated to the treatment. Two WAEs (rash) were reported for the IVIg group.

b) Intravenous immunoglobulin versus placebo

All six^{14,31,32,34,35,40} randomized, placebo-controlled trials were of good quality with Jadad scores of 4 or more, and five had adequate concealment. The method of concealment could not be ascertained for one trial.⁴⁰ The changes in the disability outcomes appear in Table 3.

| Study | IVIg Dose | Outcome | Change from Baseline Mean (SD) | | P Value* |
|-------------------------|--|---------|--------------------------------|-------------|----------|
| | | | IVIg | Placebo | |
| Hughes ⁴⁰ | 2.0 g/kg × 2 day, then 1.0 g/kg/week × 3 week | GS | 13.2 (19.3) | 1.5 (5.6) | 0.0008 |
| | | MRC-SS | 3.3 (5.6) | 0.2 (4.5) | 0.001 |
| Hahn ¹⁴ | 0.4 g/kg × 5 day | NDS | 24.4 (5.4) | 0.4 (0.3) | < 0.002 |
| | | GS | 6.3 (1.7) | -0.8 (0.9) | < 0.005 |
| | | CG | 1.0 (0) | 0.4 (0.3) | < 0.001 |
| Vermuelen ³⁴ | 0.4 g/kg × 5 day | MRC-SS | 1.6 (3.04) | 1.23 (3.2) | NSS |
| Mendell ³¹ | 1.0 g/kg × 3 day | AMS | 0.46 (0.15) | 0.02 (0.12) | 0.045 |

AMS = average muscle score (modified MRC-SS); GS = grip strength; IVIg = intravenous immunoglobulin; MRC-SS = Medical Research Council sum score;⁴⁹ NDS = neurological disability scale;⁵² NSS = not statistically significant; SD = standard deviation.

*Comparison between groups.

Larger scores mean less impairment.

Three of four trials reported statistically significant changes after IVIg treatment compared with placebo (Table 3). The maximum MRC sum score is 60, and the reported change of 3.3 may not be clinically important. A change of 20 points or more on the NDS scale or a change of one clinical grade are reported to be clinically important.¹⁴

Four trials used predefined definitions of responders, but the outcome measures that were used in the definition differed. One trial³⁴ reported that the proportion of patients showing improvement of 1 point or more on the modified Rankin scale⁵⁰ was similar between the two treatment groups (26.7% IVIg versus 23% placebo). A P value was not reported by the authors, but the calculated P value, using a chi-square test, was non-significant (P = 1.0). A second trial¹⁴ reported that the proportion of patients improving by 20 points or more in the NDS was larger in the IVIg group (63% versus 17%). The authors did not report a P value, and the calculated value using a chi-square test was significant (P < 0.001). The authors also reported the proportion of responders by disease course: 56% chronic progressive versus 71% chronic relapsing. The difference in the proportions, by disease course, is not significant. Mendell et al.³¹ reported that the proportion of responders, defined as a one-grade improvement (which is a clinically important change) in the HFDS,⁵³ was statistically significantly larger for the IVIg group (38% versus 9.5%, P = 0.019). Hughes et al.⁴⁰ reported that the IVIg group had a statistically significantly larger proportion of responders (defined as an improvement by 1 point or more on the adjusted INCAT scale) compared with placebo (54% versus 21%, P = 0.0002). A one-point improvement in the adjusted INCAT score is thought to be clinically significant in all patients, as reported by the authors. Thompson et al.³² reported that 43% of the patients showed improvement in three of the six outcome measures, but the study was stopped prematurely because of the publication of Hahn et al.'s study.¹⁴

Results that were not reported in the original IGIV-C CIDP efficacy (ICE) trial⁴⁰ were reported in two abstracts that were presented at the AAN annual meeting. Merkies et al.¹² reported a statistically significant improvement of 3.4 points in the SF-36 physical component summary score after IVIg therapy ($P = 0.001$). This equates to less than four-tenths of a SD, which may not be a clinically important difference.⁴⁸ Vermeulen et al.³⁴ reported statistically significant improvements for three of the 16 electrophysiological measures with IVIg therapy: ulnar distal latency ($P = 0.005$), tibial distal CMAP ($P = 0.003$), and peroneal nerve conduction velocity ($P = 0.003$). Hughes et al.⁴⁰ reported a statistically significant improvement in the INCAT sensory score after IVIg therapy: mean \pm SD 1.2 ± 3.4 versus 0.2 ± 3.9 ($P = 0.021$). Hahn et al.¹⁴ reported the results of a secondary analysis of the electrophysiological data at the end of the first phase of the crossover trial. The MCV and distal motor latencies improved statistically significantly with IVIg therapy compared with placebo therapy. MCV improved by mean \pm SD 15.3 ± 44.1 metres per second with IVIg therapy versus a deterioration of -13.2 ± 39.9 with placebo ($P < 0.0001$). The distal motor latency improvement was mean \pm SD 3.9 ± 14.5 milliseconds versus a -1.2 ± 15.4 millisecond deterioration with placebo ($P < 0.004$). The CMAP measured in three trials^{14,35,40} showed numerically greater but not statistically significant improvements with IVIg therapy. Brill et al.⁴⁴ reported that there was a statistically non-significant trend favouring IVIg in all the electrophysiological measures.

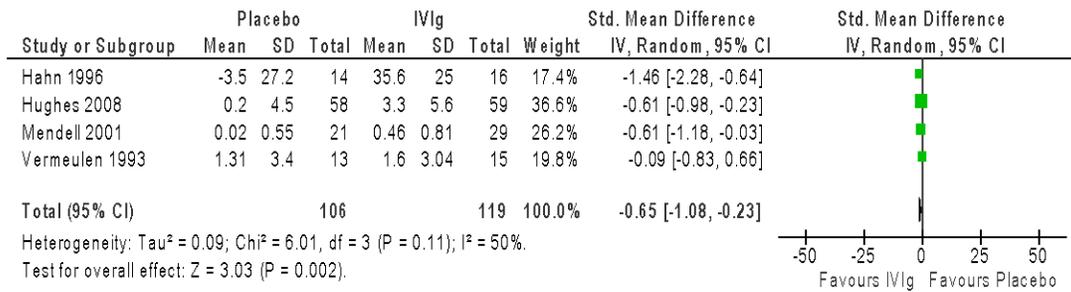
Hughes et al.⁴⁰ reported a statistically significantly smaller proportion of patients using IVIg (13%) had relapsed after 21 weeks compared with patients on placebo (45%) ($P = 0.011$). Van Doorn et al.³⁵ reported a mean of 11 weeks (minimum of four to a maximum of 24) until patients deteriorated after IVIg treatments were discontinued. When these patients were randomized to receive IVIg or placebo, van Doorn et al. reported that the time to deterioration after one treatment was statistically significantly longer for IVIg therapy compared with placebo (6.4 weeks versus 1.3 weeks, $P = 0.02$). This statistically significant increase in time to deterioration was also reported by Hughes et al.⁴⁰ during the extension phase (for responders only) of the ICE trial ($P = 0.01$).

AEs were not reported for the two trials,^{32,34} and one trial reported that no patients experienced AEs.³⁵ Numerically higher proportions of patients on IVIg, compared with those on placebo, experienced the common AEs of headache, nausea, chills, and fever, and comparable proportions experienced transient hypotension.³¹ A total of 15 patients experienced a SAE (seven patients on IVIg^{14,40} and eight on placebo).⁴⁰ Two WAEs after IVIg therapy were reported: urticaria,³¹ and lack of efficacy.⁴⁰ The patient who was experiencing lack of efficacy subsequently died of sepsis. The authors deemed the death to be unrelated to therapy.

c) Meta-analyses

Data from four^{14,31,35,40} of the six placebo-controlled trials were included in a meta-analysis of standardized mean differences. The four trials reported the disability score changes from baseline in scales that measured muscle strength and weakness. Figure 2 shows the effect of IVIg in each study and the overall pooled estimate. A statistically significant moderate treatment effect of -0.65 (95% CI -1.08 to -0.23) in favour of IVIg was found.

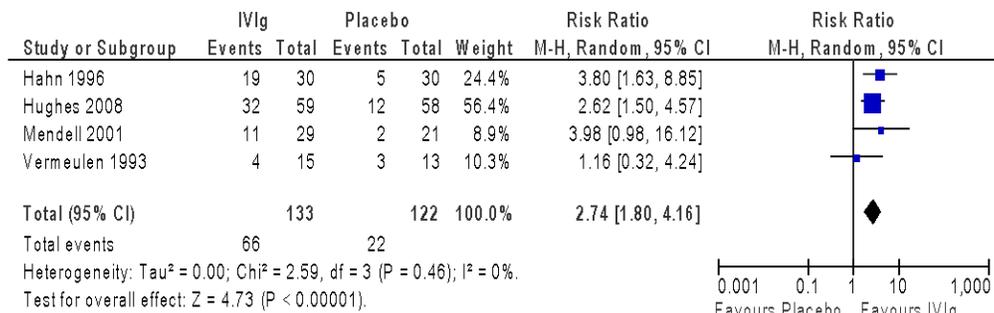
Figure 2: Change in Disability Scores



CI = confidence interval; IVIg = intravenous immunoglobulin; SD = standard deviation; Std. = standard.; IV = inverse variance

The pooled analysis of the proportion of treatment responders, as defined by the investigators in each trial, resulted in a RR of 2.74 (95% CI 1.80 to 4.16) in favour of IVIg (Figure 3).

Figure 3: Number of Patients Achieving a Treatment Response



CI = confidence interval; IVIg = intravenous immunoglobulin. ; M-H = Mantel–Haenszel

None of the trials reported results for patient subgroups (adult versus children, progressive versus relapsing-remitting, or disease variant). Therefore, no sensitivity analysis was conducted.

5 ECONOMIC ANALYSIS

5.1 Review of Economic Studies: Methods

A protocol for the review was written a priori and followed throughout the review process.

5.1.1 Literature searches

A systematic search was undertaken to locate full economic evaluations assessing IVIg for CIDP. The search strategy was developed by an information specialist (KC) with input from the project team. The search strategy underwent peer review by a CADTH information specialist.

All search results were imported into a Reference Manager Version 11 database for removal of duplicates and title and abstract screening.

The following bibliographic databases were searched through the Ovid interface: MEDLINE (1950 to present; In-Process & Other Non-Indexed Citations), EMBASE (1980 to present), and CINAHL (1982 to present). Parallel searches were run in PubMed (for non-MEDLINE records only), Wiley's Cochrane Library (NHS Economic Evaluation Database and Health Technology Assessment Database) and Health Economic Evaluations Database (HEED), Thomson's Social Sciences Citation Index and Biosis Previews, and Scholar's Portal's EconLit.

The search strategy, with controlled vocabulary and keywords, focused on "CIDP" and "IVIg." An unvalidated methodological filter was applied to limit retrieval to primary economic studies or reviews of economic studies. No year or language limits were used. Appendix H shows the search strategy.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies and health economic research groups and their associated databases. Google and AlltheWeb search engines were used to search for additional information. These searches were supplemented by reviewing the bibliographies and abstracts of key papers and conference proceedings.

Ovid and PubMed AutoAlerts were set up to send monthly updates with any new literature. Monthly updates were performed on the HEED and NHSEED databases.

5.1.2 Selection criteria

Inclusion criteria for full-text screening of studies were analysis of CIDP, IVIg being a treatment comparator, measurement of costs, and measurement of effectiveness.

5.1.3 Selection method

Study selection was done in two phases: title and abstract review, and full-text review. Two independent reviewers (GB, FX) conducted the title and abstract review using prespecified inclusion and exclusion criteria. Based on the titles and abstracts (when available), studies were excluded if both reviewers agreed that they did not include an economic evaluation, did not include IVIg as a comparator, or did not have CIDP as the patient population. The resolution of disagreement occurred through consensus. Studies that were not excluded based on title and abstract screening were retrieved in full text and assessed by one reviewer (GB) to determine if they should be included for data abstraction.

5.1.4 Data extraction strategy

One reviewer (GB) abstracted data from the economic evaluations using standard forms that were created for this project (Appendix I). A second reviewer (FX) verified the abstracted data. Completed data abstraction forms appear in Appendix J.

5.1.5 Data analysis methods

Because of the difficulty in pooling results from economic evaluations, the economic literature is analyzed using qualitative descriptions only.

5.2 Review of Economic Studies: Results

Three hundred and thirty articles were initially identified (Figure 4). Of these, 24 articles were retrieved for scrutiny, with 23 being excluded (Appendix K), leaving one economic article for review.⁵⁴

McCrone et al.⁵⁴ conducted a patient-level economic evaluation on patients with CIDP who were participating in an international clinical trial that used a crossover design. Patients were randomized to receive IVIg (single dose 2 g/kg weight) or oral prednisolone (60 mg per day for the first two weeks, 40 mg per day in week 3, 30 mg per day in week 4, 20 mg per day in week 5, 20 mg per day in week 6). The economic evaluation was conducted over the initial six-week treatment period of the crossover trial. There were 12 patients in the IVIg group and 13 in the prednisone group. The primary economic outcome was the incremental cost per quality-adjusted life-year (QALY).

The resources that were captured included IVIg and prednisolone use, stays in hospital, outpatient visits, and day hospital visits. The number of contacts with health care providers such as physiotherapists, nurses, occupational therapists, and social workers was also captured, as was the number of caregiver hours. Resource utilization data were collected four times.

The unit costs were based on UK pounds that were converted into Euros (2002). The cost of IVIg that was assumed in the analysis was €26 per gram, which equated to €3,911 for one course of IVIg. The cost of prednisolone that was assumed in the analysis was €8. The authors did not provide a source for the cost of IVIg or of prednisolone. For other costs, the paper refers to a document by Netten et al.⁵⁵ EQ5D questionnaires were provided to patients to capture the change in utility values over the six-month initial study period.

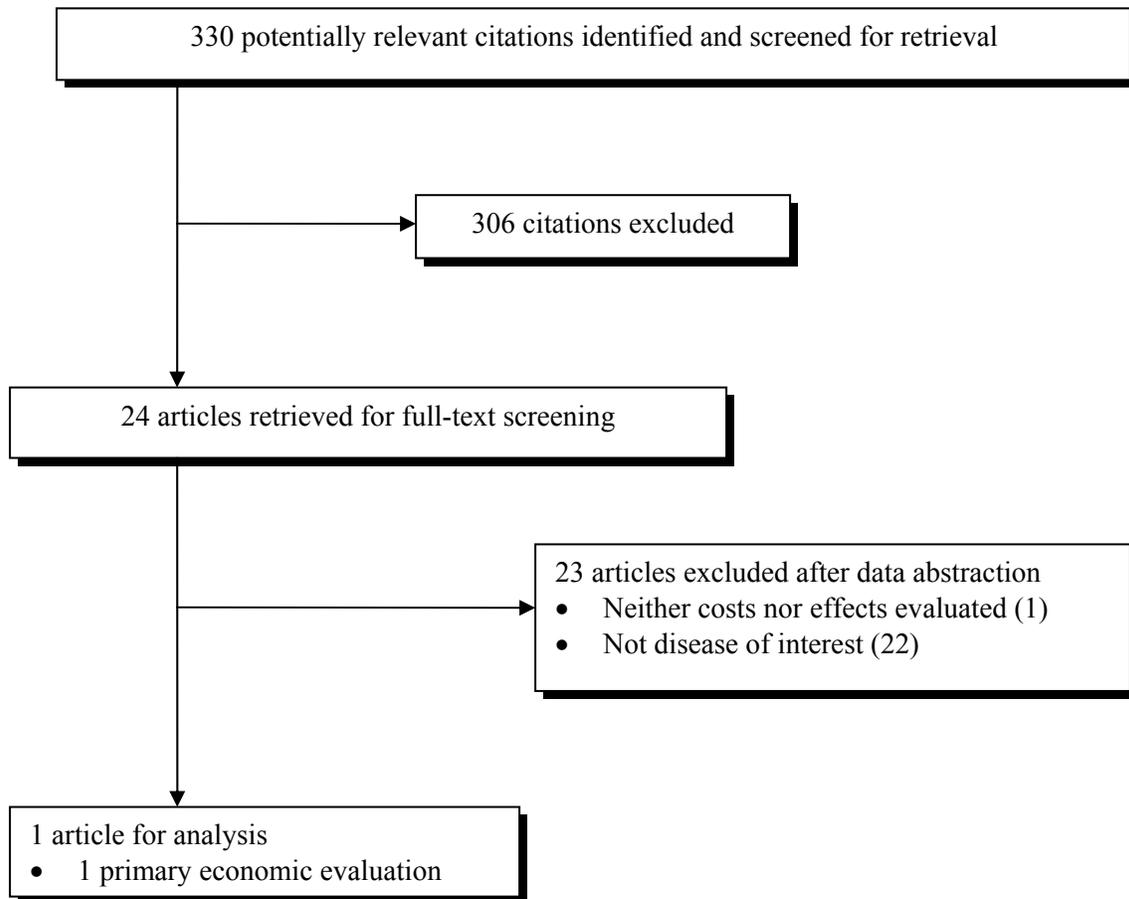
After adjusting for baseline costs, patients on IVIg incurred €3,439 higher costs than those in the prednisolone group. IVIg was also found to result in 0.12 greater utility gain compared with prednisolone. This six-week utility gain translated to 0.014 QALYs ($0.12 \times 6/52$).

The authors presented the results as cost-effectiveness acceptability curves (CEACs) instead of cost-effectiveness ratios. Uncertainty in the results was generated using non-parametric bootstrapping techniques. The authors stated that the probability that IVIg is cost-effective is greater than 50% if society values one QALY at €250,000.

Based on the incremental differences in costs and QALYs reported, a traditional cost-effectiveness ratio can be calculated as €245,643 per QALY ($€3,439/0.014$). Based on current exchange rates,⁵⁶ this is the equivalent of C\$388,110 per QALY. The authors do not make statements about the cost-effectiveness of IVIg. They do refer to cost-effectiveness ratios for other technologies that were all lower than what was found in their study. They state that one should be cautious about comparing

cost-effectiveness results, because of the differences in the methods that were used and that the high cost per QALY may be acceptable if there are no alternative treatments or if the budget impact is low. Financial support for the study was provided by industry and the Guillain-Barré Syndrome Support Group.

Figure 4: QUOROM Flowchart



5.3 Primary Economic Evaluation: Methods

5.3.1 Types of economic evaluation

A cost-utility analysis was conducted using a Markov model for patients with CIDP. Using a cost-utility analysis (cost per QALY) allows for the incorporation of the quality-of-life impact of the clinical effects of CIDP treatment strategies. The use of the cost per QALY outcome also allows for comparison with evaluations of other disease areas that use this outcome.

5.3.2 Target population

The population entering the model are adult patients with CIDP. The model cohort is assumed to be 54 years of age and weighing 75 kg. The starting age is based on the average age of patients in the trial that compared IVIg and corticosteroid treatment in patients with CIDP.³⁰ Patient weight is based on the assumption made by McCrone et al.⁵⁴

5.3.3 Comparators

Two treatment comparators are considered in the analysis: IVIg and oral corticosteroids.

5.3.4 Perspective

The analysis was taken from the perspective of a publicly funded health care system. The costs include hospital-related costs, physician fees for services that are covered by provincial fee schedules, costs of inpatient and hospital clinic administered drugs, and costs of drugs that are covered by the provincial formularies for eligible patients. Indirect costs, such as productivity losses, were not considered. Although IVIg forms part of the budget for Canadian Blood Services, its costs are borne by Canadian public health care payers as part of payments to Canadian Blood Services.¹

5.3.5 Effectiveness

The effectiveness measure is QALYs.

5.3.6 Time horizon

In the base-case analysis of the model, a five-year time horizon was chosen to capture the adverse effects of corticosteroid use. A longer time horizon may better capture these long-term AEs. The impact of IVIg therapy on utility, however, was based on six-week data.⁵⁴ Therefore, a longer time horizon was not used in the base-case analysis. Alternative time horizons are assumed in a sensitivity analysis.

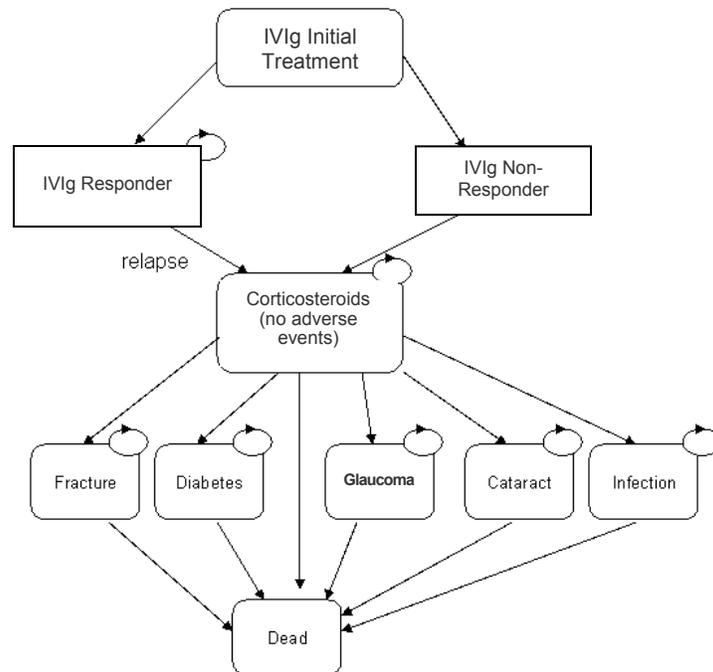
5.3.7 Modelling

The structure of the model, including the transitions between health states, appears in Figures 5 and 6. Figure 5 presents the model structure for the IVIg treatment strategy. Each box represents different health states. Transitions from one health state to another are indicated by straight

arrows. Circled arrows indicate patients can stay in a health state from one model cycle to the next. All patients enter the model in the IVIg initial treatment health state. After this initial six-week cycle, a proportion of patients are IVIg responders or IVIg non-responders. It is assumed that patients who respond to treatment receive maintenance IVIg each six-week cycle until they relapse and no longer respond to treatment. It is assumed that when patients relapse, they switch to corticosteroid treatment. It is assumed that patients who are not responding to initial IVIg treatment switch to corticosteroid treatment. It is assumed that patients who are not responding to initial IVIg treatment switch to corticosteroid treatment.

When patients start corticosteroid treatment, they are at risk of AEs in each six-week cycle. The AEs that are used in the model are fracture, diabetes, glaucoma, cataract, and serious infection. This is not an exhaustive list of side effects that are associated with steroid use. We evaluated these because they were incorporated into an economic evaluation of corticosteroids for the treatment of rheumatoid arthritis.⁵⁷ Other AEs that are associated with long-term use include hypertension, electrolyte disturbances, peptic ulceration, pancreatitis, and adrenal suppression.⁵⁸ This study was used as the source for AE-related model inputs. It is assumed that when patients have an AE, they discontinue steroid treatment. It is assumed that when treatment is stopped, HbA1C (diabetes) and elevated intraocular pressure (glaucoma) return to normal. It is assumed that these conditions last for one year before discovery and steroid discontinuation. For each AE, patients are assigned an increased risk of mortality, increased costs, and a reduction in quality of life.

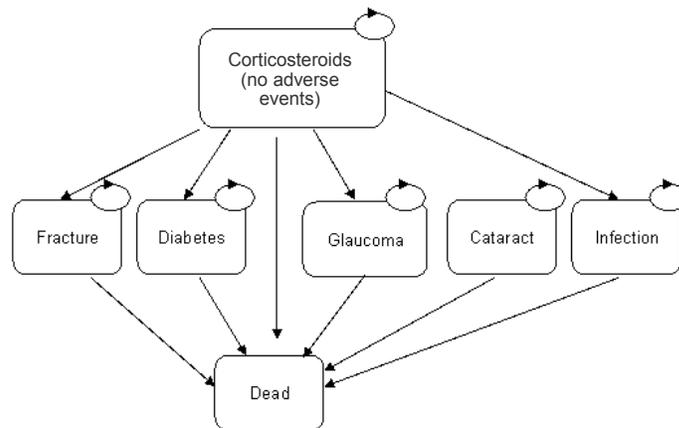
Figure 5: Structure of Intravenous Immunoglobulin Treatment Arm of Model



IVIg = intravenous immunoglobulin.

Figure 6 presents the model for the corticosteroid treatment strategy. It is similar to the structure of the IVIg arm, except that no distinction is made between steroid responders and steroid non-responders. There are several reasons why no distinction is made. First, the clinical trial comparing IVIg with corticosteroids in patients with CIDP³⁰ did not report treatment response or relapse as an outcome. Second, because IVIg treatment is more expensive than corticosteroid treatment, the proportion of patients who respond to IVIg can incur maintenance treatment costs, compared with those who respond to corticosteroids. Finally, the only study that compared utility values in IVIg and corticosteroid-treated patients with CIDP⁵⁴ did not report utility values by responder status.

Figure 6: Structure of Corticosteroid Treatment Arm of Model



5.3.8 Valuing outcomes

Several clinical input parameters were used to populate the model and estimate the number of expected QALYs for each treatment strategy. These include initial IVIg response rate, IVIg relapse rates, corticosteroid AE rates, mortality rates, and utility values that are associated with treatments and AEs.

a) ***Intravenous immunoglobulin response and relapse rates***

IVIg response rates were pooled using a random effects meta-analysis.²⁴ The studies that were included in the estimation of response rates mirrored the studies that were pooled in the clinical review. Appendix L presents the IVIg response rates that were reported in the trials with the pooled estimate. The pooled IVIg response rate was estimated to be 46.9% (95% CI 32.4% to 61.4%). The IVIg relapse rate was based on data from ICE,⁴⁰ which was the only study that reported relapse rates over a six-month period. This was also the only study that used a formal survival analysis of IVIg relapse rates. The 25-week relapse rate for IVIg in this study was estimated to be 13%. This is equivalent to a 6.5% constant relapse rate every six weeks.

b) ***Corticosteroid-related adverse event probabilities***

The probabilities of corticosteroid-related AEs were taken from a cost-effectiveness study comparing corticosteroids with Cox-2 inhibitors for the treatment of rheumatoid arthritis.⁵⁷ Bae et al.⁵⁷ used Saag et al.'s⁵⁹ study as the source for fracture and cataract probabilities. McDougall

et al.’s⁶⁰ study was used as the source for the probabilities of diabetes, glaucoma, and infection. Table 4 presents the annual AE probabilities that were used in the model.

| Table 4: Annual Probabilities of Corticosteroid Adverse Events | |
|---|---------------------------|
| Adverse Event | Annual Probability |
| Fracture | 0.0098 |
| Diabetes mellitus | 0.0043 |
| Cataract | 0.0114 |
| Glaucoma | 0.0008 |
| Infection | 0.0035 |

c) Utilities

Background utility values for the model were based on utilities from a UK general population.⁶¹ Utility values by age and gender appear in Appendix M. Utility gains from IVIg treatment were added to the background utility values, whereas utility losses from corticosteroid-related AEs were subtracted from background utility values.

The incremental gain in utility from IVIg treatment compared with corticosteroid treatment was assumed to be 0.12. This was based on findings from McCrone et al.⁵⁴ who measured utility at baseline and at 12 weeks in patients with CIDP who were treated with IVIg or corticosteroids. This utility gain was added to the baseline utility values for all IVIg-treated patients during the first 12-week model cycle. This utility gain was also applied to patients for the full duration of each subsequent cycle where they remain IVIg responders.

The disutility due to fracture was estimated using an unpublished Canadian model evaluating treatments for corticosteroid-induced osteoporosis. This model is a modification of Goeree et al.’s⁶² osteoporosis model. The model considers hip, vertebral, and wrist fractures. Disutility per fracture was estimated as a weighted average of disutilities that were associated with each fracture type. Appendix N presents the disutility per fracture by age for the initial year and subsequent years after fracture.

The disutility that was associated with diabetes was estimated using the Ontario Diabetes Economic Model (ODEM).⁶³ The ODEM predicts the occurrence of seven diabetes-related complications (ischemic heart disease, myocardial infarction, heart failure, stroke, amputation, blindness, renal failure) based on risk factors such as HbA1C, cholesterol levels, and systemic blood pressure. The long-term costs, quality of life, and mortality that are related to these complications are also predicted. The ODEM was run for 30 years using different scenarios. First it was run assuming an elevated HbA1C during the first year. Second it was run assuming no elevated HbA1C during the first year. Disutilities were calculated as the difference in utilities that were predicted by ODEM in these two scenarios. Appendix O presents the disutility that was associated with the occurrence of diabetes by age group in the first and subsequent years.

The disutility that was associated with the development of cataracts in the model was assumed to be 0.38 while waiting for surgery and 0.10 after surgery.⁶⁴ These values were based on those in a cost-effectiveness study on reducing wait times for cataract surgery in Ontario.⁶⁴ It was assumed that patients would have a 109-day wait for cataract surgery.⁶⁴ The disutility for glaucoma was

assumed to be 0.061.⁶⁵ For serious infection, the disutility of 1.0 for two weeks duration that was used was the same value that Bae et al.⁵⁷ used.

d) Mortality

General population mortality rates by age were based on 2002 Canadian lifetable data.⁶⁶ The average of male and female mortality rates were used in the model. The increased risk of death after fracture was derived from the model that provided the utilities.⁶² Increased mortality rates by age for the first and subsequent years appear in Appendix P. The increased risk of death from diabetes was estimated using the ODEM.⁶³ The increased risk of death by age group appears in Appendix Q. The acute risk of death from serious infection was based on data from a Canadian study on in-hospital mortality from community acquired pneumonia.⁶⁷ This study reported mortality rates of 0.018 and 0.111 for patients aged between 25 years and 65 years and those over 65 years respectively. No increase in the probability of death was assumed for the other corticosteroid-related AEs.

5.3.9 Resource use and costs

a) Intravenous immunoglobulin

The initial and maintenance IVIg treatment cost estimates were based on two components. The first was the dose and frequency of IVIg administration. The second component was the cost per IVIg administration. The dose and frequency of IVIg treatment that were assumed in the model were based on the information in the monograph of the product that was approved for CIDP treatment in Canada.⁶⁸ This includes an initial loading dose of 2 g of IVIg/kg of body weight over two to four days with maintenance dosing of 1 g/kg over one to two days every three weeks. This is the same dosing regimen that was used in the study to estimate IVIg relapse rates.⁴⁰ For the model, it is assumed that the initial treatment is given as two 1 mg/kg doses and that maintenance IVIg treatment is given as a 1 g/kg dose every three weeks.

Table 5 shows the unit costs and total cost per IVIg administration that were used in the model. The cost per gram of IVIg (\$59.19) was provided by Canadian Blood Services (Mathias Haun: personal communication, 2008 Apr). The cost per hour for a nurse (\$32) was based on data from the Canadian Salary Survey.⁶⁹ Based on a 1 g/kg dose, a 75 kg patient, and 3.5 hours of nurse supervision, the total cost per IVIg administration is \$4,551.25. Table 6 shows the total cost of IVIg by model cycle based on the number of administrations. In the initial 12-week cycle patients are given two 1 g/kg administrations of IVIg, resulting in a total cost of \$9,102.50. It was assumed that during subsequent 12-week cycles, patients have four 1 g/kg IVIg administrations, resulting in IVIg costs of \$18,205. This cost is applied to patients who remain IVIg responders.

| Resource | Unit Cost (\$) | Resource per IVIg Administered (75 kg patient) | Cost per IVIg Administration (\$) |
|-----------------|-----------------------|---|--|
| IVIg (0.4 g/kg) | 59.19/g | 30 g | 4,439.25 |
| Nurse wage | 32 per hour | 3.5 hours | 112.00 |
| Total | | | 4,551.25 |

IVIg = intravenous immunoglobulin.

| Cycle | Cost per IVIg Administration (\$) | Number of Administrations per Cycle | IVIg Administration Cost per 3-month Cycle (\$) |
|------------|-----------------------------------|-------------------------------------|---|
| Initial | 4,551.25 | 2 | 9,102.50 |
| Subsequent | 4,551.25 | 4 | 18,205 |

IVIg = intravenous immunoglobulin.

b) Corticosteroids

Table 7 presents the unit costs that were used when estimating the cost of corticosteroid treatment. The cost per 5 mg and 50 mg pill of prednisone was the reimbursement rate that was listed in the Ontario Drug Benefit formulary.⁷⁰ An 8% pharmacy markup and a \$7.00 pharmacy dispensing fee were applied. It was assumed that a 90-day supply of prednisone would be dispensed each time. The cost of prednisone is underestimated based on the use of the 50 mg tablet, which is not commonly used because it limits the ability to taper the dose down. It is assumed that patients on corticosteroids take a biphosphonate to help protect them from fracture. The cost of etidronate was derived from the Ontario Drug Benefit formulary.⁷⁰ An 8% pharmacy markup and \$7.00 dispensing fee per 12 weeks were applied to the biphosphonates.

| Resource | Unit Cost |
|---|-----------|
| Prednisone 50 mg | \$0.0913 |
| Prednisone 5 mg | \$0.0220 |
| Etidronate disodium / calcium carbonate 400 mg / 500 mg 90-tablet kit | \$19.99 |
| Pharmacy markup | 8% |
| Dispensing fee | \$7.00 |

It was assumed that patients would be prescribed 60 mg per day of prednisone for the first four weeks of treatment. The dose would then be reduced by 10 mg per day in each of the next 20 weeks. It was assumed that after 24 weeks, the dose was tapered down to 5 mg per day. Table 8 shows the corticosteroid treatment cost by 12-week model cycle.

| Cycle | Corticosteroid (including 8% pharmacy markup) (\$) | Biphosphonates (including 8% pharmacy markup) (\$) | Dispensing Fee (\$) | Total (\$) |
|------------|--|--|---------------------|------------|
| 1st | 12.17 | 21.59 | 14.00 | 47.76 |
| 2nd | 7.98 | 21.59 | 14.00 | 43.57 |
| Subsequent | 2.00 | 21.59 | 14.00 | 37.59 |

c) Corticosteroid-related adverse events

The cost of fracture was estimated using the same model that provided the utility and risk of death after fracture values.⁶² Appendix R shows the cost of fracture by age group in the first and subsequent years after fracture. The cost of diabetes was estimated using the ODEM.⁶³ The diabetes-related costs that were used in the model for the first and subsequent years appear in

Appendix S. The cost that is related to the development of cataracts (\$6,218) was taken from Hopkins et al.'s⁶⁴ study and primarily comprises surgery costs. The costs that are related to the development of glaucoma (\$152) and serious infection (\$24,334) were based on the estimates that were used by Bae et al.⁵⁷ inflated to 2008 Canadian dollars. This conversion from US to Canadian dollars was based on the December 2008 currency exchange rate.⁵⁶ The inflation from 1999 Canadian dollars to 2008 Canadian dollars was based on the health care component of the consumer price index.⁷¹

5.3.10 Discount rate

In accordance with CADTH guidelines⁷² a 5% discount was applied to costs and QALYs. The discount was varied in a sensitivity analysis.

5.3.11 Variability and uncertainty

The variability of cost-effectiveness results according to patient characteristics was assessed using one-way sensitivity analysis. The model was run assuming different patient weights and starting ages. Because patient weight affects IVIg dosing, it also affects the costs. The structural uncertainty of the model was evaluated using one-way sensitivity analyses varying the discount rates and the model duration. The model was also evaluated using different assumptions about the dosing and frequency of maintenance IVIg treatment and on the utility gain from IVIg treatment. Parameter uncertainty was evaluated using probabilistic sensitivity analysis and expressed in CEACs. The distributions and parameters that were used in the probabilistic sensitivity analysis appear in Appendix T.

5.4 Primary Economic Evaluation: Results

5.4.1 Analysis and results

Table 9 presents the base-case cost-effectiveness results. The total cost of the IVIg treatment arm over the five-year duration of the model is estimated to be \$104,943 compared with \$2,196 for the corticosteroid treatment cost, resulting in an incremental cost of IVIg compared with corticosteroids of \$102,747. Over five years, IVIg was estimated to have 3.970 QALYs compared with 3.783 QALYs for corticosteroids. The resulting incremental cost-utility ratio of IVIg compared with corticosteroids is \$549,449 per QALY gained.

| Table 9: Base-Case Cost-Effectiveness Analysis | | | | | |
|---|-------------------|--------------|-------------------------------|--------------------------|------------------|
| | Costs (\$) | QALYs | Incremental Costs (\$) | Incremental QALYs | ICUR (\$) |
| Corticosteroids | 2,196 | 3.783 | reference | reference | reference |
| IVIg | 104,943 | 3.970 | 102,747 | 0.187 | 549,449 |

ICUR = incremental cost-utility ratio; IVIg = intravenous immunoglobulin; QALYs = quality-adjusted life-years.

5.4.2 Results of variability analysis

One-way sensitivity analyses were conducted varying patient weight from 35 kg to 95 kg and patient age from 35 years old to 75 years old (Table 10).

| Table 10: Sensitivity Analyses by Patient Weight and Age | | | |
|---|--|---|---|
| Patient Characteristic Varied | Incremental Costs (IVIg-corticosteroids) (\$) | Incremental QALYs (IVIg-corticosteroids) | Cost per QALY IVIg versus Corticosteroids (\$) |
| Patient weight | | | |
| 35 kg | 48,930 | 0.187 | 262,260 |
| 45 kg | 62,385 | 0.187 | 334,372 |
| 55 kg | 75,839 | 0.187 | 406,485 |
| 65 kg | 89,293 | 0.187 | 478,597 |
| 75 kg | 102,747 | 0.187 | 549,449 |
| 85 kg | 116,201 | 0.187 | 622,821 |
| 95 kg | 129,655 | 0.187 | 694,933 |
| Starting age | | | |
| 35 years old | 102,763 | 0.180 | 569,590 |
| 45 years old | 102,754 | 0.183 | 561,208 |
| 55 years old | 102,748 | 0.191 | 538,696 |
| 65 years old | 102,721 | 0.212 | 485,028 |
| 75 years old | 102,661 | 0.257 | 399,656 |

IVIg = intravenous immunoglobulin; QALYs = quality-adjusted life-years. Numbers may not be exact because of rounding.

5.4.3 Results of uncertainty analysis

Table 11 presents the incremental costs, incremental QALYs, and the cost per QALY of IVIg compared with corticosteroids after varying structural model assumptions. Assuming different discount rates or model time horizons has little impact on the cost-utility estimates. Assuming a larger incremental utility impact of IVIg does have an impact on the results. If a 0.25 utility gain is assumed, the cost per QALY becomes \$275,739. If a 0.50 utility gain is assumed, the cost per QALY becomes \$140,669. Incorporating a switch from corticosteroids to IVIg does have an impact on incremental cost and incremental effects. The cost per QALY (\$558,685), however, is not greatly affected. In the base-case analysis, it was assumed that maintenance IVIg was given in 1 mg/kg doses, once every three weeks. If it is assumed that maintenance IVIg is 1 mg/kg once every eight weeks, the cost per QALY of IVIg becomes \$235,814. If it is assumed that maintenance IVIg is 0.4 mg/kg once every eight weeks, the cost per QALY of IVIg becomes \$125,241.

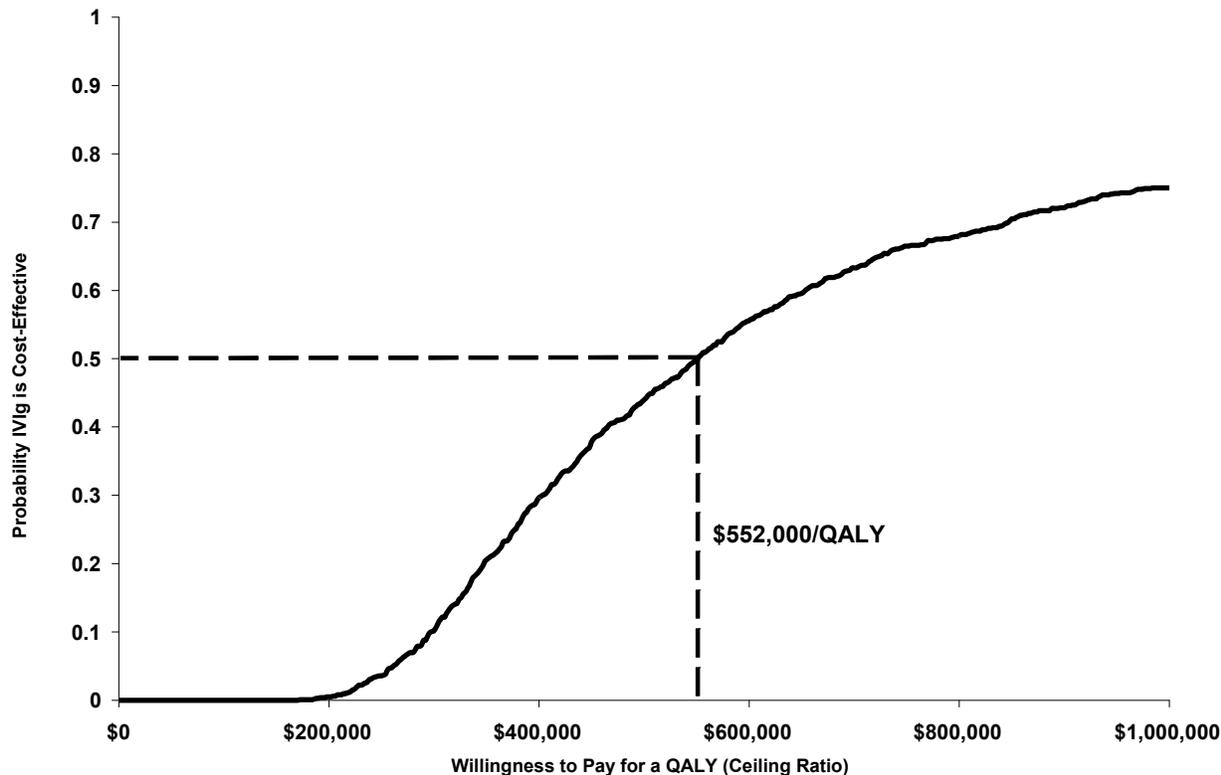
Figure 7 presents the CEAC for the IVIg treatment arm using the base-case model assumptions. At a willingness to pay for a QALY threshold of \$552,000, the probability that IVIg is cost-effective is 50%. At a willingness to pay of \$50,000, the probability that IVIg is cost-effective is less than 1%.

Table 11: Sensitivity Analysis on Model Structural Assumptions

| Structural Assumption Varied | Incremental Costs (IVIg-corticosteroids) (\$) | Incremental QALYs (IVIg-corticosteroids) | Cost per QALY IVIg versus Corticosteroids (\$) |
|--|--|---|---|
| Discount rate | | | |
| 0% | 107,935 | 0.196 | 551,700 |
| 3% | 104,705 | 0.190 | 551,129 |
| Model time horizon | | | |
| 1 year | 40,415 | 0.078 | 518,563 |
| 3 years | 83,222 | 0.150 | 556,334 |
| 5 years | 102,747 | 0.187 | 550,709 |
| 10 years | 121,260 | 0.236 | 514,222 |
| 20 years | 125,244 | 0.272 | 459,901 |
| Incremental IVIg utility gain | | | |
| 0.25 | 102,747 | 0.373 | 275,739 |
| 0.50 | 102,747 | 0.730 | 140,669 |
| Assume corticosteroid arm switching to IVIg | | | |
| | 45,653 | 0.082 | 558,685 |
| Maintenance IVIg dose and frequency | | | |
| 1.0 mg/kg every 3 weeks | 102,747 | 0.187 | 549,449 |
| 1.0 mg/kg every 6 weeks | 55,746 | 0.187 | 298,793 |
| 1.0 mg/kg every 8 weeks | 43,996 | 0.187 | 235,814 |
| 0.4 mg/kg every 3 weeks | 47,734 | 0.187 | 255,849 |
| 0.4 mg/kg every 6 weeks | 28,240 | 0.187 | 151,363 |
| 0.4 mg/kg every 8 weeks | 23,367 | 0.187 | 125,241 |

IVIg = intravenous immunoglobulin; QALY = quality-adjusted life-year.
Numbers may not be exact because of rounding.

Figure 7: Cost-Effectiveness Acceptability Curve



IVIg = intravenous immunoglobulin; QALY = quality-adjusted life-year.

6 HEALTH SERVICES IMPACT

6.1 Population Impact

Because there are no relevant Canadian prevalence and incidence data, the number of Canadians with CIDP was estimated using international estimates. The prevalence and incidence estimates that were reported in the literature vary depending on country, age, gender, and diagnoses. Some authors report a prevalence estimate for a diagnosis of definite CIDP. Others use a diagnosis of definite and probable CIDP when reporting the prevalence estimate. The numbers of prevalent and incident CIDP cases in Canada were calculated using a range of the reported estimates and the 2008 Canadian population estimates. If the authors did not provide an incidence estimate, it was assumed to be 10% of the prevalence estimate.

Table 12 shows the number of annual CIDP cases in Canada.

| Table 12: Estimated Annual Number of Cases of Chronic Inflammatory Demyelinating Polyneuropathy | | | | |
|--|--|------------------------|---|-----------------------|
| Reporting Study | Overall Prevalence per 100,000 People | Prevalent Cases | Overall Incidence per 100,000 People | Incident Cases |
| Lunn ⁵ | 0.46 | 145 | 0.04* | 13 |
| Lunn ⁵ | 1.0 | 316 | 0.1* | 32 |
| Iijima ⁸ | 1.61 | 509 | 0.48 | 152 |
| McLeod ⁴ | 1.87 | 591 | 0.15 | 47 |
| Chiò ⁶ | 3.4 | 1075 | 0.36 | 114 |
| Mygland ⁷ | 7.7 | 2,434 | 0.77* | 243 |

*Rate assumed to be 10% of the prevalence estimate.

6.2 Budget Impact

Several steps were undertaken to estimate the potential budget impact if everyone in Canada with CIDP was to be treated with IVIg. First, the annual number of patients in Canada who could be treated for CIDP was estimated based on published prevalence and incidence data. Second, a targeted literature search was used to identify Canadian recommendations for IVIg treatment regimens for CIDP (Table 13). Third, using the treatment regimens, the assumed cost of IVIg, and average patient weight, the annual treatment costs for acute and chronic treatment were estimated. Finally, the annual per patient treatment costs were multiplied by the number of people in Canada with CIDP (Table 12) to estimate the potential budget impact of IVIg if all patients were treated.

Treatment regimens for CIDP were based on the Gamunex product monograph.⁶⁸ The treatment recommendations, with the assumptions that were used in the budget impact analysis, appear in Table 13.

| Table 13: Treatment Regimens for Chronic Inflammatory Demyelinating Polyneuropathy | | |
|---|--|---|
| | Treatment Recommendation | Assumption Made for Analysis |
| Initial (acute) | 2 g/kg over 1 to 2 days | 2 g/kg over 1 to 2 days |
| Maintenance (chronic) | 1 dose of 1.0 g/kg may be needed every 3 weeks | 1.0 g/kg every 3 weeks (17.3 treatments per year) |

Based on the assumed annual treatment regimens for CIDP (Table 13), IVIg cost of \$59.19/g, and an assumed adult weight of 70 kg, the cost of an initial treatment is \$8,286.60, and the cost of one year of maintenance therapy is \$71,679.09. These costs were multiplied by the number of patients estimated to have these conditions to determine the potential annual budget for managing CIDP with IVIg. This analysis assumes incident cases will receive the initial treatment whereas prevalent cases receive maintenance therapy.

Table 14: Estimate of the Potential Annual Budget Impact of Managing Chronic Inflammatory Demyelinating Polyneuropathy with Intravenous Immunoglobulin in Canada

| Reporting Study | Initial (thousands of \$) | Maintenance (thousands of \$) | Total (thousands of \$) |
|----------------------|------------------------------|----------------------------------|----------------------------|
| Lunn ⁵ | 108 | 10,501 | 10,609 |
| Lunn ⁵ | 265 | 22,916 | 23,181 |
| Iijima ⁸ | 1,260 | 37,744 | 39,004 |
| McLeod ⁴ | 389 | 42,752 | 43,142 |
| Chiò ⁶ | 945 | 78,000 | 78,945 |
| Mygland ⁷ | 2,014 | 176,481 | 178,495 |

Table 14 presents the estimates of the potential budget impact if all patients with CIDP were treated with IVIg. The annual estimates range from \$10.6 million to \$178.5 million. McLeod et al.⁴ and Lunn et al.⁵ report estimates from countries with population demographics that would be the most similar to those of Canada. Therefore, it can be assumed that the annual cost of IVIg therapy for patients with CIDP in Canada would be in the range of \$10.6 million to \$43.1 million. It is assumed for this estimate that all patients with CIDP would be treated with IVIg. Assuming the prevalence rates from McLeod et al.'s study, if the percentage of CIDP that was managed with IVIg in Canada were 5%, 10%, or 20%, the annual cost would be \$2.2 million, \$4.3 million, and \$8.6 million respectively. Assuming the prevalence rates from Lunn et al.'s study, if the percentage of CIDP that was managed with IVIg in Canada were 5%, 10%, or 20%, the annual cost would be \$0.5 million, \$1.0 million, and \$2.1 million respectively.

6.3 Planning, Implementation, Utilization, and Legal or Regulatory Issues

The criteria for the diagnosis of CIDP may be looser for patients in clinical practice who are treated with IVIg compared with those in research trials. This raises the issues of cost-effectiveness and utilization²⁹ and implies that there could be more patients with CIDP who could be treated compared with the prevalence numbers that are reported in the literature.

To use IVIg in the most cost-effective manner, clinics would have to implement a strategy for vial sharing so that no IVIg is wasted. This would require more vigorous monitoring of the IVIg supply with a focus on lot numbers, dates opened, and storage.

6.4 Ethical Considerations

Nine clinical papers^{14,29-35,40} and one economic paper⁵⁴ on patients with CIDP mentioned ethical, equity, or psychosocial issues. A CADTH report⁷³ that reviewed IVIg for the treatment of idiopathic thrombocytopenic purpura (ITP) discusses the related issues, because of the large quantity of published IVIg literature that was available on ITP. The issues of AEs, product safety, rationale for use, quality of life, and costs, which were raised in the ITP report, would also be relevant for patients with CIDP.

6.4.1 Efficiency versus equity

The aggravation of normal renal function and changes in blood viscosity bear the risk of cardiovascular (especially blood pressure) and thromboembolic events when treating elderly patients with IVIg, although the risks of renal impairment or stroke seem to be low.³³ IVIg is safer to administer than plasma exchange.³²

The cost of IVIg is a concern, but the expense of treatment may be less when compared with the health care costs arising from and the disability caused by the long-term side effects that are associated with steroid use^{30,40} or the cost of the special equipment that is needed for plasma exchange.³³ There is a potential for cost savings if the dose is adjusted so that it is just sufficient to obtain and maintain improvement.³³ This may require, however, an increase in patient follow-up visits.

6.4.2 Process or procedural issues

IVIg is a blood product that carries the theoretical risk of transmitting known and unknown infectious agents. Patients must be informed of this risk in the treatment consent process. The risks of transmission have decreased as the manufacturing processes evolve, but there are new emergent adverse effects.²⁸ Certain features of an IVIg product must be considered in relation to the patient's clinical situation. Product features that may affect tolerance are sodium content, type and concentration of sugar, osmolarity and osmolality, pH, IgA content, and volume load.

IVIg is often said to be in short supply,³¹ but there are newer preparations that require fewer manufacturing steps, yield a larger quantity of IgG, and provide a purer product.⁴⁰ This may lead to a greater supply of IVIg in the future. Also, IVIg is more readily available than plasma exchange.³²

6.5 Psychosocial considerations

The AEs that are associated with the long-term use of corticosteroids and immunosuppressives remain a concern.^{30,32,40} This has an impact on patients' willingness to use long-term immunosuppressive therapy.

7 DISCUSSION

7.1 Summary of Results

Nine identified RCTs provided evidence about IVIg treatment in patients with CIDP. The intervention periods were short (eight days to six months) and the total sample included 314 patients. Three trials evaluated IVIg therapy with an active comparator: corticosteroids³⁰ or immunoglobulin depletion through plasma exchange³³ or extracorporeal immunoadsorption.²⁹

Each active comparator and IVIg produced similar improvements from baseline when measured on disability or impairment scales and as electrophysiological parameters. Two of the three studies have methodological issues including low Jadad score, limited study power to detect a difference in the treatments, and potential carryover effect. There was no incremental benefit in the primary outcomes when comparing IVIg therapy and the active comparator. There was a benefit with IVIg therapy in one secondary outcome measure (grip strength), when IVIg therapy was compared with prednisolone therapy.³⁰

Five of the six placebo-controlled trials showed IVIg therapy to be superior to placebo, based on disability or impairment outcomes (proportion of responders,^{31,40} statistically significant improvement,^{14,35} or numerically greater improvement³²). These trials included other measures that showed similar improvements with IVIg and placebo therapy.

Among the six trials, three^{14,34,40} demonstrated a statistically significant improvement in any of the electrophysiological parameters when IVIg therapy was compared with placebo.

AEs were not reported consistently among the nine trials. Authors generally reported that “IVIg was well tolerated.” Serious AEs were reported in six trials.^{14,29-31,33} Three deaths that were deemed to be unrelated to the IVIg treatment by the authors were included.^{29,40} Specific AEs were reported in four trials^{29-31,40} with numerically higher frequencies among patients on IVIg compared with those on placebo in all except one trial. The frequency of headache was reported to be higher with placebo treatment in Zinman et al.’s trial.²⁹ No statistical comparison of the AE frequency between treatment groups was reported.

The inconsistent results that were reported in the nine trials are due to many factors. Fourteen disability or impairment scales were used among the nine trials. Some scales emphasized mobility and provided little information about arm function (HFDS, Rankin). The INCAT score combines arm and leg functionality.³⁰ Scales providing measures of muscle strength were reported as a summed score (MRC summed) versus individual muscle strength scores. Other scales provided a measure of muscle weakness (NDS). Unlike the NDS, which is a continuous variable, the MRC score is a categorical variable. As a result, summing the individual grades of muscle strength may lead to statistical issues. With the MRC, the muscle testing is done manually and is subjective in terms of grading strengths, because there are no standardized joint positions for testing, and the point at which counter-force is administered is selected by the investigator. Because there is no operational definition of “normal” strength, criteria for MRC grades 4 and 5 (normal) tend to be ambiguous. Mild to moderate weakness may be overlooked during manual testing. It would be ideal in future research if one to two validated scales were to be used as the basis for all assessments to enhance the comparability of outcomes.

Electrophysiological outcomes were reported as single nerve conduction velocities or compound action potentials for single muscles, or as summed velocities or action potentials of many nerves and muscles. The scales being used as efficacy outcomes in these trials have been validated in patients with stroke,⁷⁴ diabetes,⁵² and GBS,⁷⁵ and therefore may not be generalizable to a CIDP population.

Some inconsistency may be due to the population that is included in the trials (known IVIg responders versus previously untreated patients), the concomitant therapies that are allowed versus those that are not allowed, and the patients with different courses of the disease. The definition of a clinical responder was not standardized among the trials. Four trials defined a responder as those with improvement using one scale.^{14,31,40,76} Two trials defined a responder as those with improvement in two of four measures²⁹ or three of six measures.³² The proportion of responders varied between 27% and 64% among these trials.

Methodological quality may have contributed to the inconsistent results that are seen among the trials. Two of the nine trials were of poor quality based on the Jadad score,^{29,33} and the concealment method that was used for the treatment allocation could not be ascertained in three trials.^{29,33,40} The poor-quality studies were single-blind with active comparators (immunoabsorption). Therefore, the results have to be viewed with caution. In single-blinded trials, where the assessment of outcomes for patients with CIDP is based on ratings on scales or questionnaires, the patients' or investigators' knowledge of the assigned treatment may bias the trial results (treatment effect estimates).²² One problem arising in crossover trials is a carry-over effect that may confound the effect estimates (in any direction) and that may occur with an inadequate length of wash-out period. In placebo-controlled crossover trials, the carryover effect may lead to the dilution of the treatment effect estimates.⁷⁷ Also, the washout periods in the crossover trials varied, so that non-responders were allowed to crossover to the second treatment early, and responders were left in the washout period until their condition deteriorated. The mean length of the washout periods and the number of patients crossing early were not reported.

Even with these limitations, IVIg therapy statistically significantly improved disability and impairment compared with placebo therapy and provided the same clinical benefit when compared with plasma exchange and oral prednisolone.

One published economic evaluation of IVIg treatment of CIDP was identified. This was a patient-level analysis using EQ5D and health care resource utilization data from patients in Hughes et al.'s⁴⁰ study. The authors found that IVIg-treated patients experienced a 0.12 greater increase in utility from baseline compared with corticosteroid-treated patients. This difference was not statistically significant. The authors stated that mean disability improvement was greater in the prednisolone group. The difference in disability improvement was not statistically significant.

Using a six-week time horizon, the authors stated that the probability that IVIg is cost-effective is more than 0.5 if society values one QALY at €250,000. Based on the incremental differences in costs and QALYs reported, a traditional cost-effectiveness ratio was calculated to be €245,643 per QALY (€3,439/0.014).

Because there was no Canadian economic evidence on IVIg treatment of CIDP, a primary cost-utility analysis was conducted. The model comparators were IVIg and oral corticosteroids, and the time horizon was five years. The model incorporated the utility gain from IVIg treatment that was reported by McCrone et al.⁵⁴ The model also incorporated the costs, quality of life, and mortality impacts of corticosteroid-related AEs.

The IVIg treatment arm in the model was estimated to incur \$102,747 more costs and result in 0.187 more QALYs compared with the corticosteroid treatment arm over five years. The resulting incremental cost-utility ratio of IVIg compared with corticosteroids is \$549,449 per QALY gained. The incremental cost-utility ratio varied from \$262,260 to \$694,933 when the patient weight was decreased to 35 kg and increased to 95 kg respectively. Assuming that maintenance treatment with IVIg consists of 0.4 mg/kg doses every eight weeks instead of 1.0 mg/kg doses every three weeks resulted in a cost per QALY estimate of \$125,241. In a probabilistic sensitivity analysis, it was found that at a willingness to pay for a QALY threshold of \$552,000, the probability that IVIg is cost-effective is 50%. At a willingness-to-pay threshold of \$50,000, the probability that IVIg is cost-effective is less than 1%. Based on current decisions for the reimbursement of health care technology, this might not be perceived as a cost-effective use of health care resources.⁷⁸

7.2 Study Limitations

Because of the small sample sizes that were used in these trials and the short durations, rare SAEs were not found. There are case reports that describe stroke after IVIg administration.⁷⁹⁻⁸¹ Caress et al.⁸⁰ reviewed the charts of outpatients and inpatients who were receiving IVIg therapy at one hospital, over a four-year period. The authors reported the clinical features of 16 patients. Most (15/16) had one or more stroke risk factors, and 2/16 patients with stroke had minimal risk factors. Alexandrescu et al.⁷⁹ suggested that the risk of stroke with IVIg therapy points to the need for clinical evaluation, with attention to history and focused vascular work-up before administering IVIg.

An observational study⁴¹ looked at the 10-year safety of one IVIg preparation (Octagam), which has been licensed for sale in Canada. In this prospective cohort, 6,357 patients received 92,958 infusions. Included in this cohort were 36 patients with CIDP who received 719 IVIg infusions. Three (8.3%) patients reported an AE. The most common AEs reported for the group that included patients with CIDP, in descending order of frequency, were headache, flushing, fatigue, and nausea. The authors concluded that this IVIg preparation is well tolerated in routine daily use, with an overall AE rate of 4.2% of all patients and 0.35% of all infusions. Most of the adverse reactions were classified as non-serious (94.8%) and of mild (55.9%) or moderate intensity (34.3%).

Because of the short intervention periods, the long-term effects of IVIg could not be ascertained from these trials. Vucic et al.⁴² conducted a retrospective chart review for neurophysiological data in 11 patients with CIDP. These patients were using no concomitant therapy with IVIg treatment. The mean duration of treatment and follow-up was 3.6 years (1.5 years to six years). IVIg doses were administered on five consecutive days during three consecutive months. Doses were tailored to each patient so that no weakness developed before the next dose. The authors reported that long-term IVIg treatment resulted in reversal of conduction block, improvement in distal CMAP and SNAP amplitudes, and a reduction in spontaneous activity.

The primary economic analysis has limitations. As in all models, we had to make several assumptions in our analysis, including the extrapolation of the non-statistically significant 0.12 (P = 0.07) utility gain from IVIg found by McCrone et al.⁵⁴ over the five-year time horizon of the

model. Another limitation is the reliance on this one source of utility gain from IVIg treatment.⁵⁴ The reliance on a single source⁵⁷ to define the corticosteroid-related AEs that were used in the model may be considered to be a limiting factor. Because a public health care payer perspective was taken, indirect costs were not included. If a societal perspective were taken and indirect costs taken into consideration, the cost-utility of IVIg compared with corticosteroids may have been more favourable. In addition, the analysis did not consider plasma exchange as a CIDP treatment comparator. There is no available evidence of better response rates or utility gains for patients who were treated with IVIg compared with those who were treated with plasma exchange. A publication from the Canadian apheresis registry⁸² estimated the cost per plasma exchange procedure to be \$950. This is about a quarter of the cost of a 1 mg/kg IVIg administration (for a 75 kg patient).

7.3 Generalizability of findings

Our findings are consistent with those of an earlier Cochrane systematic review of IVIg therapy for CIDP that included six trials.²⁹⁻³⁴ The authors pooled data from the trials and concluded that IVIg improves disability for at least two to six weeks compared with placebo. The number needed to treat is three.⁸³

The criteria for the diagnosis of CIDP may be looser for patients in clinical practice who are treated with IVIg compared with the criteria that are used in research trials. This may have an impact on the generalizability of the effectiveness of IVIg to clinical practice and the overall utilization of IVIg.

Depending on the manufacturing process, different IVIg preparations vary in composition²⁸ and, in turn, potential effectiveness and AE profile could also vary.

7.4 Knowledge Gaps

There are areas where rigorous research is needed to ascertain the true effectiveness of IVIg in the treatment of patients with CIDP. The approved dosing of IVIg is 2 g/kg loading dose followed by a maintenance dose of 1 g/kg every three weeks. The dosing in this review ranged from 0.4 g/kg to 2.0 g/kg. The dose frequency for maintenance therapy varied among the trials that followed patients who were using open-label IVIg. One trial reported that they administered 0.4 g/kg every three to four days to neutralize the patients' neurological deficits, which returned to normal, thereby allowing the patients to return to work. The frequency of treatments could be reduced later.³³ Would initial higher doses allow the patients to achieve remission and, therefore, avoid maintenance therapy? What is the lowest dose and treatment interval that can normalize neurological deficits?

The dosing for methylprednisolone is unknown. Conservative doses (60 mg tapered over six weeks) have been effective in some patients with CIDP. The doses that are used to manage multiple sclerosis relapses are higher (1,000 mg of intravenous or oral methylprednisolone). Would patients with CIDP who use this dose achieve remission?

IVIg does not work for all patients (the proportion of IVIg responders that was reported in this review is less than 65%). There is a need for studies that identify the predictors of response to IVIg. These may be clinical, patient-level predictors that may be associated with the infusion process or be IVIg product-specific. The study that reported the number of responders by disease course¹⁴ reported no difference in the proportion of responders. The sample size was small in this trial, and both groups responded equally well to IVIg therapy. Larger trials that stratify patients by disease course are needed to determine if the disease course is a predictor of treatment response.

Even with improvement in disability and impairment, patients remain IVIg-dependent, and new conduction blocks developed while on treatment. There is a need for clinical trials that investigate new and old immunosuppressant therapies alone or in combination with IVIg to determine if there is a combination that will be effective in the treatment of CIDP.

8 CONCLUSIONS

IVIg therapy is statistically significantly superior to placebo treatment in reducing the disability and impairment of patients with CIDP. It provides a statistically significantly lower relapse rate and increases the time to deterioration. IVIg demonstrates similar effectiveness as the alternative treatment strategies of plasma exchange and methylprednisolone. With the concern about the AEs that are associated with long-term corticosteroid use, and the cost and access to plasma exchange, IVIg is an attractive alternative.

No deaths that were directly attributable to IVIg therapy were reported. The long-term effects of IVIg therapy are emerging. Our primary economic evaluation and a previously published economic evaluation found the cost per QALY of IVIg compared with corticosteroids for CIDP treatment to be higher than what might be viewed to be a cost-effective use of health care resources.

Conclusions cannot be drawn about appropriate use, because of the potential heterogeneity of the populations (and outcomes) under investigation and the small sample sizes that are reported in the selected trials. There does not seem to be a strategy with clear therapeutic advantages for the management of CIDP.

With the concern about the AEs that are associated with long-term corticosteroid use and access to plasma exchange, IVIg may be an attractive alternative. IVIg, however, is expensive. Our primary economic analysis found the cost per QALY of IVIg compared with prednisone to be \$549,449. At a willingness to pay threshold of \$50,000, the probability that IVIg is cost-effective is less than 1%. This might not be viewed as a cost-effective use of health care resources.

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APPENDICES

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