# Intravenous immunoglobulin for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis

Kathryn Gaebel, Gord Blackhouse, Kaitryn Campbell, Diana Robertson, Feng Xie, Nazila Assasi, Colin Chalk, Mitchell Levine, Ron Goeree

## ABSTRACT

**Background:** Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated inflammatory disorder that targets the myelin sheaths of the peripheral nervous system. Intravenous immunoglobulin (IVIg) is a blood product containing immunoglobulin G pooled from many human donors. In fall 2008, CIDP became an approved indication for IVIg in the United States and Canada.

**Objective:** To evaluate the clinical effectiveness and safety of IVIg for the treatment of CIDP through a systematic review of published randomized controlled trials.

**Methods:** We searched the MEDLINE (1950–2009, including in-process and other non-indexed citations), Embase (1980–2009) and other databases through the Ovid interface. We applied a methodological filter to limit retrieval to controlled clinical trials, meta-analyses and systematic reviews, and health technology assessments. Retrieval was limited to studies involving humans, and no language restrictions were employed. We pooled extracted data to estimate the effect size of IVIg treatment based on the random-effects model.

**Results:** We identified 9 unique randomized controlled trials. Of these, 3 compared IVIg therapy with an active comparator (plasma exchange, plasma exchange using extracorporeal immunoadsorption, oral prednisolone, respectively); the other 6 trials had placebo controls. No incremental benefit was seen in terms of primary outcomes for comparisons of IVIg therapy and an active comparator. Data from 4 of the 6 placebo-controlled trials were included in a meta-analysis. A significant improvement in disability (i.e., reduction in disability score) was found, with a standardized mean difference of 0.65 (95% confidence interval [CI] 0.23 to 1.08) in favour of IVIg. A pooled analysis of the proportion of patients with a response to treatment, as defined by the investigators of each of the trials, resulted in a risk ratio of 2.74 (95% CI 1.80 to 4.15) favouring IVIg.

**Interpretation:** IVIg therapy was statistically superior to placebo in reducing disability and impairment among patients with CIDP. The effectiveness of IVIg was similar to that of the alternative treatment strategies of plasma exchange and oral prednisolone

**Kathryn Gaebel,** MSc, is a senior projects manager in the Centre for Evaluation of Medicines, St. Joseph's Healthcare, and the Programs for Assessment of Technology in Health (PATH), McMaster University, Hamilton, Ontario, Canada. **Gord Blackhouse,** MSc, is the manager of the Health Technology Assessment Program for PATH and a part-time faculty member in the Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton. **Kaitryn Campbell,** MLIS, is an information specialist for PATH and the Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton. **Diana Robertson,** MLIS, is an information specialist for PATH and the Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton. **Feng Xie,** PhD, is the faculty director of the Health Technology Assessment Program of PATH and an assistant professor in the Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton. **Nazila Assasi,** MD, PhD, is a senior research coordinator for PATH and the Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton. **Colin Chalk,** MD, FRCPC, is a neurologist and an associate professor in the Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, and the director of the Division of Neurology at the Montreal General Hospital, Montreal. **Mitchell Levine,** MD, FRCPC, is a clinical pharmacologist and internist at St. Joseph's Healthcare, Hamilton, the director of the Centre for Evaluation of Medicines, St. Joseph's Healthcare, and a professor in the Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton. **Ron Goeree,** MSc, is the director of PATH and an associate professor in the Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton.

**Competing interests:** Kathryn Gaebel has received funds from Abbott Laboratories Ltd. for a speaking engagement. Gord Blackhouse received funding from Eli Lilly Canada Inc. and GlaxoSmithKline Inc. for consulting. Colin Chalk received funding from Talecris Biotherapeutics Ltd., and he is the primary investigator in a multi-centre study funded by Baxter Canada. Mitchell Levine received funding from AstraZeneca Canada Inc., Eli Lilly Canada Inc., Pfizer Canada Inc. and Merck Frosst Canada Inc. He has acted as an expert witness for Novartis Pharmaceuticals Canada Inc. and for Wyeth Pharmaceuticals. He has also chaired the Expert Drug Committee for Health Canada. Ron Goeree was advisory board member to Janssen-Ortho Inc. and Hoffmann-La Roche Ltd. He has been a consultant for Eli Lilly Canada Inc.

**Funding:** The Canadian Agency for Drugs and Technologies in Health (CADTH) provided the funding to complete the original review and this updated review. No one at CADTH had any involvement in the collection, analysis and interpretation of data, the writing of the report, or the decision to submit the report for publication.

**Correspondence:** Kathryn Gaebel, PATH Research Institute, St. Joseph's Healthcare/McMaster University, 25 Main St. W, Ste. 2000, Hamilton ON L8P 1H1; tel. 905 523-7284 ext. 3826, fax 905-522-0568; gaebk@mcmaster.ca

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated inflammatory disorder that targets the myelin sheaths of the peripheral nervous system. The motor weakness symptoms of CIDP resemble those of the Guillain–Barré syndrome, but the 2 disorders are arbitrarily differentiated by the time to maximum deficit.[1] Patients with CIDP reach maximum clinical deficit about 8 weeks or more after the onset of symptoms, whereas patients with Guillain–Barré syndrome reach maximum deficit within 3–4 weeks. In addition, Guillain–Barré syndrome 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]

Given the ambiguities of diagnosing CIDP, the true prevalence of the disease may be underestimated or overestimated. Reported mean prevalence estimates from 6 studies ranged from 0.46 to 7.7 per 100 000 population.[3–8] Reported prevalence estimates vary by age and sex, the highest estimates of 3.12, 9.47 and 19.24 per 100 000 population having been reported for men 55 years of age and older,[8] 70–79 years of age[4] and 80 years of age and older,[6] respectively. Regional differences within the same country have also been reported.[3,5] Prevalence and incidence rates have not been reported for Canada, but it can be assumed that rates for this country will fall within the ranges reported in trials from other countries with similar demographic characteristics, such as England[5] and Australia:[4] 1.0–1.9 per 100 000 population.

Patients with CIDP have shown improvement after treatment with corticosteroids or plasma exchange,[9,10] but both therapies have disadvantages. Because of the chronic nature of the disease, long-term use of corticosteroids is usually required, which carries the risk of numerous adverse events, some of which may be serious.[11] The benefit of plasma exchange is typically transient, and it is therefore usually employed concomitantly with some other form of therapy.[10] Plasma exchange is also associated with several adverse effects, including anaphylactic reactions, cardiac arrhythmias and death.[12] Furthermore, plasma exchange must be carried out in specialized centres, and the repeated procedures require good vascular access.[13]

Intravenous immunoglobulin (IVIg) is a blood product containing immunoglobulin G pooled from many human donors. In fall 2008, both the US Food and Drug Administration[14] and the Health Products and Food Branch of Health Canada[15] granted Talecris Biotherapeutics supplemental licences for its IVIg product to include CIDP as an indication.

The objective of this systematic review of published randomized controlled trials (RCTs) was to evaluate the clinical effectiveness and safety of IVIg for the treatment of CIDP.

## Methods

**Protocol.** A protocol was written a priori and was followed throughout the review process. A copy of the protocol was filed with the Canadian Agency for Drugs and Technologies in Health (CADTH). The original protocol defined the population of interest as adults 18 years of age or older. However, there was no valid rationale to limit the search to adults, and this age limit was subsequently removed.

**Sources of information.** An unpublished CADTH technology report[16] served as the starting point for this research. To update the original search used in the unpublished report, we undertook a systematic search to locate relevant clinical trials, meta-analyses, systematic reviews and health technology assessments evaluating IVIg for CIDP. The search strategy was developed by an information specialist (KC), with input from the project team. Before the search strategy was executed, it underwent peer review by a CADTH information specialist. All search results were imported into a Reference Manager version 11 database for the purposes of removing duplicates and screening the titles and abstracts.

We searched the following bibliographic databases through the Ovid interface: MEDLINE (1996 to 2009, including in-process and other non-indexed citations), Embase (1996 to 2009) and CINAHL (1982 to 2009). 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 2009).

A search strategy with controlled vocabulary and keywords focusing on the concepts of "CIDP" and "IVIg" was executed.

A methodological filter was applied to limit retrieval to controlled clinical trials, meta-analyses, systematic reviews and health technology assessments. Furthermore, retrieval was limited to articles with a database entry date of December 2007 to 2009 (when possible) or a publication date in 2007 or 2008 and to studies of the human population (the latter criterion could be applied only within the Ovid interface and was applied only to the search for controlled clinical trials). No language restrictions were employed. An attempt was made to translate all relevant articles published in languages

other than English, but translation was limited to the capabilities of available staff to translate from French, German and Chinese. See online Appendix A for the detailed search strategy.

We identified grey literature (literature that is not commercially published) by searching the websites of health technology assessment and related agencies and their associated databases, the websites of the manufacturers of IVIg products (Talecris Biotherapeutics and Baxter) and clinical trial registers. We also searched the 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 for relevant evidence (including conference abstracts from 2007 and 2008, if available). We used Google and AlltheWeb search engines to search for additional web-based materials and information. We supplemented these searches 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 1 Nov. 2008. We updated our searches of The Cochrane Library quarterly, with the last update search performed on 8 Oct. 2008 (Issue 4, 2008).

We also requested information directly from the manufacturers of IVIg, Talecris Biopharmaceutics and Baxter (see online Appendix B).

**Study selection and assessment of methodological quality.** Studies selected for inclusion met the following criteria: trial was an RCT; participants had definite or probable CIDP; trial compared any dose of IVIg with placebo, corticosteroid or plasma exchange; and trial reported a change from baseline in both a disability score and an electrophysiological outcome (e.g., conduction velocity, latency, muscle or nerve action potential). There was no a priori selection of disability scales or electrophysiological outcomes.

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

We used the Jadad scale[17] to assess study quality, and we used the Schultz treatment allocation concealment questionnaire[18] to rate allocation concealment as adequate, inadequate or unclear (see online Appendix D).

**Data synthesis and analysis.** We described all trials qualitatively and did not include in the pooled data results from studies with poor quality (Jadad score of 2 or less). Studies that had Jadad scores of 3 or more and that reported the mean change (and standard deviation [SD]) from baseline for the disability outcomes were pooled to estimate the effect size of IVIg treatment. For continuous outcomes, we calculated the difference between study arms and 95% confidence intervals (CIs), using Review Manager (RevMan), version 5 (The Cochrane Collaboration, Copenhagen, Denmark). The meta-analyses were based on the random-effects model of DerSimonian and Laird.[19] For the aggregated continuous outcomes, we calculated standardized mean differences with 95% CIs. We used a conservative approach when combining results from crossover and parallel trials, with only the data from the first arm of a crossover trial being included.
For binary outcomes, we calculated a risk ratio and 95% CI for each individual study, also using RevMan. A pooled risk ratio estimate of greater than 1 indicates that more patients in the IVIg arm relative to the control or comparator arm had a favourable outcome.

Sensitivity analyses were planned to examine whether the effect of IVIg varied with trial design or quality (e.g., comparison of those with and without adequate allocation concealment). Subgroup analyses were planned to examine if the effect of IVIg differed depending on the duration or dose of IVIg treatment or the subtypes of CIDP (e.g., pure motor variant). We did not consider differences between various IVIg preparations.

## Results

**Studies included in analysis.** Together, the original search and the updated search identified a total of 495 citations, of which 325 were excluded after level 1 screening (citation, title and abstract, if available). An additional 11 citations were added from other sources, and 181 citations were subjected to full-text screening. Of these, 19 publications were identified as potentially relevant.[10,13,20–36] A total of 8 articles were excluded, 2 because they were not RCTs;[22,35] 1 (an RCT)[26] because the study population included patients with multifocal motor neuropathy, and data for patients with CIDP were not reported separately; and 5[20,23,25,29,31] because they were not full study reports (i.e., abstracts or conference proceedings only), and the corresponding full articles were

included for data abstraction.[13,28,30] Thus, 11 relevant full-text records reporting 9 unique RCTs,[10,13,21,24,27,28,30,32–34,36] including 2 abstracts reporting outcomes that were not reported in the corresponding published RCT,[10,21] were retained.

A modified PRISMA flow diagram is presented in Fig. 1, and a list of the excluded studies appears in Appendix E.

The 9 RCTs included a total of 312 patients with CIDP (Table 1). Of the 9 trials, 3 compared IVIg therapy with an active comparator (plasma exchange,[24] plasma exchange using extracorporeal immunoadsorption,[36] or oral prednisolone[27]), and the other 6 trials had placebo controls.[13,28,30,32–34] Because of the small number of studies, we could not use funnel plots to assess publication bias. Typically, the minimum number of studies required to properly assess publication bias with funnel plots is suggested to be 10.[45]

**Study characteristics.** Three of the studies[13,30,32] used the American Academy of Neurology criteria to confirm the diagnosis of CIDP,[44] and 2 of the studies[27,28] used the inflammatory neuropathy cause and treatment (INCAT) criteria.[27] The other 4 studies[24,33,34,36] used symptomatology and electrophysiological testing (nerve conduction velocities and conduction blocks) as the criteria for diagnosis. The intervention periods for the trials were 6 months or less.

All 6 crossover trials[13,24,27,28,32,33] had a conditional crossover depending upon the patient's response to the first treatment: patients with a response to treatment did not cross over to the second treatment until they experienced deterioration in their disease. Washout periods were fixed in 3 of the trials at 8 days,[33] 4 weeks[32] and 6 weeks,[24] with the remaining 3 trials allowing patients with deterioration to cross over to the second treatment early.[13,27,28]

A variety of disability scales and electrophysiological parameters were reported as outcomes (see Table 1 for details). Six of the trials[13,28,32–34,36] used a response to treatment as an outcome; however, the criteria used to define improvements varied across trials.

**IVIg versus active comparator.** Prednisolone was the active comparator in one randomized crossover trial.[27] This study compared IVIg 1.0 g/kg given on 2 consecutive days (or 2.0 g/kg delivered in 24 hours) with a 6-week course of oral prednisolone, with an initial dose of 60 mg/d for 2 weeks, tapered to 10 mg/d over 4 weeks. The trial had a Jadad score of 5 and was stopped early because the study medication expired. Thirty-two patients had been randomly assigned to treatment, all of whom completed the first treatment period. Only 25 patients were crossed over to the second treatment period, 24 of whom completed both treatment periods. Six patients who were initially assigned to receive IVIg therapy did not continue for the following reasons: further treatment deemed unnecessary (3 patients), withdrawal from study because of worsening symptoms (2 patients, who went on to receive open-label IVIg) and discovery

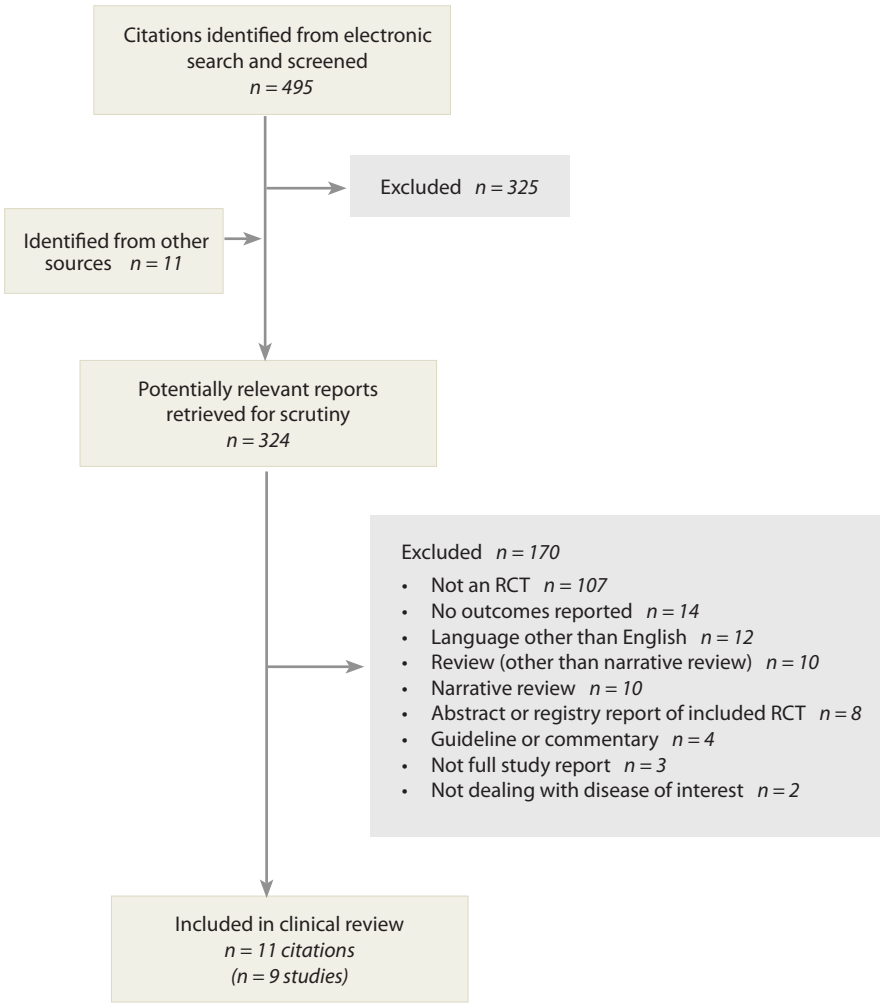


**Figure 1. Flow diagram for reports selected for clinical review.**
RCT = randomized controlled trial

**Table 1: Study characteristics**

| Study | Patients Total | IVIg | C | Comparison | Outcomes | Quality* | Notes |
|---|---|---|---|---|---|---|---|
| Vermeulen 1993[34] | 28† | 15 | 13 | 0.4 g/kg daily x 5 d v. placebo (albumin 3 g/50 mL) | MRC-SS, RS, CMAP, NCV (16 electro physiological measures in total) | 5, A | Patients previously treated with immunosupressants excluded; minimum disability score required for inclusion; predefinition of response to therapy |
| Mendell 2001[30] | 53 | 30 | 23 | 1.0 g/kg daily x 2 d, then again on d 21 v. placebo (albumin) | AMS, HFDS, NCS | 5, A | No immunotherapy for any indication in previous 3 mo |
| **Single-blind parallel** | | | | | | | |
| Zinman 2005[36] | 18 | 13 (of whom 4 were excluded from analysis)§ | 5 | 1 g/kg daily x 2 d for 6 mo v. plasma exchange (3 txs over 7 d for 6 mo | AMS, TCNS, HFDS, NCV, CMAP, F-wave latencies | 2, I | Patients previously treated with IVIg or plasma exchange excluded; no immunosuppressant therapy in previous 6 mo; predefinition of response to therapy |
| **Single-blind crossover** | | | | | | | |
| Dyck 1994[24] | 20 | 15 | 17 | 0.4 g/kg per wk x 3 wk followed by 0.2 g/kg per wk x 3 wk v. plasma exchange twice wkly x 3 wk followed by once wkly x 3 wk | NDS, NDS-W, ∑CMAP, SNAP, VDT great toe | 1, I | No plasma exchange or IVIg in previous 6 wk; minimum disability score required for inclusion; fixed washout period |
| **Double-blind crossover** | | | | | | | |
| Hughes 2001[27] | 32‡ | 24 | 24 | 1.0 g/kg daily x 2 d or 2.0 g/kg over 24 h v. oral prednisolone, 60 mg/d x 2 wk, then tapered | INCAT disability scale, 10-m walk, 9-hole peg test, MRC-SS, GS, RHS, RS, SF-36 physical function score, SSS | 5, A | No immunosuppressants in previous 6 wk; stable AZA dose allowed; predefined rules for washout period, predefinition of response to therapy |
| Hughes 2008[28] | 117‡ | 59 | 58 | 2.0 g/kg over 2–4 d followed by 1 g/kg over 1–2 d every 3 wk for 24 wk v. placebo (0.1% albumin) | INCAT disability score, GS, MRC-SS, time to relapse for patients with response in first period, INCAT SS, CMAP | 4, U | No steroids, IVIg or plasma exchange in previous 3 mo; no immunomodulatory or immunosuppressive agents in previous 6 mo; minimum disability score required for inclusion; predefined rules for washout period; predefinition of response to therapy |
| Hahn 1996[13] | 30† | 25 | 25 | 0.4 g/kg daily x 5 d v. placebo (10% dextrose) | NDS, CG, GS, MCV, distal motor latencies, CMAP | 4, A | Patients with previous exposure to IVIg excluded; low dose prednisone (< 20 mg/day) allowed if treatment initiated > 3 mo before; minimum disability score required for inclusion; predefined rules for washout period; predefinition of response to therapy |
| Thompson 1996[32] | 7† | 7 | 7 | 0.4 g/kg daily x 5 d v. placebo (albumin) | Ambulation index, 10-m walk time, E-MRC-SS, 9-hole peg test, myometer score, HMAS, CMAP distal motor latency, MCV, F-wave latency | 4, A | Patients with previous exposure to IVIg excluded; fixed washout period; predefinition of response to therapy |
| van Doorn 1990[33] | 7 | 7 | 7 | 0.4 g/kg daily x 5 d v. placebo (3 g/50 mL 20% albumin) | RS, CMAP, NCV, mean time to clinical deterioration | 4, A | Previous response to IVIg treatment required for inclusion; fixed washout period; predefinition of response to therapy |

AMS = average muscle strength (modified Medical Research Council),[30] AZA = azathioprine, C = control, CG = clinical grade, CMAP = compound muscle action potential, E-MRC-SS = expanded Medical Research Council sum score, GS = grip strength, HFDS = Hughes functional disability scale,[37] HMAS = Hammersmith motor ability score,[38] INCAT = inflammatory neuropathy cause and treatment,[27] INCAT SS = INCAT sensory score, IVIg = intravenous immunoglobulin, MCV = motor conduction velocity, MRC-SS = Medical Research Council sum score,[39] NCS = nerve conduction study, NCV = nerve conduction velocity, NDS = neurological disability score,[40] NDS-W = neurological disability score weakness subscore,[40] RHS = Rotterdam handicap scale,[41] RS = Rankin scale,[42] SF-36 = medical outcome study 36-item short-form health status scale,[43] SNAP = sensory nerve action potential, SSS = sensory sum score, TCNS = Toronto clinical neuropathy score,[36] txs = treatments, VDT = vibratory detection threshold

* Quality assessed using Jadad scale[17] (numeric value) and Schultz treatment allocation concealment questionnaire[18] (where A = adequate, I = inadequate, and U = unclear)

† Diagnosis according to criteria of American Academy of Neurology[44]

‡ Diagnosis according to the INCAT criteria[27]

§ One intervention arm, with 4 patients, used a low dose of IVIg (0.5 g/kg daily), but 2 of the patients died of unrelated causes, and the remaining 2 patients were therefore excluded from the analysis

of a small-cell carcinoma (1 patient). Two patients who received prednisolone first did not continue with the second treatment period: 1 had psychosis, and the other preferred not to start the second treatment.

The primary outcome in this study was the change in INCAT disability score[27] at 2 weeks, relative to baseline. For all patients who completed both arms of the trial, the INCAT disability score improved from baseline, but there were no significant differences between treatment arms in the extent of improvement. There were also no differences between treatments for any of the secondary outcomes: Medical Research Council (MRC) sum scores (for muscle strength),[39] grip strength, 10-metre walk time, 9-hole peg test, modified Rankin scale score,[42] Rotterdam Handicap Score,[41] medical outcomes study short-form 36[43] or any of the electrophysiological measures.

The incidence of total adverse events was similar between the 2 treatments. Three serious adverse events causing the patients' withdrawal from the study were reported: carcinoma and psychosis with prednisolone treatment and heart failure with IVIg therapy.

Plasma exchange was the active comparator in another randomized crossover trial.[24] That study compared IVIg 0.4 g/kg once a week for 3 weeks followed by 0.2 g/kg once a week for 3 weeks with plasma exchange twice a week for 3 weeks followed by plasma exchange weekly for 3 weeks. The quality of the trial was low (Jadad score 1). Twenty patients were enrolled, 19 of whom completed the first treatment period and 13 of whom completed the second treatment period. Of the 6 patients who completed the first treatment but did not receive the second treatment, 2 withdrew to undergo treatment elsewhere and 4 did not require the second treatment.

The primary outcomes were changes after 6 weeks in the neurological disability score (NDS),[40] NDS weakness subscore and summed compound muscle action potential (∑CMAP) of the ulnar, median and peroneal nerves. There were no significant differences between the 2 treatment groups. There was also no significant difference between treatment arms for the secondary outcomes of summed sensory nerve action potential of the median and sural nerves or vibratory detection threshold of the great toe.

Total and serious adverse events were not reported, and there was 1 withdrawal due to an adverse event, an infection associated with an indwelling catheter in a patient who underwent plasma exchange. Lightheadedness, rash and nausea were reported as adverse events, but their frequency was not reported.

Plasma exchange was also studied in a randomized, 3-arm parallel group trial[36] that compared IVIg 1 g/kg daily for 2 consecutive days, 0.5 g/kg daily for 2 consecutive days, and 3 plasma exchange treatments with special staphylococcal protein immunoadsorption columns (Excorim, Lund, Sweden) over 7 days. The quality of this trial was also low (Jadad score 2). Twenty patients were enrolled, and 18 received treatment before the study was halted because of cessation of funding. Nine patients received the higher-dose IVIg, 4 received the lower-dose IVIg, and 5 underwent plasma exchange. Two of the patients in the lower-dose IVIg treatment arm died of illnesses unrelated to their treatment (pneumonia and sepsis for one, congestive heart failure for the other), which left only 2 patients in that arm. Because of this small sample size, the data for lower-dose IVIg were not included in the final analysis. Therefore, the final analysis consisted of data for 9 patients who received IVIg and 5 who underwent plasma exchange.

The primary outcome measure was a determination of patients with a clinical response to treatment. As defined by the authors, a patient with clinical response showed improvement in 2 of 4 measures (average muscle strength,[30] grip strength, Toronto clinical neuropathy score[36] and Hughes functional disability score[37]) without deterioration in the other measures. However, the authors did not specify the criteria for improvement for each of these assessment scales. There was no significant difference in the proportion of patients with a clinical response between the 2 treatment groups. At 2 months, 50% of patients in the IVIg group and 80% of those in the plasma exchange group were considered to have a clinical response ($p$ = 0.56). There were no significant differences between the treatment groups in terms of nerve conduction changes, even though the conduction velocity in sensory nerves, CMAP and F-wave latencies improved numerically with plasma exchange and worsened with IVIg therapy.

Two serious adverse events were reported in the IVIg treatment arm (heart failure and pneumonia with sepsis, both resulting in death). The authors deemed both deaths to be unrelated to the treatment. Two withdrawals due to adverse events (a rash in both cases) were also reported for the IVIg group.

**IVIg versus placebo.** All 6 of the randomized, placebo-controlled trials[13,28,30,32–34] were of good quality, with Jadad scores of 4 or higher, and all but 1[28] had adequate concealment. Two studies used a parallel group design,[30,34] and 4 studies used a crossover design.[13,28,32,33]

In 1 of the 2 studies with parallel group design, Vermeulen and colleagues[34] randomly assigned 15 patients to receive 0.4 g/kg IVIg for 5 consecutive days and 13

patients to receive placebo. All 28 patients completed the final assessment between 16 and 21 days after receiving the trial treatments. To be eligible for inclusion, patients had to have a disability of at least 3 on the modified Rankin scale.[42] The primary outcome, the proportion of patients showing an improvement of 1 point or greater on the Rankin scale, was similar between the 2 treatment groups (26.7% for IVIg group v. 23.0% for placebo group). The mean improvement in the MRC sum score was also similar for the 2 groups (mean [SD] 1.60 [SD 3.04] for IVIg group v. 1.23 [SD 3.2] for placebo group). The authors reported significant improvements after IVIg therapy for only 3 of the 16 electrophysiological measures recorded: ulnar distal latency ($p = 0.005$), tibial distal CMAP ($p = 0.003$) and peroneal nerve conduction velocity ($p = 0.003$). The authors did not comment on adverse events for this trial.[34]

The second trial with parallel group design[30] compared IVIg (1 g/kg given on 2 consecutive days with a third dose on day 21) with placebo. Thirty patients were randomly assigned to IVIg therapy, and 29 completed the final assessment at day 42. A single patient was excluded because of incomplete data collection at the institutional study site. Of the 23 patients randomly assigned to receive placebo, 2 dropped out (because of urticaria and patient choice to quit), and 21 completed the final assessment at day 42. The primary outcome was muscle strength as measured with a modified MRC scale,[39] referred to as average muscle strength. The average muscle strength improved significantly with IVIg therapy (mean difference 0.44, standard error 0.21, $p = 0.045$). The percentage of patients with an improvement of at least 1 grade in the Hughes functional disability score was significantly larger for the IVIg group (34.0% v. 9.5%, $p = 0.019$). The groups did not differ in terms of motor nerve conduction studies on the median, ulnar, peroneal and tibial nerves. There were no serious adverse events and only 1 withdrawal due to an adverse event in the IVIg group. Higher proportions of patients receiving IVIg experienced the common adverse events of headache, nausea, chills and fever, and comparable proportions of the two treatment groups experienced transient hypotension.[30]

In 1 of the 4 crossover trials comparing IVIg with placebo, Hughes and colleagues[28] compared a loading dose of IVIg (2.0 g/kg) given over 2–4 days, followed by 1.0 g/kg over 1–2 days given every 3 weeks for 24 weeks with placebo. The study design allowed patients with no response (where response was defined as an improvement of 1 point or more on the adjusted INCAT scale) to cross over to the second treatment any time after week 6. All of the patients who had a response were randomly reassigned at the end of 24 weeks to either IVIg or placebo in a parallel group design.

Of 59 patients initially randomly assigned to receive IVIg, 3 withdrew (because of an adverse event, withdrawal of consent and a protocol violation, respectively), 23 were deemed to have no response and crossed over to placebo, and 33 completed the 24 weeks of therapy. Of the 23 who crossed over to placebo, 16 had no response, 2 withdrew their consent, and 5 had a response. Of 58 patients initially randomly assigned to receive placebo, 1 withdrew because of an adverse event, 45 had no response and crossed over to IVIg therapy, and 12 completed the 24-week trial. Of the 45 patients who crossed over to IVIg treatment, 16 had no response, 2 experienced an adverse event, 1 was lost to follow-up, and 26 completed the 24-week trial. The IVIg group had a significantly larger proportion of patients with response than did the placebo group (54% v. 21%, $p = 0.0002$).

There was also significantly greater improvement after IVIg therapy than placebo therapy in grip strength (improvement of 13.2 [SD 19.3] v. 1.5 [SD 15.6] points, respectively; $p = 0.0008$) and the MRC sum score (improvement of 3.3 [SD 5.6] v. 0.2 [SD 4.5] points, respectively; $p = 0.001$). The probability of relapse was lower among patients who were randomly reassigned to IVIg than among those randomly reassigned to placebo (13% v. 45%), and the time to relapse was significantly longer for patients who received IVIg than for those who received placebo ($p = 0.011$). Results not reported in this original paper were reported in 2 abstracts presented at meetings of the American Academy of Neurology and the American Neurological Association in 2008. Merkies and colleagues[10] reported significant improvement (by 3.4 points) in the 36-item short-form health status scale (physical component summary score) after IVIg therapy ($p = 0.001$). Bril and colleagues[21] reported a nonsignificant trend favouring IVIg in all of the electrophysiological measures.

In another crossover study, Hahn and colleagues[13] assigned 16 patients to receive IVIg 0.4 g/kg for 5 consecutive days and 14 patients to receive placebo treatment for 5 consecutive days, with a 28-day follow-up period. Patients who experienced a deterioration of more than 20 points in the NDS were allowed to cross over to the second treatment at day 21. A response was predefined as a change in the NDS of 20 points or more or improvement by 1 clinical grade or more. Both NDS and CIDP clinical grade improved significantly after treatment with IVIg ($p < 0.002$ and $p < 0.005$, respectively). The authors also reported a significant improvement in grip strength after

treatment with IVIg compared with placebo (6.3 [SD 1.7] v. –0.8 [SD 0.9], respectively; $p < 0.005$).

There was also significantly greater improvement in the following electrophysiological outcomes after IVIg therapy relative to placebo therapy: summed motor conduction velocity 15.3 (SD 44.1) v. –13.2 (SD 39.9) points ($p < 0.0001$) and summed distal motor latency 3.9 (SD 14.5) v. –1.2 (SD 15.4) points ($p < 0.04$).[13]

In these 2 trials,[13,28] a total of 15 patients experienced a serious adverse event (1 of those receiving IVIg in the trial by Hahn and colleagues;[13] 6 of those receiving IVIg and 8 of those receiving placebo in the trial by Hughes and colleagues[28]). Hahn and colleagues[13] reported that one patient had symptoms resembling aseptic meningitis after IVIg therapy, but the patient continued with treatments. Hughes and colleagues[28] reported common adverse events of headache (4.0% in IVIg group v. 1.2% in placebo group) and pyrexia (2.4% in IVIg group v. 0% in placebo group), with the data reported as percentages of infusions not patients. Hughes and colleagues[28] reported only 1 withdrawal due to an adverse event. The patient withdrew because of lack of efficacy and subsequently died of sepsis.

An additional 2 placebo-controlled crossover trials[32,33] each had 7 patients. In both trials, the patients were assigned to receive IVIg 0.4 g/kg for 5 consecutive days or placebo. In 1 of these studies,[32] the investigators judged the patients' response after 28 days, and those with no response crossed over to the second treatment. For patients with a response, the second treatment was withheld until the patient required further treatment. The authors defined a response as at least 3 of the following: improvement of at least 1 grade in the ambulation index, improvement of more than 2 seconds in 10-metre walk time, improvement of 4 or more units in the expanded MRC sum score, improvement of more than 3 seconds in time for the 9-hole peg test, improvement of 10% or more in mean myometer score for 2 individual muscle groups, and improvement of at least 2 points on the Hammersmith motor ability score. Thompson and colleagues[32] had assigned 4 patients to IVIg treatment and 3 patients to placebo (with both groups crossing over to the second treatment, either IVIG or placebo) by the time the trial by Hahn and colleagues,[13] described above, was published, at which point Thompson and colleagues stopped their trial. They reported that 43% of the 7 patients showed improvement in 3 of the 6 outcome measures.

In the other small crossover trial, Van Doorn and colleagues[33] investigated the time to deterioration after IVIg therapy was stopped. Seven patients who had previously been receiving IVIg therapy stopped their treatments and were randomly assigned to receive 5 days of treatment with IVIg (0.4 g/kg) or placebo. All patients were seen at regular intervals. When a deterioration of at least 1 point on the Rankin scale was detected for a patient, he or she received the first assigned treatment. If by day 8 after treatment the patient's condition was still deteriorating, the second (crossover) treatment was given. If there was no deterioration, the second treatment was withheld until deemed necessary. Van Doorn and colleagues[33] reported a significantly greater time to deterioration with IVIg therapy than with placebo (6.4 [SD 3.0] weeks v. 1.3 [SD 1.3] weeks, $p = 0.02$). A significantly greater time to deterioration was also reported by Hughes and colleagues[28] during the extension phase of their trial (for patients with a response to treatment) ($p = 0.01$). Neither Thompson and colleagues[32] nor Van Doorn and colleagues[33] reported significant changes in electrophysiological parameters. No patients experienced side effects in the trial by van Doorn and colleagues,[33] and adverse events were not reported by Thompson and colleagues.[32]

We included data from 4[13,28,30,34] of the 6 placebo-controlled trials described above in a meta-analysis. These 4 trials reported changes from baseline in a disability score (i.e., a scale that measured muscle strength or weakness). The meta-analysis revealed a significant treatment effect, with a standardized mean difference of 0.65 (95% CI 0.23 to 1.08) in favour of IVIg (Fig. 2). A pooled analysis of the proportion of patients with a response to treatment, as defined by the investigators of each of the trials, resulted in a risk ratio of 2.74 (95% CI 1.80 to 4.16) in favour of IVIg (Fig. 3).

**Sensitivity analysis.** Given the small number of trials identified, the variety of comparators, the variety of doses and administration regimens for IVIg and the variety of outcome measures used by the original investigators, we did not perform any sensitivity analyses.

## Interpretation

We identified 9 RCTs providing evidence related to IVIg treatment for patients with CIDP. All used short intervention periods (8 days to 6 months), and the total sample size was 312 patients. Each active comparator and IVIg produced similar improvements from baseline, but there was no incremental benefit in the primary outcomes in comparisons between IVIg therapy and an active comparator. Five of the 6 placebo-controlled trials showed that IVIg therapy was superior to placebo on the basis of a variety of disability or impairment outcomes (in terms of greater proportion of patients with a response,[28,30] significant

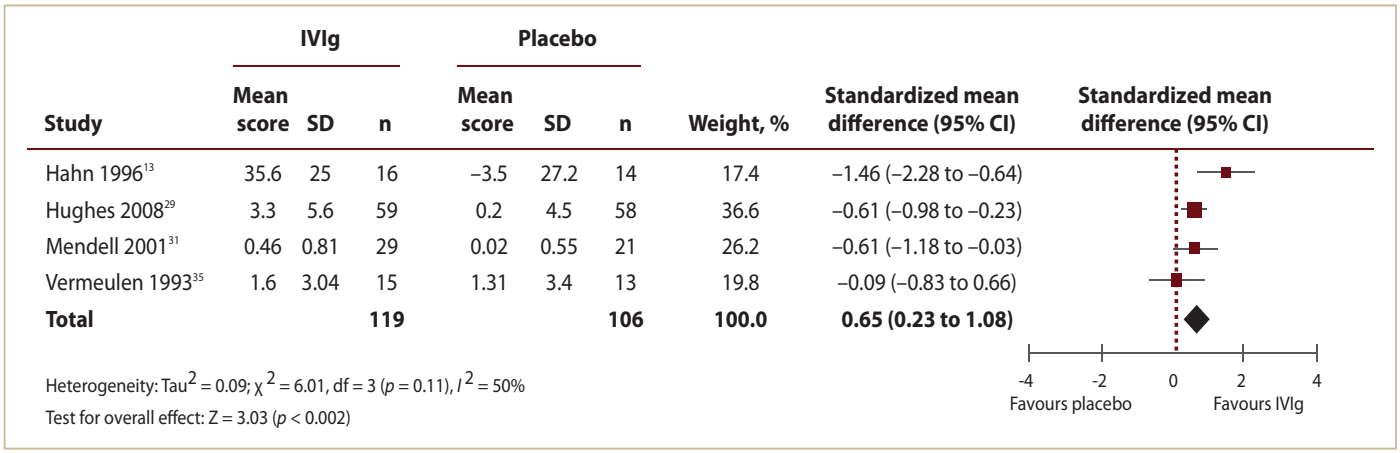


**Figure 2. Forest plot showing the effect of intravenous immunoglobulin (IVIg) within each study and the overall pooled estimate, as standardized mean difference in disability score.** CI = confidence interval, df = degrees of freedom, IV = inverse variance, IVIg = intravenous immunoglobulin, SD = standard deviation

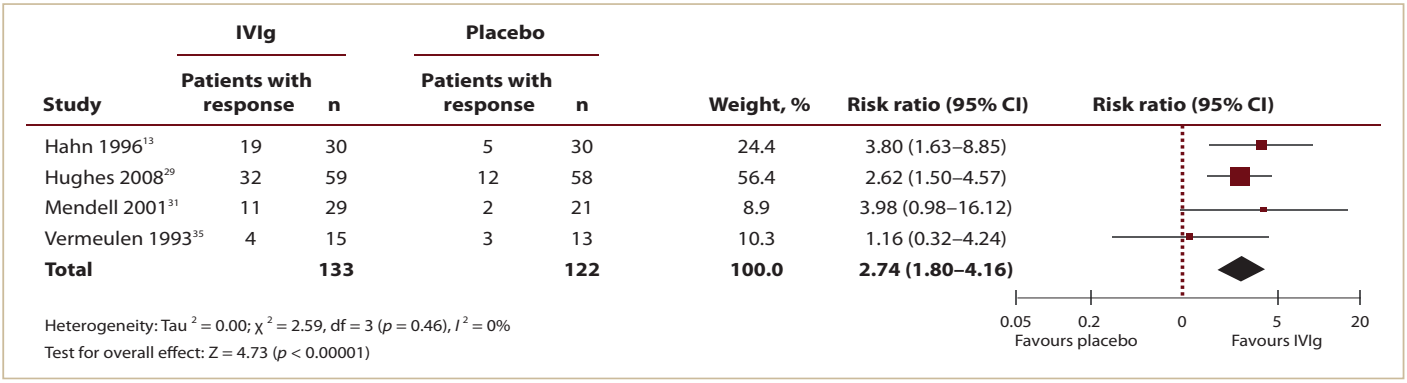


**Figure 3. Forest plot for the pooled analysis of the proportion of patients with a response to treatment.** CI = confidence interval, df = degrees of freedome, IVIg = intravenous immunoglobulin

improvement[13,33] or numerically greater improvement[32]). Only 3 trials[13,28,34] demonstrated a significantly greater improvement in any of the electrophysiological parameters with IVIg therapy compared with placebo.

A total of 14 different disability or impairment scales were used across the 9 trials. Some scales emphasized mobility, providing little information about arm function (e.g., Hughes functional disability score, Rankin scale), whereas the INCAT sensory score combined both arm and leg functionality. Scales providing measures of muscle strength were reported as a summed score (e.g., MRC sum score) or as individual muscle strength scores, whereas others provided a measure of muscle weakness (e.g., NDS weakness subscore). Electrophysiological outcomes were also reported as either single-nerve conduction velocities or compound action potentials for single muscles or as summed velocities or action potentials of many nerves and muscles.

The definition of clinical response was not standardized across the trials. Four trials defined a response as an improvement based on a single scale,[13,24,28,30] and 2 trials defined a response as improvement in 2 of 4 measures[36] or 3 of 6 measures.[32] The proportion of patients with a response ranged from 27% to 64% across these trials.

The variety of trial designs, especially crossover trials without a fixed wash-out period, and the presence of trials allowing the use of concomitant therapies and others not allowing their use, contributed to the inconsistent treatment effect sizes reported. The variety of outcome measures used across the trials (as described above) was also a contributing factor. Some of this inconsistency may also have been due to the populations included in the trials: patients with a known response to IVIg versus previously untreated patients and patients with different courses of the disease.

Even with these study limitations, IVIg therapy improved disability and impairment significantly relative to placebo over the short term (6 months or less) and provided clinical benefits similar to those realized with plasma exchange and oral prednisolone. Our findings

are consistent with a recent Cochrane systematic review of IVIg therapy for CIDP that was published after we had submitted a copy of our final report[46] to the funding agency (CADTH). In that review,[47] Eftimov and colleagues asked original authors for their data and contacted investigators in the field to identify unpublished or overlooked studies, neither of which we did. Their primary outcome measure was a change in disability according to the Rankin scale. If a particular study had not used this disability scale, the authors transformed the data to fit the Rankin scale. They also excluded 2 trials[33,36] that we included in our review; however, we did not pool the data from either of these 2 studies. Eftimov and colleagues[47] concluded that IVIg improves disability relative to placebo, and their reported standardized mean difference in disability scores of 0.54 (95% CI 0.24 to 0.84) is comparable to our pooled standardized mean difference of 0.65 (95% CI 0.23 to 1.08). If we had excluded from our meta-analysis another trial that Eftimov and colleagues also excluded,[13] then our point estimate would have been 0.53 (95% CI 0.24 to 0.82), even closer to theirs. Even though the study by Hahn and colleagues[13] was a crossover trial, we used data from the first treatment arm in our meta-analysis. Eftimov and colleagues[47] also reported a number needed to treat of 3, but we did not perform that type of analysis.

Because of the small sample sizes and the short durations of the trials included in our review, rare but serious adverse events were not observed. However, case reports describing stroke after administration of IVIg have been published.[48–50]

An observational study,[22] which we did not include in our meta-analysis, looked at the 10-year safety of the IVIg preparation Octagam (Octapharma Canada Inc., Scarborough ON), which was very recently licensed for sale in Canada. This prospective cohort enrolled a total of 6357 patients, of whom 1093 patients were using the IVIg preparation for treatment of an autoimmune disease. Among these 1093 patients were 36 patients with CIDP who underwent a total of 719 IVIg infusions, and 3 (8%) of these patients reported an adverse event. The most common adverse events reported for patients with an autoimmune disease, in descending order of frequency, were headache, flushing, fatigue and nausea. The authors concluded that this IVIg preparation was well tolerated in routine daily use, with an overall adverse event rate of 4.2% of all patients and 0.35% of all infusions. The vast majority of adverse events were classified as nonserious (94.8%) and of mild (55.9%) or moderate (34.3%) intensity.

Because of the short intervention periods, the long-term effects of IVIg could not be ascertained from the trials included in our review. In a chart review of neurophysiological data for 11 patients with CIDP, Vucic and colleagues[35] reported that long-term IVIg treatment resulted in reversal of conduction block, improvement in distal amplitudes of CMAP and sensory nerve action potential, and reduction in spontaneous activity indicative of ongoing denervation.

IVIg does not work for all patients: in this review, the proportion of patients with a response to IVIg was less than 65%. Even with significant improvements in disability and impairment, patients remain dependent on IVIg, and new conduction blocks may develop while they are receiving treatment. As such, there is a need for future clinical trials to investigate immunosuppressant therapies (e.g., novel and older agents, higher doses than previously used) alone or in combination with IVIg to determine if there is some other approach that will reliably induce remission in patients with CIDP. A very recently published RCT[51] investigated the addition of methotrexate 7.5 mg weekly to the existing treatment regimens of patients with CIDP. After 40 weeks of treatment, the methotrexate had no significant benefit relative to placebo. The authors stated that the negative trial results might have been due to study limitations and suggested that a different dose of methotrexate might have had more favourable results.

One or 2 outcome measures should be identified as the standard outcomes to be used in future CIDP research, which would facilitate comparisons across treatment regimens. This may assist in identifying a truly superior therapeutic regimen for the management of this disease.

As part of our original review,[46] we performed an economic review and primary economic analysis. The latter was a cost–utility primary economic analysis, from the perspective of a publicly funded health care system using a Markov model of adult patients with CIDP (weighing 75 kg). The treatment comparators were IVIg and oral corticosteroids, and the time horizon was 5 years. Taking into account both the gain in utility from IVIg treatment and the disutility from adverse events, we found that patients in the IVIg treatment arm had 0.187 more quality-adjusted life years (QALYs) than those in the corticosteroid arm. The resulting incremental cost–utility ratio of IVIg compared with corticosteroids was $549 449 per QALY gained. The incremental cost–utility ratio varied with patient weight, from $262 260 for a 35-kg patient to $694 933 for a 95-kg patient.

## Conclusions

In statistical terms, IVIg therapy is superior to placebo in reducing the disability and impairment experienced

by patients with CIDP. In addition, the relapse rate with this therapy is significantly lower, and the time to deterioration significantly greater. The effectiveness of IVIg is similar to that of the alternative treatment strategies of plasma exchange and oral prednisolone. Given concerns about adverse events associated with long-term corticosteroid use, and the cost of and limited access to plasma exchange, IVIg may be suitable for patients who cannot tolerate or access the alternative therapies, provided society is willing to pay the financial cost of more than $200 000 per QALY.

**Contributors:** Kathryn Gaebel, as the clinical lead for the project, conducted the clinical literature review, data abstraction and meta-analyses, and wrote the first draft of the article. She is the guarantor for the study. Gord Blackhouse, as the economic lead for the project, assisted with the data abstraction and interpretation and critically reviewed the draft article. Feng Xie assisted with the data interpretation and critically reviewed the draft article. Nazila Assasi assisted with the clinical literature review, data abstraction and interpretation and critically reviewed the draft article. Kaitryn Campbell was responsible for designing the literature retrieval search strategy for the clinical literature and critically reviewed the draft article. Diana Robertson assisted with the data acquisition and critically reviewed the draft article. Colin Chalk assisted with the data interpretation and critically reviewed the draft article. Mitchell Levine assisted with the data interpretation and critically reviewed the draft article. Ron Goeree assisted with overall design and execution of study and critically reviewed the draft article. All of the authors gave final approval of the version to be published.

## References

1. van Schaik I, Van den Bergh P, de Haan R, Vermeulen M. Intravenous immunoglobulin for multifocal motor neuropathy. *Cochrane Database Syst Rev* 2006;2,2006.
2. Lewis RA. Chronic inflammatory demyelinating polyneuropathy. *Neurol Clin* 2007;25(1):71–87.
3. Kasumi M, Nakashima K, Nakayama H, Takahashi K. Epidemiology of inflammatory neurological and inflammatory neuromuscular disease in Tottor Prefecture, Japan. *Psychiatr Clin Neurosci* 1995;49(3):169–174.
4. McLeod JG, Pollard JD, Macaskill P, Mohamed A, Spring P, Khurana V. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. *Ann Neurol* 1999;46(6):910–913.
5. Lunn MP, Manji H, Choudhary PP, Hughes RA, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. *J Neurol Neurosurg Psychiatry* 1999;66(5):677–680.
6. Chiò A, Cocito D, Bottacchi E, Buffa C, Leone M, Plano F, et al. Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. *J Neurol Neurosurg Psychiatry* 2007;78(12):1349–1353.
7. Mygland A, Monstad P. Chronic polyneuropathies in Vest-Agder, Norway. *Eur J Neurol* 2001;8(2):157–165.
8. Iijima M, Koike H, Hattori N, Tamakoshi A, Katsuno M, Tanaka F, et al. Prevalence and incidence rates of chronic inflammatory demyelinating polyneuropathy in the Japanese population. *J Neurol Neurosurg Psychiatry* 2008;79(9):1040–1043.
9. Dyck PJ, O'Brien PC, Oviatt KF, Dinapoli RP, Daube JR, Bartleson JD, et al. Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. *Ann Neurol* 1982;11(2):136–141.
10. Merkies ISJ, Bril V, Dalakas MC, Deng C, Donofrio P, Hanna K. Quality-of-Life (QoL) Improvements with Immune Globulin Intravenous, 10% Caprylate/Chromatography Purified (IGIV-C) in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [abstract M-3]. 133rd Annual Meeting of the American Neurological Association; September 22, 2008; Salt Lake City. 2008. Available: http://www.abstracts2view.com/ana/view.php?nu=ANA08L_M-3 (accessed 2008 Oct 17).
11. Dyck PJ. Intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy and in neuropathy associated with IgM monoclonal gammopathy of unknown significance. *Neurology* 1990;40(2):327–328.
12. Shumak KH, Rock GA. Therapeutic plasma exchange. *N Engl J Med* 1984;310(12):762–771.
13. Hahn AF, Bolton CF, Zochodne D, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. *Brain* 1996;119(4):1067–1077.
14. *Gamunex [FDA product approval information].* Rockville (MD): Center for Biologics Evaluation and Research, U.S. Food and Drug Administration; 2008 Sep 12. Available: http://www.fda.gov/cber/products/gamunex.htm (accessed 2008 Oct 17).
15. Gamunex. *Notices of compliance* [database online]. Ottawa: Health Canada; 2008. Available: http://205.193.93.51/NocWeb/viewnoce.jsp?noc=kqig (accessed 2009 Jan 19).
16. Chen S, Desjardins B, Chalk C, Pi D, Banks R. *Polyclonal intravenous immunoglobulin (IVIG) in patients with immune thrombocytopenic purpura (ITP) or chronic inflammatory demyelinating polyneuropathy (CIDP): a clinical systematic review.* Unpublished report. Report 298, February 2008. Ottawa: Canadian Agency for Drugs and Technologies in Health.
17. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1–12.
18. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002;359(9306):614–618.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7(3):177–188.
20. Bril V, Dalakas M, Donofrio P, van Doorn P, Hartung H, Hughes R, et al. Intravenous immunoglobulin chromatography (IGIV-C) 10% for treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an adequately powered placebo-controlled clinical trial to evaluate efficacy of IGIV-C 10% in CIDP. *Neurology* 2007;68(Suppl 1):A68 (PO2.108).
21. Bril V, Katzberg H, Dalakas M, Deng C, Donofrio P, Hanna K, et al. Nerve conduction studies (NCS) in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) treated with intravenous immunoglobulin therapy versus placebo [abstract P07.097]. 60th Annual Meeting of the American Academy of Neurology; April 12–19, 2008; Chicago. 2008. Available: http://www.abstracts2view.com/aan2008chicago/search.php?search=do&intMaxHits=10&where%5B%5D=&andornot%5B%5D=&query=CIDP&startat=1 (accessed 2008 Oct 17).
22. Debes A, Bauer M, Kremer S. Tolerability and safety of the intravenous immunoglobulin Octagam: A 10-year prospective observation study. *Pharmacoepidemiol Drug Saf* 2007;16(9):1038–1047.
23. Donofrio P, Bril V, Dalakas M, Deng C, Hanna K, Hartung H. Long-term efficacy of immune globulin intravenous, 10% capryl-

ate/chromatography purified (IGIV-C; Gamunex) maintenance therapy for chronic inflammatory demyelinating dolyneuropathy (CIDP) [abstract S47-005]. 60th Annual Meeting of the American Academy of Neurology; April 12–19, 2008; Chicago; 2008. Available: http://www.abstracts2view.com/aan2008chicago/search.php?search=do&intMaxHits=10&where%5B%5D=&andornot%5B%5D=&query=CIDP&startat=1 (accessed 2008 Oct 17).

24. Dyck PJ, Litchy WJ, Kratz KM, Suarez GA, Low PA, Pineda AA, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 1994;36(6):838–845.
25. Hahn A, Bolton C, Vandervoort P, Feasby T, Zochodne D. Intravenous immunoglobulin treatment (IvIg) in chronic inflammatory demyelinating polyneuropathy (CIDP): A double-blind, placebo-controlled, crossover study. *Neurology* 1995;45(4 Suppl 4).
26. Hirose G, Kimura J, Arimura K, Baba M, Hara H, Hirayama K, et al. A trial study of chronic inflammatory demyelinating polyneuropathy with intravenous immunoglobulin. *International Congress Series; Recent advances in clinical neurophysiology*. New York: Elsevier Science Publishing; 1996. p.879–883.
27. Hughes R, Bensa S, Willison H, Van Den BP, Comi G, Illa I, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 2001;50(2):195–201.
28. Hughes RAC, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol* 2008;7(2):136–144.
29. Latov N, Bril V, Dalakas M, Deng C, Donofrio P, Hanna K. Timing of clinical response to immune globulin intravenous, 10% caprylate/chromatography purified (IGIV-C) in chronic inflammatory demyelinating polyneuropathy (CIDP) [abstract M-18]. 133rd Annual Meeting of the American Neurological Association, September 21–24, 2008; Salt Lake City. 2008. Available: http://www.abstracts2view.com/ana/view.php?nu=ANA08L_M-18 (accessed 2008 Oct 17).
30. Mendell JR, Barohn RJ, Freimer ML, Kissel JT, King W, Nagaraja HN, et al. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 2001;56(4):445–449.
31. Mendell JR, Barohn RJ, Kissel JT, Sanders MC, King WM, Campbell WW, et al. Intravenous immunoglobulin (IVIg) in untreated patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Neurology* 2000;54(7 suppl 3):A212.
32. Thompson N, Choudhary P, Hughes RA, Quinlivan RM. A novel trial design to study the effect of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol* 1996;243(3):280–285.
33. Van Doorn PA, Brand A, Strengers PF, Meulstee J, Vermeulen M. High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: A double-blind, placebo-controlled, crossover study. Neurology 1990;40(2):209-212.
34. Vermeulen M, van Doorn PA, Brand A, Strengers PF, Jennekens FGI, Busch HF. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1993;56(1):36–39.
35. Vucic S, Black K, Baldassari LE, Tick CPS, Dawson KT, Cros D. Long-term effects of intravenous immunoglobulin in CIDP. *Clin Neurophysiol* 2007;118(9):1980–1984.
36. Zinman LH, Sutton D, Ng E, Nwe P, Ngo M, Bril V. A pilot study to compare the use of the Excorim staphylococcal protein immunoadsorption system and IVIG in chronic inflammatory demyelinating polyneuropathy. *Transfus Apher Sci* 2005;33(3):317–324.
37. Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial prednisolone in acute polyneuropathy. *Lancet* 1978;2(8093):750–753.
38. Scott OM, Hyde SA, Goddard C, Dubowitz V. Quantitation of muscle function in children: a prospective study in Duchenne muscular dystrophy. *Muscle Nerve* 1982;5(4):291–301.
39. Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve* 1991;14(11):1103–1109.
40. Dyck PJ, Sherman WR, Hallcher LM, Service FJ, O'Brien PC, Grina LA, et al. Human diabetic endoneurial sorbitol, fructose, and myo-inositol related to sural nerve morphometry. *Ann Neurol* 1980;8(6):590–596.
41. Merkies ISJ, Schmitz PIM, van der Meché FGA, Samijn JPA, van Doorn PA. Psychometric evaluation of a new handicap scale in immune-mediated polyneuropathies. *Muscle Nerve* 2002;25(3):370–377.
42. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19(5):604–607.
43. Ware JE Jr, Sherbourne C. The MOS 36-item short-form health survey (SF-36). I: Conceptual framework and item selection, *Med Care* 1992;30(6):472–483.
44. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. *Neurology* 1991;41(5):617–618.
45. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med* 2001;20(4):641–654.
46. Gaebel K, Blackhouse G, Campbell K, Robertson D, Xie F, Assasi N, et al. *Intravenous immunoglobulin for chronic inflammatory demyelinating polyneuropathy: clinical and cost-effectiveness analyses* [Technology report number 117]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
47. Eftimov F, Winer JB, Vermeulen M, de Haan R, Van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev.* 2009; (1). Chichester (UK): John Wiley & Sons, Ltd; 2009.
48. Alexandrescu DT, Dutcher JP, Hughes JT, Kaplan J, Wiernik PH. Strokes after intravenous gamma globulin: thrombotic phenomenon in patients with risk factors or just coincidence? *Am J Hematol* 2005;78(3):216–220.
49. Caress JB, Cartwright MS, Donofrio PD, Peacock JE Jr. The clinical features of 16 cases of stroke associated with administration of IVIg. *Neurology* 2003;60(11):1822–1824.
50. Doss-Esper CE, Singhal AB, Smith MSA, Henderson GV. Reversible posterior leukoencephalopathy, cerebral vasoconstriction, and strokes after intravenous immune globulin therapy in guillain-barre syndrome. *J Neuroimaging* 2005;15(2):188–192.
51. RMC Trial Group. Randomised controlled trial of methotrexate for chronic inflammatory demyelinating polyradiculoneuropathy (RMC trial): a pilot, multicentre study. *Lancet Neurol* 2009;8(2):158–164.

**Citation:** Gaebel K, Blackhouse G, Campbell K, Robertson D, Xie F, Assasi N, et al. Intravenous immunoglobulin for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis. *Open Med* 2010;4(3)e154-e166.

**Published:** 31 August 2010. Revised 2 September 2010.