A systematic review and meta-analysis of Intravenous Immunoglobulin for the treatment of CIDP

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Ron Goeree was advisory board member to Janssen-Ortho Inc, and Hoffman-La Roche Ltd. He has been a consultant for Eli Lilly Canada Inc.

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 (IgG) that has been pooled from many human donors. In the fall of 2008 CIDP became an approved indication for IVIg in the USA and Canada.

Objective

To evaluate the clinical effectiveness and safety of IVIg for the treatment of CIDP through a systematic review of the literature.

Methods

The Medline (1950-2009; In-Process & Other Non-Indexed Citations) and EMBASE (1980-2009) databases were searched through the Ovid interface. A methodological filter was applied to limit retrieval to randomized clinical trials (RCT), meta-analyses, or systematic reviews. Retrieval was limited to humans and no language restrictions were employed. Extracted data were pooled to estimate the effect size of IVIg treatment based on the random-effects model using RevMan version 5.

Results

Nine unique RCTs were identified. Three of the nine trials compared IVIg therapy to an active comparator (plasma exchange (PE), PE using extracorporeal immunoadsorption, or oral prednisolone), and the other six trials were placebo-controlled. There was no incremental benefit seen in the primary outcomes when comparing IVIg therapy and the active comparator. Data from four of the six placebo-controlled trials were included in a meta-analysis. A significant treatment effect of -0.65 (95% CI, -1.08 to -0.23) in favour of IVIg was found. A pooled analysis of the proportion of treatment responders, as defined by the investigators of each of the trials, resulted in a rate ratio of 2.74 (95% CI, 1.80 to 4.15), favouring IVIg.

Conclusion

IVIg therapy is statistically superior to placebo treatment in reducing the disability and impairment for CIDP patients. IVIg demonstrates similar effectiveness as the alternative treatment strategies of PE and methyprednisolone.

Introduction

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-Barre syndrome (GBS), and CIDP is sometimes considered to be the chronic counterpart of GBS.[1] Patients with CIDP will reach their maximum clinical deficit approximately eight weeks or more after symptom onset. CIDP has a prolonged course over months to years, which may be steadily progressive or relapsing-remitting.[2]

Due to the ambiguities in diagnosing CIDP the true prevalence of the disease may be underestimated. Reported mean prevalence estimates from six studies varied from 0.46 to 7.7 per 100,000 population.[3-8] Reported prevalence estimates vary by age and gender, and regional differences within the same country have been reported. The prevalence and incidence rates have not been reported for Canada, but one could assume that Canada's rate should fall within the range reported in the trials from other countries with similar demographic characteristics such as England[4] and Australia;[5] 1.0 – 1.9 per 100,000 population.

Patients with CIDP have shown improvement after treatment with corticosteroids or plasma exchange (PE)[9,10] but both therapies

have disadvantages. Due to the chronic nature of the disease, long-term use of corticosteroids is usually required, and this carries the risk of numerous adverse events (AEs) and serious adverse events (SAE).[11] The benefit from PE is usually transient, therefore it is usually employed concomitantly with other therapy.[10] PE is also associated with complications that include anaphylactic reactions, cardiac arrhythmias and patient death.[12] Also, PE 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 (IgG) that has been pooled from many human donors. Both the FDA[14] and the Health Products and Food Branch of Health Canada[15] granted Talecris Biotherapeutics supplemental licenses for their IVIg product to include CIDP as an indication in the fall of 2008.

The objective of this systematic review of the literature was to evaluate the clinical effectiveness and safety of IVIg for the treatment of CIDP.

Methods

The Medline (1950-2009; In-Process & Other Non-Indexed Citations) and EMBASE (1980-2009) databases were searched through the Ovid

interface. A search strategy with controlled vocabulary and keywords focused on the concepts of "CIDP" and "IVIG" was executed. This review was sponsored by the Canadian Agency for Drugs and Technologies in Health and their information specilaist provided feedback regarding the search stratgies. They had no involvement in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

A methodological filter was applied to limit retrieval to randomized clinical trials (RCT), meta-analyses or systematic reviews. Retrieval was limited to humans and no language restrictions were employed (see Appendix 1 for a detailed search strategy).

Study Selection and assessment of methodological quality

Studies selected for inclusion met the following criteria: RCT design; participants had definite or probable CIDP; trial compared any dose of IVIg to placebo, corticosteroid or plasma exchange (PE); and reported a change from baseline in a disability score and an electrophysiological outcome. Study quality was assessed using the Jadad scale[16] and allocation concealment was rated as adequate, inadequate or unclear using the Schultz treatment allocation concealment questionnaire.[17]

Data analysis methods

Studies with Jadad[16] scores ≥3, 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 the difference between study arms and 95% CIs were calculated, using RevMan Version 5.[18] The meta-analyses were based on the random-effects model of DerSimonian and Laird.[19] For the aggregated continuous outcomes, a standardized mean difference (SMD) was calculated with 95% CIs. A conservative approach was used when combining crossover and parallel trial results; only the data from the first arm of a crossover trial were pooled.

For binary outcomes a risk ratio (RR) and 95% confidence intervals (CIs) were calculated for each individual study also using RevMan. A pooled RR estimate >1 would indicate that more patients in the IVIg arm relative to the control or comparator arm developed a favourable outcome.

Results

Nine unique RCTs,[13,20-27] were retained for this review. Table 1 gives details of the nine RCTs. The nine trials included a total

of 314 patients with CIDP. Three of the nine trials compared IVIg therapy to an active comparator (plasma exchange (PE),[24] PE using extracorporeal immunoadsorption,[20] or oral prednisolone[21]), and the other six trials were placebo-controlled.[13,22,23,25-27]

All studies included patients with a diagnosis of probable or definite CIDP; three[13,22,23] used American Academy of Neurology (AAN) criteria,[28] and two studies[21,26] used the inflammatory neuropathy cause and treatment (INCAT) criteria.[21] The intervention periods for the trials were six months or less. All six crossover trials had a conditional crossover depending upon the patient's response to the first treatment, i.e. responders were not crossed-over to second treatment until their disease had deteriorated.[13,21,23,24,26,27] Washout periods were fixed in three trials at eight days,[27] four weeks,[23] and six weeks,[24] with the remaining three allowing patients who had deteriorated to crossover to the second treatment early.[13,21,26]

Outcomes were a variety of disability scales and electrophysiological parameters (see Table 1 for outcome details). Six trials[13,20,23,25-27] used a significant or clinical response to treatment as an outcome, however the criteria used to define the improvement varied across trials.

IVIg versus active comparator

Prednisolone

One randomized crossover trial[21] compared 1.0g/kg IVIg given on two consecutive days to a six week course of oral prednisolone, initial dose 60mg/d for two weeks, then tapered to 10mg/d over four weeks. The trial had a Jadad score of 5 and was stopped early due to expiration of study medication. Twenty-four patients provided data for the primary analysis.

The primary outcome was an improvement from baseline in the INCAT disability score[21] at two weeks for all patients completing both arms of the trial. Each group showed significant improvement from baseline after therapy initiation, with a mean(SD) improvement seen with IVIg therapy of 0.58 (0.93) grades (p=0.005), and 0.71 (1.27) grades with prednisolone (p=0.012). An improvement from grade 0 to grade 1 on the INCAT scale is not clinically important but all other one point improvements are clinically important.[26] There were no significant differences seen in the disability scores between treatment arms. The change from baseline in the secondary outcomes, which included: the Medical Research Council (MRC) sum scores (muscle strength),[29] grip strength, 10-meter walk time, nine-hole peg test, modified Rankin scale score[30] and the Rotterdam Handicap Score,[31] were not statistically

significant except for grip strength at six weeks in the IVIg group (scores not reported).

Plasma exchange (PE)

One randomized, crossover trial[24] compared IVIg 0.4g/kg once a week for three weeks followed by 0.2g/kg once a week for three weeks, to PE twice a week for 3 weeks followed by PE weekly for the remaining three weeks. Quality of the trial was low (Jadad=1). Twenty patients were enrolled, with 19 completing the first treatment period and 13 completing the second treatment period. Two patients withdrew to receive treatment elsewhere, with the remaining four patients not requiring a second treatment.

The primary outcomes were the changes after 6 weeks in the neurological disability score (NDS),[32] NDS weakness subset score and the summated compound muscle action potential (∑CAMP) of the ulnar, median and peroneal nerves. There was significant improvement from baseline in the primary outcomes after both treatments. Scores for the PE group were: average NDS (SD) 38.3 (34.6) points, ($p<0.001$); weakness score 33.4 (29.5) points, ($p<0.001$); ∑CAMP 3.7 (3.5) mV ($p<0.001$). The corresponding changes seen with IVIg therapy for the NDS, weakness score and ∑CAMP were 36.1 (32.0) points, ($p=0.006$); 31.4 (31.5) points,

(p<0.002); 3.3 (2.8) mV, (p<0.001). There were no significant differences between the two treatment groups. The maximum impairment on the NDS scale is 132 and 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.[13] There was also no significant difference seen between treatments for the secondary outcomes of summated sensory nerve action potential (∑SNAP) of the median and sural nerves, and the vibratory threshold of the great toe.

A randomized, three arm parallel group trial[20] compared IVIg 1g/kg/d for two consecutive days, 0.5g/kg/d for two consecutive days, and 3 treatments of PE using special Excorim staphylococcal protein immunoadsorption columns over 7 days. Quality of this trail was also low (Jadad= 2). Twenty patients were enrolled and 18 received treatment before the study was halted due to cessation in funding. Therefore, data from nine IVIg patients and five PE patients 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 (AMS)[22], grip strength, Toronto clinical neurology score (TCNS)[33], Hughes functional disability score (HFDS)[34]]

without deterioration in the other measures. The authors did not specify the criteria for improvement for each of the four assessment scales. There was no significant difference in the proportion of responders between the two treatment groups. At two months, 50% of the IVIg group were considered clinical responders versus 80% in the PE group (p=0.56). There were no significant differences between the treatment groups, when evaluating nerve conduction changes, even though the sensory nerve conduction velocity and the F-wave latencies improved numerically with PE and worsened with IVIg.

IVIg versus Placebo

Meta-analyses

Data from four[13,22,26,27] of the six placebo-controlled trials were included in a meta-analysis. These four trials reported changes from baseline in a disability score scales that measured muscle strength/weakness. Figure 1 is the forest plot showing the effect of IVIg within each study and the overall pooled estimate. A significant treatment effect of -0.65 (95% CI, -1.08 to -0.23) in favour of IVIg was found. A pooled analysis of the proportion of treatment responders, as defined by the investigators of each of the trials, resulted in a RR of 2.74 (95% CI, 1.80 to 4.15), favouring IVIg. Figure 2 shows the forest plot for this analysis.

Other Disability Outcomes

Mendell *et al.*[22] reported a significant improvement in the AMS after IVIg therapy: mean difference±SD; 0.46±0.15 versus 0.02±0.12 with placebo, p=0.045, and the mean change in the AMS reported by Hahn *et al.*[13] was 6.3±1.7 compared to -0.8±.9 with placebo (p<0.005). Hughes *et al.*[26] reported a mean change±SD in grip strength of 13.2±19.3 for the IVIg group versus 1.5±15.6 for the placebo group (p=0.0008).

Hughes *et al.*[26] reported a significantly smaller proportion of IVIg patients (13%) that had relapsed after 21 weeks compared to placebo patients (45%) (p=0.011). Another study[27] reported a mean of 11 weeks (min-max: 4 to 24) until deterioration after IVIg treatments were discontinued.Van Doorn and colleagues[27] also investigated the time to deterioration after stopping IVIg therapy and found a significant increase in this time with IVIg therapy compared with placebo (6.4 weeks versus 1.3 weeks, p=0.02).

Electrophysiological outcomes

Three[22,23,27] of the six placebo-controlled trials reported no significant changes in the electrophysiological parameters, although some measures were numerically higher with IVIg

therapy.[27] Vermulen *et al.*[25] reported significant improvements with IVIg therapy (compared with placebo) for three of the sixteen electrophysiological measures; ulnar distal latency (p=0.005), tibial distal CMAP (p=0.003), and peroneal nerve conduction velocity (p=0.003).

Hughes *et al.*[26] reported a significant improvement in the INCAT sensory score (ISS) after IVIg therapy, (mean±SD), 1.2±3.4 versus 0.2±3.9 (p=0.021). Hahn *et al.*[13] reported the results of a secondary analysis of the electrophysiological data at the end of the first phase of the crossover trial. The MCV improved by (mean±SD) 15.3±44.1 meters per second with IVIg therapy versus a deterioration of -13.2±39.9 with placebo (p<0.0001). The distal motor latency improvement was 3.9±14.5 milliseconds versus a -1.2±15.4 millisecond deterioration with placebo (p<0.004).

Safety

There were 10 serious adverse events (SAEs) reported in patients receiving IVIg,[13,20,21,26] two SAEs with prednisolone,[21] and eight SAEs with placebo[26] therapy. This equates to advere event rates of 0.004 per patient week for IVIg and placebo, and 0.02 per patient week for prenisolone. Three SAEs were fatal: two occurances of sepsis,[20,26] and one occurance of congestive heart failure.[20] None of these deaths were deemed, by the

investigators, to be related to the IVIg therapy. Withdrawals from IVIg therapy because of adverse events occurred in three patients: two with rash[20], one with urticaria,[21] and one patient withdrew because of lack of efficacy.[26]

Most common AEs reported, after IVIg therapy, were: headache, pyrexia, hypertension, asthenia, chills, back pain, rash, arthralgia, nausea, dizziness, influenza, indigestion, hypotension, light-headedness, and nausea.

Discussion

There are nine RCTs providing evidence for IVIg treatment in patients with CIDP. They all used short intervention periods (eight days to six months), with a total sample size of 314 patients. Each active comparator and IVIg produced similar improvements from baseline but there was no incremental benefit seen in the primary outcomes when comparing IVIg therapy and an active comparator. Five of the six placebo-controlled trials showed IVIg therapy to be superior to placebo based upon a variety of disability or impairment outcomes (proportion of responders,[22,26] significant improvement,[13,27] or numerically greater improvement[23]). Only three trials[13,25,26] were able to demonstrate a

significant improvement in any of the electrophysiological parameters with IVIg therapy compared with placebo.

There were 14 different disability or impairment scales used across the nine trials. Some scales emphasized mobility, providing little information about arm function (HFDS, Rankin), whereas the INCAT score combines both arm and leg functionality.[21] Scales providing measures of muscle strength were reported as a summed score (MRC summed) versus individual muscle strength scores, while others provided a measure of muscle weakness (NDS). 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 a clinical responder was not standardized across the trials. Four trials defined a responder as improvement using one single scale,[13,22,24,26] and two trials defined a responder by improvement in two of four measures,[20] or three of six measures.[23] The proportion of responders varied between 27 and 64 percent across these trials.

The variety of different outcome measures used across the trials contributes to the inconsistent treatment effect sizes reported. Some of the inconsistency may also be due to the population being included in the trials: known IVIg responders versus previously untreated patients, concomitant therapies allowed versus not allowed, and patients with different courses of the disease.

Even with these limitations IVIg therapy improved disability and impairment significantly compared with placebo therapy, and provided similar clinical benefit compared to PE and oral prednisolone. Our findings are consistent with an earlier Cochrane systematic review of IVIg therapy for CIDP where the authors pooled data from the trials and concluded that IVIg improves disability for at least 2-6 weeks compared with placebo, with a number needed to treat of three.[35]

Due to the small sample sizes used in these trials and the short durations, rare SAEs were not observed. Case reports describing stroke after IVIg administration do exist in the literature.[36-38]

An observational study[39] (not included in the meta-analysis) looked at the 10 year safety of the IVIg preparation Octagam®,which was very recently licensed for sale in Canada.

This prospective cohort enrolled 6357 patients which included 36 CIDP patients who underwent 719 IVIg infusions and three (8.3%) patients reported an AE. The most common AEs reported for the group that included CIDP patients, 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. The vast majority of adverse reactions were classified as non-serious (94.8%) and of mild or moderate intensity, 55.9% and 34.3%, respectively.

Because of their short intervention periods the long term effects of IVIg could not be ascertained from these trials. Vucic *et al.*[40] conducted a retrospective chart review for neurophysiological data in 11 CIDP patients. 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.

IVIg does not work for all patients; the proportion of IVIg responders reported in this review is <65 percent. Even with significant improvement in disability and impairment patients remain IVIg dependent and new conduction blocks develope while on treatment. There is a need for future clinical trials to

investigate immunosuppressant therapies (novel and old, higher doses than previously used, etc.) alone or in combination with IVIg to determine if there is a combination that will provide effective treatment for inducing remission in patients with CIDP. A very recently published RCT[41] did investigate the addition of methotrexate (MTX), 7.5 mg weekly, to existing treatment regimens of patients with CIDP. After 40 weeks of treatment, MTX did not have any significant benefit compared with placebo. These authors do state that the study limitations may have lead to the negative trial and suggest that a different MTX dose may have had more favourable results.

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

Conclusions

IVIg therapy is statistically superior to placebo treatment in reducing the disability and impairment for CIDP patients. It also provides a significant lower relapse rate and increases the time to deterioration. IVIg demonstrates similar effectiveness as the alternative treatment strategies of plasma exchange and

methyprednisolone. With the concern of AEs associated with long-term corticosteroid use, and the cost and access to PE, IVIg is an attractive alternative.

Table 1: Study characteristics

Ref	Design	Patients			Comparison	Outcomes	Quality	Notes
		Total	IVIg	C				
Vermeulen 1993[25]	Double-blind Parallel	28†	15	13	0.4g/kg dailyx5d vs placebo (albumin 3g/50ml)	MRC-SS, RS, CMAP, NCV	5, Y	Patients previously treated with immunosuppressants excluded; minimum disability score required for inclusion; responder predefined
Mendell 2001[22]	Double-blind Parallel	53	30	23	1.0g/kg dailyx2d, then again on d20 vs placebo (albumin)	AMS, HFDS, NCS	5, Y	no immunotherapy for any indication in previous 3 months
Zinman 2005[20]	Single-blind Parallel	14	9	5	1g/kg dailyx2d, monthly x 6mos vs PE (3 txs over 7d, monthly x 6mos	AMS, TCNS, HFDS, NCV, CMAP, F-wave latencies;	2, N	Patients previously treated with IVIg or PE excluded, no immunosuppressant therapy in previous 6 months, responder predefined
Dyck 1994[24]	Single-blind Crossover	20	15	17	0.4g/kg/wk x3wks followed by 0.2g/kg/wk x3wks vs PE twice wkly	NDS, NDS-W, CMAP, SNAP, VDT great toe	1, N	No PE or IVIg in previous 6 wks; minimum disability score required for inclusion; fixed washout period

					x3wks followed by once wkly x3wks			
Hughes 2001[21]	Double-blind Crossover	32‡	24	24	1.0g/kg daily x2d or or 2.0g/kg over 24hrs vs oral prednisolone, 60mg/d x 2wks then tapered	INCAT disability scale, 10-meter walk 9 hole peg board MRC-SS, GS, RHS, RS, SF-36 physical function score, SSS	5, Y	no immunosuppressants in previous 6wks; stable AZA dose allowed; predefined rules for washout period, responder predefined
Hughes 2008[26]	Double-blind Crossover	117‡	45	23	2.0g/kg over 2-4d followed by 1g/kg over 1-2d every 3wks for 24 wks vs placebo (0.1% albumin)	INCAT disability score, GS; MRC-SS, time to re-lapse for first period responders INCAT SS, CMAP,	4, U	no steroids, IVIg or PE in previous 3 mos; no immunomodulatory or immunosuppressive agents in previous 6 mos; minimum disability score required for inclusion; predefined rules for washout period; responder predefined
Hahn 1996[13]	Double-blind	30†	25	25	0.4g/kg daily x 5d vs	NDS, CG, GS, MCV, distal	4, Y	Patients with previous exposure

	Crossover				placebo (10% dextrose)	motor latencies, CMAP		to IVIg excluded; low dose prednisone (<20mg/day) allowed if treatment initiated > 3 mos; minimum disability score required for inclusion; predefined rules for washout period; responder predefined
Thompson 1996[23]	Double-blind Crossover	7†	7	7	0.4g/kg daily x5d vs placebo (albumin)	ambulation index, 10-m walk time, E-MRC-SS, 9-hole peg test, myometer, HMAS, CMAP distal motor latency, MCV, F-wave latency	4, Y	Patients with previous IVIg excluded; fixed washout period, responder predefined
vanDoorn 1990[27]	Double-blind Crossover	7	7	7	0.4g/kg daily x5d vs placebo (3g/50ml 20% albumin)	RS, CMAP, NCV, Mean time to clinical deterioration		Patients had to have previously responded to IVIg treatment, fixed washout period, responder

								predefined

AMS=average muscle strength (modified MRC), AZA=azathioprine, CMAP=compound muscle action potential, CG=clinical grade, d=day, E-MRC-SS=expanded Medical Research Council sum score, GS= grip strength, HFDS= Hughes functional disability scale,[34] HMAS= Hammersmith motor ability score[42], INCAT= inflammatory neurology cause and treatment,[21] INCAT SS= INCAT sensory score, IVIg= intravenous immunoglobulin, MCV= motor conduction velocity, mos=month, MRC-SS= Medical Research Council sum score,[30] NCS= nerve conduction study, NCV= nerve conduction velocity, NDS= Neurological disability score,[32] NDS-W=Neurological disability score weakness subscore,[32] PE=plasma exchange, RS=Rankin scale,[30] RHS= Rotterdam handicap scale,[31] SF36=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,[33] txs=treatment, VDT= Vibratory detection threshold, wks=weeks, †=patients diagnosed using the AAN criteria[28], ‡ patients diagnosed using the INCAT criteria[21], Quality assessed using Jadad scale[16] and Schultz treatment allocation concealment questionnaire[17] where Y is Yes, N is No and U is unclear.

Table 2: Disability scores for Forest plot 1

Study	placebo			IVIG			weight	Std. mean difference [95% CI]
	Mean score	SD	N	Mean score	SD	N		
Vermeulen 1993	1.31	3.4	13	1.6	3.04	15	19.8%	-0.09 [-0.83, 0.66]
Mendell 2001	0.02	0.55	21	0.46	0.81	29	26.2%	-0.61 [-1.18, -0.03]
Hughes 2008	0.2	4.5	58	3.3	5.6	59	36.6%	-0.61 [-0.98, -0.23]
Hahn 1996	-3.5	27.2	14	35.6	25	16	17.4%	-1.46 [-2.28, -0.64]

SD: standard deviation, N: number of patients, IVIG: intravenous immunoglobulin, STD.: standardized, CI: confidence interval

Table 3: Number of responders for Forest plot 2

Study	IVIG		placebo		weight	Risk Ratio [95% CI]
	Responders	N	Responders	N		
Vermeulen 1993	4	15	3	13	10.3%	1.16 [0.32, 4.24]
Mendell 2001	11	29	2	21	8.9%	3.98 [0.98, 16.12]
Hughes 2008	32	59	12	58	56.4%	2.62 [1.50, 4.57]
Hahn 1996	19	30	5	30	24.4%	3.80 [1.63, 8.85]

N: number of patients, IVIG: intravenous immunoglobulin, CI: confidence interval

Appendix 1 Literature search Strategy

EMBASE, Ovid MEDLINE(R)

#	Searches	Results	Search Type
1	Immunoglobulins, Intravenous.sh.	7030	Advanced
2	((intravenous$ adj (antibod$ or gammaglobulin$ or gamma globulin$ or immunoglobulin? or immune globulin?)) or iv immunoglobulin? or intravenous ig or modified immune globulin?).ti,ab.	14283	Advanced
3	(ivig or igiv or igv or ivigg or ivgg).ti,ab.	7392	Advanced
4	(alphaglobin$ or baygam$ or endobulin$ or gamagard$ or gamimmune$ or gamimune$ or gamunex$ or gammimune$ or gammimmune$ or gam?agard$ or gam?aguard$ or gammaglobulin$ or gammonativ$ or (globulin adj n) or igivnex$ or intraglobin$ or intraglobulin$ or iveegam$ or octagam$ or polygam$ or sandoglobulin$ or venimmune$ or venoglobulin$).ti,ab,tn.	5558	Advanced
5	Immunoglobulin.sh.	36133	Advanced
6	4 or 1 or 3 or 2	22239	Advanced
7	4 or 3 or 2 or 5	48860	Advanced
8	Polyradiculoneuropathy, Chronic Inflammatory Demyelinating.sh.	535	Advanced
9	(chronic inflammatory demyelinating polyradiculoneuropath$ or chronic inflammatory polyradiculoneuropath$ or CIDP).ti,ab.	1799	Advanced

10	Chronic Inflammatory Demyelinating Polyneuropathy.sh.	691	Advanced
11	8 or 9	1954	Advanced
12	10 or 9	2143	Advanced
13	exp Controlled Clinical Trials as Topic/ or Double-Blind Method.sh. or Random Allocation.sh. or Single-Blind Method.sh. or Multicenter Studies.sh.	222913	Advanced
14	(Multicenter Study or Randomized Controlled Trial or Controlled Clinical Trial).pt.	407986	Advanced
15	(random$ or rct$ or sham$ or placebo$ or (singl$ adj (blind$ or dumm$ or mask$)) or (doubl$ adj (blind$ or dumm$ or mask$))).ti,ab.	1014107	Advanced
16	((tripl$ adj (blind$ or dumm$ or mask$)) or (trebl$ adj (blind$ or dumm$ or mask$))).ti,ab.	371	Advanced
17	(control$ adj (study or studies or trial$)).ti,ab.	257158	Advanced
18	or/13-17	1345095	Advanced
19	Meta-Analysis.pt.	20758	Advanced
20	Meta-Analysis.sh. or exp Technology Assessment, Biomedical/	68857	Advanced
21	((systematic$ adj (literature review$ or review$ or overview$)) or (methodologic$ adj (literature review$ or review$ or overview$))).ti,ab.	37065	Advanced
22	((quantitative adj (review$ or overview$ or synthes$)) or	1141	Advanced

	(research adj (integration$ or overview$))).ti,ab.		
23	((integrative adj2 (review$ or overview$)) or (collaborative adj (review$ or overview$)) or pool$ analy$).ti,ab.	4339	Advanced
24	(data synthes$ or data extraction$ or data abstraction$).ti,ab.	15146	Advanced
25	(handsearch$ or hand search$).ti,ab.	4656	Advanced
26	(meta analy$ or metaanaly$ or met analy$ or metanaly$ or health technology assessment$ or HTA or HTAs or biomedical technology assessment$ or bio-medical technology assessment$).ti,ab.	51917	Advanced
27	(meta regression$ or metaregression$ or mega regression$).ti,ab.	1436	Advanced
28	(Meta Analysis or Systematic Review or Biomedical Technology Assessment).sh.	73576	Advanced
29	or/19-27	133458	Advanced
30	or/20-28	139839	Advanced
31	6 and 11 and 18	132	Advanced
32	6 and 11 and 29	18	Advanced
33	18 and 7 and 12	146	Advanced
34	30 and 7 and 12	27	Advanced
35	32 or 31	134	Advanced
36	33 or 34	155	Advanced
37	35 or 36	168	Advanced

38	limit 37 to human	163	Advanced
39	limit 38 to humans	163	Advanced
40	remove duplicates from 39	118	Advanced