Treatment for IgG and IgA paraproteinaemic neuropathy (Review)

Stork ACJ, Lunn MPT, Nobile-Orazio E, Notermans NC

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 3

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Treatment for IgG and IgA paraproteinaemic neuropathy

Abraham CJ Stork[1], Michael PT Lunn[2], Eduardo Nobile-Orazio[3], Nicolette C Notermans[1]

[1]Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands. [2]Department of Neurology and MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, London, UK. [3]IRCCS Humanitas Clinical Institute, Neurology 2, Milan University, Milan, Italy

Contact address: Abraham CJ Stork, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands. A.C.J.Stork@umcutrecht.nl.

Editorial group: Cochrane Neuromuscular Disease Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2015.
Review content assessed as up-to-date: 18 January 2014.

Citation: Stork ACJ, Lunn MPT, Nobile-Orazio E, Notermans NC. Treatment for IgG and IgA paraproteinaemic neuropathy. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD005376. DOI: 10.1002/14651858.CD005376.pub3.

ABSTRACT

Background

Paraproteinaemic neuropathy refers to those neuropathies associated with a monoclonal gammopathy or paraprotein. The most common of these present with a chronic, predominantly sensory, symmetrical neuropathy, similar to chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) but with relatively more sensory involvement, both clinically and neurophysiologically. The optimal treatment for neuropathies associated with IgG and IgA monoclonal gammopathy of uncertain significance is not known. This is an update of a review first published in 2007.

Objectives

To assess the effects of any treatment for IgG or IgA paraproteinaemic peripheral neuropathy.

Search methods

On 18 January 2014 we searched the Cochrane Neuromuscular Disease Group Trials Specialized Register, CENTRAL, MEDLINE and EMBASE. We also checked bibliographies for controlled trials of treatments for IgG or IgA paraproteinaemic peripheral neuropathy. We checked clinical trials registries for ongoing studies in November 2014.

Selection criteria

We considered for inclusion randomised controlled trials (RCTs) and quasi-RCTs using any treatment for IgG or IgA paraproteinaemic peripheral neuropathy. We excluded people with IgM paraproteins. We excluded people where the monoclonal gammopathy was considered secondary to an underlying disorder. We included participants of any age with a diagnosis of monoclonal gammopathy of uncertain significance with a paraprotein of the IgG or IgA class and a neuropathy. Included participants were not required to fulfil specific electrophysiological diagnostic criteria.

Data collection and analysis

We used standard Cochrane methodology to select studies, extract data and analyse results. One trial author provided additional data and clarification.

Main results

We identified one RCT, with 18 participants, that fulfilled the predetermined inclusion criteria. The trial compared plasma exchange to sham plasma exchange in participants with IgG or IgA paraproteinaemic neuropathy over a three-week follow-up period. We identified four other studies but these were not RCTs or quasi-RCTs. The included RCT did not report our predefined primary outcome measure, change in disability six months after randomisation. The trial revealed a modest benefit of plasma exchange in the weakness component of the Neuropathy Disability Score (NDS, now the Neuropathy Impairment Score); the mean improvement with plasma exchange was 17 points (95% confidence interval (CI) 5.2 to 28.8 points) versus 1 point (95% CI -7.7 to 9.7 points) in the sham exchange group at three weeks' follow-up (mean difference (MD) 16.00; 95% CI 1.37 to 30.63, low quality evidence). There was no statistically significant difference in the overall NDS (MD 18.00; 95% CI -2.03 to 38.03, low quality evidence), vibration thresholds or neurophysiological indices. Adverse events were not reported. The trial was at low risk of bias overall, although limitations of trial size and duration reduce the quality of the evidence in support of its conclusions.

Authors' conclusions

The evidence from RCTs for the treatment of IgG or IgA paraproteinaemic neuropathy is currently inadequate. More RCTs of treatments are required. These should have adequate follow-up periods and contain larger numbers of participants, perhaps through multicentre collaboration, considering the relative infrequency of this condition. Observational or open trial data provide limited support for the use of treatments such as plasma exchange, cyclophosphamide combined with prednisolone, intravenous immunoglobulin, and corticosteroids. These interventions show potential therapeutic promise but the potential benefits must be weighed against adverse effects. Their optimal use and the long-term benefits need to be considered and validated with well-designed RCTs.

PLAIN LANGUAGE SUMMARY

Treatment for neuropathies associated with abnormal antibodies in the blood (IgG and IgA paraproteinaemic neuropathies)

Review question

What are the benefits and harms of treatments for nerve damage associated with abnormal IgG and IgA proteins in the blood?

Background

Paraproteinaemic neuropathy refers to those neuropathies associated with a paraprotein (an abnormal antibody or immunoglobulin (Ig) present in relative excess in the blood). Paraproteins come from a group of blood disorders called monoclonal gammopathies. If the paraprotein is present without evidence of any underlying disease, this is known as a monoclonal gammopathy of uncertain significance (MGUS). This review looked at the treatments for neuropathy associated with and possibly caused by IgG and IgA paraproteins. The optimal treatment is not known. Treatments that act on the immune system such as plasma exchange, corticosteroids or intravenous immunoglobulin have been examined in nonrandomised studies of people with IgG and IgA paraproteinaemic neuropathy.

Study characteristics

We identified only one randomised controlled trial (RCT), which compared plasma exchange with sham exchange, in 18 participants with either IgA or IgG paraproteinaemic neuropathy. The results were reported after three weeks of treatment.

Key results and quality of the evidence

The trial did not report our primary outcome measure, which was improvement in disability measured by a validated scale six months after randomisation, or our other specified outcomes at six months. The trial demonstrated a modest benefit in improvement of weakness and overall disability as measured by the neuropathy disability score (NDS) over a period of three weeks. There was no improvement in this timescale in measures of sensory disturbance or electrical studies of the nerves. Adverse events were not reported. Further RCTs of this and other treatments with larger numbers of participants are needed.

This is an update of a review first published in 2007. We found no additional trials for inclusion. The evidence is current to January 2014.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Plasma exchange (PE) versus sham exchange for IgG and IgA paraproteinaemic neuropathy

Patient or population: people with IgG and IgA paraproteinaemic neuropathy
Settings: hospital, ambulatory care
Intervention: plasma exchange
Comparison: sham exchange

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sham exchange	Plasma exchange				
Change in disability Neuropathy Disability Score Follow-up: 3 weeks[1]	The mean improvement in disability in the control group was **2 points**	The mean improvement in disability in the intervention groups was **18 points higher** (2.03 lower to 38.03 higher)		18 (1 study)	⊕⊕◯◯ **low**[2]	A higher score is less disability (impairment)
Change in sensation using a validated scale (e.g. INCAT sensory sum score) - not measured	See comment	See comment	Not estimable	-	See comment	Not an outcome in the included study (Dyck 1991)
Change in strength Neuropathy Disability Score (weakness) Follow-up: 3 weeks[1]	The mean improvement in strength in the control group was **1 point**	The mean improvement in strength in the intervention groups was **16 points higher** (1.37 to 30.63 higher)		18 (1 study)	⊕⊕◯◯ **low**[2]	A higher score is less weakness
Adverse events - not reported	See comment	See comment	Not estimable	-	See comment	Not reported in (Dyck 1991)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **INCAT**: Inflammatory Neuropathy Cause and Treatment

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Our prespecified time point was six months. We report three-week outcomes here; this was the duration of the included study.
[2]We found one randomised controlled trial, with a small number of participants (serious imprecision) and outcome measured after three weeks instead of the more relevant six months pre-specified for this review (serious indirectness). It is unclear if paraprotein is incidental or causative in neuropathies treated.

BACKGROUND

Paraproteinaemic neuropathy refers to a group of neuropathies associated with a monoclonal gammopathy or paraprotein. A paraprotein is an immunoglobulin (Ig) molecule produced by a monoclonal plasma cell expansion. The monoclonal protein is present in relative excess and is often nonfunctional. If the monoclonal protein is present without evidence of an underlying causative disease, this is known as a monoclonal gammopathy of uncertain significance (MGUS). Treatment for IgM paraprotein-associated neuropathy has been reviewed previously (Lunn 2012). The treatment of neuropathies occurring in people with IgG or IgA MGUS is covered in this review.

Where the only clinical manifestation of the MGUS is neuropathy, the neuropathy dictates treatment (Nobile-Orazio 2002), as the monoclonal gammopathy usually remains benign and nonprogressive. Kyle found that one per cent per year of all people with MGUS progressed to develop a malignant plasma cell dyscrasia (Kyle 1993). In Ponsford's series of 50 people with IgG or IgA MGUS neuropathy, six per cent developed malignancy after a median follow-up of 14 years (Ponsford 2000). Others have found malignant transformation more often occurs earlier in the natural history of MGUS in people with neuropathy and is associated with worsening neuropathy (Eurelings 2001). Where MGUS transforms into myeloma, the malignancy is more likely to determine treatment.

The prevalence of MGUS increases with age. The most common paraprotein type is IgG, accounting for 61% of cases in one review (Kyle 1992). Most people with MGUS do not have a symptomatic neuropathy. Kelly found a monoclonal protein in 10% of people with neuropathy of unknown aetiology (Kelly 1981). Conversely, in series of people with MGUS, the prevalence of symptomatic neuropathy ranged from 1% to 36% and was higher in MGUS associated with IgM than with IgG or IgA paraproteins (Gosselin 1991; Nobile-Orazio 2002; Vrethem 1993; Yeung 1991).

Typically, paraproteinaemic neuropathy affects men in their sixth to eighth decade. It presents with a chronic, predominantly sensory, symmetrical neuropathy, similar to chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). People with MGUS neuropathy (IgM, IgG and IgA) often have less weakness and relatively more sensory involvement, both clinically and neurophysiologically, than do people with idiopathic CIDP (Gorson 1997b; Simmons 1993; Simmons 1995). Some have found less clinical or neurophysiological sensory involvement in IgG and IgA paraproteinaemic neuropathy compared to IgM (Magy 2003; Notermans 2000). There is some diagnostic controversy, and debate continues about whether a person with an IgG MGUS and otherwise typical CIDP justifies a separate diagnosis (Bleasel 1993; Simmons 1995); some authors classify it as a concurrent illness with CIDP (EFNS/PNS 2010; Saperstein 2001). Some have found a difference in the clinical features between people with IgM and IgG MGUS neuropathy (Gosselin 1991; Nobile-Orazio 1992; Vrethem 2010), but others have not (Bromberg 1992; Yeung 1991).

The majority of the cases reported in the literature are associated with IgG as opposed to IgA. The clinical and electrophysiological features of 205 IgG and 27 IgA reported cases have been reviewed (Nobile-Orazio 2002). The review highlights the heterogeneity of both IgG and IgA MGUS neuropathy patients, noted previously in smaller studies by others (Di Troia 1999; Gorson 1997a; Hermosilla 1996; Notermans 1994). People with IgG and IgA paraproteinaemic neuropathy have either demyelinating or axonal/mixed neuropathies, in approximately equal numbers. Those with a slowly progressive distal axonal polyneuropathy tend to show a poor response to immunotherapy (treatments that have a mechanism of action via modulation of the immune system). Others with a sensorimotor demyelinating neuropathy frequently respond to immunotherapy (Magy 2003).

Initial screening with serum protein electrophoresis is nonspecific but may identify the presence of a serum paraprotein in higher concentrations. Immunofixation is required to detect those at low concentrations (< 0.2 g/L), which may not be detected by electrophoresis. Immunofixation is also necessary to identify the exact isotype of the heavy and light chains. Occasionally light chains in the urine can identify the presence of a serum paraprotein.

The pathogenic role of IgG and IgA paraproteins is debated. Monoclonal gammopathy may become apparent after the onset of neuropathy (Nobile-Orazio 1992; Simmons 1995). Serum levels of the paraprotein fluctuate and may not correlate with the clinical course (Bleasel 1993). Some researchers have suggested that the paraprotein is part of a secondary autoimmune response (Di Troia 1999). Others argue that it is a coincidental finding, particularly in the setting of a chronic axonal neuropathy (Kyle 1987; Notermans 1996a; Ritzmann 1975; Saleun 1982).

The paraprotein antibodies are sometimes found to have specific antigen targeted activity. In people with IgG MGUS, Di Troia et al. found no differences in the frequency of antibodies to various neural glycoprotein and glycolipid antigens between people with and without neuropathy (Di Troia 1999). Others have found antibodies to neurofilament antigens in people with neuropathy (Fazio 1992; Stubbs 2003). The immunological characteristics of people with IgG and IgA paraproteinaemic neuropathy have been reviewed (Nobile-Orazio 2002). A few cases demonstrated IgA or IgG deposition in the nerves (Bailey 1986; Mehndiratta 2004; Vallat 2000), but the pathogenic significance of this finding remains uncertain. In a histological study, sural nerve biopsies in eight people with IgG paraproteins were indistinguishable from those of idiopathic CIDP (Vital 2000). Other biopsy studies have suggested more T cell involvement in paraproteinaemic neuropathy (Eurelings 2002; Eurelings 2003) than in CIDP without a paraprotein.

The optimal treatment for IgG and IgA MGUS neuropathies is not known. In two published observational studies people with 'CIDP-MGUS' responded less well to immunotherapy than those with idiopathic CIDP (Simmons 1993; Simmons 1995). In a third study, the responses were similar (Gorson 1997b). A review of 124 people with IgG MGUS and neuropathy considered treatment with immune therapies (most commonly corticosteroids and plasma exchange) (Nobile-Orazio 2002). Of these 124 people, 67 had a demyelinating neuropathy and of these, 54 (81%) responded to immunotherapies, compared with only seven of 34 people (21%) with an axonal neuropathy. In the same review, seven of 13 IgA cases responded to immune therapies. In a double-blind controlled trial of plasma exchange versus sham plasma exchange in 39 participants with polyneuropathy associated with MGUS (21 IgM and 18 IgG/IgA), plasma exchange produced more marked improvement in the neuropathy disability score (now referred to as the neuropathy impairment score (Dyck 2005)) and neurophysiological improvement, in those with IgG or IgA (Dyck 1991). Gorson reported improvement with IVIg in eight of 20 people who had IgG MGUS (Gorson 2002). In one series of people with axonal neuropathy and IgG MGUS, authors reported improvement in one out of three people treated with corticosteroids (Di Troia 1999).

This is an update of a review first published in 2007.

OBJECTIVES

To assess the effects of any treatment for IgG or IgA paraproteinaemic peripheral neuropathy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs using any treatment for IgG or IgA paraproteinaemic peripheral neuropathy.

Types of participants

We followed the International Myeloma Working Group 2003 diagnostic criteria for MGUS: monoclonal protein < 30 g/L and clonal plasma cell population < 10% with no evidence of multiple myeloma, other B-cell proliferative disorders or amyloidosis (Myeloma 2003). We therefore excluded people in whom the monoclonal gammopathy was considered to be due to an underlying disorder, such as multiple myeloma, plasmocytoma, malignant lymphoproliferative diseases or amyloidosis.

We included people of any age who had a diagnosis of MGUS with a paraprotein of the IgG or IgA class and a neuropathy. We excluded individuals with IgM paraproteins. We also ruled out other causes of peripheral neuropathy. The clinical picture was a recognised presentation of peripheral neuropathy (Nobile-Orazio 2002), being typically a symmetrical sensory or sensorimotor neuropathy. Neurophysiologically the neuropathy could be demyelinating, axonal or of mixed type, and therefore it did not need to fit any published electrophysiological diagnostic criteria. We included studies that did not exactly fulfil these criteria, provided the review authors agreed that IgG or IgA paraproteinaemic peripheral neuropathy was the preferred diagnosis, if necessary after consultation with the original study authors. We noted any departures from the diagnostic criteria.

Types of interventions

We included any treatment used for IgG or IgA paraproteinaemic peripheral neuropathy. Treatments could be administered using various protocols (for example as a single agent, in combination or sequentially). The control arm did not necessarily include a placebo, but if the control arm received a treatment then the participants in the experimental arm also had to have received that same treatment. We considered any route of administration, provided that it had been defined. We also required dosages and the frequency and length of administration to have been defined in the studies.

Types of outcome measures

Primary outcomes

The predefined primary outcome measure was: change in disability at six months after randomisation, measured by a validated scale such as the Overall Disability Scale (ODS) (Merkies 2003a).
We selected a disability score for the primary outcome, as such scores are considered to be the most relevant measures in immune-mediated neuropathies (Merkies 2003b). They are also potentially easy to derive retrospectively from collected data. We predefined six months as a favoured time point for re-evaluation, on the basis that IgG or IgA paraproteinaemic peripheral neuropathy is a chronic and slowly progressive or relapsing-remitting disorder. However, to avoid limiting the scope of the review we considered trials using other trial periods and follow-up intervals, and made appropriate adjustments in our analysis.

Secondary outcomes

Secondary outcome measures were as follows.

1. Change at six months in sensation, measured by a validated scale such as the Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score (Merkies 2000).

2. Change in strength at six months, measured by a validated scale such as the Medical Research Council (MRC) sum score (Kleyweg 1991).

3. Neurophysiology: change at six months, measured by the distally evoked summed compound muscle action potential (CMAP) amplitudes.

4. Neurophysiology: change at six months, measured by a change in the number of sites of conduction block, as defined by the American Association of Neurology diagnostic criteria for CIDP (CIDP 1991).

5. Adverse events - adverse events defined as those which are fatal, life threatening or required or resulted in hospitalisation.

We would have adjusted the rate for differing follow-up periods as necessary.

Search methods for identification of studies

On 18 January 2014 we searched the Cochrane Neuromuscular Disease Group Trials Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 12), MEDLINE (January 1966 to January 2014) and EMBASE (January 1980 to January 2014). There were no language limitations. We searched the US National Institutes for Health Clinical Trials Registry, www.ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Portal (ICTRP) (apps.who.int/trialsearch/) for ongoing studies on 18 November 2014.

Electronic searches

We provided the detailed search strategies in the appendices: MEDLINE (Appendix 1), EMBASE (Appendix 2) and CENTRAL (Appendix 3).

Searching other resources

We reviewed bibliographies to identify other controlled trials.

Data collection and analysis

Selection of studies

Two review authors (ACJS and NCN at this update) independently checked titles and abstracts identified from the Cochrane Neuromuscular Disease Group Specialized Register, MEDLINE and EMBASE searches and bibliographies. The review authors obtained the full texts of potentially relevant studies, and three authors (ACJS, MPTL and NCN) carried out independent assessments to decide which trials met the inclusion criteria. There were no disagreements about study selection.

Data extraction and management

Two review authors (ACJS and NCN) independently extracted data. An author of the included study provided some additional data and clarification (Dyck 1991).

Assessment of risk of bias in included studies

The 'Risk of bias' assessment took into account seven predefined domains, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. For each domain two review authors independently made a judgement of 'low risk of bias', 'high risk of bias', or 'unclear risk of bias' (Higgins 2011). There were no disagreements.

Measures of treatment effect

The trial provided continuous data. We reported the mean difference (MD) in improvement from baseline, with corresponding 95% confidence interval (CI).

To allow meta-analysis where different trials used different measurement scales for outcomes that were conceptually the same, we would have either dichotomised changes or use standard deviations (SDs) as the units and report standardised mean differences with 95% CI, either using the SD of the population at baseline or of the control population.

Data synthesis

We did not perform meta-analysis, test for heterogeneity across trials or conduct the planned subgroup analyses described in the protocol (Allen 2005) because of the lack of included trials and the lack of data available.

We considered nonrandomised evidence concerning adverse events, cost-effectiveness and treatments currently in use in the Discussion.

We created a 'Summary of findings' table using the following outcomes: change in disability (NDS), change in strength (NDS weakness) and change in sensation (INCAT sensory sum score).

We used the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software (GRADEpro 2008). We justified all decisions to downgrade the quality of studies using footnotes and we made comments to aid reader's understanding of the review where necessary.

RESULTS

Description of studies

Results of the search

The number of papers found by the new, current strategies, which were run on 18 January 2014, were:

- MEDLINE - 1343
- EMBASE - 478
- Cochrane Neuromuscular Disease Group Specialized Register - 74
- CENTRAL - 113

We identified no additional published or unpublished data. The systematic database searches in 2005 revealed five possible trials. One trial met the inclusion criteria (Dyck 1991) (Characteristics of included studies). We excluded the four other trials (see Characteristics of excluded studies). The review authors identified no new published or ongoing trials from the searches for this updated review.

Included studies

There were 18 participants with IgG or IgA paraproteinaemic neuropathy in the included trial (Dyck 1991). This trial was a randomised double-blind, parallel-group, sham-controlled trial of plasma exchange. The trial also included participants with IgM paraproteinaemic neuropathy, but the report discussed results for the different types of paraprotein separately, allowing the use of these data. The criteria for the paraprotein specifically being a MGUS were not as strictly defined as those used for this review, but we still considered that they fulfilled the criteria adequately. The participants' neuropathies were deemed to be either stable or worsening at the time of enrolment. The intervention in this trial was a twice-weekly 3.5 L plasma exchange for three weeks, totalling six exchanges. No additional treatments were given. Participants remained on other treatments that they were already taking but had received no other immunotherapy in the six weeks prior to plasma exchange. Eight participants with IgG or IgA paraproteinaemic neuropathy initially received treatment. Ten control participants with IgG or IgA paraproteinaemic neuropathy received full sham exchanges, with plasma extraction, separation, recombination and re-infusion. Nine of these control participants subsequently underwent treatment with plasma exchange following the same protocol. The results of this open phase of the trial were also reported.

Excluded studies

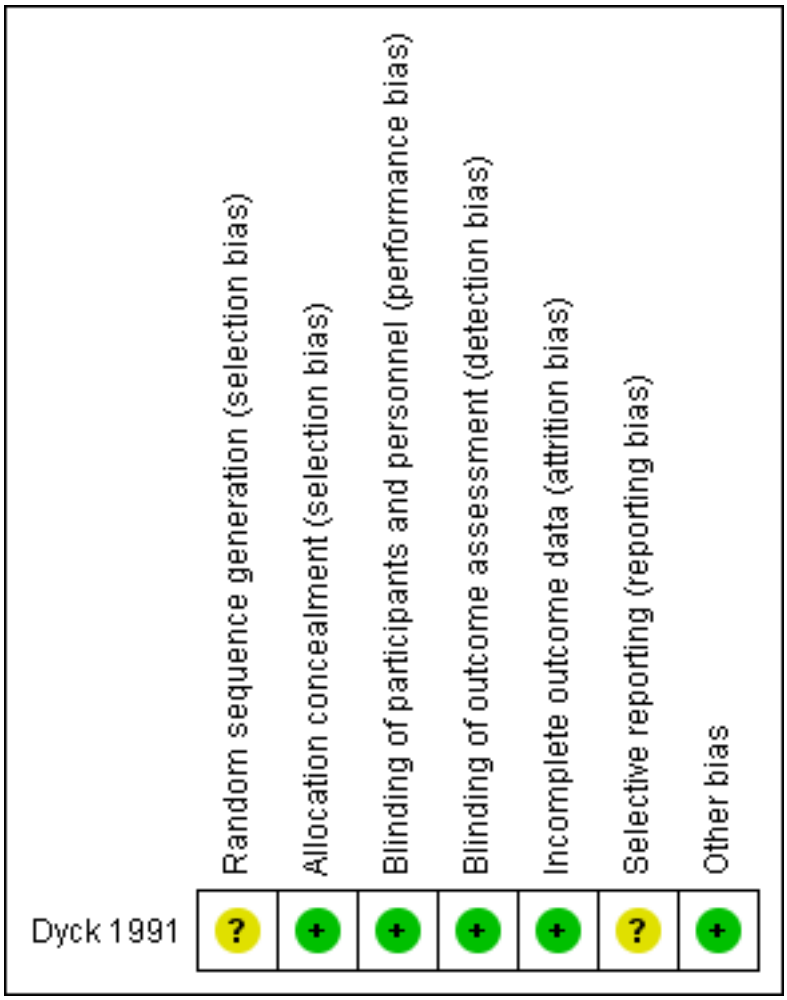
We excluded the four remaining trials for various reasons: Notermans 1996a performed an uncontrolled open prospective trial of intermittent cyclophosphamide and prednisolone. Five of the sixteen participants included had IgG MGUS neuropathy. We also excluded a trial of pulsed high-dose dexamethasone as it was an uncontrolled open trial of six participants with paraproteinaemic neuropathy (Notermans 1997). Only one had an IgG MGUS, the others had IgM MGUS. Léger 1994 performed a trial of IVIg that included four participants with IgG paraproteinaemic neuropathy. This was an uncontrolled open prospective trial, for which the diagnostic criteria were unclear, and which used no clear outcome criteria. Sghirlanzoni 2000 reported a trial of 60 participants, which included nine with IgG paraproteinaemic neuropathy. This trial included various immunosuppressant treatments. The trial was a prospective, uncontrolled, nonrandomised cohort study and the results for the IgG paraproteinaemic neuropathy participants were not reported separately from those with an IgM paraproteinaemic neuropathy.

Risk of bias in included studies

In Dyck 1991, participants underwent 'restricted randomisation'. This was done to ensure that the baseline characteristics of age and sex were approximately equal. The study authors state that the groups at baseline were 'reasonably balanced' with respect to neuropathic abnormalities. We deemed the blinding process to have been adequate and explicit clinical and outcome criteria to have been used. We judged completeness of follow-up as partially adequate, and there were no drop-outs. The study initially aimed to include 40 participants, including participants with IgM MGUS neuropathy. The results section describes 39 participants being enrolled in the study and one developing myeloma. The results state that the trial authors did not use the data for this participant in the analysis. It is unclear whether this participant took part in the trial or even underwent plasma exchange. The review authors have presumed that the participant did not receive any treatment and was not enrolled, consistent with the 39 participants that are included in the baseline and post-treatment results. The follow-up period was only three weeks.

Figure 1 summarises the review authors' 'Risk of bias' assessments.

Figure 1. Risk of bias summary: review authors' judgements about each 'Risk of bias' item for each included study. Green (+) = low risk of bias; yellow (?) = unclear risk of bias; red (-) = high risk of bias (not shown).



Effects of interventions

See: **Summary of findings for the main comparison** Plasma exchange (PE) versus sham exchange for IgG and IgA paraproteinaemic neuropathy

Plasma exchange versus sham exchange

The only eligible trial provided results for 18 participants with IgG or IgA paraproteinaemic neuropathy at a follow-up interval of three weeks (Dyck 1991). The trial authors did not separate results with respect to the individual IgG or IgA subgroups. The trial used the NDS (subsequently renamed the Neuropathy Impairment Score) as the primary outcome measure. Scores could range from zero to 244 points, with 244 being maximal neurological disability (impairment). Included participants had an average NDS of 60.5. The report provided neurophysiological improvement data for the group but did not provide a neurophysiological classification of the neuropathy (in terms of being predominantly axonal or demyelinating) at baseline.

Primary outcome measure: change in disability

In the randomised controlled phase of the trial, the trial did not report our predefined primary outcome measure, although it did measure disability at three weeks. Comparing the overall NDS, the treatment group improved by a mean of 20 points (95% CI 3.4 to 36.6) compared to 2 points (95% CI -9.2 to 13.2) for the control group (MD 18.00; 95% CI -2.03 to 38.03; Analysis 1.1). This was not statistically significant.

Secondary outcome measures

Change in sensation

The trial authors did not report changes in sensation using a validated sum score as specified previously. Instead the trial measured vibration detection thresholds at three weeks, and mean scores were not statistically significantly better with plasma exchange (MD 0.10; 95% CI -0.50 to 0.70; Analysis 1.2).

Change in strength

The trial also assessed strength measurements at three weeks. Overall, the 19 participants (including those with IgM as well as IgG and IgA paraproteins) who underwent plasma exchange improved on average more than the 20 who underwent sham exchange. Participants with IgG or IgA paraproteinaemic neuropathy improved more in weakness (P value = 0.03) when compared to participants with IgM paraproteins. When assessing the participants with IgG or IgA in isolation, improvement in the weakness score of the NDS was significantly greater in the eight participants given plasma exchange in comparison to the 10 given sham exchange. The plasma exchange group showed mean score improvements of 17 (95% CI 5.2 to 28.8) versus 1 (95% CI -7.7 to 9.7) in the sham exchange group (MD 16.00; 95% CI 1.37 to 30.63; Analysis 1.3). The report did not specify the actual number of participants who showed improvement.

Neurophysiology: change in CMAP amplitude

The mean scores for summed CMAP measurements were also not statistically significantly different (MD 2.00 mV; 95% CI -0.94 to 4.94; Analysis 1.4). Subjective assessment was not recorded. Motor nerve conduction studies showed no significant differences (MD 4.00 m/s; 95% CI -12.30 to 20.30; Analysis 1.5), and sensory nerve studies were not reported on follow-up.

Neurophysiology: change in the number of sites with conduction block

The number of sites with conduction block was not reported

Adverse events

Details of adverse events were not reported.

DISCUSSION

Only one trial fulfilled the predetermined inclusion criteria (Dyck 1991). Four other studies were not RCTs but we have discussed some of their findings. Dyck 1991 included 39 participants of whom 18 had either IgG or IgA paraproteinaemic neuropathy. The risk of bias was low. The blinding process was well described and performed. The trial used clear outcome criteria but did not report all of the data, and the time points used were much shorter than our predefined criteria. Baseline characteristics were reasonably balanced; completeness of follow-up and randomisation were, however, only partially adequate, based upon the descriptions provided. The trial did not use our primary outcome measure, but did use some of our secondary outcome measures. In particular, there was a statistically significant but modest increase in strength with plasma exchange compared to sham exchange. The small number of participants limited the power of the trial. Adverse events were not reported. Due to the limited number of participants and a short follow-up period we rated the quality of the evidence provided by this trial as low following the GRADE working group rating system (see Summary of findings for the main comparison).

In the open trial stage of Dyck 1991, not included in the results section above, nine of the 10 participants with IgG or IgA paraproteinaemic neuropathy who had initially received sham exchange in the controlled trial, then received plasma exchange. This group subsequently showed very similar overall mean improvements when compared to those of the initial treatment group from the randomised trial phase. However, when the NIS, the weakness score of the NIS, vibration detection threshold score and summed CMAP scores were compared to the nine participants own original (sham control) scores, the results were not statistically significantly different. The overall results from the open trial phase did reveal some statistically significant findings but only when the results for all the IgG, IgA and IgM participants were included. The assessing physicians were unblinded at this stage.

Although not included in this review, a trial of intermittent cyclophosphamide (300 mg/m^2 body surface daily for four days) combined with prednisone (40 mg/m^2 body surface daily for five days) in 16 participants provided relevant data (Notermans 1996a). Four of the five participants with IgG paraproteinaemic neuropathy improved or stabilised following treatment, and this was maintained for three years of follow-up. Of these five participants, two had mixed axonal and demyelinating findings on motor nerve conduction studies and three had predominantly demyelinating findings. Side effects were a severe but reversible leukopenia after one cycle of cyclophosphamide and prednisolone in one participant, necessitating withdrawal of treatment. Other participants suffered hair loss and nausea.

Another trial, of pulsed high dose dexamethasone (40 mg/day orally for four days, once a month, in up to six cycles) in six participants with paraproteinaemic neuropathy, showed a stable Rankin scale and a two-point improvement in the MRC sum score at follow-up in the single participant with IgG paraproteinaemic neuropathy (Notermans 1997). However, this participant, like two others, developed proximal lower limb weakness as a side effect. Electrophysiologically, the single participant with IgG parapro-

teinaemic neuropathy had a mixed axonal and demyelinating neuropathy. Further enrolment in the study was stopped due to serious side effects in four out of six participants, with three experiencing severe mood disturbance.

Other reviews and some of the retrospective series discussed below provide support for the use of immunotherapy. In a review which included 124 people with IgG MGUS neuropathy, Nobile-Orazio found that 81% of the 67 people with a predominantly demyelinating neuropathy responded favourably to therapies such as steroids and plasma exchange (Nobile-Orazio 2002). In a retrospective review of 20 people with IgG MGUS neuropathy who all received intravenous immunoglobulin, Gorson 2002 found a beneficial response in eight.

Other studies have reported beneficial responses in some patients to various therapies (Di Troia 1999; Magy 2003; Yeung 1991). In a retrospective observational study, Magy reported that eight out of nine people experienced a sustained clinical improvement with either corticosteroids, plasma exchange or intravenous immunoglobulin. Yeung reported that four out of five people with IgG experienced a good response to corticosteroids in another retrospective observational study. Four also received cytotoxic drugs but without additional benefit. Three IgA patients treated with corticosteroids (one with a concomitant cytotoxic drug) also improved but another person treated with plasma exchange showed no benefit. In one series of people with axonal neuropathy and IgG MGUS reported by Di Troia, improvement was reported in one out of three treated with corticosteroids.

This review has revealed that only one RCT relating to the treatment of IgG or IgA paraproteinaemic neuropathy exists. This may be partly due to the relatively low prevalence of this disease. Unfortunately, retrospective reviews are potentially open to bias. They are not blinded, often do not consistently report useful assessment scores and are not controlled. Furthermore, people with a demyelinating neuropathy associated with IgG or IgA monoclonal gammopathy are considered to have CIDP (European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria for CIDP) as far as they fulfil the diagnostic criteria for CIDP. These people are considered eligible for RCTs on CIDP, making the initiation of new RCTs specifically on polyneuropathy associated with IgG or IgA monoclonal gammopathy less likely.

Searches were comprehensive and the review authors are confident that they have identified eligible studies. The review methods do not allow for the detection of rare adverse events, because of the small numbers of trial participants with this rare condition.

Although not addressed in trials so far, evaluation of treatments should be made in people with both predominantly axonal and demyelinating neuropathies associated with IgG or IgA MGUS. It is uncertain whether the presence or absence of electrophysiological characteristics predict response to treatment.

In the UK the cost of five single plasma volume plasma exchange procedures is about the same as a course of IVIg 2.0 g/kg, namely about GBP 4000. Patients may require multiple courses of plasma exchange, each possessing inherent risks. In a large series of plasma exchange for various indications, adverse reactions, including citrate toxicity (3%), vasovagal reactions and vascular access complications, occurred in 3.9% of 17,940 procedures on 3583 people (Kiprov 2001). As with any treatment the potential benefits of plasma exchange treatment should be balanced against the costs and potential side effects of that treatment.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from randomised controlled trials for the treatment of IgG or IgA paraproteinaemic neuropathy is currently inadequate. One small trial showed significant short-term benefit from plasma exchange in measures of weakness but not in a composite impairment score (Neuropathy Disability Score), sensory function or neurophysiology measures. The long-term benefits and side effects of repeated plasma exchange have not been investigated.

Implications for research

More randomised controlled trials of existing and new treatments are required. These should have adequate follow-up periods and contain larger numbers of participants, perhaps through multicentre collaboration because of the relative infrequency of this condition.

Future trials should use sensitive and validated disability and clinical scores that are likely to extract meaningful effects (Merkies 2006). Quality of life assessment and cost effectiveness measurements should also be considered in future studies, as the treatments that have been used and those that are likely to be used in the future are expensive. These treatments are also time consuming to receive or provide, may be invasive and are not without side effects. Trial endpoints should also be appropriate to the chronicity of the disorder and meaningful in patient terms, particularly overall disability. We had suggested a predefined endpoint of six months or a year.

Some observational data provide limited support for the use of plasma exchange, cyclophosphamide combined with prednisolone, intravenous immunoglobulin and corticosteroids. Their possible potential benefits must be weighed against their sometimes severe adverse effects. Their optimal use and long-term benefits need to be considered and validated with well-designed randomised controlled trials.

ACKNOWLEDGEMENTS

David Allen and Jikke-Mien Niermeijer contributed to an earlier version of this review.

The Cochrane Neuromuscular Disease Group Trials Search Co-ordinator developed search strategies in collaboration with the review authors. The Group's Managing Editor, Ruth Brassington, helped authors draft the 'Summary of findings' table.

This project was supported by the National Institute for Health Research via Cochrane Infrastructure funding to the Cochrane Neuromuscular Disease Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health. The Cochrane Neuromuscular Disease Group also receives support from the MRC Centre for Neuromuscular Diseases.

REFERENCES

References to studies included in this review

Dyck 1991 *{published and unpublished data}*
Dyck P, Low PA, Windebank AJ, Jaradeh SS, Gosselin S, Bourque P, et al. Plasma exchange in polyneuropathy associated with monoclonal gammopathy of undetermined significance. *New England Journal of Medicine* 1991;**325** (21):1482–6. [PUBMED: 1658648]

References to studies excluded from this review

Léger 1994 *{published data only}*
Léger JM, Younes-Chennoufi AB, Chassande B, Davila G, Bouche P, Baumann N, et al. Human immunoglobulin treatment of multifocal motor neuropathy and polyneuropathy associated with monoclonal gammopathy. *Journal of Neurology, Neurosurgery & Psychiatry* 1994;**57 Suppl**:46–9.

Notermans 1996 *{published data only}*
Notermans NC, Lokhorst HM, Franssen H, Van der Graaf Y, Teunissen LL, Jennekens FG, et al. Intermittent cyclophosphamide and prednisone treatment of polyneuropathy associated with monoclonal gammopathy of undetermined significance. *Neurology* 1996;**47**(5): 1227–33.

Notermans 1997 *{published data only}*
Notermans NC, Vermeulen M, Van Doorn PA, Van den Berg LH, Teunissen LL, Wokke JH. Pulsed high-dose dexamethasone treatment of polyneuropathy associated with monoclonal gammopathy. *Journal of Neurology* 1997; **244**(7):462–3.

Sghirlanzoni 2000 *{published data only}*
Sghirlanzoni A, Solari A, Ciano C, Mariotti C, Fallica E, Pareyson D. Chronic inflammatory demyelinating polyradiculoneuropathy: long-term course and treatment of 60 patients. *Neurological Sciences* 2000;**21**(1):31–7.

Additional references

Bailey 1986
Bailey RO, Ritaccio AL, Bishop MB, Wu AY. Benign monoclonal IgAK gammopathy associated with polyneuropathy and dysautonomia. *Acta Neurologica Scandinavica* 1986;**73**(6):574–80.

Bleasel 1993
Bleasel AF, Hawke SH, Pollard JD, McLeod JG. IgG monoclonal paraproteinaemia and peripheral neuropathy. *Journal of Neurology, Neurosurgery & Psychiatry* 1993;**56**(1): 52–7.

Bromberg 1992
Bromberg MB, Feldman EL, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy: comparison of patients with and without an associated monoclonal gammopathy. *Neurology* 1992;**42**(6):1157–63.

CIDP 1991
Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Research criteria for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Neurology* 1991;**41**(5): 617–8.

Di Troia 1999
Di Troia A, Carpo M, Meucci N, Pellegrino C, Allaria S, Gemignani F, et al. Clinical features and anti-neural reactivity in neuropathy associated with IgG monoclonal gammopathy of undetermined significance. *Journal of the Neurological Sciences* 1999;**164**(1):64–71.

Dyck 2005
Dyck PJ, Boes CJ, Mulder D, Millikan C, Windebank AJ, Dyck PJ, et al. History of standard scoring, notation, and summation of neuromuscular signs. A current survey and recommendation. *Journal of the Peripheral Nervous System* 2005;**10**(2):158–73.

EFNS/PNS 2010
Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the treatment of chronic inflammatory demyelinating polyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - First Edition. *Journal of the Peripheral Nervous System* 2010;**15**(3):185–95.

Eurelings 2001
Eurelings M, Notermans NC, Van de Donk NW, Lokhorst HM. Risk factors for haematological malignancy in polyneuropathy associated with monoclonal gammopathy. *Muscle & Nerve* 2001;**24**(10):1295–302.

Eurelings 2002
Eurelings M, Notermans NC, Wokke JH, Bosboom WM, Van den Berg LH. Sural nerve T cells in demyelinating polyneuropathy associated with monoclonal gammopathy. *Acta Neuropathologica* 2002;**103**(2):107–14.

Eurelings 2003
Eurelings M, Van den Berg LH, Wokke JHJ, Franssen H, Vrancken AFJ, Notermans NC. Increase of sural nerve T cells in progressive axonal polyneuropathy and monoclonal gammopathy. *Neurology* 2003;**61**(5):707–9.

Fazio 1992
Fazio R, Nemni R, Quattrini A, Lorenzetti I, Canal N. IgG monoclonal proteins from patients with axonal peripheral neuropathies bind to different epitopes of the 68kDa neurofilament protein. *Journal of Neuroimmunology* 1992; **36**(2-3):97–104.

Gorson 1997a
Gorson KC, Ropper AH. Axonal neuropathy associated with monoclonal gammopathy of undetermined significance. *Journal of Neurology, Neurosurgery & Psychiatry* 1997;**63**(2): 163–8.

Gorson 1997b
Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. *Neurology* 1997;**48**(2): 321–8.

Gorson 2002
Gorson KC, Ropper AH, Weinberg DH, Weinstein R. Efficacy of intravenous immunoglobulin in patients with IgG monoclonal gammopathy and polyneuropathy. *Archives of Neurology* 2002;**59**(5):766–72.

Gosselin 1991
Gosselin S, Kyle RA, Dyck PJ. Neuropathy associated with monoclonal gammopathies of undetermined significance. *Annals of Neurology* 1991;**30**(1):54–61.

GRADEpro 2008
Jan Brozek, Andrew Oxman, Holger Schünemann. GRADEpro. 3.2 for Windows. Jan Brozek, Andrew Oxman, Holger Schünemann, 2008.

Hermosilla 1996
Hermosilla E, Lagueny A, Vital C, Vital A, Ferrer X, Steck A, et al. Peripheral neuropathy associated with monoclonal IgG of undetermined significance: clinical, electrophysiologic, pathologic and therapeutic study of 14 cases. *Journal of the Peripheral Nervous System* 1996;**1**(2): 139–48.

Higgins 2011
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011) March 2011. Available from www.cochrane–handbook.org.

Kelly 1981
Kelly JJ, Kyle RA, O'Brien P, Dyck PJ. Prevalence of monoclonal protein in peripheral neuropathy. *Neurology* 1981;**31**(11):1480–3.

Kiprov 2001
Kiprov DD, Golden P, Rohe R, Smith S, Hofmann J, Hunnicutt J. Adverse reactions associated with mobile therapeutic apheresis: analysis of 17,940 procedures. *Journal of Clinical Apheresis* 2001;**16(3)**:130–3.

Kleyweg 1991
Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. *Muscle & Nerve* 1991;**14**(11):1103–9.

Kyle 1987
Kyle R. Plasma cell dyscrasia: definition and diagnostic evaluation. In: Kelly J, Kyle R, Latov N editor(s). *Polyneuropathies associated with plasma cell dyscrasias*. Boston: Martinus Nijhoff Publishing, 1987:1–28.

Kyle 1992
Kyle RA. Diagnostic criteria of multiple myeloma. *Hematology/Oncology Clinics of North America* 1992;**6**(2): 347–58.

Kyle 1993
Kyle RA. 'Benign' monoclonal gammopathy-after 20 to 35 years of follow up. *Mayo Clinic Proceedings* 1993;**68**(1): 26–36.

Lunn 2012
Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. *Cochrane Database of Systematic Reviews* 2012, Issue 5. [DOI: 10.1002/ 14651858.CD002827.pub3]

Magy 2003
Magy L, Chassande B, Maisonobe T, Bouche P, Vallat J, Léger J. Polyneuropathy associated with IgG/IgA monoclonal gammopathy: a clinical and electrophysiological study of 15 cases. *European Journal of Neurology* 2003;**10** (6):677–85.

Mehndiratta 2004
Mehndiratta MM, Sen K, Tatke M, Bajaj BK. IgA monoclonal gammopathy of undetermined significance with peripheral neuropathy. *Journal of Neurological Sciences* 2004;**221**(1-2):99–104.

Merkies 2000
Merkies IS, Schmitz PI, van der Meche FG, van Doorn PA, for the European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Psychometric evaluation of a new sensory scale in immune-mediated neuropathies. *Neurology* 2000;**54**(4):943–9.

Merkies 2003a
Merkies I, Schmitz P, van der Meche F, Samijn J, van Doorn P, for the Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Psychometric evaluation of an overall disability scale in immune-mediated neuropathies. *Journal of Neurology, Neurosurgery & Psychiatry* 2003;**74**(1):99–104.

Merkies 2003b
Merkies IS, Schmitz PI, van der Meche FG, van Doorn PA. Comparison between impairment and disability scales in immune-mediated polyneuropathies. *Muscle & Nerve* 2003; **28**(1):93–100.

Merkies 2006
Merkies IS, Lauria G. 131st ENMC international workshop: selection of outcome measures for peripheral neuropathy clinical trials 10-12 December 2004, Narden, The Netherlands. *Neuromuscular Disorders* 2006;**16(2)**: 149–56.

Myeloma 2003
International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *British Journal of Haematology* 2003;**121**(5):749–57.

Nobile-Orazio 1992
Nobile-Orazio E, Barbieri S, Baldini L, Marmiroli P, Carpo M, Premoselli S, et al. Peripheral neuropathy in monoclonal gammopathy of undetermined significance: prevalence and immunopathogenic studies. *Acta Neurologica Scandinavica* 1992;**85**(6):383–90.

Nobile-Orazio 2002
Nobile-Orazio E, Casellato C, Di Troia A. Neuropathies associated with IgG and IgA monoclonal gammopathy. *Revue Neurologique* 2002;**158**(10 Pt 1):979–87.

Notermans 1994
Notermans NC, Wokke JHJ, Lokhorst HM, Franssen H, van der Graaf Y, Jennekens FG. Polyneuropathy associated with monoclonal gammopathy of undetermined significance. A prospective study of the prognostic value of clinical and laboratory abnormalities. *Brain* 1994;**117**(Pt 6):1385–93.

Notermans 1996a
Notermans NC, Wokke JHJ, van den Berg L, van der Graaf Y, Franssen H, Teunissen LL, et al. Chronic idiopathic axonal polyneuropathy. Comparison of patients with and without monoclonal gammopathy. *Brain* 1996;**119**(Pt 2): 421–7.

Notermans 2000
Notermans NC, Franssen H, Eurelings M, Van der Graaf Y, Wokke JH. Diagnostic criteria for demyelinating polyneuropathy associated with monoclonal gammopathy. *Muscle & Nerve* 2000;**23**(1):73–9.

Ponsford 2000
Ponsford S, Willison H, Veitch J, Morris R, Thomas PK. Long term clinical and neurophysiological follow up of patients with peripheral neuropathy associated with benign monoclonal gammopathy. *Muscle & Nerve* 2000;**23**(2): 150–2.

Ritzmann 1975
Ritzmann S, Loukas D, Sakai H, Daniels JC, Levin WC. Idiopathic (asymptomatic) monoclonal gammopathies. *Archives of Internal Medicine* 1975;**135**(1):95–106.

Saleun 1982
Saleun JP, Vicariot M, Deroff P, Morin J. Monoclonal gammopathies in the adult population of Finistere, France. *Journal of Clinical Pathology* 1982;**35**(1):63–8.

Saperstein 2001
Saperstein DS, Katz JS, Amato AA, Barohn RJ. Clinical spectrum of chronic acquired demyelinating polyneuropathies. *Muscle & Nerve* 2001;**24**(3):311–24.

Simmons 1993
Simmons Z, Albers JW, Bromberg MB, Feldman EL. Presentation and initial clinical course in patients with chronic inflammatory demyelinating polyradiculoneuropathy: comparison of patients without and with monoclonal gammopathy. *Neurology* 1993;**43** (11):2202–9.

Simmons 1995
Simmons Z, Albers JW, Bromberg MB, Feldman EL. Long term follow up of patients with chronic inflammatory demyelinating polyradiculoneuropathy, without and with monoclonal gammopathy. *Brain* 1995;**118**(Pt 2):359–68.

Stubbs 2003
Stubbs EB, Lawlor MW, Richards MP, Siddiqui K, Fisher MA, Bhoopalam N, et al. Anti-neurofilament antibodies in neuropathy with monoclonal gammopathy of undetermined significance produce experimental motor nerve conduction block. *Acta Neuropathologica* 2003;**105**(2):109–16.

Vallat 2000
Vallat J, Tabaraud F, Sindou P, Preux M, Van den Berghe A, Steck A. Myelin widenings and MGUS-IgA: an immunoelectronmicroscopic study. *Annals of Neurology* 2000;**47**(6):808–11.

Vital 2000
Vital A, Lagueny A, Julien J, Farrer X, Barat M, Hermosilla E, et al. Chronic inflammatory demyelinating polyneuropathy associated with dysglobulinaemia: a peripheral nerve biopsy study in 18 cases. *Acta Neuropathologica* 2000;**100**(1):63–8.

Vrethem 1993
Vrethem M, Cruz M, Wen-Xin H, Malm C, Holmgren H, Ernerudh J. Clinical, neurophysiological and immunological evidence of polyneuropathy in patients with monoclonal gammopathies. *Journal of the Neurological Sciences* 1993; **114**(2):193–9.

Vrethem 2010

Vrethem M, Reiser N, Lauermann C, Svanborg E. Polyneuropathy associated with IgM vs IgG monoclonal gammopathy: comparison between clinical and electrophysiological findings. *Acta Neurologica Scandinavica* 2010;**122**(1):52–57.

Yeung 1991

Yeung KB, Thomas PK, King RH, Waddy H, Will RG, Hughes RA, et al. The clinical spectrum of peripheral neuropathies associated with benign monoclonal IgM, IgG and IgA paraproteinaemia. Comparative clinical, immunological and nerve biopsy findings. *Journal of Neurology* 1991;**238**(7):383–91.

References to other published versions of this review

Allen 2005

Allen D, Lunn MPT, Niermeijer J, Nobile-Orazio E. Treatment for IgG and IgA paraproteinaemic neuropathy. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD005376]

Allen 2007

Allen D, Lunn MPT, Niermeijer J, Nobile-Orazio E. Treatment for IgG and IgA paraproteinaemic neuropathy. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD005376.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dyck 1991

Methods	Parallel group, randomised double-blind sham controlled trial, with subsequent open trial treatment for control participants
Participants	39 participants completed the trial. 18 of these had either IgA or IgG paraproteinaemic neuropathy and were stable or deteriorating at the time of enrolment. 8 had plasma exchange and 10 sham exchange
Interventions	Plasma exchange. 3.5 L exchange, twice weekly for 3 weeks. Total of 6 exchanges
Outcomes	Follow-up at 3 weeks. Outcomes were: Neuropathy Impairment Score, muscle weakness score, vibration detection threshold and summed neurophysiological scores of compound muscle action potentials, motor nerve conduction velocities and sensory nerve action potentials
Notes	Adverse events not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: patients were assigned... by restricted randomization
Allocation concealment (selection bias)	Low risk	Quote: the only investigators not blinded to treatment allocations were the patient coordinator, the biostatistician and the bloodbank consultant and personnel. The patient and the examining physician were unaware of the nature of the treatment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: a curtain separated the apheresis equipment from the patient. For sham exchange, blood was drawn, separated into cells and plasma...recombined, and reinfused
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: the only investigators not blinded to treatment allocations were the patient coordinator, the biostatistician and the bloodbank consultant and personnel. The patient and the examining physician were unaware of the nature of the treatment

Dyck 1991 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: one patient was found to have osteosclerotic myeloma and therefore the data on this patient were not used in the analysis. Neurophysiological data were provided for 8 out of 18 participants
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information on whether the selected outcome measures were predefined
Other bias	Low risk	Comment: none found

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Léger 1994	Uncontrolled open prospective trial of intravenous immunoglobulin, including 4 participants with IgG MGUS neuropathy. Diagnostic criteria unclear. No clear outcome criteria used
Notermans 1996	Uncontrolled open prospective trial of intermittent cyclophosphamide and prednisolone. 5 of the 16 participants included had IgG MGUS neuropathy
Notermans 1997	Uncontrolled open trial of pulsed high-dose dexamethasone. Only 1 had an IgG MGUS neuropathy
Sghirlanzoni 2000	Prospective uncontrolled, nonrandomised cohort study. A trial of 60 participants, included 9 with IgG MGUS neuropathy. Various immunosuppressant treatments included. Results for participants with IgG MGUS neuropathy not reported separately from those with an IgM MGUS neuropathy

MGUS: monoclonal gammopathy of uncertain significance

DATA AND ANALYSES

Comparison 1. Plasma exchange (PE) versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in Neuropathy Disability Score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Change in Neuropathy Disability Score (weakness)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Change in vibration detection threshold	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Change in summed compound muscle action potential (CMAP) (mV)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 Change in summed motor nerve conduction velocity (m/s)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

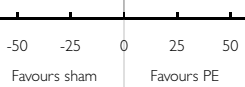
Analysis 1.1. Comparison 1 Plasma exchange (PE) versus control, Outcome 1 Change in Neuropathy Disability Score.

Review: Treatment for IgG and IgA paraproteinaemic neuropathy

Comparison: 1 Plasma exchange (PE) versus control

Outcome: 1 Change in Neuropathy Disability Score

Study or subgroup	PE N	Mean(SD)	Sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dyck 1991	8	20 (24)	10	2 (18)			18.00 [-2.03, 38.03]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							



Analysis 1.2. Comparison 1 Plasma exchange (PE) versus control, Outcome 2 Change in Neuropathy Disability Score (weakness).

Review: Treatment for IgG and IgA paraproteinaemic neuropathy

Comparison: 1 Plasma exchange (PE) versus control

Outcome: 2 Change in Neuropathy Disability Score (weakness)

Study or subgroup	PE N	Mean(SD)	Sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dyck 1991	8	17 (17)	10	1 (14)			16.00 [1.37, 30.63]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							

Analysis 1.3. Comparison 1 Plasma exchange (PE) versus control, Outcome 3 Change in vibration detection threshold.

Review: Treatment for IgG and IgA paraproteinaemic neuropathy

Comparison: 1 Plasma exchange (PE) versus control

Outcome: 3 Change in vibration detection threshold

Study or subgroup	Sham N	Mean(SD)	PE N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dyck 1991	10	0.1 (0.5)	7	0 (0.7)			0.10 [-0.50, 0.70]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							

Analysis 1.4. Comparison 1 Plasma exchange (PE) versus control, Outcome 4 Change in summed compound muscle action potential (CMAP) (mV).

Review: Treatment for IgG and IgA paraproteinaemic neuropathy

Comparison: 1 Plasma exchange (PE) versus control

Outcome: 4 Change in summed compound muscle action potential (CMAP) (mV)

Study or subgroup	PE N	Mean(SD)	Sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dyck 1991	5	0.4 (3)	9	-1.6 (2)			2.00 [-0.94, 4.94]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							

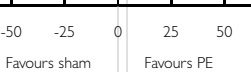
Analysis 1.5. Comparison 1 Plasma exchange (PE) versus control, Outcome 5 Change in summed motor nerve conduction velocity (m/s).

Review: Treatment for IgG and IgA paraproteinaemic neuropathy

Comparison: 1 Plasma exchange (PE) versus control

Outcome: 5 Change in summed motor nerve conduction velocity (m/s)

Study or subgroup	PE N	Mean(SD)	Sham N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dyck 1991	3	-2 (13)	5	-6 (8)			4.00 [-12.30, 20.30]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							



APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to January Week 2 2014>
Search Strategy:
---
1 randomized controlled trial.pt. (358644)
2 controlled clinical trial.pt. (86849)
3 randomized.ab. (259903)
4 placebo.ab. (140993)
5 drug therapy.fs. (1648210)
6 randomly.ab. (185772)
7 trial.ab. (267479)
8 groups.ab. (1200237)
9 or/1-8 (3085266)
10 exp animals/ not humans.sh. (3863199)
11 9 not 10 (2622734)
12 exp "Hereditary Motor and Sensory Neuropathies"/ (4894)
13 exp Peripheral Nervous System Diseases/ (111767)
14 peripheral nervous system disease$.tw. (113)
15 polyradiculoneuropath$.mp. (4855)
16 paraprotein$ peripheral neuropath$.mp. (3)
17 chronic demyelinat$ neuropath$.mp. (48)
18 chronic$ inflammatory demyelinat$ polyradiculoneuropath$.mp. (515)
19 exp Demyelinating Diseases/ (75068)
20 demyelinat$ disease$.tw. (4295)
21 or/12-20 (176286)
22 Monoclonal Gammopathies, Benign/ or exp Paraproteinemias/ or MGUS.mp. (40448)
23 exp Immunoglobulin A/ or exp Immunoglobulin G/ or exp PARAPROTEINS/ (142301)
24 Myelin-Associated Glycoprotein/ or MAG.mp. (3464)
25 or/22-24 (179430)
26 21 and 25 (6909)
27 ((IgG-MGUS or IgA-MGUS or IgA or IgG or Immunoglobulin G or Immunoglobulin A or paraprotein$ or monoclonal gammopath$ or MAG or (myelin and glycoprotein$)) and (((demyelinat$ or peripheral) and (nerv$ or neuro$)) or (radiculoneuropath$ or polyradiculoneuropath$ or polyneuropath$ or neuropath$))).mp. (5215)
28 26 or 27 (9782)
29 (intervention or treatment).mp. (3161497)
30 exp Therapeutics/ (3256670)
31 (rituximab or plasma exchange or plasmapheresis or fludarabine or azathioprine or cyclosporine or methotrexate or prednisolone).mp. (145508)
32 exp cyclophosphamide/ (46176)
33 exp dexamethasone/ (43145)
34 exp interferons/ (110039)
35 exp adrenal cortex hormones/ (329196)
36 (stem cell adj2 transplantation).mp. (55373)
37 (Intravenous adj2 immunoglobulin$).mp. (12461)
38 (ivig or interferon$1 or cyclophosphamide or dexamethasone or corticosteroid$).tw. (252798)
39 or/29-38 (5671547)
40 11 and 28 and 39 (1771)
41 40 not (ms or multiple sclerosis).mp. (1356)
42 remove duplicates from 41 (1343)

Appendix 2. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2014 Week 03>
Search Strategy:
---

1 crossover-procedure/ (39502)
2 double-blind procedure/ (119737)
3 randomized controlled trial/ (364698)
4 single-blind procedure/ (18828)
5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw. (1326805)
6 or/1-5 (1410344)
7 exp animals/ (19245302)
8 exp humans/ (15189009)
9 7 not (7 and 8) (4056293)
10 6 not 9 (1267260)
11 limit 10 to embase (980920)
12 Hereditary Motor Sensory Neuropathy/ (6413)
13 exp Peripheral Neuropathy/ (50281)
14 peripheral$ nervous$ system$ disease$.tw. (146)
15 polyradiculoneuropath$.tw. (1513)
16 paraprotein$ peripheral$ neuropath$.tw. (4)
17 chronic$ demyelinat$ neuropath$.tw. (65)
18 chronic$ inflammator$ demyelinat$ polyradiculoneuropath$.tw. (767)
19 exp Demyelinating Disease/ (103068)
20 demyelinat$ disease$.tw. (6174)
21 or/12-20 (158165)
22 Monoclonal immunoglobulinemia/ or exp Paraproteinemia/ or MGUS.tw. (90854)
23 exp Immunoglobulin A/ or exp Immunoglobulin G/ or exp PARAPROTEINS/ (138964)
24 Myelin-Associated Glycoprotein/ or MAG.tw. (4174)
25 or/22-24 (226681)
26 21 and 25 (8550)
27 ((IgG-MGUS or IgA-MGUS or IgA or IgG or Immunoglobulin G or Immunoglobulin A or paraprotein$ or monoclonal gammopath$ or MAG or (myelin and glycoprotein$)) and (((demyelinat$ or peripheral) and (nerv$ or neuro$)) or (radiculoneuropath$ or polyradiculoneuropath$ or polyneuropath$ or neuropath$))).tw. (5404)
28 26 or 27 (12332)
29 (intervention or treatment).tw. (3954612)
30 exp Therapy/ (5819757)
31 exp corticosteroids/ (682376)
32 Stem cell transplantation/ (28286)
33 (stem cell adj2 transplantation).tw. (38654)
34 ((Intravenous adj2 immunoglobulin$) or ivig or interferon$1 or corticosteroid$).tw. (250495)
35 (rituximab or plasma exchange or plasmapheresis or fludarabine or cyclophosphamide or azathioprine or cyclosporine or methotrexate or dexamethasone or prednisolone or immunotherapy or interferon).mp. (817582)
36 or/29-35 (8357448)
37 11 and 28 and 36 (590)
38 (ms or multiple sclerosis or optic neuritis or encephalomyelitis).ti. (75877)
39 multiple sclerosis/ or optic neuritis/ or encephalomyelitis/ (83685)
40 (international MS journal or MS forum or IM).jn. (241)
41 or/38-40 (110195)
42 37 not 41 (480)
43 remove duplicates from 42 (478)

Appendix 3. CENTRAL search strategy

#1 MeSH descriptor: [Hereditary Motor and Sensory Neuropathies] explode all trees
#2 MeSH descriptor: [Peripheral Nervous System Diseases] explode all trees
#3 (peripheral* next nervous* next system* next disease*)
#4 polyradiculoneuropath*
#5 paraprotein* next peripheral* next neuropath*
#6 chronic* next demyelinat* next neuropath*
#7 chronic* near (inflammator* next demyelinat* next polyradiculoneurop*)
#8 MeSH descriptor: [Demyelinating Diseases] explode all trees
#9 demyelinat* near disease*
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 MeSH descriptor: [Monoclonal Gammopathies, Benign] this term only
#12 MeSH descriptor: [Paraproteinemias] explode all trees
#13 MGUS
#14 MeSH descriptor: [Paraproteins] explode all trees
#15 MeSH descriptor: [Myelin-Associated Glycoprotein] this term only
#16 MAG
#17 #11 or #12 or #13 or #14 or #15 or #16
#18 #10 and #17
#19 IgG-MGUS or IgA-MGUS or paraprotein$ or monoclonal next gammopath$ or MAG or (myelin and glycoprotein*)
#20 (((demyelinat* or peripheral) and (nerv* or neuro*)) or (radiculoneuropath* or polyradiculoneuropath* or polyneuropath* or neuropath*))
#21 #19 and #20
#22 #18 or #21
#23 intervention or therap* or treatment*
#24 MeSH descriptor: [Therapeutics] explode all trees
#25 rituximab or plasma next exchange or plasmapheresis or fludarabine or interferon* or azathioprine or cyclosporine or methotrexate or prednisolone
#26 stem next cell near/2 transplantation
#27 Intravenous near/2 immunoglobulin
#28 ivig or interferon* or cyclophosphamide or corticosteroid:ti and ivig or interferon* or cyclophosphamide or corticosteroid:ab
#29 MeSH descriptor: [Cyclophosphamide] explode all trees
#30 MeSH descriptor: [Dexamethasone] explode all trees
#31 MeSH descriptor: [Interferons] explode all trees
#32 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#33 #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34 #22 and #33
#35 ("multiple sclerosis" or ms):ti
#36 ("international MS journal" or "MS forum"):so
#37 #35 or #36
#38 #34 not #37

Appendix 4. NMD Register (CRS) search strategy

#1 MeSH DESCRIPTOR Hereditary Sensory and Motor Neuropathy Explode All [REFERENCE] [STANDARD]
#2 MeSH DESCRIPTOR Peripheral Nervous System Diseases Explode All [REFERENCE] [STANDARD]
#3 "peripheral nervous system diseases" [REFERENCE] [STANDARD]
#4 polyradiculoneuropath* [REFERENCE] [STANDARD]
#5 paraprotein* NEAR/1 "peripheral neuropathy" [REFERENCE] [STANDARD]
#6 paraprotein* NEAR/1 "peripheral neuropathies" [REFERENCE] [STANDARD]
#7 "chronic demyelinating neuropathy" or "chronic demyelinating neuropathies" [REFERENCE] [STANDARD]
#8 "chronic inflammatory demyelinating polyradiculoneuropathy" or "chronic inflammatory demyelinating polyradiculoneuropathies" [REFERENCE] [STANDARD]
#9 MeSH DESCRIPTOR Demyelinating Diseases Explode All [REFERENCE] [STANDARD]
#10 "demyelinating disease" or "demyelinating diseases" [REFERENCE] [STANDARD]
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 [REFERENCE] [STANDARD]
#12 MeSH DESCRIPTOR Monoclonal Gammapathies, Benign [REFERENCE] [STANDARD]
#13 MeSH DESCRIPTOR Paraproteinemias Explode All [REFERENCE] [STANDARD]
#14 MeSH DESCRIPTOR Immunoglobulin A Explode All [REFERENCE] [STANDARD]
#15 MeSH DESCRIPTOR Immunoglobulin G Explode All [REFERENCE] [STANDARD]
#16 MeSH DESCRIPTOR Paraproteins Explode All [REFERENCE] [STANDARD]
#17 MeSH DESCRIPTOR Myelin-Associated Glycoprotein [REFERENCE] [STANDARD]
#18 MAG or MGUS [REFERENCE] [STANDARD]
#19 #12 or #13 or #14 or #15 or #16 or #17 or #18 [REFERENCE] [STANDARD]
#20 #11 and #19 [REFERENCE] [STANDARD]
#21 (IgG-MGUS or IgA-MGUS or IgA or IgG or "Immunoglobulin G" or "Immunoglobulin A" or paraprotein* or "monoclonal gammopathy" or MAG or (myelin and glycoprotein*)) and (((demyelinat* or peripheral) and (nerv* or neuro*)) or (radiculoneuropath* or polyradiculoneuropath* or polyneuropathy* or neuropath*)) [REFERENCE] [STANDARD]
#22 #20 or #21 [REFERENCE] [STANDARD]
#23 MeSH DESCRIPTOR Therapeutics Explode All [REFERENCE] [STANDARD]
#24 intervention or treatment [REFERENCE] [STANDARD]
#25 rituximab or" plasma exchange" or plasmapheresis or fludarabine or azathioprine or cyclosporine or methotrexate or prednisolone [REFERENCE] [STANDARD]
#26 MeSH DESCRIPTOR Cyclophosphamide Explode All [REFERENCE] [STANDARD]
#27 MeSH DESCRIPTOR Dexamethasone Explode All [REFERENCE] [STANDARD]
#28 MeSH DESCRIPTOR Interferons Explode All [REFERENCE] [STANDARD]
#29 MeSH DESCRIPTOR Adrenal Cortex Hormones Explode All [REFERENCE] [STANDARD]
#30 "stem cell" NEAR2 transplantation [REFERENCE] [STANDARD]
#31 Intravenous NEAR2 immunoglobulin or Intravenous NEAR2 immunoglobulins [REFERENCE] [STANDARD]
#32 ivig or interferon or interferons or cyclophosphamide or dexamethasone or corticosteroid* [REFERENCE] [STANDARD]
#33 #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 [REFERENCE] [STANDARD]
#34 #22 and #33 [REFERENCE] [STANDARD]
#35 (#22 and #33) AND (INREGISTER) [REFERENCE] [STANDARD]

WHAT'S NEW

Last assessed as up-to-date: 18 January 2014.

Date	Event	Description
9 April 2014	New citation required but conclusions have not changed	Abraham Stork joined the review team at this update. David Allen and Jikke-Mien Niermeijer withdrew
9 April 2014	New search has been performed	New searches run to January 2014. We identified no new trials. We revised the text throughout, assessed 'Risk of bias' according to current methodology and added a 'Summary of findings' table

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 1, 2007

Date	Event	Description
28 October 2008	Amended	Converted to new review format.
24 October 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

ACJS prepared the first draft of the background and protocol and prepared the data extraction form. EN-O, MPTL and NCN edited the draft and agreed the text.

ACJS and NCN independently identified potential randomised controlled trials from the register and searches. MPTL, ACJS and NCN independently assessed the identified trials, graded their risk of bias and performed independent data extraction.

ACJS prepared the draft of the results and the discussion. EN-O, MPTL and NCN edited the draft and agreed the text.

DECLARATIONS OF INTEREST

ACJS: no disclosures.

MPTL has received honoraria for consultation from Baxter Pharmaceuticals, CSL Behring and LfB and a travel support grant from Grifols, all manufacturers of IVIG. He was a blinded investigator in the study of Comi et al 2002.

EN-O reports personal compensation for serving in the Steering or Advisory Board of Baxter, Italy, CSL Behring, Italy, Kedrion, Italy, and Novartis, Switzerland. He received honoraria for lecturing from Baxter, Italy, CSL Behring, Italy, Grifols, Spain, and Kedrion, Italy and travel support for scientific meetings from Baxter, CSL and Kedrion. He was the principal investigator of a RCT comparing the efficacy of IVIg and intravenous methylprednisolone in a related condition, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), for which financial support was provided by Kedrion, Italy.

NCN: no disclosures.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review has a published protocol (Allen 2005). We assessed the included trial using the Cochrane 'Risk of bias' tool (Higgins 2011), which replaces the previous methodological assessment. We noted in the methods that for continuous outcomes we reported MD with 95% CI.

We included a 'Summary of findings' table at this update.

At this update, two authors withdrew (D Allen and J Niermeijer). Two new authors revised the review (ACJS and NCN).

INDEX TERMS

Medical Subject Headings (MeSH)

*Immunoglobulin A; *Immunoglobulin G; Monoclonal Gammopathy of Undetermined Significance [*therapy]; Peripheral Nervous System Diseases [*therapy]; Plasma Exchange

MeSH check words

Humans