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Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies.
Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD002827.
DOI: 10.1002/14651858.CD002827.pub4.

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[Intervention Review]

Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies

Michael PT Lunn[1], Eduardo Nobile-Orazio[2]

[1]Department of Neurology and MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, London, UK. [2]IRCCS Humanitas Clinical Institute, Neurology 2, Milan University, Milan, Italy

Contact address: Michael PT Lunn, Department of Neurology and MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK. michael.lunn@uclh.nhs.uk.

Editorial group: Cochrane Neuromuscular Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 10, 2016.
Review content assessed as up-to-date: 1 February 2016.

Citation: Lunn MPT, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No.: CD002827. DOI: 10.1002/14651858.CD002827.pub4.

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ABSTRACT

Background

Serum monoclonal anti-myelin-associated glycoprotein (anti-MAG) antibodies may be pathogenic in some people with immunoglobulin M (IgM) paraprotein and demyelinating neuropathy. Immunotherapies aimed at reducing the level of these antibodies might be expected to be beneficial. This is an update of a review first published in 2003 and previously updated in 2006 and 2012.

Objectives

To assess the effects of immunotherapy for IgM anti-MAG paraprotein-associated demyelinating peripheral neuropathy.

Search methods

On 1 February 2016 we searched the Cochrane Neuromuscular Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase for randomised controlled trials (RCTs). We also checked trials registers and bibliographies, and contacted authors and experts in the field.

Selection criteria

We included randomised controlled trials (RCTs) or quasi-RCTs involving participants of any age treated with any type of immunotherapy for anti-MAG antibody-associated demyelinating peripheral neuropathy with monoclonal gammopathy of undetermined significance and of any severity.

Our primary outcome measures were numbers of participants improved in disability assessed with either or both of the Neuropathy Impairment Scale (NIS) or the modified Rankin Scale (mRS) at six months after randomisation. Secondary outcome measures were: mean improvement in disability, assessed with either the NIS or the mRS, 12 months after randomisation; change in impairment as measured by improvement in the 10-metre walk time, change in a validated linear disability measure such as the Rasch-built Overall Disability Scale (R-ODS) at six and 12 months after randomisation, change in subjective clinical scores and electrophysiological parameters at six and 12 months after randomisation; change in serum IgM paraprotein concentration or anti-MAG antibody titre at six months after randomisation; and adverse effects of treatments.

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Data collection and analysis

We followed standard methodological procedures expected by Cochrane.

Main results

We identified eight eligible trials (236 participants), which tested intravenous immunoglobulin (IVIg), interferon alfa-2a, plasma exchange, cyclophosphamide and steroids, and rituximab. Two trials of IVIg (22 and 11 participants, including 20 with antibodies against MAG), had comparable interventions and outcomes, but both were short-term trials. We also included two trials of rituximab with comparable interventions and outcomes.

There were very few clinical or statistically significant benefits of the treatments used on the outcomes predefined for this review, but not all the predefined outcomes were used in every included trial and more responsive outcomes are being developed. A well-performed trial of IVIg, which was at low risk of bias, showed a statistical benefit in terms of improvement in mRS at two weeks and 10-metre walk time at four weeks, but these short-term outcomes are of questionable clinical significance. Cyclophosphamide failed to show any benefit in the single trial's primary outcome, and showed a barely significant benefit in the primary outcome specified here, but some toxic adverse events were identified.

Two trials of rituximab (80 participants) have been published, one of which (26 participants) was at high risk of bias. In the meta-analysis, although the data are of low quality, rituximab is beneficial in improving disability scales (Inflammatory Neuropathy Cause and Treatment (INCAT) improved at eight to 12 months (risk ratio (RR) 3.51, 95% confidence interval (CI) 1.30 to 9.45; 73 participants)) and significantly more participants improve in the global impression of change score (RR 1.86, 95% CI 1.27 to 2.71; 70 participants). Other measures did not improve significantly, but wide CIs do not preclude some effect. Reported adverse effects of rituximab were few, and mostly minor.

There were few serious adverse events in the other trials.

Authors' conclusions

There is inadequate reliable evidence from trials of immunotherapies in anti-MAG paraproteinaemic neuropathy to form an evidence base supporting any particular immunotherapy treatment. IVIg has a statistically but probably not clinically significant benefit in the short term. The meta-analysis of two trials of rituximab provides, however, low-quality evidence of a benefit from this agent. The conclusions of this meta-analysis await confirmation, as one of the two included studies is of very low quality. We require large well-designed randomised trials of at least 12 months' duration to assess existing or novel therapies, preferably employing unified, consistent, well-designed, responsive, and valid outcome measures.

PLAIN LANGUAGE SUMMARY

Immune treatments for peripheral neuropathy caused by an IgM paraprotein antibody, which may bind to MAG, a protein on the myelin sheath of nerves

Review question

What are the benefits and harms of immune treatments for peripheral neuropathy caused by an IgM paraprotein antibody that may bind to myelin-associated glycoprotein (MAG)?

Background

There are several types of antibodies in the human body. They are more or less specifically adapted to recognise a target, usually a 'foreign' protein such as a bit of a bacterium, virus or tumour. In some people too much of one type of antibody is made, called a paraprotein. Some of these paraproteins are of the IgM class (IgM antibodies are usually an 'early attack force' type of antibody). Some of these antibodies may react against myelin-associated glycoprotein, also known as MAG. MAG is a molecule on the insulating myelin sheath of nerves. The antibody probably results in damage to the nerve myelin to which it is bound and thus causes a specific type of damage to the nerves, known as a peripheral neuropathy. Anti-MAG paraprotein-associated peripheral neuropathy is a condition affecting more men than women, most commonly over the age of 60 years. It causes progressive sensory symptoms, unsteadiness and tremor, and sometimes some weakness of the feet and lower legs.

Treatments that act on the immune system such as plasma exchange (which removes circulating antibodies and replaces blood plasma with a clean plasma substitute), intravenous immunoglobulin (IVIg; antibodies that have been purified from donated blood), rituximab

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(which kills some of the cells that produce the antibody), corticosteroids, or anticancer drugs might be expected to reduce levels of these neuropathy-causing IgM antibodies and slow or prevent progression of the disease.

Study characteristics

Many of these therapies have been tried in non-randomised studies, but we found only eight small randomised controlled trials (RCTs), involving 236 participants, that met our criteria for inclusion.

Results and quality of the evidence

Two trials with 22 and 11 participants (20 with antibodies against MAG) suggest that IVIg may sometimes produce short-term measurable benefit and is relatively safe, but the benefit is of doubtful clinical significance. No severe adverse effects related to IVIg were reported in these trials. A trial of cyclophosphamide and corticosteroids showed some mild benefit. Two trials of rituximab demonstrated a positive benefit of rituximab, but this evidence was of low quality because of small numbers of participants and concerns about the design of one of the two studies. Reported adverse effects of rituximab were few, and mostly minor. Other trials did not allow us to draw conclusions about the efficacy of other agents and reported few serious adverse events. We need large, well-designed RCTs to assess the efficacy of the existing and new therapies, and better ways for doctors and researchers to detect changes that people report in response to treatments.

The evidence is up to date to February 2016.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Should rituximab versus placebo be used for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies?

Patient or population: people with IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies
Setting: hospital and outpatient treatment centres
Intervention: rituximab
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with rituximab				
Number of participants improved in disability Assessed with: INCAT score or INCAT Leg Disability Score Follow-up: range 8 to 12 months[1]	**Study population**		RR 3.51 (1.30 to 9.45)	73 (2 RCTs)	⊕⊕○○ **low**[2]	Statistically significant effect in meta-analysis
	74 per 1000	260 per 1000 (96 to 700)				
Mean improvement in disability Assessed with: INCAT score or INCAT leg disability score Scale from: 0 to 12 in INCAT and 0 to 7 in INCAT leg disability. Follow-up: range 8 to 12 months[1]	The mean improvement in INCAT score (see text) at 8 to 12 months was -0.18	The mean improvement in INCAT score (see text) at 8 to 12 months in the intervention group was 0.45 lower (0.85 lower to 0.05 lower)	-	73 (2 RCTs)	⊕⊕○○ **low**[2]	Statistically significant improvement versus placebo but probably less than MCID
Improvement in 10-metre walk time at 8 to 12 months[1]	The mean improvement in 10-metre walk time at 8 to 12 months was 0.14 seconds	The mean improvement in 10-metre walk time at 8 to 12 months in the intervention group was 0.35 seconds more (1.	-	68 (2 RCTs)	⊕⊕⊕○ **moderate**[4]	MCID for 10-metre walk approximately 0.4 seconds. Borders on clinically significant improvement, but wide CIs

		89 more to 1.19 less)				
Participant subjective impression of change stable or improved at 8 to 12 months Assessed with: VAS from: 0 to 10 Follow-up: mean 8 months[1]	**Study population**		RR 1.86 (1.27 to 2.71)	70 (2 RCTs)	⊕⊕○○ **low**[3]	Patient global impression of change improved similarly in both studies in a time-dependent manner (see data tables)
	447 per 1000	832 per 1000 (568 to 1000)				
Change in serum IgM paraprotein concentration 8 months after treatment[1]	The mean change in IgM level 8 months after treatment was 32.3 mg/L	The mean change in IgM level 8 months after treatment in the intervention group was 287.7 mg/L lower (328.98 lower to 244.42 lower)	-	26 (1 RCT)	⊕⊕⊕○ **moderate**[4]	An unsurprising reduction in IgM in the rituximab-treated group
Any adverse event	**Study population**		RR 1.18 (0.84 to 1.66)	80 (2 RCTs)	⊕○○○ **very low**[5]	No statistically significant difference in adverse effects. Serious adverse effects too few to make comment. Consistency of adverse event collection always suspect
	561 per 1000	662 per 1000 (471 to 931)				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IgM:** immunoglobulin M; **INCAT score:** Inflammatory Neuropathy Cause and Treatment score;**MCID:** minimum clinically important difference; **RR:** risk ratio; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1]The outcomes in the rituximab study were recorded at between 8 and 12 months, which is rational for the treatment of a disease with rituximab. Thus we have reported this interval for this intervention (see text).

[2]Downgraded twice for imprecision (small underpowered studies) and unresponsive outcome measures.

[3]Downgraded twice for imprecision (small underpowered studies) and indirectness (patient impression of change).

[4]Downgraded once for imprecision (small underpowered studies).

[5]Downgraded three times for imprecision (small studies and small even numbers), trial design and inconsistent adverse event recording.

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BACKGROUND

Up to 10% of people with a peripheral neuropathy which is not secondary to another primary illness have a paraprotein in the serum (Kelly 1981). A paraprotein is an abnormal protein produced by bone marrow cells and may belong to one of the three classes of immunoglobulin (Ig), IgG, IgA or IgM. The majority of paraproteins in people with peripheral neuropathy are IgM, produced by an initially benign condition of blood cells called monoclonal gammopathy of undetermined significance (MGUS). Of this group of paraproteins, 50% react with the CD57/HNK-1 carbohydrate epitope found on myelin-associated glycoprotein (MAG). This epitope is also found on other peripheral nerve myelin molecules (myelin protein zero, peripheral myelin protein 22, sulphated glucuronyl paragloboside (SGPG), sulphated glucuronyl lactosaminyl paragloboside (SGLPG) and others) but the antibodies are commonly referred to as anti-MAG.

Description of the condition

The clinical neuropathy associated with anti-MAG antibodies is usually relatively phenotypically homogeneous, and consists of a slowly progressive distal sensorimotor neuropathy with a variable degree of ataxia and prominent tremor (Chassande 1998; Smith 1983; Smith 1987; Yeung 1991). The neurophysiological features are demyelination, characteristically with more slowing of conduction in the distal than the proximal nerve segments (Kaku 1994). The term anti-MAG IgM paraproteinaemic demyelinating peripheral neuropathy (PDPN) is therefore sometimes used to refer to this condition.

Other antibody reactivities exist in people with neuropathy and an IgM paraprotein and they have tentatively been classified into small homogeneous groupings. Examples include motor neuropathies with anti-GM1 antibodies (Steck 1996), chronic sensory ataxic neuropathy associated with antibodies to GQ1b and other gangliosides with at least two sialic acid groups called CANOMAD (Willison 2001), and sensory demyelinating neuropathies with anti-sulfatide antibodies (Ferrari 1998). However, the most clearly described, relatively homogeneous group remains the neuropathy associated with IgM anti-MAG antibodies, the subject of this review.

Considerable evidence exists that anti-MAG antibodies are pathogenic. Deposits of the IgM paraprotein have been demonstrated in sural nerves of affected people (Takatsu 1985). The paraprotein is bound to myelin in a similar distribution to MAG. In some cases the binding has been associated with the deposition of activated complement components (Hays 1988; Monaco 1990). Demyelination has also been induced in some animal models by the passive transfer of anti-MAG antibodies (Tatum 1993; Willison 1988), and more recently by immunisation with SGPG (Ilyas 2008). People have been reported to respond to immunotherapies, the improvement sometimes correlating with a reduction in levels of IgM (Wilson 1999).

Description of the intervention

There are a number of possible therapies which have been described as effective in the treatment of anti-MAG paraproteinaemic neuropathy, including plasma exchange, corticosteroids, intravenous immunoglobulin (IVIg), cyclophosphamide, fludarabine and cytarabine, chlorambucil, alpha-interferon, rituximab or combinations of these agents. These are described below in the Results and Discussion sections.

Currently, treatment is largely decided on the informed choice of the individual. Many people are too old or too mildly affected to make the risks of treatment worthwhile. There are only eight randomised controlled trials (RCTs) testing the efficacy of the various immunosuppressive regimens in IgM paraproteinaemic neuropathies (Comi 2002; Dalakas 1996; Dalakas 2009; Dyck 1991; Léger 2013; Mariette 1997; Mariette 2000; Niermeijer 2007; Oksenhendler 1995). Most case series have been small, included diverse groups of participants and have not presented results of efficacy clearly.

How the intervention might work

Treatment strategies have either aimed to reduce the IgM paraprotein concentration, by removing the antibody or targeting the presumed monoclonal B-cell clone and reducing its production, or to interfere with the presumed effector mechanisms such as complement activation or macrophage recruitment.

OBJECTIVES

To assess the effects of immunotherapy for IgM anti-MAG paraprotein-associated demyelinating peripheral neuropathy.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs and quasi-RCTs using any immunotherapy in anti-MAG paraproteinaemic demyelinating peripheral neuropathy (PDPN).

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Types of participants

We included participants of any age with a diagnosis of MGUS, demyelinating neuropathy and anti-MAG antibodies. Other causes of peripheral neuropathy should have been ruled out.
Paraproteins were to be of the IgM class and shown to be reactive with MAG or SGPG by a validated method which could be:

- western blotting against human sciatic nerve homogenate;
- enzyme-linked immunosorbent assay (ELISA) for MAG or SGPG or SGLPG;
- complement fixation test against human sciatic nerve homogenate (confirmed by a second method);
- thin layer chromatographic immuno-overlay against SGPG or SGLPG.

As anti-MAG methods varied, we accepted positive anti-MAG results as reported by the trial authors and we did not define a threshold titre for positivity.
The neuropathy was to be typical distal symmetrical sensory or sensorimotor and should fit published criteria for slowing of motor nerve conduction in chronic inflammatory demyelinating polyradiculoneuropathy (Ad Hoc 1991 or Nicolas 2002), with or without prominent slowing in distal nerve segments. The occurrence of conduction block in this neuropathy is debated and was not an exclusion criterion.
We included studies that did not exactly fulfil these criteria, if necessary after consultation with the original study authors, provided the review authors agreed that IgM anti-MAG-associated demyelinating neuropathy was the preferred diagnosis. We noted any departure from the diagnostic criteria.

Types of interventions

We included any type of immunotherapy used for the treatment of IgM paraprotein-associated demyelinating peripheral neuropathy with anti-MAG antibodies. We considered the following therapies for inclusion: plasmapheresis or plasma exchange or selective apheresis, intravenous immunoglobulin (IVIg), corticosteroids (prednisolone, prednisone, methylprednisolone, dexamethasone), chlorambucil, cyclophosphamide, azathioprine, fludarabine,cladribine, interferon alfa-2a, adriamycin, melphalan, and monoclonal antibody-based therapies (for example, rituximab). We considered comparisons versus placebo, another treatment, or an alternative dosage or treatment protocol. Therapies could be administered using any protocol (for example, single agent, combined therapy or sequential administration). If the control arm received a co-intervention then the experimental arm had to also receive that same treatment.

Types of outcome measures

Primary outcomes

Predefined primary outcome measures were numbers of participants improved in disability at six months after randomisation assessed with either or both of:
(a) the Neuropathy Impairment Scale (NIS) (Dyck 1980; Dyck 2005) by at least 10% (maximum score 244);
(b) the modified Rankin Scale (mRS) (Bamford 1989) (scale 0 to 6).
We selected the NIS and mRS as primary outcome measures, as we considered them to be broad, commonly-used scores that were potentially easy to retrospectively derive from collected data. We predefined six months as the favoured time point for re-evaluation on the basis that IgM anti-MAG paraprotein-associated neuropathy is a chronic and slowly progressive disorder. A reduction in either score indicates improvement and as there is no published minimum clinically important difference for the NIS, we defined a 10% change as improvement.

Secondary outcomes

Secondary outcome measures were:

1. mean improvement in disability assessed with either the NIS or the mRS, or both, 12 months after randomisation;
2. change in impairment as measured by improvement in 10-metre walk time six and 12 months after randomisation (improvement is reduction in walk time);
3. change in a validated linear disability measure such as the Rasch-built Overall Disability Scale (R-ODS) at six and 12 months after randomisation;
4. change in subjective clinical scores at six and 12 months after randomisation;
5. change in electrophysiological measures:
   i) reappearance of sural sensory nerve action potentials (SNAPs) or compound muscle action potentials (CMAPs) in previously inexcitable nerves, or
   ii) electrophysiological change in at least two nerves (where improvement was defined as more than a 20% increase in motor or sensory nerve conduction velocities or more than a 20% decrease in motor distal latencies) compared to baseline at six and 12 months after randomisation;
6. change in serum IgM paraprotein concentration or anti-MAG titre (significant improvement defined as at least a 20% reduction in IgM or a 50% reduction of anti-MAG titre compared to baseline at six months after randomisation);
7. adverse effects from treatment during the trial period, graded as:
   - minor - not requiring action;
   - moderate - requiring alteration in dosage, drug regimen or other intervention; or
   - severe - requiring withdrawal from study or resulting in hospitalisation or death.

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Search methods for identification of studies

We searched the Cochrane Neuromuscular Specialised Register (1 February 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) (2016, Issue 1 in the Cochrane Library), MEDLINE (January 1966 to January 2016) and Embase (January 1980 to January 2016) for randomised controlled trials. We reviewed bibliographies to identify other controlled trials. We contacted trial authors and experts in the field to identify additional published or unpublished data.

We also searched ClinicalTrials.gov (ClinicalTrials.gov) and the World Health Organization International Clinical trials Registry Platform (ICTRP) (www.who.int/ictrp/en/), on 23 October 2014. The detailed search strategies are in the appendices: MEDLINE (Appendix 1), Embase (Appendix 2), CENTRAL (Appendix 3) and Cochrane Neuromuscular Specialised Register (Appendix 4). We searched clinical trials registries from within their search engines with the terms "myelin associated glycoprotein", "anti-MAG neuropathy" and "paraproteinaemic neuropathy" (Appendix 5).

Data collection and analysis

Selection of studies

Two review authors independently checked titles and abstracts identified from database searches and bibliographies. Both review authors obtained and assessed the full text of all potentially relevant studies. Both review authors decided which trials fitted the inclusion criteria, resolving disagreements about inclusion by discussion.

Data extraction and management

Both review authors independently performed data extraction onto a custom-designed data extraction sheet, cross-checked the data and resolved differences by discussion. We requested and obtained missing data from the trial authors whenever possible.

Assessment of risk of bias in included studies

The review authors assessed the risk of bias in included studies using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). They considered: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential sources of bias.

We graded these items as at low risk of bias, high risk of bias or unclear. Each review author graded the risk of bias independently; we then compared the results and reached agreement about differences by consensus.

Data synthesis

We pooled trial outcomes for interventions when possible. We calculated a weighted treatment effect across trials (using a fixed-effect model) with the Cochrane statistical package Review Manager 5 (RevMan 2014). We expressed results as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes, and mean differences (MDs) with 95% CIs for continuous outcomes. We tried to analyse all the primary and secondary outcomes under consideration. Because very little meta-analysis was possible, we did not perform sensitivity analysis. We did not plan any subgroup analyses.

'Summary of findings' tables

We included 'Summary of findings' tables where it was possible to populate these with meaningful data. Where possible, we reported all outcomes at six months after randomisation:

1. number of participants improved in disability assessed with either or both of the NIS and the mRS;
2. mean improvement in disability assessed with either the NIS or the mRS;
3. change in impairment as measured by improvement in 10-metre walk time;
4. change in subjective clinical scores (participant subjective impression of change stable or improved);
5. change in serum IgM paraprotein concentration; and
6. any adverse event.

RESULTS

Description of studies

Results of the search

Up to 2006, a search of the Cochrane Neuromuscular Specialised Register revealed 12 possible trials. Searching MEDLINE and Embase with the same strategy and handsearching bibliographies failed to reveal further trials. A further search to July 2009 for the update identified trials and papers as follows: CENTRAL: 4, MEDLINE: 679 (13 papers reviewed), and Embase: 212 (seven reviewed). Review of the full texts identified two new eligible studies (Dalakas 2009; Niermeijer 2007). A further search for the 2012 update identified the following numbers of papers: Cochrane Neuromuscular Specialised Register: 3, CENTRAL: 52, MEDLINE: 116, and Embase: 317, with no new trials identified. In 2015, searches identified the following numbers of papers: Cochrane Neuromuscular Specialised Register: 27 papers, CENTRAL: 76 papers, MEDLINE: 65 new papers (1035 total), Embase: 112 new

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papers (1645 total). A search of the Database of Abstracts of Reviews of Effectiveness (DARE) identified four papers and searches of ClinicalTrials.gov and ICTRP (www.who.int/ictrp/en/) identified three each (identified from the resources above).

Figure 1 presents a flow chart of the study selection process for this update.

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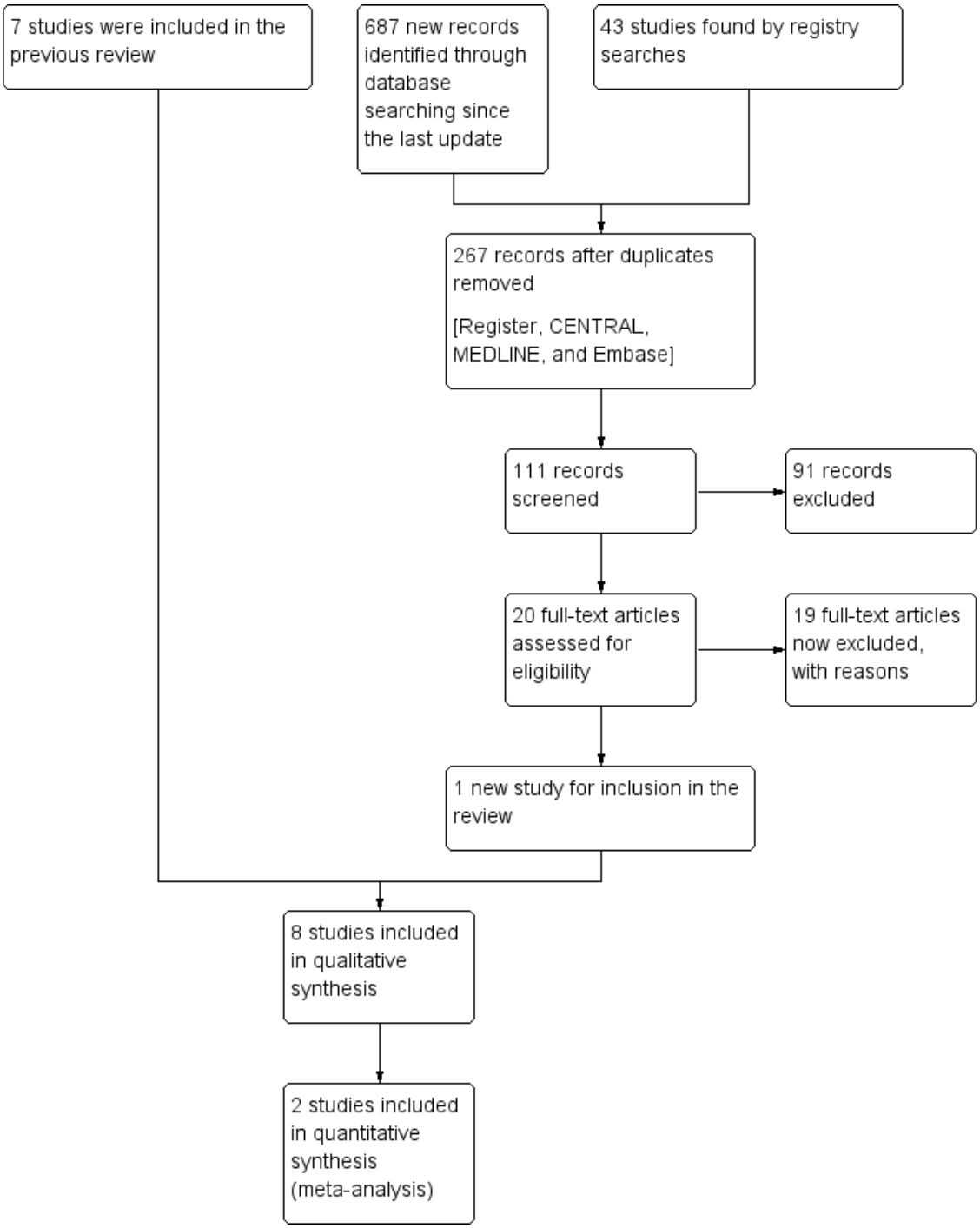
Figure 1. PRISMA chart for searched to included studies of IgM paraproteinaemic neuropathy



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Included studies

The eight included studies enrolled 236 participants (see Characteristics of included studies; Figure 1), of whom 104 were treated at some stage with the study intervention. In only three trials were all the predeclared inclusion criteria met (Comi 2002; Dalakas 2009; Niermeijer 2007). Three studies stated that the participants had benign monoclonal gammopathy or monoclonal gammopathy of undetermined significance (Comi 2002; Dalakas 2009; Niermeijer 2007). Other studies may have included participants with Waldenstrom's macroglobulinaemia (Mariette 1997; Mariette 2000; Oksenhendler 1995), or participants with other causes of neuropathy (Dalakas 1996). Three studies stated that all participants had a demyelinating neuropathy (Comi 2002; Dalakas 1996; Dalakas 2009), but only one of these stipulated the electrophysiological criteria for demyelination used (Comi 2002). All of the included participants had serum IgM anti-MAG activity tested but this was established by various methods of western blotting, immunofluorescence or anti-SGPG ELISA testing. In total, 194 of 236 participants had anti-MAG activity, and in four of eight studies all the participants in the study had anti-MAG activity (Dalakas 2009; Léger 2013; Mariette 1997; Mariette 2000). Niermeijer 2007 stated that numbers of participants were too small to establish an effect of anti-MAG antibodies and no original data were available to analyse the subgroup of anti-MAG participants in the other three studies.

The interventions and trial designs of the eight included studies were widely different. Two studies compared IVIg with placebo in a placebo-controlled cross-over design (Comi 2002; Dalakas 1996). Both of these studies included a one-month minimum washout period between the cross-over arms, considered rather short given the half-life of IgG, even though Comi 2002 gave a single dose of IVIg compared to the three monthly doses in Dalakas 1996. One study compared interferon alfa-2a with IVIg in an open-label design (Mariette 1997) and another with placebo in a double-blind design (Mariette 2000). One study compared chlorambucil alone with a combination of chlorambucil and plasma exchange (Oksenhendler 1995). The most recent trials studied the effect of cyclophosphamide and prednisolone (Niermeijer 2007), or rituximab (Dalakas 2009; Léger 2013). We included all eight studies, despite the lack of fulfilment of all inclusion criteria by five of them.

Excluded studies

We excluded 19 studies that had been considered at the title selection stage (see Excluded studies). Of these, we excluded one trial as serum IgM anti-MAG activity was not tested in the 21 participants with IgM-associated neuropathy and specific criteria for demyelinating neuropathies were not an entry criterion (Dyck 1991). We excluded two rituximab trials: as one (with seven participants) was open (Renaud 2003), the other (including nine participants) had a non-randomised control group and unblinded assessments (Pestronk 2003). Other reasons for excluding studies are shown in Characteristics of excluded studies.

Risk of bias in included studies

See Figure 2 for a summary of the review authors' 'Risk of bias' assessments for the included studies.

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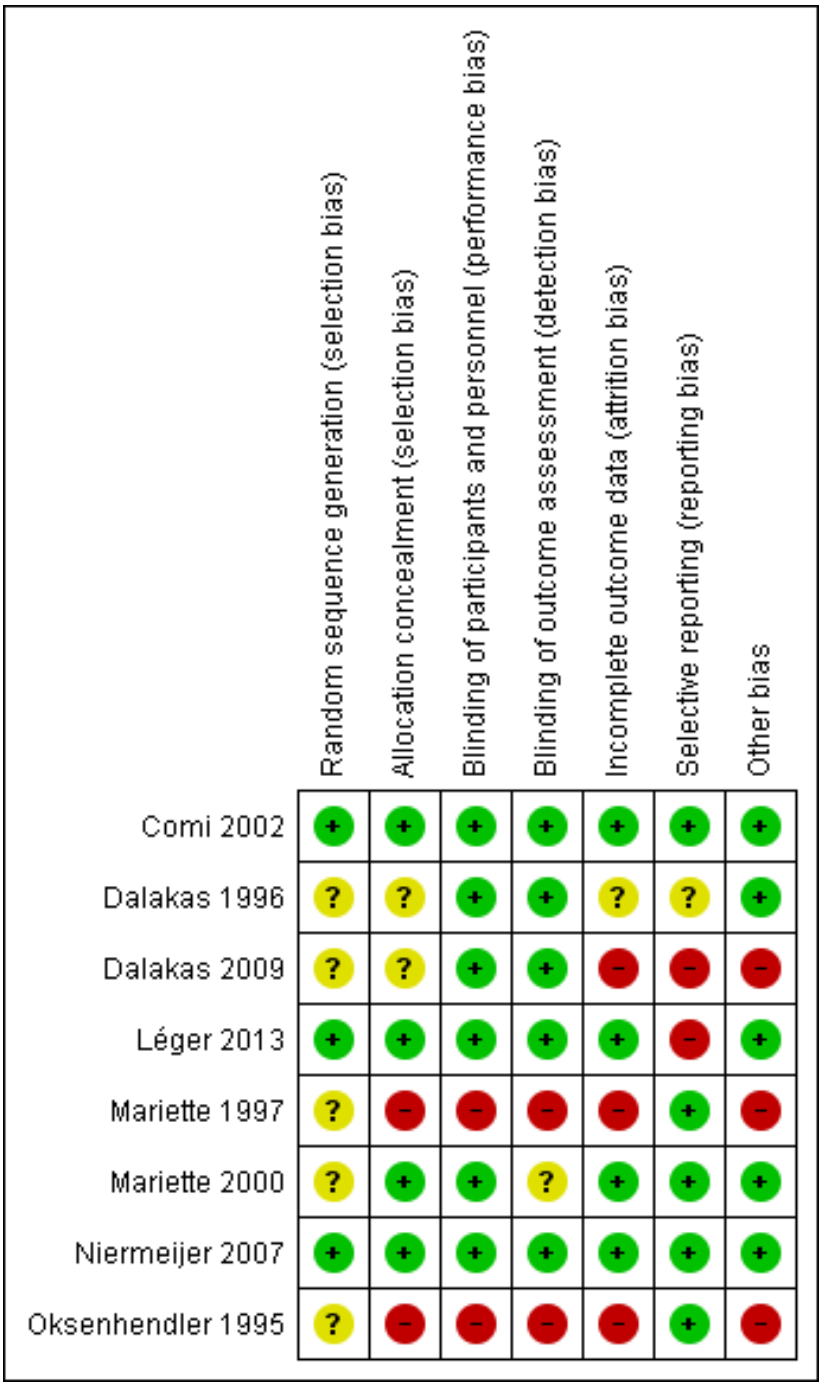
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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All the included trials had a randomised design and participants were randomly assigned to receive the intervention or control for the whole trial, or the first arm in cross-over studies (see Characteristics of included studies). All but one of the studies stipulated explicit diagnostic criteria (Dalakas 1996). Baseline characteristics were not significantly different in six of the studies, but in Dalakas 2009 the groups were very unbalanced with very few men in the rituximab-treated group at randomisation. Differences in baseline characteristics were also present in Dalakas 1996.

The trials of IVIg both had low risk of bias (Comi 2002; Dalakas 1996). In Dalakas 1996, the risk of bias was a little greater, as allocation concealment was unclear and the participants randomised to placebo were much older than in the IVIg arm, although this did not reach significance with the nine anti-MAG participants included. However, the sensory scores were significantly higher in the placebo group than the IVIg-treated group. Furthermore, this study did not state explicit diagnostic criteria. Both trials suffer from a short washout period and a potential carry-over effect, although this would be expected to reduce the significance of any therapeutic effect of IVIg.

Mariette et al studied interferon alfa-2a in two studies (Mariette 1997; Mariette 2000). The second study was blinded and controlled and at a much lower risk of bias than the preliminary randomised open trial. Four of 10 participants in the IVIg group in Mariette 1997 and three of 12 in the interferon group in Mariette 2000 dropped out early in the trial, which may confound results in these small groups.

Oksenhendler 1995 studied plasma exchange plus chlorambucil versus chlorambucil alone. As a result of the plasma exchange procedure, the blinding and allocation concealment were inadequate. Furthermore, although dropouts were balanced in the two groups (four of 22 in one group and four of 23 in the other), and the investigators performed an intention-to-treat analysis, the dropout numbers were deemed significant given the small number of included participants. Overall, we judged the risk of bias in this small study to be high.

The first published RCT of rituximab for paraproteinaemic demyelinating peripheral neuropathy (PDPN) was at high overall risk of bias (Dalakas 2009). The treatment groups at entry were unbalanced with respect to sex distribution (PDPN affects more men than women, but only two of 13 participants randomised to treatment were men). The randomisation method was not clear, and although the National Institutes of Health (NIH) pharmacy provided drug and placebo, it is not clear that the trial maintained allocation concealment. Most importantly, one participant was randomised and then removed from the trial having received rituximab and suffered an adverse event; this participant's data were not analysed. A further participant was removed at the analysis stage when it became clear the person did not fulfil the inclusion criteria; statistical analyses were done including and excluding this participant. We judged a second trial of rituximab to be at low risk of bias. The trial was entered in ClinicalTrials.gov, but the published protocol does not contain all outcomes presented in the trial report, which appear to have been added post protocol publication. To clarify the meta-analysis, we requested trial data from the authors of these two studies. Data were provided for Léger 2013. The authors of Dalakas 2009 were unable to provide any outcome data for their trial, which were lost with a retiring colleague.

We considered the study of cyclophosphamide and steroid to be at low risk of bias in all domains (Niermeijer 2007). We analysed the first six months of the trial, as after this point participants who experienced a clinical decline were rerandomised to treatment with a different corticosteroid or cyclophosphamide.

Effects of interventions

See: **Summary of findings for the main comparison** Rituximab versus placebo for treating IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathy

General comment

Two trials compared IVIg with placebo (Comi 2002; Dalakas 1996). Their designs differed in IVIg dose and outcome measures and neither provided six- or 12-month assessments.

Two trials tested rituximab in a very similar group of participants, using fairly similar outcomes. In Dalakas 2009, 26 participants were randomised to rituximab or a placebo infusion. There were concerns about the validity of the statistical manipulations used in this trial (see above and below) and corroborative data were not available. Léger 2013 also studied rituximab and randomised 54 participants to rituximab or placebo. The study produced similar results to Dalakas 2009 (see analysis below). The trial data were analysed at slightly different time points, but the review authors considered eight- and 12- month outcomes similar enough in this slowly changing disease.

The other four trials tested different interventions or combinations of treatment. Oksenhendler 1995 compared plasma exchange with no plasma exchange in participants receiving chlorambucil. Mariette et al compared IVIg with interferon alfa-2a (Mariette 1997), and, in a follow-up study, interferon alfa-2a with placebo (Mariette 2000). Niermeijer 2007 randomised participants to cyclophosphamide and prednisolone pulses or placebo in a six-month-long phase one of a 24-month trial. To satisfy ethical concerns, any participant who deteriorated in phase one was reassigned to cyclophosphamide and prednisolone (if they had received placebo in phase one) or dexamethasone (if they had received cyclophosphamide and prednisolone) (termed phase 2 of the study), making the 24-month outcomes difficult to assess. In phase two the placebo group was not truly randomised, as phase two contained only participants who had not improved on placebo, nine of 19

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participants having switched to active treatment in phase two. After discussion of the trial data released by the trial authors, we did not include six-month to 24-month outcomes in the analysis.
The primary and secondary outcome measures used in all these trials varied widely and those predefined for this review were rarely provided.

Intravenous immunoglobulin versus placebo

Investigated in Comi 2002 and Dalakas 1996. See 'Summary of findings' (Additional Table 1).

Primary outcome measures

One trial with 22 participants (Comi 2002), of IVIg versus placebo in IgM paraprotein-associated neuropathy used the modified Rankin Scale (mRS). However, this was a short trial and the investigators only measured the primary outcome at two and four weeks, not at six months. Eleven of 22 participants had anti-MAG antibodies but the data concerning the anti-MAG participant subgroup were not available. At two weeks, the mRS score showed a significant improvement with IVIg (-0.38, standard deviation (SD) 0.58) over placebo (+0.19, SD 0.51) at two weeks (P = 0.008), a difference that may not be clinically significant. No significant difference between the groups was present at four weeks.
The primary outcome of Comi 2002 was the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score at four weeks. This was not one of our prespecified outcome measures (see Discussion). After two weeks, the INCAT disability score did not change significantly; there was no difference between the groups and no evidence of a carry-over effect. After four weeks, the INCAT disability score decreased by a mean of 0.55 (SD 0.67) grades in the IVIg period (P = 0.001), with no significant change (mean 0.05 (SD 0.90)) in the placebo period. Only the mean difference (MD) between the treatment effects in the two four-week periods was significant (0.5 of a grade, 95% confidence interval (CI) 0.00 to 1.00).

Secondary outcome measures

The secondary outcomes at time points selected for this review were not available because the trials were both so short.
Related secondary outcomes were measured at different time points (two and four weeks) and the results were presented as MD between treatments.
a. One trial assessed the 10-metre walk (Comi 2002), but only at four weeks in the first arm of the study, as there was significant evidence of a carry-over effect into the second arm. There was a significant reduction in 10-metre walk time with IVIg compared with placebo in the whole IgM treatment group (MD 2.77 seconds, 95% CI 0.01 to 5.54). No data were available on the anti-MAG participants alone, but the trial authors state that MAG antibodies "did not influence the response to IVIg treatment".
b. Serum data: not enough information was available on anti-MAG titres or serum IgM concentrations in Dalakas 1996 to make a meaningful comment.
No 12-month outcomes were available.

Adverse events

Two studies compared IVIg and placebo (Comi 2002; Dalakas 1996), but data for the anti-MAG subgroup were not available. In Comi 2002, one participant had an aseptic meningitis and a rash after IVIg treatment. It is not clear whether she completed the three-month trial period. Two moderate adverse events occurred in the placebo treatment arm in Comi 2002, one retinal vein thrombosis and one episode of transient diplopia. In Dalakas 1996, no serious adverse events occurred as a result of IVIg infusion, but mild and transient effects were "more common in the IVIg than the placebo group". No further analysis was possible.
For adverse events of IVIg in the interferon alfa-2a versus IVIg trial (Mariette 1997), see below.

Interferon alfa-2a versus placebo or IVIg

Investigated in Mariette 1997 and Mariette 2000.

Primary outcome measures

The mRS was not assessed. The Neuropathy Impairment Scale (NIS) was the primary outcome in both studies involving interferon alfa-2a (referred to as the Clinical Neuropathy Disability Score (CNDS), a scale derived with minor modifications from the NIS, maximum score 93 (higher scores indicate greater disability)). In the initial randomised but open parallel-group study of interferon alfa-2a versus IVIg (Mariette 1997), participants in the IVIg group worsened by a mean of 2.3 (SD 7.6) points on the NIS at six months, and those in the interferon alfa-2a group improved by 7.5 (11.1) points, a MD of 9.80 (95% CI 1.46 to 18.14, n = 20) in favour of interferon alfa-2a (Analysis 1.1). However, Mariette 2000 (n = 24), a randomised and blinded trial of interferon alfa-2a versus placebo at low risk of bias, failed to confirm the beneficial effect of interferon alfa-2a in the primary outcome at six months (Analysis 2.1).

Secondary outcome measures

Neither trial assessed the 10-metre walk at any time point.
The two trials derived a subjective clinical score (Mariette 1997; Mariette 2000). In the unblinded 1997 study, the subjective scores improved significantly in favour of interferon alfa-2a over IVIg (MD 3.10, 95% CI 1.02 to 5.18, n = 20; Analysis 1.2). In the later blinded and reported 'negative' placebo-controlled study of

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interferon alfa-2a, the subjective scores were not presented in the published data.

The presence of sural sensory nerve action potentials (SNAPs) was examined at six months in both studies. The number of participants with detectable sural nerve SNAPs did not improve with either interferon alfa-2a or IVIg in the first study and exhibited "no significant improvement" in the second (data not presented). More participants had recordable median SNAPs after six months treatment with interferon alfa-2a (2/7 improved to 5/7) compared to IVIg (4/8 declined to 1/8) in the first study (Mariette 1997).

In Mariette 1997, IgM paraprotein bands and anti-MAG activity were still detectable at six months in all participants but only decreased significantly in two participants receiving interferon alfa-2a (50% reduction each). No 12-month outcome data for serum data were published.

Adverse events

In both interferon alfa-2a trials all included participants had anti-MAG serum activity (Mariette 1997; Mariette 2000). Interferon alfa-2a caused flu-like symptoms in all 10 participants in the open study (Mariette 1997), which were persistent and required tapering of the dose in three (moderate side effects). A further three participants required dose-tapering for systemic adverse effects (also moderate). One of 10 participants in the IVIg treatment group withdrew because of self-limiting erythroderma (Mariette 1997). No other mild or moderate side effects were reported with IVIg.

In the placebo-controlled, blinded study, two of 12 participants withdrew from the study because of side effects (severe), one with diarrhoea and one with flu-like symptoms (Mariette 2000). One participant withdrew with worsening of neuropathy. There were no other severe side effects reported for interferon alfa-2a.

Chlorambucil and plasma exchange versus chlorambucil alone

Investigated in Oksenhendler 1995.

Primary outcome measures

In a comparison of chlorambucil and plasma exchange versus chlorambucil alone in IgM paraprotein-associated neuropathy, the NIS at four months showed no statistically significant difference in outcome (Oksenhendler 1995). The trialists assessed neither the NIS nor the mRS at the six-month time point specified for this review. Data were not available for the anti-MAG subgroup alone, as participants with anti-MAG activity were not differentiated from those without.

Secondary outcome measures

The change in NIS at 12 months was no different between the plasma exchange plus chlorambucil and the chlorambucil-alone groups.

The 10-metre walk time was not recorded at six months.

A subjective clinical score was not recorded at six months. There was "no difference" in the subjective clinical score at 12 months between the groups.

SNAPs were not recorded at six months.

IgM paraprotein concentrations and anti-MAG (anti-myelin IgM) titres were determined prior to entry but no results were given for later time points other than a comment in the paper that the response was not associated with a significant decrease in the serum IgM concentration.

Adverse events

In Oksenhendler 1995, there were no serious adverse events from plasma exchange, but side effects of chlorambucil were common. Ten of the 44 participants required temporary suspension or tapering of the chlorambucil dosage because of haematotoxicity, but none had to cease treatment.

Rituximab versus placebo

In 2012 only one study had been published using rituximab as an intervention for paraproteinaemic neuropathy that fulfilled our inclusion criteria (Dalakas 2009). A second study called RiMAG has now been published and we include it here (Léger 2013). See Summary of findings for the main comparison.

Dalakas 2009 randomised 26 participants to receive either rituximab or placebo at a standard dose of four infusions of 375 mg/m^2 every week for four weeks. Outcomes were measured at eight months (which for the purposes of this review we have used as six-month outcomes). One randomised participant had a severe anaphylactic adverse event with the first infusion of the drug. The participant was replaced and not included in any further analysis. One further participant randomised to rituximab and treated in accord with the protocol was found to have had an INCAT leg score at entry of zero (inadvertently assigned as 1 at entry). He could not therefore have improved. We have performed the analysis here with the participant included as in the protocol for this review.

Some discrepancies exist in the results in the published paper (see below) (Dalakas 2009). These were resolved through enquiry with the trial author. Original trial data were not made available in 2012 and further requests in 2014 and 2015 were not fruitful. Trial data were "entered directly by the statistician who retired more than 10 years ago" and he was untraceable.

Léger 2013 randomised 54 participants to receive either rituximab in a standard 375 mg/m^2 dose or placebo. Outcomes were measured at 0 and 12 months, but upon request, the trial authors also made nine-month data available for the INCAT scale, change

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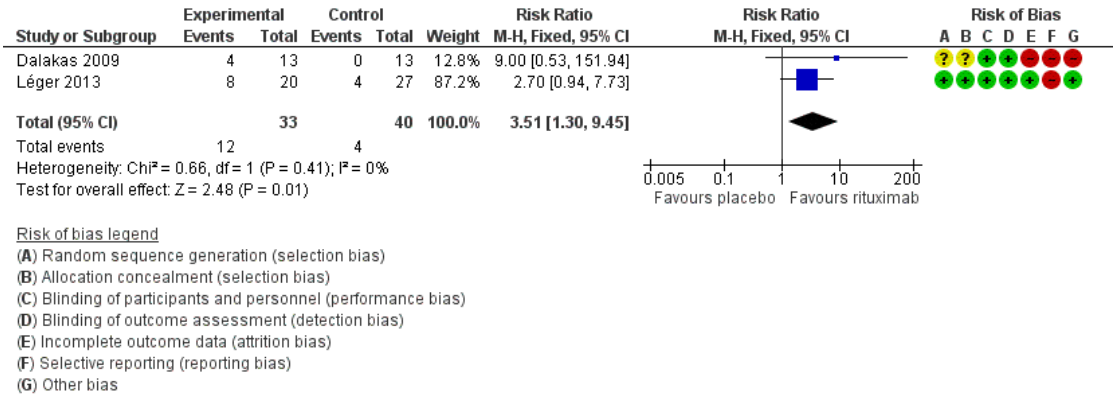
in INCAT scale and IgM levels, to correspond to outcomes of Dalakas 2009. We requested data for the leg subscale of the INCAT score but these were not available. The outcomes in the published and amended ClinicalTrials.gov protocol are limited and do not fully correspond to the outcomes in the methods section of the published paper (which are those with results). There is no suggestion of suppression of negative outcome data or selective reporting, but these outcomes could have been decided post hoc.

Primary outcome measures

These two studies included neither the NIS nor the mRS as outcomes. The INCAT leg score reported in Dalakas 2009 corresponds broadly to the mRS and thus we used this in our analysis both as a continuous and a dichotomous outcome. For the dichotomous improvement we have compared the leg score at eight months from Dalakas 2009 with the dichotomous complete INCAT score at 12 months from Léger 2013 (Analysis 3.1; Figure 3). The RR for improvement was 3.51, 95% CI 1.30 to 9.45 (I^2 = 0%, 73 participants). We will perform a six-month meta-analysis if other studies become available. Using the published eight-month data from Dalakas 2009 and 12-month data from Léger 2013, the mean improvement in the INCAT leg disability score (MD -0.45, 95% CI -0.85 to -0.05; I^2 = 0%) was statistically significant, whether the INCAT 0-score participant from Dalakas 2009 was included in the analysis or not (Summary of findings for the main comparison; Analysis 3.2). Participant-level data obtained for nine-month improvement from Léger 2013 (not published), which are at a more comparable time point to Dalakas 2009, give a MD of -0.33, 95% CI -0.73 to 0.07 (I^2 = 0%, 70 participants) in the same direction as the longer time point but including the possibility of no effect (Analysis 3.3).

Figure 3. Forest plot of comparison: 3 Rituximab versus placebo, outcome: 3.1 Number of participants improved on INCAT score (see text) at 8-12 months.



(Note: in the published paper of Dalakas 2009 there is a discrepancy between the data for the INCAT leg score in the text and in the published table. We checked the data with the trial authors who gave verbal clarification and we included the correct figures. No recorded trial data were made available.)

Secondary outcome measures

Secondary outcomes that we could include in our analyses were the 10-metre walk time, the change in IgM levels, and anti-MAG titre, but these were all measured at eight months in Dalakas 2009 and at 12 months in Léger 2013. Nine-month data were not available for Léger 2013 except for the IgM levels.

The 10-metre walk times did not improve significantly, either in terms of time to walk (MD -0.35 seconds, 95% CI -1.89 to 1.19; I^2 = 0%, 68 participants) or numbers of participants improved (RR 1.80, 95% CI 0.83 to 3.92; 26 participants; Dalakas 2009 only - data from Léger requested; Analysis 3.5; Analysis 3.6). As might be expected, there was a measurable and significant decrease in the level of serum IgM eight months after rituximab (reduction of 286 mg/dL, 95% CI 329 to 244; 26 participants; Analysis 3.7). Less expected (from reports of other studies of treatment of anti-MAG neuropathy) but not surprising was a decrease in the titre of anti-MAG activity of -17.79 units/mL (95% CI -33.33 to -2.25; Analysis 3.8; I^2 = 0%, 71 participants).

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Outcome measures not prespecified in this protocol

Both studies included participant "clinical assessments and questionnaires" (not further described). The RR for "stable or improved" at eight to 12 months was 1.86 (95% CI 1.27 to 2.71; I^2 = 0%, 70 participants) in favour of rituximab (Analysis 3.9). For participants "improved" only at eight to 12 months, the RR was 9.67 with a wide CI (95% CI 1.84 to 50.85; I^2 = 0%, 70 participants) albeit statistically significant (Analysis 3.10). Léger 2013 presented results for the Short Form 36 Health Survey (SF36) with a MD improvement of 15.50 (95% CI 5.24 to 25.76; 37 participants) in the physical subscores (Analysis 3.11) but no statistically significant change in the mental subscores (MD 6.60, 95% CI -0.35 to 13.55; 41 participants; Analysis 3.12). These assessments were not prespecified as primary or secondary outcomes.

Adverse events

There were not significantly more adverse events in the rituximab group (RR 1.18, 95% CI 0.84 to 1.66; I^2 = 0%, 80 participants; Analysis 3.13). Most adverse events were minor, including mild temperature increases and chills, headaches and mild hypotension, nausea, vomiting, dizziness and lightheadedness, and rash. One severe adverse event of bronchospasm led to the participant being removed from Dalakas 2009, despite receiving the drug; his data were not included in the published results. In Léger 2013, one participant with rituximab was withdrawn from the study after developing a bradycardia. The RR for severe adverse events was 3.11 (95% CI 0.34 to 28.54; I^2 = 0%, 80 participants; Analysis 3.14), but this figure should be interpreted with caution, given the small number of participants and single-integer events.

Cyclophosphamide and prednisolone combination versus placebo

The only trial to use this combination as an intervention was Niermeijer 2007. See 'Summary of findings' Additional Table 2. Values for outcomes in this study were presented as means and 95% CIs. We calculated SDs from the 95% CIs.

The trial authors made original trial data available and we considered whether to carry out further statistical analysis to use the data after six months from phase two (see Effects of interventions above). However, after discussion we did not consider the data to be valid, as the re-allocation of participants was not truly random and the results would therefore be significantly biased.

Primary outcome measures

The mRS at six months was included as one of the outcomes of phase one of this trial, the only disability data that could be included in this review. At six months a (barely) significant improvement in the mean mRS was present, with a MD of -0.31 points (95% CI -0.61 to -0.01; 34 participants; Analysis 4.1), with no significant difference in the number of participants improved at six months when we extracted the dichotomous data from the dataset provided by the authors (3/16 improved with cyclophosphamide and prednisolone combination versus 1/19 with placebo, RR 3.56, 95% CI 0.41 to 30.99; 35 participants; Analysis 4.2.

Secondary outcome measures

The authors of this trial used the Rivermead Mobility Index (RMI) as their primary outcome measure. We included the RMI as a secondary outcome under subjective clinical scores. No significant improvement in the RMI was present after six months of cyclophosphamide and prednisolone (MD 0.42, 95% CI -0.41 to 1.25; 34 participants; Analysis 4.3).

Adverse events

Adverse events were not specifically sought in this trial. One participant receiving cyclophosphamide withdrew because of angina and was lost to follow-up, and one participant withdrew because of rapid progression of neuropathy. A further participant, who was also cyclophosphamide-treated, withdrew during the seven-month to 12-month phase. The trialists reported that nausea was significantly more common in the cyclophosphamide-treated group (P = 0.001), but provided no further details.

Three of 35 participants (8.6%) who had received cyclophosphamide developed an immunocytoma not requiring further treatment at five years of follow-up.

DISCUSSION

Randomised controlled trials (RCTs)

We identified eight RCTs for this update. Four fulfilled all our strict predefined inclusion criteria (Comi 2002; Dalakas 2009; Léger 2013; Niermeijer 2007). The trials of Comi, Leger and Niermeijer had a low risk of bias, whereas Dalakas 2009 had a high risk of bias in multiple domains (Figure 2). We included the four other RCTs that did not fulfil all the inclusion criteria, because their inclusion criteria closely approximated to those intended.

According to evidence from two trials, IVIg may produce some short-term benefit in the treatment of anti-MAG IgM paraproteinaemic neuropathy. One double-blind, placebo-controlled study with minimal bias showed benefit of IVIg at four weeks in one of the primary outcome measures (mRS) and the 10-metre walk time secondary outcome measure but no other significant outcomes (Comi 2002). The outcomes were available only at four weeks and were not available for the predefined endpoints of six and 12 months; it is not clear whether any short-term benefit would be sustained or whether IVIg is clinically useful. Furthermore, this trial was of IgM paraproteinaemic neuropathy and not

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all the included participants had associated anti-MAG activity. Evidence for any benefit from IVIg should be regarded with caution. Two trials with interferon alfa-2a gave contradictory results. Interferon alfa-2a appeared to be of benefit in treating anti-MAG neuropathy when tested in an open trial with IVIg (Mariette 1997). Because this trial was not blinded it was at high risk of bias. The later, less biased, double-blind, placebo-controlled study of interferon alfa-2a did not demonstrate any significant benefit from interferon alfa-2a (Mariette 2000).

A single trial assessed the use of plasma exchange as additional treatment to chlorambucil (Oksenhendler 1995). No additional benefit was gained from the addition of plasma exchange in the predefined outcome measures at four or 12 months. This relatively large study lacked blinding and allocation concealment, and the results should therefore be interpreted with caution. Since the trial showed no additional benefit from plasma exchange, any possible bias did not lead to a significant result.

A number of case reports and small case series have described use of rituximab for the treatment of paraproteinaemic neuropathy (Barohn 2005; Benedetti 2005; Benedetti 2007; Benedetti 2008; Canavan 2002; Delmont 2010; Goldfarb 2005; Gono 2006; Gorson 2007; Kelly 2006; Kilidireas 2006; Latov 1999; Levine 1999; Pestronk 2003; Renaud 2003; Renaud 2006; Weide 2000; Niermeijer 2009). The results were varied, with most reporting positive outcomes in the majority of participants but some very usefully reporting no response in all their reported cases (Barohn 2005; Rojas-García 2003), and some reporting deteriorations (Broglio 2005; Gironi 2006; Noronha 2006). We included the first rituximab RCT in the 2012 update (Dalakas 2009), and we now include a further RCT (Léger 2013). Dalakas 2009 had a high risk of bias in two assessed domains and unclear risks in three others of the six assessed. As such, we assessed the evidence from this trial as very low quality across the outcomes stipulated. The results should therefore be regarded with caution. With the removal of a participant from the analysis who should perhaps not have been randomised, the trial reported improvements in the INCAT leg score and the 10-metre walk time, and in the whole group, the IgM levels and anti-MAG titres. The study reported seven of 13 rituximab-treated participants compared to none of the 13 participants in the placebo group experiencing improvement in "patient clinical assessments and questionnaires". In our analysis, although there was a trend in favour of the treatment group in all analyses, none of the clinical outcomes were statistically significantly different from placebo. However, rituximab did reduce IgM levels and anti-MAG titres, as would be expected. The interpretation of the results in the original paper by the trial authors concludes that "The results warrant confirmation with a larger trial". We have now added the data from the larger and less biased Léger 2013 to the meta-analysis. Léger 2013 was reported as demonstrating no change in its primary and secondary outcomes. However, the outcome changes, where they are comparable, are all in a similar direction and of similar magnitude to those of Dalakas 2009 (I^2 = 0% throughout). In meta-analysis, comparing rituximab to placebo, significant improvements are seen in numbers of participants improved on the INCAT score (although the magnitude of this does not reach clinical significance), the biological parameters (IgM, anti-MAG titres), the physical subscores of the SF36 (but not the mental), and perhaps importantly the patient clinical impression of change scores, both for improvement alone and stabilisation and improvement. The numbers of participants are small but the results demonstrate no heterogeneity. The results of Léger 2013 are more robust, at less risk of bias and more reliable, and support an effect of rituximab in stabilising or improving anti-MAG neuropathy.

Niermeijer 2007 trialed cyclophosphamide and corticosteroids (CP) in combination, versus placebo. Ethical concerns led to modification of the protocol such that we could not use the data after the sixth month in the meta-analysis. We found no significant improvements in the functional scales used (mRS and RMI), as displayed here, from moderate-quality evidence. The trial reports significant improvements in validated impairment measures of strength and sensory dysfunction (not predefined outcomes in this meta-analysis), which did not translate into functional benefits.

This review has identified many problems with the trials of treatment for this indication, including variations in trial design, participant inclusion and exclusion criteria, analysis points, and outcome measures. Only six of the eight trials were blinded. Some trials employed a cross-over design, which must be allowed for in analysis. In one study an alteration in the trial design for ethical reasons meant that data beyond the six-month time point were not usable in this analysis (Niermeijer 2007). Most studies did not use validated clinical and disability scales that are likely to detect changes (for example, the INCAT Sensory Sum Score (Merkies 2000)) and these should be considered in future studies. Further, more sensitive scales measuring both disability and specific domains of impairment that are affected in this predominantly sensory neuropathy are being developed. Although Comi 2002 was possibly too short to detect meaningful changes, it did include validated, clinically useful, and reproducible endpoints such as the sensory sum score, 10-metre walking time, nine-hole peg test, the Rotterdam Scale (a handicap score), and the SF36 quality-of-life scale. Dalakas 2009 also used more up-to-date outcomes, although the trial was probably too small to detect significant change, and bias makes the results unreliable. Further work is ongoing to develop valid disability measures (see for example the PeriNomS project). Objective endpoints such as presence of SNAPs were infrequently used, but in clinical practice these seldom change in the short to medium term. No study has included a measure of fatigue (Merkies 1999), which is prevalent in chronic inflammatory demyelinating polyradiculoneuropathy but has not been investigated in anti-MAG neuropathy. Furthermore, effective treatments, if identified, are likely to be expensive and possibly invasive, and investigators should therefore consider measures of quality of

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life and cost effectiveness in all trials.

Only four trials confined recruitment to participants with anti-MAG antibodies (Dalakas 2009; Léger 2013; Mariette 1997; Mariette 2000). The anti-MAG neuropathies constitute the majority of the IgM paraproteinaemic demyelinating neuropathies in terms of immunoreactivity. They are relatively homogeneous in their clinical features and are distinct from some other rare but identified subgroups (for example, those with IgM anti-GM1/GD1b reactivity). Many IgM paraproteinaemic neuropathies have no identified antigen target and yet are not clinically very different from those with anti-MAG antibodies. This is often used as an argument that anti-MAG antibodies are not relevant in the pathogenesis. Although this may be the case, there is a considerable body of evidence in favour of anti-MAG antibodies causing demyelination, as described in the Background. Lack of anti-MAG antibodies may simply reflect low detection through inadequate immunological identification, or alternative antigenic targets yet to be described. Subgroup analysis by anti-MAG activity should be reported in future trials.

Cochrane is increasingly concerned about the quality of data supplied for systematic reviews from original trials where a number of instances of fraudulent publishing have been uncovered. Any future trials in the area should eradicate the need for suspicion about the data published, by publishing, in full, the trial protocol on a clinical trials website, making minimal change (but being transparent with the change if required), publishing all the predefined outcomes for all trials, and making the data available for scrutiny.

Non-randomised studies

As part of our systematic search of the literature for RCTs, we identified many case reports and small non-randomised case series. These included all the therapies covered in the RCTs above, as well as other therapies not subjected to RCTs. These are documented in Table 3 but this should not be regarded as a systematic presentation of the non-randomised literature.

Plasma exchange and apheresis

Dyck 1991 compared plasma exchange to sham exchange in a parallel-group RCT with 39 participants, 21 of whom had an IgM paraprotein. We excluded this study, as there were no criteria specified for demyelination and the anti-MAG status was not clear. Dyck 1991 found a significant improvement in the weakness component of the Neuropathy Disability Score (now known as the Neuropathy Impairment Score) in favour of plasma exchange in the IgG and IgA, but not the IgM subgroups. Functional changes were not reported. In eight case series of plasma exchange as monotherapy, improvement was reported in 24 of 48 cases of IgM paraprotein-associated neuropathy (Ellie 1996; Ernerudh 1986; Ernerudh 1992; Frayne 1985; Gorson 1997; Gorson 2001; Haas 1988; Hafler 1986; Latov 1988; Nobile-Orazio 2000; Smith 1987) (see Table 3). When described, the improvement was sustained at between eight and 36 months. Siciliano 1994 reported benefit in one person with an IgM paraprotein treated with selective apheresis, and Niemierko 1999 reported another. Improvement with plasma exchange in combination with either pulsed intravenous cyclophosphamide, chlorambucil, protein A immunoadsorption, melphalan or adriamycin, with or without steroid, has been reported in 25% to 100% of participants, all in small studies (one to eight participants per treatment group) with follow-up periods ranging from two to 34 months (Bland 1985; Blume 1995; Dubas 1987; Gorson 2001; Kelly 1988; Latov 1980; Latov 1988; Meier 1984; Nobile-Orazio 2000; Oksenhendler 1995; Rudnicki 1998; Sherman 1984; Smith 1987; Stefansson 1983; Tagawa 2001).

Corticosteroids

Less information is available regarding response to steroid therapy. Four of five people treated with pulsed high-dose intravenous dexamethasone improved, but the incidence of psychiatric side effects (three of six, one with IgG MGUS) was unacceptably high (Notermans 1997). Oral prednisolone alone objectively improved only three of 30 people treated with monotherapy (Cook 1990; Dalakas 1981; Donofrio 1989; Ernerudh 1992; Gorson 1997; Gorson 2001; Hafler 1986; Latov 1988; Melmed 1983; Nobile-Orazio 2000). Corticoteroids have been used in combination with azathioprine, cyclophosphamide, chlorambucil, and plasma exchange in several small studies, with improvement or stabilisation in 0% to 100% of participants at 14 to 54 months follow-up (Dalakas 1981; Donofrio 1989; Ellie 1996; Ernerudh 1992; Kelly 1988; Latov 1988; Melmed 1983; Niermeijer 2007; Nobile-Orazio 1988; Nobile-Orazio 2000; Notermans 1996; Stefansson 1983).

Intravenous immunoglobulin

We have described the two RCTs of intravenous immunoglobulin (IVIg) versus placebo above (Comi 2002: Dalakas 1996), which provide low-quality evidence for very short-term improvement. Six other uncontrolled studies reported transient improvement, in 22 of 50 participants, with IVIg (Cook 1990; Ellie 1996; Gorson 1997; Gorson 2001; Hoang-Xuan 1993; Léger 1994), whereas another did not report improvement (Nobile-Orazio 2000).

Interferon alfa-2a

A well-performed randomised, double-blind, placebo-controlled study of 24 people (Mariette 2000) confirmed the efficacy of interferon alfa-2a as suggested by an earlier open study (see above). One of eight people treated with interferon alfa-2a in a study by Gorson et al improved (Gorson 2001). This participant remained stable (mild bilateral foot drop and pinprick and vibration loss in the feet, mRS 1) off all therapy for three years. Furthermore, the IgM paraprotein and anti-MAG titre became unrecordable.

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A group of seven people treated with interferon alfa-2a, and assessed with a novel measure of postural stability, improved (Pouget 2000).

Cytotoxic therapies

Chemotherapeutic (or cytotoxic) therapies have been used singly or in combination with other drugs, but none (except Niermeijer 2007 using cyclophosphamide and corticosteroids, as above) in a controlled trial. These agents include cyclophosphamide (Blume 1995; Gorson 1997; Gorson 2001; Hafler 1986; Hamidou 2005; Kelly 1988; Niermeijer 2007; Nobile-Orazio 2000; Tagawa 2001), fludarabine (29 participants, 11 anti-MAG and nine of these with clinical improvement) (Niermeijer 2006; Rudnicki 1998; Sherman 1994; Wilson 1999), fludarabine and rituximab (Gruson 2011, see below), cladribine (one participant) (Ghosh 2002), azathioprine (Gorson 2001), mycophenolate (Gorson 2004), chlorambucil alone (Andres 2001; Gorson 2001; Latov 1988; Nobile-Orazio 2000), and melphalan and chlorambucil (Ernerudh 1992). Responses to treatment were variable. More extensive chemotherapy has been used in non-MGUS associated anti-MAG neuropathies, which are outside the scope of this review (Andres 2001).

Rituximab

Rituximab has been used in multiple cases in non-randomised cohorts and cases series (Barohn 2005; Benedetti 2005; Benedetti 2007; Benedetti 2008; Canavan 2002; Delmont 2010; Goldfarb 2005; Gono 2006; Gorson 2007; Kelly 2006; Kilidireas 2006; Latov 1999; Levine 1999; Niermeijer 2009; Pestronk 2003; Renaud 2003; Renaud 2006; Smith 2011; Weide 2000). About 50% to 60% of participants seem to respond in these uncontrolled studies, but two studies failed to show any benefit in five participants (Barohn 2005; Rojas-García 2003), and three studies reported worsening (Broglio 2005; Gironi 2006; Noronha 2006). Three fully-published studies included 42 participants with anti-MAG neuropathy treated with rituximab and documented improvements in strength, neurophysiological indices, and functional score up to two years (Dalakas 2009; Pestronk 2003; Renaud 2003). However, neither Pestronk 2003 nor Renaud 2003 were adequately controlled. Renaud 2003 had no controls and Pestronk 2003 had a semi-historical non-randomised control group without blinding of the assessment of outcome measures. We describe the first two RCTs of rituximab above (Dalakas 2009; Léger 2013) A recent study describes the use of rituximab in combination with fludarabine in five participants, four of whom improved clinically and electrophysiologically, with serum IgM and anti-MAG titre responses too. Improvement was sustained and, in this small series, treatment was without significant toxicity (Gruson 2011).

Others

Some more novel therapies have been tried, including ciclosporin in two participants (Hodgkinson 1990), and a single participant underwent autologous stem cell transplantation (ASCT) (Rudnicki 1998). In this one person, the ASCT was followed after two years by improvements in symptoms, signs, and neurophysiological indices, although he had been treated with other agents including fludarabine prior to the transplant. Neither ciclosporin nor ASCT have been subjected to a RCT.

Economic considerations

The treatments discussed are all expensive. In 2005, the approximate cost of IVIg was about GBP 3600 for the standard 2.0 g/kg dose in a 70 kg adult, and in 2012 about GBP 4500. Fludarabine and rituximab cost approximately GBP 5000 per course, and an autologous stem cell transplant costs approximately GBP 25,000 to 35,000. We cannot overstate the importance of subjecting such agents to early and adequate clinical trials.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from trials of immunotherapies in anti-myelin-associated glycoprotein (anti-MAG) paraprotein-associated peripheral neuropathies is inadequate to identify whether any particular immunotherapy treatment is significantly beneficial. The eight published randomised controlled trials (RCTs) of immunotherapy in anti-MAG IgM paraproteinaemic neuropathy were all individually either too small, too short or too flawed for us to draw confident conclusions about the efficacy of individual treatments or comparisons between them.

In meta-analysis there is low-quality evidence (two small studies, one significantly biased including inconsistency, indirectness), that rituximab is of benefit in stabilising or improving anti-MAG neuropathy.

Implications for research

The statistically significant short-term benefit from IVIg may not be clinically significant. The evidence is of low quality and needs further confirmation. More large, carefully-constructed, collaborative studies are required to identify whether anti-CD20 therapies or other treatments are effective.

The IgM paraproteinaemic neuropathies are chronic and slowly progressive. We chose to measure our outcomes at six and 12 months as these are more likely to reflect a time course over which measurable progression or recovery might occur. Endpoints of four weeks or even three to four months may not be long enough to

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detect clinical stabilisation or improvement. Dalakas 2009, Léger 2013 and Niermeijer 2007 used sensible longer-term outcomes and future studies should replicate this. We would encourage the authors of future trials to collect consistent, comparable and clinically-meaningful endpoint data. We predefined our primary outcome measures as improvement in the Neuropathy Impairment Scale and modified Rankin Scale (disability) at six months. The inclusion of a disability measure in future trials would be appropriate, being relevant both to patients and to healthcare providers. We have included Rasch-built disability scores in the secondary outcome measures for future studies, as these show promise in reflecting change and more effectively representing a greater range of disability. These remain in development and have not so far appeared in any trial. Predictive scoring systems which allow the clinician to estimate the trajectory and likely outcome of patients at an early stage will allow people who warrant treatment to be identified earlier in the disease; work needs to be undertaken to study the natural history of the disease progression.

The Perinoms study is completed and a further study (Perinoms 2) is underway at the time of publication, which will define appropriate outcome measures for clinical and research outcome measurement in this condition.

Studies of other novel agents such as cladribine or fludarabine may be indicated.

ACKNOWLEDGEMENTS

MPTL was supported by the Patrick Berthoud Charitable Trust and the Brain Neurology Entry Scholarship. This work was undertaken at University College London NHS Hospitals Trust/University College London.

This project was supported by the National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to Cochrane Neuromuscular. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service, or the Department of Health. Cochrane Neuromuscular is also supported by the MRC Centre for Neuromuscular Diseases.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Comi 2002

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	22 participants (11 with anti-MAG antibodies) with monoclonal gammopathy of undetermined significance, a stable or worsening demyelinating neuropathy and significant limb disability. No other cause for neuropathy, treatment with IVIg, plasma exchange or corticosteroids in the 6 weeks before randomisation or failure to respond to IVIg previously
Interventions	IVIg (2 g/kg) over 24 to 48 hours or placebo. Washout period and then cross-over
Outcomes	Difference in overall disability grade 2 weeks from treatment Secondary endpoints (2 and 4 weeks) were change in 10-metre walk time, average of right and left hand times for 9-hole peg test, grip strength and vibration threshold, MRC sum score, INCAT sensory sum score, sensory symptom score, Rotterdam Handicap Scale, mRS and SF36 Nerve conduction studies at 4 weeks: distal CMAP amplitude, proximal CMAP amplitude; motor conduction velocity
Funding	Support from EUBIOMED project no. BMH4-CT96-0324. Novartis supplied Sandoglobulin and placebo infusions, and provided financial support
Conflicts of interest among main investigators	Not provided
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	According to a sequence of random numbers provided by the trial statistician to the manufacturers who prepared the randomisation packs
Allocation concealment (selection bias)	Low risk	"The sequences were stratified by centre with a block size of two according to a sequence of random numbers provided by the trial statistician to the manufacturers who prepared the randomisation packs. The block size was not revealed to the trialists. Each centre was provided with coded packs, prepared by Novartis, containing ei-

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		ther Sandoglobulin or placebo."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The placebo infusions contained albumin 6 mg % and were identical in appearance to the IVIg infusions"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The placebo infusions contained albumin 6 mg % and were identical in appearance to the IVIg infusions"; "The assessing neurologist, who did not have access to laboratory data or to possible side effects, performed all trial assessments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"According the intention-to-treat principle with the methods described by Senn" (Senn 1993). "All participants completed study."
Selective reporting (reporting bias)	Low risk	None
Other bias	Low risk	None

Dalakas 1996

Methods	Randomised, placebo-controlled cross-over trial
Participants	11 participants were randomised of whom 9 had IgM anti-SGPG activity. All had demyelinating neuropathy. All had subjective worsening in the 9 to 12 months prior to study and 9 were unresponsive to prior therapies
Interventions	IVIg (2 g/kg) or placebo over 2 days monthly for 3 months. Washout period and then crossed over to alternative arm
Outcomes	MRC muscle strength, neuromuscular symptoms score and sensory sum score at baseline, end of washout and end of each treatment period. Anti-MAG titres at various times during the protocol. No primary outcome measure was predefined
Funding	Bayer Pharmaceuticals provided the IVIg
Conflicts of interest among main investigators	Not declared
Notes	No criteria for demyelination were stated. No explicit exclusion of other causes of neuropathy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Random sequence generation (selection bias)	Unclear risk	Possibly generated in National Institutes of Health pharmacy, but unclear by what methodology "Randomized" but no method given. A block-randomisation procedure was used in 1993 dermatomyositis trial which is referenced Participants randomised to placebo were much older than in the IVIg arm, although this did not reach significance with the nine anti-MAG participants included. Sensory scores were significantly higher in the placebo group than the IVIg-treated group
Allocation concealment (selection bias)	Unclear risk	Generated in National Institutes of Health pharmacy but placebo was dextrose in half-normal saline. The code was broken when all participants completed the study. Allocation concealment is referred to as having been performed as per the 1993 dermatomyositis trial referenced in the paper
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The whole intravenous set was covered by an opaque plastic bag so that any possible fluid turbidity or frothing would not be evident to the investigators or patients. None of the laboratory values were entered into the computer or the patients' charts." - derived from referenced 1993 study. "The physicians, nurses, physical therapists, photographer, and statistician were unaware of which treatment was administered"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The whole intravenous set was covered by an opaque plastic bag so that any possible fluid turbidity or frothing would not be evident to the investigators or patients. None of the laboratory values were entered into the computer or the patients' charts." - derived from referenced 1993 study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how incomplete data analysed - participant 7 did not participate in arm 2 but data presented - thus no treatment given
Selective reporting (reporting bias)	Unclear risk	None identified but predates ClinicalTrials.gov

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Other bias	Low risk	None identified

Dalakas 2009

Methods	Randomised, double-blind parallel-group study
Participants	26 participants, selected if they had clinical and electrophysiological evidence of a demyelinating neuropathy, a benign IgM monoclonal spike, and anti-MAG or SGPG antibodies. Participants should not have received any immunosuppressive therapy for at least 6 months before enrolment. At entry, all participants should have impaired function as evidenced by affected balance, co-ordination, frequent falls, or muscle weakness, reflected in an INCAT disability (leg) score > 1
Interventions	Rituximab 375 mg/m^2 i.v. 4 times, given weekly
Outcomes	The primary outcome was a change of 1 point in INCAT disability scale score in the lower extremities at month 8 Secondary measures included assessment of sensory function using the SNS scale and muscle strength measurements using the MRC scale. Electrophysiological outcomes: median, ulnar, tibial, and peroneal motor and sensory nerve conduction velocities were determined before therapy and at the end of the 12-month follow-up period
Funding	"The study was conducted at the National Institutes of Health under a Cooperative Research and Development Agreement between National Institute of Neurological Disorders and Stroke and Genetech [sic]"
Conflicts of interest among main investigators	"Nothing to report"
Notes	Statistical manipulations cause concern. One participant was removed from the study after randomisation because a severe adverse event occurred on 1st infusion of the drug, and was not analysed. One participant was mis-scored with INCAT 1 but on analysis was found to be INCAT 0 and hence excluded from the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Paper states "Randomized" only
Allocation concealment (selection bias)	Unclear risk	Not clear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both drug and placebo were supplied by the National Institutes of Health pharmacy and sent to the floor covered so that all in-

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		vestigators, assessors, evaluators, and nurses remained blinded to the study code
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both drug and placebo were supplied by the National Institutes of Health pharmacy and sent to the floor covered so that all investigators, assessors, evaluators, and nurses remained blinded to the study code
Incomplete outcome data (attrition bias) All outcomes	High risk	One participant removed after randomisation following adverse events replaced by another and not included in the analysis. One participant admitted to study who could not have improved and thus removed from the analysis. The analysis was performed both with and without this participant
Selective reporting (reporting bias)	High risk	See section above
Other bias	High risk	Data check of publication inconsistencies verbally clarified. Study authors unable to provide participant-level data for outcomes checking and reformatting Trial not registered on ClinicalTrials.gov Non-balanced groups with respect to sex at admission, not representative of disease Drug company provided drug

Léger 2013

Methods	A randomised, double-blind, placebo-controlled study
Participants	54 participants between 18 and 82 years of age with demyelinating sensory ataxic neuropathy associated with anti-MAG IgM gammopathy, a demyelinating neuropathy according to EFNS/PNS criteria, and either monoclonal gammopathy of unknown significance or a low-grade non-Hodgkin B-cell lymphoma not necessitating treatment by itself. The presence of serum anti-MAG antibodies at significant titres was assessed by 1 reference laboratory. For inclusion in the trial, the patients had an INCAT score 4 or more, and VAS pain score > 4 or an ataxia score of 2 or more
Interventions	Either weekly infusions of 375 mg/m^2 rituximab for 4 weeks (n = 26) or identical infusions of placebo (n = 28)
Outcomes	Primary outcome: 20% improvement of the INCAT score at 12 months Secondary outcome measures: sensory part of the Neurological Disability Score, MRC scale in distal muscles in both upper and lower limbs, ataxia score, 10-meter walking time, self-evaluation scale, electrophysiological and immunological data

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Funding	Roche France provided the rituximab and placebo. Study supported by academic grant	
Conflicts of interest among main investigators	Full disclosures made by authors (see www.neurology.org). No author reported conflicts related to Roche or Genentech	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Using a stratified (by centre) and blocked (with variable block length) randomisation list (created by a statistician) to ensure that the 2 parallel groups were comparable at baseline, participants were randomised by fax to 1 of 2 groups (1:1 ratio)
Allocation concealment (selection bias)	Low risk	"The first group received 4 weekly infusions of 375 mg/m^2 rituximab (as in regimens used in previous trials for IgM anti-MAG demyelinating neuropathy) and the second group received placebo" It is not clear that allocation concealment to group was maintained. However, "Randomization was centralized and carried out independently of the clinicians."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Drug and placebo were supplied by Roche France." "All investigators, assessors, evaluators, and nurses remained blinded to the randomization codes."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All investigators, assessors, evaluators, and nurses remained blinded to the randomization codes."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome measures from the methods reported
Selective reporting (reporting bias)	High risk	None identified. The trial protocol on ClinicalTrials.gov does not specify all the outcomes listed in the methods, giving only functional scales (MRC), quality of life, serum lymphocyte, anti-MAG titres and electrophysiological parameters
Other bias	Low risk	None

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Mariette 1997

Methods	Randomised, open, parallel-group trial
Participants	20 participants with stable or progressive anti-MAG neuropathy with CNDS > 10, with no other cause for neuropathy and no treatment in preceding 3 months
Interventions	IVIg (2 g/kg) over 4 days, then IVIg 1 g/kg over 2 days every 3 weeks for 6 months, then every 6 weeks for 6 months if CNDS improvement > 20% Or interferon alfa-2a 3 MU/m^2 3 times a week for 6 months and then twice a week if CNDS improvement > 20%. If no improvements at 6 months then participants crossed over
Outcomes	Change in CNDS at 6 months. Secondary endpoints were proportion of participants with 20% improvement in CNDS, improvement in CNDS at 12 months, change in electrophysiological data, change in level of monoclonal component, change in anti-MAG titre, subjective score
Funding	"Drug and placebo were supplied by Roche France."
Conflicts of interest among main investigators	None declared
Notes	11 participants treated with plasma exchange (3) or chlorambucil (8) without benefit prior to trial Some participants changed over to the alternate (open) arm if they failed to respond at 6 months or declined sooner (one participant in the IVIg arms switched at 4 months). Data for this participant or those who dropped out were included on a 'last observation carried forward' intention-to-treat basis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation according to previous treatment through a blinded telephone assignment procedure
Allocation concealment (selection bias)	High risk	No - open
Blinding of participants and personnel (performance bias) All outcomes	High risk	No - open
Blinding of outcome assessment (detection bias) All outcomes	High risk	No - open
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat analysis using 'last observation carried forward'. Small numbers of participants, with a high level of dropout, and

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		early cross-over
Selective reporting (reporting bias)	Low risk	No selective reporting identified
Other bias	High risk	4/10 participants dropped out of IVIg group, and study interrupted after first interim analysis

Mariette 2000

Methods	Prospective, randomised, double-blind, placebo-controlled trial
Participants	24 participants with stable or progressive anti-MAG neuropathy with CNDS > 10, no other cause for neuropathy and no treatment in preceding 3 months
Interventions	Interferon alfa-2a 4.5 MU 3 times a week for 6 months, or visually identical placebo
Outcomes	Change in CNDS at 6 months. Secondary endpoints were proportion of participants with a 20% improvement in CNDS and a participant subjective score
Funding	Academic grant from public body - unclear if drug supply also from company as in Mariette 1997
Conflicts of interest among main investigators	None declared
Notes	11 (5 in interferon, 6 in placebo group) had been previously treated with chlorambucil with no effect and 10 also with plasma exchange

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation according to the existence of a previous treatment, through a blinded telephone assignment procedure "Randomly Allocated"
Allocation concealment (selection bias)	Low risk	Blinded telephone assignment procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The reconstituted vials of interferon alfa-2a or placebo were delivered by the pharmacy of each centre and appeared identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear

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Mariette 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Yes - explained in the report. Intention-to-treat analysis using 'last observation carried forward'
Selective reporting (reporting bias)	Low risk	Yes
Other bias	Low risk	Yes - except trial stopped early because no placebo left

Niermeijer 2007

Methods	Randomised, double-blind, placebo-controlled, partial cross-over study of 24 months duration. Participants who declined at 6 months were crossed-over to the other group. Analysis at 6 months then again with 2nd treatment group
Participants	35 participants, 17/35 with anti-MAG antibodies. Men or women. Inclusion criteria were a diagnosis of symmetric motor and sensory polyneuropathy confirmed by electrophysiologic examination; presence of a monoclonal IgM gammopathy, progression of symptoms defined as a ?1 point deterioration on the mRS or RMI, or a ?5% deterioration of the MRC sum score or sensory sum score in a time interval of 6 months; no other causes for polyneuropathy; age over 25 years and completed family for reasons of fertility; no underlying haematologic malignancies as excluded by a haematologist; no contraindications for the use of corticosteroids or cyclophosphamide; no other immunotherapy for polyneuropathy in the previous 5 years
Interventions	Cyclophosphamide 500 mg orally once daily for 4 days with prednisone 60 mg orally once daily for 5 days. Given every 28 days for 6 to 12 months, depending upon cross-over
Outcomes	Primary outcome - revised RMI: Change from baseline on the RMI was compared between the treatment group and placebo group, as well as percentage responders from 6 to 24 months after start of treatment. Response was defined as 1 point improvement on the RMI Secondary outcome measures: Changes from baseline at 6, 12, 18, and 24 months using mRS, MRC sum score (0 to 140 points), manual muscle testing (MMT) using the MRC scale in 28 muscles of both arms and legs. Sensory sum score (0 to 56 points). Ataxia was scored with a standardised tapping test of the dominant hand and foot measuring the number of taps using a device with 2 buttons attached to an automatic counter. Quality of life - Dutch SF 36 questionnaire. M-protein levels Electrophysiologic studies (before and 6 months after start of treatment): motor conduction with stimulation of the median, ulnar, peroneal nerve and tibial nerve. Sensory conduction of musculocutaneous, median, ulnar, radial, and sural nerves on distal stimulation was measured
Funding	Not declared
Conflicts of interest among main investigators	"The authors report no conflicts of interest."

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Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were allocated to treatment or placebo using a computer-generated list with permuted blocks of randomly varying size stratified by anti-MAG activity
Allocation concealment (selection bias)	Low risk	Physicians and participants were unaware of treatment allocation throughout the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were unaware of treatment allocation throughout the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physicians were unaware of treatment allocation throughout the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat 8/35 participants dropped out over 2 years. Only 1 participant dropped out and lost to follow-up before 6 months. Another stopped drug but continued follow-up. Only 1 analysed in final by intention-to-treat
Selective reporting (reporting bias)	Low risk	None
Other bias	Low risk	None identified

Oksenhendler 1995

Methods	Prospective randomised open, parallel-group trial
Participants	44 participants with IgM associated peripheral neuropathy of whom 33 had serum IgM anti-myelin activity. Not necessarily demyelinating
Interventions	Chlorambucil alone (0.1 mg/kg/day orally) for 12 months or in association with 15 1½-volume plasma exchanges over 4 months
Outcomes	Primary outcome measure was the NDS after 12 months. Secondary endpoints were changes in the sensory or motor subcomponents of the NDS, participant subjective self-assessment and neurophysiological studies

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Funding	Not known	
Conflicts of interest among main investigators	None declared	
Notes	45 participants were initially enrolled. 1 randomised to the chlorambucil group had severe chronic hepatopathy and the data were excluded 10 participants had suspension or dose reduction of chlorambucil because of haematological toxicity. 8 participants (4 in each group) failed to complete the trial to 12 months, but were included in intention-to-treat analysis	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were assigned by randomisation"
Allocation concealment (selection bias)	High risk	No - open
Blinding of participants and personnel (performance bias) All outcomes	High risk	No - open to participants
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not clear for assessors - probably no
Incomplete outcome data (attrition bias) All outcomes	High risk	All outcomes are reported but incomplete follow-up and dropouts are not reported Mention of intention-to-treat analysis is passing only. Unclear whether applied to all outcomes 1 participant from chlorambucil group had a hepatopathy and their data were not included in the analysis
Selective reporting (reporting bias)	Low risk	None
Other bias	High risk	3 participants on chlorambucil stopped treatment by months 2, 7, and 9, and subsequently received plasma exchange. They were, however, included in the chlorambucil group analysis on an intention-to-treat basis but the effect of plasma exchange is unclear

anti-MAG: anti-myelin-associated glycoprotein

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CMAP: compound muscle action potential
CNDS: Clinical Neuropathy Disability Score
IgM: immunoglobulin M
INCAT: Inflammatory Neuropathy Cause and Treatment
IVIg: intravenous immunoglobulin
MRC: Medical Research Council
mRS: modified Rankin Scale
NDS: Neuropathy Disability Score
RMI: Rivermead Mobility Index
SF36: Short Form 36 Health Survey
SGPG: sulphated glucuronyl paragloboside
SNSS: sensory neuropathic sum scale

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

Study	Reason for exclusion
Barohn 2005	Uncontrolled open study
Benedetti 2005	Uncontrolled open study
Benedetti 2007	Uncontrolled open study
Benedetti 2008	Uncontrolled case series
Canavan 2002	Uncontrolled open study
Dyck 1991	Participants with IgM paraprotein had no documentation of anti-MAG status. No criteria for the diagnosis of demyelination
Goldfarb 2005	Single case
Gorson 2004	8 participants in open uncontrolled study of mycophenolate
Gorson 2007	Uncontrolled open study including single participant with anti-MAG antibody
Hamidou 2005	Uncontrolled study of 9 participants
Kilidireas 2006	Uncontrolled open study
Latov 1999	Open study
Niermeijer 2006	Open uncontrolled follow-up
Niermeijer 2009	Case series
Pestronk 2003	Non-randomised control group and unblinded assessments

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(*Continued*)

Renaud 2003	Open study
Renaud 2006	Open uncontrolled follow-up study
Sghirlanzoni 2000	Open uncontrolled study - 8 IgM in 60 participants
Smith 2011	Non-randomised phase II clinical trial - case series

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DATA AND ANALYSES

Comparison 1. IVIg versus interferon alfa-2a

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in Clinical Neuropathy Disability Score (CNDS) at six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Subjective score at six months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Number of participants improved by at least 20% on NIS at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Interferon alfa-2a versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in the CNDS at 6 months (maximum 93)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Number improved in CNDS by 20% at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Rituximab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants improved on INCAT score (see text) at 8-12 months	2	73	Risk Ratio (M-H, Fixed, 95% CI)	3.51 [1.30, 9.45]
2 Mean improvement in INCAT score (see text) at 8 - 12 months	2	73	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.85, -0.05]
3 Rituximab vs placebo. Mean improvement in INCAT score at 8 - 9 months (post hoc data)	2	70	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.73, 0.07]
4 Mean improvement in NIS at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Improvement in 10-metre walk time at 8 - 12 months	2	68	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-1.89, 1.19]
6 Number improved in 10-metre walk at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

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7 Change in IgM level 8 months after treatment	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Change in IgM anti-MAG titre at 8 - 12 months	2	71	Mean Difference (IV, Fixed, 95% CI)	-17.79 [-33.33, -2.25]
9 Participant subjective impression of change stable or improved at 8 - 12 months	2	70	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [1.27, 2.71]
10 Participant subjective impression of change improved at 8 - 12 months	2	70	Risk Ratio (M-H, Fixed, 95% CI)	9.67 [1.84, 50.85]
11 Mean change in SF36 physical subscores at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Mean change in SF36 mental health subscores at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13 Any adverse event	2	80	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.84, 1.66]
14 Severe adverse event	2	80	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [0.34, 28.54]

Comparison 4. Cyclophosphamide and steroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in modified Rankin Scale at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Number of participants improved on modified Rankin Scale at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Improvement in Rivermead Mobility Index (subjective participant score) at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

ADDITIONAL TABLES

Table 1. 'Summary of findings' table: Intravenous immunoglobulin (IVIg) versus placebo

IVIg versus placebo for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies					
Patient or population: people with IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies **Settings:** hospital and outpatient treatment centres **Intervention:** IVIg versus placebo					
Outcomes	**Anticipated absolute effects*** **(95% CI)**	**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**

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Table 1. 'Summary of findings' table: Intravenous immunoglobulin (IVIg) versus placebo (*Continued*)

	Risk with placebo	Risk with IVIg				
Number of participants improved in disability score at 6 months - not reported	See comment	See comment	Not estimable	-	See comment	Short-term outcomes only, not reported at 6 months
Mean improvement in disability score at 6 months - not reported	See comment	See comment	Not estimable	-	See comment	Short-term outcomes only, not reported at 6 months
Improvement in 10-metre walk time at 6 months - not reported	See comment	See comment	Not estimable	-	See comment	Short-term outcomes only, not reported at 6 months
Participant subjective impression of change at 6 months - number of participants reporting improvement - not reported	See comment	See comment	Not estimable	-	See comment	Short-term outcomes only, not reported at 6 months
Change in serum IgM paraprotein concentration 8 months after treatment - not reported	See comment	See comment	Not estimable	-	See comment	Short-term outcomes only, not reported at 6 months
Any adverse event	Data for the anti-MAG subgroup were not available. In one study, one participant had an aseptic meningitis and a rash after IVIg treatment, with 2 moderate adverse events in the placebo group. In the other trial, there were no serious adverse events with IVIg, but mild and transient		Not estimable	-	See comment	No further analysis was possible.

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Table 1. 'Summary of findings' table: Intravenous immunoglobulin (IVIg) versus placebo (*Continued*)

	effects were "more common in the IVIg than the placebo group"				

*__The risk in the intervention group__ (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; **RR:** risk ratio

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]Incomplete reporting of adverse events in one study.

Table 2. 'Summary of findings' table: Cyclophosphamide and prednisone versus placebo

Cyclophosphamide and corticosteroids compared to placebo for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies

Patient or population: people with IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies
Settings: hospital and outpatient treatment centres
Intervention: cyclophosphamide and corticosteroids
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with cyclophosphamide and corticosteroids				
Number of participants improved in disability score at 6 months Modifed Rankin Scale Scale from: 0 to 6 (normal to death) Follow-up: mean	**Study population**		**RR 3.56** (0.41 to 30.99)	35 (1 study)	⊕⊕⊕○ **moderate**[1]	

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Table 2. 'Summary of findings' table: Cyclophosphamide and prednisone versus placebo (*Continued*)

6 months	**53 per 1000**	**189 per 1000** (22 to 1000)				
Mean improvement in disability score at 6 months Modifed Rankin Scale Scale from: 0 to 6 (normal to death) Follow-up: 6 months[2]	The mean improvement in disability score at 6 months in the control groups was **0.11 units**	The mean improvement in disability score at 6 months in the intervention groups was **0.31 lower** (0.61 lower to 0. 01 lower)		34 (1 study)	⊕⊕⊕○ **moderate**[1]	
Improvement in 10-metre walk time at 6 months - not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Participant subjective impression of change at 6 months - number of participants reporting improvement - not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Change in serum IgM paraprotein concentration after treatment - not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Any adverse event - not measured	See comment	See comment	Not estimable	-	See comment	Adverse events not specifically collected but text notes in the paper (see text of review)

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Table 2. 'Summary of findings' table: Cyclophosphamide and prednisone versus placebo *(Continued)*

*__The risk in the intervention group__ (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; **IgM:** immunoglobulin M; **RR:** risk ratio

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]Dowgraded once for imprecision (single small study).
[2]Phase 1 of cross-over trial only.

Table 3. Details of non-randomised studies

Study ID	Study design	Participant number (total)	Participant number (IgM)	Participant number (MAG)	Intervention	Number improved (IgM)	Number improved (MAG)
Latov 1980	Case report	1	1	1 (anti-myelin Abs)	Prednisolone + chlorambucil + plasma exchange	1/1	-
Dalakas 1981	Uncontrolled case series (response to Rx recorded in Latov 1988)	11	4	?	a. Prednisolone b. Prednisolone + chlorambucil	a. 0/1 b. 1/1	-
Melmed 1983	Uncontrolled case series (response to Rx recorded in Latov 1988)	3	3	3	a. Corticosteroids b. Steroids + plasma exchange + chlorambucil	-	a. 3/3 b. 0/3
Stefansson 1983	Case report	1	1	1	Plasmapheresis + immunosuppressant	-	0/1
Meier 1984	Case report	1	1	1	Plasmapheresis + prednisolone + chlorambucil	-	1/1

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Table 3. Details of non-randomised studies (*Continued*)

Sherman 1984	Retrospective case series	10	6	?	Plasmapheresis + chlorambucil	2/5	-
Bland 1985	Case report	1	1	1	Plasmapheresis + chlorambucil	-	1/1
Frayne 1985	2 cases	2	2	-	Plasma exchange	2/2	-
Ernerudh 1986	Retrospective non-randomised	3	3	3 (anti-myelin Abs)	Plasma exchange	2/3 (temporary)	-
Hafler 1986	Uncontrolled case series (response to Rx recorded in Latov 1988)	9	9	7	a.Corticosteroids b. Plasma exchange c. Cyclophosphamide	-	a. 0/5 b. 1/5 c. 1/1
Smith 1987	Prospective non-randomised case series	13	8 (2 lymphoma)	4 (1 lymphoma)	a. Chlorambucil + plasma exchange b. Plasma exchange	a. 3/4 b. 1/2	a. 1/2 b. 1/1
Haas 1988	Case report	1	1	1	Plasma exchange	1/1	1/1
Kelly 1988	Uncontrolled case series	10	10	5	Prednisolone + cyclophosphamide (azathioprine or chlorambucil) + plasma exchange	4/4 (all 5 not treated)	2/3 (All 5 not treated)
Latov 1988	Uncontrolled case series	11	11	11	a. Plasmapheresis b. Prednisolone c. Chlorambucil d. Prednisolone + plasma exchange e. Plasma ex-	-	a. 3/3 b. 0/1 c. 3/4 d. 0/1 e. 0/1

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Table 3. Details of non-randomised studies (*Continued*)

					change + chlorambucil		
Donofrio 1989	Case report	1	1	0	a. Corticosteroids b. Plasma exchange + corticosteroids	a. 0/1 b. 1/1	-
Cook 1990	Case reports	2	2	1	a. IVIg b. prednisolone	a. 2/2	a. 1/1 b. 0/1
Hodgkinson 1990	Uncontrolled case series	8	2	?	Ciclosporin	2/2	-
Ernerudh 1992	Prospective non-randomised	5	5	5 (anti-myelin Abs)	a. Plasma exchange b. Prednisolone c. Melphalan d. Chlorambucil e. Chlorambucil and plasma exchange f. Chlorambucil + prednisolone	a. 1/1 b. 1/2 c. 0/1 d. 0/1 e. 1/1 f. 1/2	-
Hoang-Xuan 1993	Open prospective	4	4	3 (2 in Léger 1994)	IVIg	-	0/1
Léger 1994	Open prospective	7	7	5	IVIg	-	2/5
Sherman 1994	Abstract	10	10	8	Fludarabine	-	7/8
Siciliano 1994	Case report	3	1	?	Selective apheresis	1/1	-
Blume 1995	Uncontrolled case series	4	3	4	Plasma exchange + cyclophosphamide	3/3	4/4
Ellie 1996	Retrospective case series	33	33	33	a. Plasma exchange b. IVIg	a. 2/6 b. 13/17	-

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Table 3. Details of non-randomised studies (*Continued*)

Notermans 1996	Open prospective	16	11	5	Cyclophosphamide + prednisolone	-	Unclear
Gorson 1997	Retrospective case series	15	12	8	a. Plasma exchange b. Prednisolone c. IVIg d. Cyclophosphamide + plasma exchange	a. 10/12? b. 1/2 c. 2/6 d. 2/2	Unclear
Rudnicki 1998	Case report	1	1	1	a. Fludarabine + plasma exchange b. Bone marrow transplant		a. 0/1 b. 0/1
Latov 1999	Case reports	2	2	2	Rituximab	-	1/2
Levine 1999	Probably included in Pestronk 2003 - unclear	-	-	-	Rituximab	-	-
Wilson 1999	Open prospective	4	4	4	Fludarabine	-	4/4
Nobile-Orazio 2000	Retrospective case series	25	25	25	a. Plasma exchange b. Plasma exchange + chlorambucil c. Prednisolone d. IVIg e. Cyclophosphamide		a. 2/5 b. 2/2 c. 0/6 d. 0/2 e. 1/5
Gorson 2001	Retrospective case series (NB some cases in Gorson 1997)	24	22	24	a. Plasma exchange b. IVIg c. Prednisolone d. Cyclophosphamide e. Plasma exchange + cyclophosphamide f. In-	-	a. 8/20 b. 3/19 c. 0/8 d. 3/6 e. 2/8 f. 1/8 g. 0/2 h. 0/2

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Table 3. Details of non-randomised studies (*Continued*)

					terferon alfa-2a g. Chlorambucil h. Azathioprine		
Tagawa 2001	Case report	1	1	1	Plasmapheresis + cyclophosphamide	-	1/1
Canavan 2002	Retrospective case reports (abstract)	3	3	2	Rituximab	-	1/2
Ghosh 2002	Case report	1	1	1	Cladribine	-	1/1
Pestronk 2003	Prospective open study	21	21	7	Rituximab	-	Unclear - improvement
Renaud 2003	Prospective open phase II study	9	9	9	Rituximab	-	6/9
Barohn 2005	Uncontrolled case series	5	5	3	Rituximab	0/5	0/3
Benedetti 2005	Uncontrolled ?prospective (abstract)	13	13	13	Rituximab	-	8/13
Broglio 2005	Case report	1	1	1	Rituximab	-	Worse
Hamidou 2005	Uncontrolled case series	9	9	-	Cyclophosphamide	7/9 improved, 2 stable	-
Kilidireas 2006	Uncontrolled case series	4	4	2	Rituximab	3/4 improved	
Niermeijer 2006	Open prospective	16	16	6	Fludarabine	3/ 10 improved, all others stabilised	2/6 improved all others stabilised
Renaud 2006	Prospective follow-up study to 2003	8	8	8	High-dose rituximab	-	4/7 improved (1 death)
Gironi 2006	Case report	1	1	1	Rituximab	-	Worse

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Table 3. Details of non-randomised studies (*Continued*)

Noronha 2006	Case report	1	1		Rituximab	-	Worse
Niermeijer 2009	Case series	17	17	6	Rituximab	Improvement in: ODSS 2/17, MRC sum score 11/17, Sensory sum score 10/17	3/6
Delmont 2010	Case report	1	1	0	Rituximab (after IVIg, corticosteroids, chlorambucil)	1	N/A
Gruson 2011	Case series	5	5 (2 MGUS, 3 WM)	5	Rituximab and fludarabine	4/5 improved clinically, electrophysiologically, IgM level and anti-MAG titre	All MAG
Smith 2011	Phase II non-randomised case series	21	21	N/K	Rituximab	NIS significant (>10 pts) improvement at 6 months 13/21, and 24 months 8/21	N/A

Abs: antibodies; anti-MAG; anti-myelin-associated glycoprotein; IgM: immunoglobulin M; IVIg; intravenous immunoglobulin; pts: participants; Rx: treatment; WM: Waldenstrom's macroglobulinemia

WHAT'S NEW

Last assessed as up-to-date: 1 February 2016.

Date	Event	Description
1 February 2016	New citation required and conclusions have changed	New trials have been incorporated, which change the conclusions of the review

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(*Continued*)

1 February 2016	New search has been performed	We added a new secondary outcome measure of a R-ODS score or similar to bring the review into line with current thinking on outcome measures in paraproteinaemic neuropathies

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 1, 2003

Date	Event	Description
22 November 2011	New citation required and conclusions have changed	New studies that included new interventions were included and these changed the conclusions of the review
25 October 2011	New search has been performed	Searches were updated to June 2011. New 'Risk of bias' methodology was included. In this update, data were extracted independently and cross-checked; in the previously published version, data were extracted by one author and checked by the other
29 May 2008	Amended	Converted to new review format.
2 January 2006	New citation required and conclusions have changed	We updated the Cochrane Neuromuscular Disease Group Register in March 2005 and searched MEDLINE (January 1966 to March 2005) and EMBASE (January 1980 to March 2005). We have added comments about two non-randomised trials of rituximab in the treatment of IgM anti-myelin associated glycoprotein (MAG) paraproteinaemic demyelinating peripheral neuropathy. There are three other non-randomised rituximab studies published in abstract form. We have amended the 'Discussion' and 'Conclusion' of the review accordingly

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CONTRIBUTIONS OF AUTHORS

Michael Lunn prepared the first draft of the review, prepared databases for the extraction of data from the reviews, extracted data and prepared edits in subsequent drafts.

Eduardo Nobile-Orazio extracted data independently, edited each draft and agreed the final text.

DECLARATIONS OF INTEREST

MPTL has published a pilot study of the use of fludarabine in IgM-associated paraproteinaemic neuropathy (Wilson 1999) and was a blinded investigator in Comi 2002. He has received honoraria for consultation from Baxter Pharmaceuticals, CSL Behring, UCB and LFB and a travel support grant from CSL Behring and Grifols, all manufacturers of IVIg. He was a blinded Site Investigator on the FORCIDP study (fingolimod in CIDP (Novartis) who in August 2015 purchased ofatumumab (not included in this review). He is Joint Co-ordinating Editor of Cochrane Neuromuscular. He did not have a role in editorial assessment or the decision to publish this updated review.

EN-O has received honoraria from CSL Behring (Italy and USA), UCB (UK), and Kedrion (Italy) for Scientific Advisory Board participation and from Novartis (Switzerland) for being part of a Steering Committee for a trial with fingolimod on CIDP. He received compensation from Baxalta, Italy for preparing a teaching course on Multifocal Motor Neuropathy. He received compensation for lectures from Kedrion, Italy, CSL Behring, Italy and Baxter, USA. He received support for Meeting attendance from CSL Behring, Italy and Kedrion Italy. He has published a study of long-term prognosis of IgM neuropathies and their immunotherapy (Nobile-Orazio 2000) and was a member of the BIOMED INCAT Group which conducted the Comi 2002 study. He was the principal investigator in a RCT sponsored by Kedrion comparing the efficacy of intravenous corticosteroids with IVIg in CIDP. He is the Principal Investigator of a trial on IVIg in CIDP sponsored by LFB, France. He states that no part of the above-mentioned financial support had any influence on his work in preparing this review.

Both review authors were investigators in Comi 2002. The Cochrane Neuromuscular Managing Editor carried out an independent risk of bias assessment and data extraction of outcome data for this study, and checked these against the data entered in the review.

This review was first published in 2003. One new trial, of rituximab, has been added at this update. Both review authors have declared financial remuneration for consultancy work relating to IVIg. The most recent trial of IVIg was published in 2002, the conclusion of the review being that the short-term effects of this intervention are of doubtful clinical significance in this condition, a conclusion unchanged at this update.

Although the authorship of this updated review does not fully comply with the current Conflict of Interests policy, it did at the time of original publication. This has been discussed with the Funding Arbiters who have agreed that there is a low risk of significant bias resulting from the declared financial and academic interests.

SOURCES OF SUPPORT

Internal sources

- King's College London School of Medicine, UK.

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External sources

- Patrick Berthoud Charitable Trust, UK.
- Brain Neurology Entry Scholarship, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2012 and 2016 updates, both review authors extracted data independently and cross-checked data.

We have added a further outcome measure, but no trials have used this.

In the 2012 update, we included a 'Summary of findings' table and updated the 'Risk of bias' methodology.

INDEX TERMS

Medical Subject Headings (MeSH)

Demyelinating Diseases [immunology; *therapy]; Immunoglobulin M [blood; *immunology]; Immunoglobulins, Intravenous [therapeutic use]; Immunosuppressive Agents [therapeutic use]; Immunotherapy [*methods]; Myelin-Associated Glycoprotein [*immunology]; Paraproteinemias [immunology; *therapy]; Paraproteins [immunology]; Peripheral Nervous System Diseases [immunology; *therapy]; Plasma Exchange [methods]; Randomized Controlled Trials as Topic; Rituximab [therapeutic use]

MeSH check words

Humans

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