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[Intervention Review]

Immunotherapy for diabetic amyotrophy

Yee Cheun Chan¹, Yew Long Lo², Edwin SY Chan³

¹Division of Neurology, National University Hospital, Singapore, Singapore. ²National Neuroscience Institute (Singapore General Hospital Campus), Singapore, Singapore. ³Epidemiology, Singapore Clinical Research Institute Pte Ltd, Singapore, Singapore

Contact address: Yee Cheun Chan, Division of Neurology, National University Hospital, 1E, Kent Ridge Road, NUHS Tower Block, Level 10, Singapore, 119228, Singapore. yeecheun@yahoo.com.sg.

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ABSTRACT

Background

People with diabetes mellitus (DM) sometimes present with acute or subacute, progressive, asymmetrical pain and weakness of the proximal lower limb muscles. The various names for the condition include diabetic amyotrophy, diabetic lumbosacral radiculoplexus neuropathies, diabetic femoral neuropathy or Bruns-Garland syndrome. Some studies suggest that diabetic amyotrophy may be an immune-mediated inflammatory microvasculitis causing ischaemic damage of the nerves. Immunotherapies would therefore be expected to be beneficial. This is the second update of a review first published in 2009.

Objectives

To review the evidence from randomised trials for the efficacy of any form of immunotherapy in the treatment of diabetic amyotrophy.

Search methods

On 5 September 2016 we searched the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE and Embase. We also contacted authors of relevant publications and other experts to obtain additional references, unpublished trials, and ongoing trials.

Selection criteria

We intended to include all randomised and quasi-randomised trials of any immunotherapy in participants with the condition fulfilling all the following: diabetes mellitus as defined by internationally recognised criteria; acute or subacute onset of pain and lower motor neuron weakness involving predominantly the proximal muscles of the lower limbs; weakness that is not confined to one nerve or nerve root distribution; and exclusion of other causes of lumbosacral radiculopathies and plexopathy.

Data collection and analysis

Two authors independently examined all references retrieved by the search to select those meeting the inclusion criteria.

Main results

We found only one completed placebo-controlled trial (N = 75) using intravenous methylprednisolone in diabetic amyotrophy (Dyck 2006). The results have not been fully published and were not available for analysis. The risk of bias was unclear because there was too little information to make a judgement, but we considered the trial at high risk of selective reporting. The published abstract did not report adverse events. We found no additional trials when the searches were updated in September 2016.

Authors' conclusions

There is presently no evidence from randomised trials to support a positive or negative effect of any immunotherapy in the treatment in diabetic amyotrophy.

PLAIN LANGUAGE SUMMARY

Treatments that act on the immune system for diabetic amyotrophy

Review question

Is immunotherapy an effective and safe treatment for diabetic amyotrophy?

Background

Diabetic amyotrophy, which is also known as diabetic lumbosacral radiculoplexus neuropathy, diabetic femoral neuropathy or Bruns-Garland syndrome, is an uncommon disorder of the peripheral nerves (nerves outside the brain and spinal cord) that occurs in people with diabetes. The condition causes pain and weakness in the legs, mostly the muscles at the front of the thigh. Some researchers have found that blood vessels become inflamed and have suggested that this interrupts blood supply to the nerves. Medicines that target immune cells could be helpful.

Study characteristics

We found only one completed trial, which included 75 people who received methylprednisolone or a placebo. However the results have not been fully published and were not available for further scrutiny. The published abstract did not report adverse events. There is presently no evidence from any trial to show whether immunotherapies may benefit people with this condition.

We await results from trials to show whether corticosteroids, immunoglobulin or other treatments that act on the immune system have an effect in the treatment of diabetic amyotrophy.

Searches are up to date to September 2016.

BACKGROUND

The prevalence of diabetic peripheral neuropathy (DPN) reaches 50% for people who have had diabetes mellitus (DM) for more than 25 years (Sugimoto 2000). The most common form of DPN is a symmetrical, predominantly sensory polyneuropathy with distal onset and slow proximal progression. A less common but well-described form of the condition presents with acute or subacute, progressive, asymmetrical pain and weakness of the proximal lower limb muscles. This has been known as diabetic amyotrophy (DA), Bruns-Garland syndrome, diabetic myelopathy, diabetic mononeuritis multiplex, diabetic polyradiculopathy, femoral or femoral-sciatic neuropathy of diabetes, diabetic motor or paralytic neuropathy, proximal diabetic neuropathy, diabetic lumbosacral plexopathy or diabetic lumbosacral radiculoplexus neuropathies. The different names reflected uncertainty about the anatomical involvement and pathophysiology of the condition. Ischaemic injury, metabolic derangement, and inflammation have been proposed as causes. Many workers have also proposed that the condition has different clinical subtypes with different pathophysiology. Recent studies have helped to characterise its clinical and pathological features.

The lifelong incidence of DA is estimated to be 1% among people with diabetes (Dyck 1993; O'Hare 1994). It generally affects middle-aged or elderly people with type 2 DM. It may occur soon after diagnosis or be the presenting complaint that leads to the diagnosis of DM. Pain and weakness are the major symptoms at presentation and often begin proximally in a lower limb before progressing to other segments and the contralateral limb. The distal and proximal segments in both lower limbs may become affected to similar degrees. Severe pain occurs early, while weakness accompanied by muscle atrophy become the predominant features later. Most people have significant weight loss. Sensory symptoms of paraesthesia, allodynia and autonomic dysfunction may also be present. Some people have associated thoracic radiculopathies or upper limb weakness. The condition usually runs a monophasic course that can be protracted (up to three years) with the pain and weakness often causing significant disability. Recovery of function occurs without medical treatment in nearly everyone but may be slow and incomplete (Coppack 1991; Dyck 2002).

Cerebrospinal fluid of people with DA is usually acellular with a raised protein level. Erythrocyte sedimentation rates may be increased. Nerve conduction studies mainly show decreased amplitudes of lower limb motor and sensory action potentials and electromyography usually shows evidence of denervation in affected muscles, including paraspinal and thoracic-innervated muscles. Mildly prolonged distal latencies and F-wave minimal latencies as well as mild slowing of conduction velocities may be encountered. Biopsies of sural, superficial peroneal and lateral femoral nerves found features of ischaemic nerve injury and inflammatory infiltrates as well as immunoglobulin and complement depositions in the small blood vessel walls (Said 1994; Lewelyn 1998; Dyck 1999; Kelkar 2000). These suggest that the pathogenesis is due to immune-mediated microvasculitis. Kawamura 2008 studied sural nerve biopsies of people with DA and found increased expression of different inflammatory mediators in different cells at different disease stages, suggesting sequential involvement of the mediators in an immune-mediated inflammatory process.

A number of conditions share similar features but have unclear relationships with DA. Non-diabetic lumbosacral radiculoplexus neuropathy is a condition occurring in non-diabetic people that has similar clinical features, course, laboratory findings and outcome as DA (Dyck 2000; Dyck 2002). In diabetic neuropathic cachexia, people have weight loss and lower limb pain but no weakness (Ellenberg 1974). Occasionally, people with diabetes may present with progressive symmetrical bilateral proximal and distal lower limb weakness with little or no pain. It is uncertain if this represents a subtype of DA or the occurrence of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in DM. It has also been suggested that in the insidious onset symmetrical subtype of the condition, metabolic factors (hyperglycaemia) may be responsible for its pathophysiology (Chokroverty 1977). However, Garces-Sanchez 2011 found features of ischaemic injury and microvasculitis in the nerve biopsies of such individuals, similar to biopsies in people with DA.

Consistent with an immune-mediated microvasculitis pathogenesis, retrospective studies and prospective case series have suggested that immunotherapy for DA may be effective in reducing pain and improving strength (Bradley 1984; Krendel 1995; O'Neill 1997; Pascoe 1997; Jaradeh 1999; Kilfoyle 2003; Tamburin 2009). At present, to our knowledge and following extensive searching, only one randomised study, in which intravenous methylprednisolone (MP) was used, has been completed (Dyck 2006).

This review was first published in 2009 and updated in 2012 and 2017.

OBJECTIVES

To review the evidence from randomised trials for the efficacy of any form of immunotherapy in the treatment of diabetic amyotrophy.

METHODS

Criteria for considering studies for this review

Types of studies

We intended to include all controlled clinical trials that allocate treatment in a genuinely random fashion based on a random number table or computer algorithm or physical process (for example coin toss, dice roll, draws from a bag etc.) or in a quasi-random fashion based on an alternative non-random scheme (for example even/odd, days of the week etc.). Studies that declared themselves to be randomised controlled trials (RCTs) but did not clearly specify the randomisation method would also have been included.

Types of participants

Eligible studies had to include participants of any age or sex with diabetic amyotrophy (DA) satisfying all of the following clinical criteria.

1. Diabetes mellitus as defined by internationally recognised criteria.
2. Acute or subacute onset of pain and lower motor neuron weakness involving predominantly the proximal muscles of the lower limbs.

3. Weakness that is not confined to one nerve or nerve root distribution.
4. Exclusion of other causes of lumbosacral radiculopathies and plexopathy.

Types of interventions

We would have included results for any form of immunotherapy compared with placebo, no treatment or other treatments administered for any duration.

Types of outcome measures

Primary outcomes

- Time from randomisation to improvement in Neuropathy Impairment Scale (NIS) (Dyck 1980) by four points (time-to-event). We selected this outcome measure because the natural history of the condition without treatment is slow recovery and also because this is the outcome measure used in the only known completed RCT of immunotherapy in this condition (Dyck 1980).

Where this outcome was not available we would have used:

- time from randomisation to a clinically significant improvement with whatever scale was used by the authors (time-to-event).

Secondary outcomes

1. Change in grades of a disability scale, such as the Modified Rankin Scale (Van Swieten 1988) at least 12 weeks after treatment onset.
2. Change in sum score of an impairment scale, such as the Mayo Neuropathy Impairment Scale (Dyck 1980) or the Medical Research Council (MRC) sum score (Kleyweg 1991) at least 12 weeks after treatment onset.
3. Change in any measure of neuropathy symptoms, such as the Neuropathy Symptom and Change (NSC) score (Grant 1999) at least four weeks after treatment onset.
4. Change in analogue pain scale at least four weeks after treatment onset.
5. Change in summated compound muscle action potential (Dyck 1994) of lower limb nerves at least 12 weeks after treatment onset.
6. Adverse effects encountered during the treatment period.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Neuromuscular Specialised Register (5 September 2016), the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 8) in the Cochrane Library (searched 5 September 2016, MEDLINE (January 1966 to August 2016) and Embase (January 1980 to August 2016). There was no language restriction on searching. We tried to identify additional studies by searching www.controlled-trials.com, and www.clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/default.aspx) and we searched the reference lists of review publications. We contacted authors of relevant publications and other experts in order to obtain additional references, unpublished trials, and ongoing trials.

The detailed search strategies are in the appendices: Cochrane Neuromuscular Specialised Register (Appendix 1), CENTRAL (Appendix 2), MEDLINE (Appendix 3), Embase (Appendix 4), and clinical trials registries (Appendix 5).

Data collection and analysis

Selection of studies

Two review authors (CYC, LYL) independently examined all references retrieved by the search. They would have obtained the full text of all potentially relevant studies and independently selected those meeting the inclusion criteria had these been available. Any disagreements would have been resolved by discussion amongst the three review authors.

Data extraction and management

Two review authors (CYC, LYL) would have extracted the data independently using a piloted data extraction form if studies reported in full text had been available. We would have resolved differences in data extraction by discussion and reference to the original article. We would have contacted authors to provide missing data if necessary.

Assessment of risk of bias in included studies

We would have assessed the risk of bias of the included studies as described in Chapter 8 (Assessing risk of bias in included studies) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements would have been resolved by discussion amongst the three review authors.

Measures of treatment effect

We would have used the Cochrane software Review Manager 5 (RevMan 5) to compute the following comparative statistics and their 95% confidence intervals. We would have summarised time-to-event outcomes using hazard ratios where possible, or proportion surviving to a defined time point. We would have summarised dichotomous outcomes using risk ratios and mean differences. Any pooling of mean differences would have been by a method of differences of means. We would have dichotomised short ordinal outcomes if possible. We would have reported relevant outcome summaries that had been reported in studies as median scores but would only have pooled them if standard errors were also reported. We would have reported change scores for follow-up periods other than 12 weeks and would have pooled them with other change scores measured over a similar period of follow-up.

Assessment of heterogeneity

We would have tested for statistical heterogeneity between trials using the I^2 statistic as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

Studies judged clinically homogeneous by their design and inclusion criteria would have been candidates for pooling by the fixed-effect model. Persistent unexplained statistical heterogeneity might have resulted in a decision not to pool or to pool using a random-effects model in a sensitivity analysis.

We did not create a 'Summary of findings' table as full details of the study results were not available for adequate evaluation of outcomes.

Subgroup analysis and investigation of heterogeneity

If we had found heterogeneity, attempts would have been made to identify the studies responsible and to find clinical reasons for it.

If data had allowed, we would have undertaken a subgroup analysis to test the effect of interventions in participants presenting with asymmetrical weakness and pain and those with symmetrical weakness with minimal pain.

Sensitivity analysis

The effect of differing risks of bias (randomisation, blinding etc.) and of fixed-effect versus random-effects meta-analysis would have been explored by sensitivity analyses.

We have taken into account evidence from non-randomised studies for adverse events of treatments and presented these in the [Discussion](#).

R E S U L T S

Description of studies

Results of the search

See [Figure 1](#) for a PRISMA flow chart showing the study selection process for this (second) update. We identified 73 new records (Cochrane Neuromuscular Specialised Register 14, CENTRAL 4, MEDLINE 36, and Embase 19) and removed one duplicate. We identified no full-text reports for evaluation but included one trial, reported only as an abstract, in the review. We identified no ongoing studies.

Figure 1. Study flow diagram.

For the first version of the review, searches on MEDLINE and Embase using the adopted strategies returned 476 and 1159 results respectively. We ran a more specific search for the first update which retrieved 177 references from MEDLINE, 49 from Embase, none from CENTRAL and 16 from the Cochrane Neuromuscular Disease Group Specialised Register.

Included studies

We found only one completed controlled trial using intravenous methylprednisolone (MP) in diabetic amyotrophy (DA) ([Dyck 2006](#)). The results have been published in abstract form. This was a multicentre, double-blind controlled trial of intravenous MP in DA (see [Characteristics of included studies](#)). Seventy-five participants (44 men and 31 women) with a mean age of 65.3 years (range 36 to 81) were included. Forty-nine participants received MP,

initially 1 g three times weekly, with decreasing dosage and frequency over 12 weeks, while 26 participants received placebo. Age, gender, diabetes type, height, weight, body mass index (BMI), and impairments (Neuropathy Impairment Scale (NIS) or NIS lower limbs (NIS (LL))) in the two groups of participants were not significantly different at baseline. Participants were assessed at intervals from baseline until week 104.

A previously ongoing controlled trial of intravenous immunoglobulin (IVIg) in DA (NCT00004407) was not finished due to the lack of the intervention drug (IVIg) and funding. We found reports of immunotherapy in series of people with DA (Bradley 1984; Krendel 1995; O'Neill 1997; Pascoe 1997; Jaradeh 1999; Kilfoyle 2003; Zochodne 2003; Tamburin 2009), and have reported these in the Discussion.

Risk of bias in included studies

As Dyck 2006, the single completed study, has not undergone peer review and is currently unpublished, there is high risk of bias for selective reporting. The study was reported in the abstract as a randomised, double-blind study. However, the methods for sequence generation and allocation concealment are not known. It is unclear which group of people were blinded.

Effects of interventions

Intravenous methylprednisolone versus placebo

Predetermined outcomes cannot be reported due to incomplete details, and results were reported as given by the investigators in the published abstract of Dyck 2006.

Primary outcome: time to improvement

The mean NIS and NIS (LL) significantly improved in both groups over 104 weeks ($P < 0.0001$). The primary study endpoint — time to improve NIS (LL) by four points — was not significantly different between the two groups.

Secondary outcomes

Data on change in grades of a disability scale, change in sum score of an impairment scale, change in analogue pain scale, and change in summated compound muscle action potential of lower limb nerves after treatment onset were not available.

However, over two years, the number of neuropathic symptoms decreased more in the MP group compared to the placebo group (NSC, $P = 0.059$).

Many of the NSC subscores (including NSC-lower limb, NSC-positive neuropathic sensory symptoms, NSC-pain) were also reported as better in the MP group, especially to week 24. However complete results are not available.

The published abstract did not report adverse events.

DISCUSSION

Summary of main results

Randomised studies

The results of one multicentre, double-blind controlled trial of intravenous MP, involving 75 participants, have been presented in abstract form but not fully published (Dyck 2006). The primary

study endpoint — time to improve NIS (LL) by four points — was not significantly different between the two groups. The number of neuropathic symptoms, a secondary outcome, decreased more in the MP group compared to the placebo group. Other secondary outcomes, including NSC-lower limb, NSC-positive neuropathic sensory symptoms, and NSC-pain were also significantly better in the MP group,

Other evidence (non-randomised studies)

Prior to the controlled trial using intravenous methylprednisolone (MP) in diabetic amyotrophy (DA) (Dyck 2006), several case series reported benefits of immunotherapy in improving pain and strength (Table 1), though one did not.

A total of 15 people from the patient series of Said 1994, Krendel 1995, Pascoe 1997 and Kilfoyle 2003 were treated with corticosteroids alone. Twelve people were considered to have improved with treatment. Said and colleagues treated three people with prednisolone: all three had rapid relief of pain within days after treatment. One had no weakness; the strength in the other two recovered over several months. Kilfoyle 2003 treated 10 episodes of DA in nine people with oral or intravenous MP. They received 500 mg of MP daily for two days every two weeks for up to three months. In six episodes, there was a marked improvement in pain within days of starting treatment. Pain resolved in seven episodes within three months of symptoms onset. Moderate or severe weakness resolved or markedly improved after three months of treatment in seven episodes. The authors considered that these improvements occurred faster than the expected natural history of DA. Treatment started within two months of symptom onset was associated with rapid improvement in pain, while treatment within four weeks of symptom onset resulted in rapid improvement of both strength and pain. Pascoe 1997 did not report any adverse effects. Two people in the Said 1994 series had an increase of glycaemia requiring insulin administration. Among the six people that received prednisolone in the Krendel 1995 series, five had increased requirements or a new requirement for insulin to control glycaemia, one had heart failure, one had corticosteroid myopathy, one had insomnia, one had gastrointestinal haemorrhage and one committed suicide during treatment. Similarly in the Kilfoyle 2003 series, administrations of MP were associated with transient asymptomatic hyperglycaemia and one person required temporary insulin treatment. Another person had mild transient elevation of blood pressure and visual hallucination. Insomnia and irritability were also reported during MP treatments.

Monotherapy with IVIg was given to a total of 17 people from the patient series of Krendel 1995, Pascoe 1997 and Jaradeh 1999. All were considered to have improved from treatment. Only Krendel 1995 reported adverse effects: two people had a rash and one had staphylococcal sepsis.

Plasma exchange (PE) as monotherapy was given to 14 people from the Pascoe 1997 and Jaradeh 1999 series. All except one improved.

The 15 people in the Krendel 1995 series were treated after their DA had progressed for between one to 15 months (average five months). Eight were given IVIg, three were given prednisolone, two were given a combination of IVIg and prednisolone, one had a combination of IVIg, prednisolone and IV cyclophosphamide and another a combination of IVIg and IV cyclophosphamide as initial therapies. In all cases, worsening stopped when treatment began

and there was a subsequent improvement in strength of at least one grade on the Medical Research Council scale. Performance of activities of daily living improved in at least 12. Recovery was complete or nearly complete in five people.

[Pascoe 1997](#) retrospectively reviewed 44 people with DA seen over a 12-year period. Of 12 people who received immunotherapy, nine (75%) had improvement but 17 of 29 untreated people with DA (59%) also eventually improved. They considered those treated to have had greater deficits but faster and greater improvement than those who were untreated.

[Jaradeh 1999](#) treated 15 people with diabetes and progressive polyradiculoneuropathy with immunotherapy. Nine received PE, six received IVIg. All had proximal and distal lower limb weakness which was often asymmetrical. Most had pronounced radicular pain and significant weight loss. These features suggest the diagnosis of DA. However, of the eight people who had proximal and distal upper limb weakness, two also had facial weakness and another two required respiratory assistance, and may have had a condition closer to chronic inflammatory demyelinating polyradiculoneuropathy. After immunotherapy, all of those studied had no further deterioration and had dramatic subjective improvement, in particular rapid resolution of their pain. The improvement in neuropathy disability score weakness subset (NDSW) averaged 9.0 (SD 5.1) points at week six, and 29.1 (SD 9.3) points by week 52.

In a prospective case series ([Tamburin 2009](#)), five people with severe pain from DA received IVIg treatment after having no response to symptomatic therapy for pain and corticosteroids. Four had a decrease in pain. The authors report that scores on a visual analogue scale for pain, the Medical Research Council scale for lower limb strength and walking distance improved significantly at one month.

In contrast, [Zochodne 2003](#) reported a person who developed DA while on an immunosuppressive regimen consisting of ciclosporin and mycophenolate mofetil for an allograft cardiac transplant and two people with DA who did not respond to IVIg treatments.

Because the natural history of DA is that of spontaneous improvement, it is not possible to be certain from case series if immunotherapy had improved the condition. The single completed intravenous MP controlled trial suggested that MP may help neuropathic symptoms but does not hasten recovery of strength ([Dyck 2006](#)). However, the study data are unpublished. There is an urgent need for the data to be peer reviewed and published. Future trials are also necessary to investigate the effect of earlier treatment, different immunotherapeutic agents, dosages and schedules.

Recent studies have increased the evidence for immune-mediated inflammatory microvasculitis causing ischaemic damage

to nerves as the pathogenic process in DA. Early institution of immunotherapy may therefore be expected to improve the condition.

Overall completeness and applicability of evidence

Our review included one RCT that has not been fully published. The number of participants in the RCT is low. Full details of the methods and results are not known and there is high risk of bias from selective reporting. The evidence cannot be regarded as complete and the applicability in determining whether immunotherapy is beneficial in DA is questionable.

Quality of the evidence

Our review included one RCT that has not been fully published. The results have only been presented in abstract form and thus has a high risk of bias from selective reporting. Otherwise, only anecdotal evidence from non-randomised case series is available. Thus, this can be classified as low-quality evidence (down-graded randomised trials; or observational studies).

Potential biases in the review process

The searches were likely to have detected any other RCT on immunotherapy in DA. There was no potential bias.

Agreements and disagreements with other studies or reviews

The review by [Bhanushali 2008](#) did not include the result of the intravenous MP controlled trial ([Dyck 2006](#)). It concluded that there is limited data on the efficacy of immunotherapy for the condition. To our knowledge, there is no other systematic review on immunotherapy in DA.

AUTHORS' CONCLUSIONS

Implications for practice

There is presently no evidence from RCTs to support the use of any immunotherapy treatment in DA.

Implications for research

Results from the completed RCT in which intravenous MP was used and the closed but unpublished RCT on the use of IVIg in DA should help determine whether immunotherapy is beneficial in DA. Future trials should also evaluate the effect of earlier treatment, different immunotherapeutic agents, dosages and schedules.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Dyck 2006

Methods	Randomised, double-blind, placebo-controlled study.
Participants	75 participants (44 men and 31 women) with a mean age of 65.3 years (range 36 to 81).
Interventions	Intravenous methylprednisolone or placebo.
Outcomes	Assessments were done at baseline, weeks 1, 6, 12, 24, 36, 52 and finally at week 104. 1. Time to improve NIS (LL) by four points (primary endpoint). 2. Change in mean NIS and NIS(LL). 3. Change in NSC.
Notes	Study findings presented in abstract form but unpublished.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was a randomised study. However, it has not undergone peer review and is currently unpublished. The methods for sequence generation are not known.

Dyck 2006 (Continued)

Allocation concealment (selection bias)	Unclear risk	Study has not undergone peer review and is currently unpublished. The methods for allocation concealment are not known.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was a double blind study. However, it has not undergone peer review and is currently unpublished. It is uncertain which participants and personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was a double blind study. However, it has not undergone peer review and is currently unpublished. It is unclear who was or was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study has not undergone peer review and is currently unpublished. It is uncertain if all participants completed the study or if there were losses to follow-up and treatment withdrawal.
Selective reporting (reporting bias)	High risk	Study has not undergone peer review and is currently unpublished. The abstract provides selective reporting of the results.
Other bias	Unclear risk	Study has not undergone peer review and is currently unpublished. It is uncertain if there may be other bias.

LL: lower limb; NSC; Neuropathy Symptom and Change; NIS: Neuropathy Impairment Scale

ADDITIONAL TABLES

Table 1. Case series of immunotherapy in diabetic amyotrophy

	Treatment	Outcomes	Adverse effects
Said 1994	3 people received prednisolone.	All 3 people had rapid relief of pain within days after treatment. 1 had no weakness. The strength in the other 2 recovered over several months.	In 2 people, treatment with corticosteroids led to increase of glycaemia requiring insulin administration.
Krendel 1995	8 people received IVIg. 3 people received prednisolone. 2 people received a combination of IVIg and prednisolone. 1 people received combination of IVIg, prednisolone and IV cyclophosphamide. 1 people received combination of IVIg and IV cyclophosphamide.	In all of those treated, worsening stopped when treatment began and there was a subsequent improvement in strength of at least 1 grade on the MRC scale. Performance of activities of daily living improved in at least 12. Recovery was complete or nearly complete in 5.	Among the people that received prednisolone, 5 had increased requirements or a new requirement for insulin to control glycaemia, 1 had heart failure, 1 had corticosteroid myopathy, 1 had insomnia, 1 had gastrointestinal haemorrhage and 1 committed suicide during treatment. Among the people that received IVIg, 2 had a rash and 1 had staphylococcal sepsis.
Pascoe 1997	3 people received prednisolone. 5 people received PE. 3 people received IVIg.	All improved, except 1 who received prednisolone, 1 who received PE and the 1 who had both PE and IVIg.	Not reported

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Table 1. Case series of immunotherapy in diabetic amyotrophy *(Continued)*

	1 people received PE and IVIg.		
Jaradeh 1999	9 people received PE. 6 people received IVIg.	All had no further deterioration and had dramatic subjective improvement, in particular rapid resolution of their pain. The improvement in neuropathy disability score weakness subset averaged 9.0 (SD 5.1) points at week six, and 29.1 (SD 9.3) points by week 52.	Not reported
Kilfoyle 2003	10 episodes of DA in 9 people were treated with oral or intravenous MP.	In 6 episodes, there was a marked improvement in pain within days of starting treatment. Pain resolved in 7 episodes within 3 months of symptoms' onset. Moderate or severe weakness resolved or markedly improved after 3 months of treatment in 7 episodes.	Administrations of MP were associated with transient asymptomatic hyperglycaemia and 1 person required temporary insulin treatment. Another person had mild transient elevation of blood pressure and visual hallucination. Insomnia and irritability were also reported during MP treatments.
Zochodne 2003	1 person developed DA while on an immunosuppressive regimen consisting of ciclosporin and mycophenolate mofetil. 2 people received IVIg.	Progression of pain and weakness despite treatment.	Not reported
Tamburin 2009	5 people received IVIg. 2 of those treated had repeat IVIg treatment due to pain recurrence after 7 to 18 months.	4 had reduction of severe pain starting 5 to 10 days after IVIg infusion. Visual analogue scale for pain, MRC scale for lower limb strength and walking distance improved significantly at 1 month. The 2 with pain recurrence also improved with further IVIg treatment.	None

IVIg: intravenous immunoglobulin; MRC: Medical Research Council; PE: plasma exchange; DA: diabetic amyotrophy; MP: methylprednisolone

APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register (CRS) search strategy

("diabetic amyotrophy" or "diabetic myelopathy" or "diabetic mononeuritis" or "diabetic polyradiculoneuropathy" or (diabetic and ("motor neuropathy" or "paralytic neuropathy")) or ("diabetic neuropathy" and proximal) or (diabetic and microvasculitis) or "diabetic lumbosacral plexopathy" or "diabetic lumbosacral radiculoplexus" or "diabetic radiculopathy" or "diabetic femoral" or "diabetic sciatic" or "diabetic neuropath*") and (immunotherapy or "adrenal cortex hormones" or immunoglobulins or IGG or immunotherap* or immunologic or immunosuppress* or glucocorticoid* or cortico* or steroid* or methylprednis* or predniso*)

Appendix 2. CENTRAL (CRSO) search strategy

#1 ("bruns garland"):TI,AB,KY
 #2 ("diabetic amyotroph*"):TI,AB,KY
 #3 ("diabetic mononeuritis multiplex"):TI,AB,KY
 #4 ("diabetic polyradiculopath*"):TI,AB,KY
 #5 ("motor neuropath*" NEAR diabet*):TI,AB,KY
 #6 ("paralytic neuropath*" NEAR diabet*):TI,AB,KY
 #7 ("proximal neuropathy" NEAR diabet*):TI,AB,KY

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#8 ("diabetic neuropathy" NEAR proximal):TI,AB,KY
#9 (diabet* NEAR microvasculitis):TI,AB,KY
#10 ("diabet* lumbosacral plexopathy"):TI,AB,KY
#11 ("diabet* lumbosacral radiculoplexus"):TI,AB,KY
#12 ("diabet* radiculopath*"):TI,AB,KY
#13 ("diabet* femoral" NEAR neuropath*):TI,AB,KY
#14 ("diabetic sciatic neuropath*"):TI,AB,KY
#15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16 MESH DESCRIPTOR Immunotherapy EXPLODE ALL TREES
#17 MESH DESCRIPTOR Glucocorticoids EXPLODE ALL TREES
#18 MESH DESCRIPTOR Immunoglobulins EXPLODE ALL TREES
#19 MESH DESCRIPTOR Adrenal Cortex Hormones EXPLODE ALL TREES
#20 (immunotherapy* or immunologic or immunoglobulin* or immunosuppress* or glucocorticoid* or cortico* or steroid*):TI,AB,KY
#21 (methylprednisolone or prednisolone or prednisone):TI,AB,KY
#22 #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #15 AND #22
```

Appendix 3. MEDLINE (OvidSP) search strategy

Ovid MEDLINE(R) 1946 to August Week 4 2016

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 randomized controlled trial.pt. (429552)
2 controlled clinical trial.pt. (91634)
3 randomized.ab. (368786)
4 placebo.ab. (178430)
5 drug therapy.fs. (1902478)
6 randomly.ab. (262645)
7 trial.ab. (383644)
8 groups.ab. (1634679)
9 or/1-8 (3891094)
10 exp animals/ not humans.sh. (4306043)
11 9 not 10 (3356638)
12 bruns garland.mp. (5)
13 diabetic amyotroph$.mp. (140)
14 diabetic myelopath$.mp. (9)
15 diabetic mononeuritis multiplex.mp. (1)
16 diabetic polyradiculopath$.mp. (6)
17 ((motor neuropath$ or paralytic neuropath$) adj3 diabet$.mp. (36)
18 (proximal neuropathy adj3 diabet$.mp. (10)
19 (diabetic neuropathy adj3 proximal).mp. (25)
20 (diabet$ and microvasculitis).mp. (32)
21 diabet$ lumbosacral plexopathy.mp. (3)
22 diabet$ lumbosacral radiculoplexus.mp. (27)
23 diabet$ radiculopath$.mp. (13)
24 (diabet$ femoral adj3 neuropath$.mp. (2)
25 diabet$ sciatic neuropath$.mp. (1)
26 exp diabetic neuropathies/ (19191)
27 or/12-26 (19267)
28 11 and 27 (5389)
29 exp Immunotherapy/ (240080)
30 exp Adrenal Cortex Hormones/ (367242)
31 exp immunoglobulins/ (803904)
32 (immunotherap$ or immunologic or immunoglobulin$ or immunosuppress$ or glucocorticoid$ or cortico$ or steroid$.mp. (1192406)
33 (methylprednisolone or prednisolone or prednisone).mp. (105898)
34 or/29-33 (1913613)
35 11 and 27 and 34 (217)
36 remove duplicates from 35 (212)
```

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1980 to 2016 Week 36>

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Search Strategy:

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1 crossover-procedure.sh. (48506)
2 double-blind procedure.sh. (131292)
3 single-blind procedure.sh. (22979)
4 randomized controlled trial.sh. (416151)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (1292707)
6 trial.ti. (206846)
7 or/1-6 (1445251)
8 (animal/ or nonhuman/ or animal experiment/) and human/ (1518818)
9 animal/ or nonanimal/ or animal experiment/ (3627983)
10 9 not 8 (2995609)
11 7 not 10 (1330863)
12 limit 11 to embase (1096531)
13 diabetic neuropathies/ (11433)
14 bruns garland.mp. (9)
15 diabetic myelopath$.mp. (7)
16 diabetic amyotroph$.mp. (176)
17 diabetic mononeuritis multiplex.mp. (1)
18 diabetic polyradiculopath$.mp. (8)
19 ((motor neuropath$ or paralytic neuropath$) adj3 diabet$).mp. (46)
20 (proximal neuropathy adj3 diabet$).mp. (19)
21 (diabetic neuropathy adj3 proximal).mp. (35)
22 (diabet$ and microvasculitis).mp. (44)
23 diabet$ lumbosacral plexopath$.mp. (7)
24 diabet$ lumbosacral radiculoplexus.mp. (54)
25 diabet$ radiculopath$.mp. (16)
26 (diabet$ femoral adj3 neuropath$).mp. (2)
27 diabet$ sciatic neuropath$.mp. (1)
28 or/13-27 (11646)
29 exp immunotherapy/ (149656)
30 exp glucocorticoid/ (596688)
31 exp immunoglobulin/ (394462)
32 (immunotherap$ or immunologic or immunoglobulin$ or immunosuppress$ or glucocorticoid$ or cortico$ or steroid$).mp. (1567417)
33 (methylprednisolone or prednisolone or prednisone).mp. (298719)
34 or/29-33 (1896493)
35 12 and 28 and 34 (37)
36 remove duplicates from 35 (36)

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Appendix 5. Current Controlled Trials, ICTRP and ClinicalTrials.gov

The following terms were used:

diabetic amyotrophy

diabetic lumbosacral radiculoplexus neuropathy

diabetic neuropathy

WHAT'S NEW

Date	Event	Description
5 September 2016	New search has been performed	Searches updated.
5 September 2016	New citation required but conclusions have not changed	No new studies identified from searches. One study previously listed as 'unpublished' has been re-categorized as 'included' while one previously 'ongoing' study was re-categorized as 'excluded'.

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 3, 2009

Date	Event	Description
20 March 2012	New citation required but conclusions have not changed	New searches were run in February 2012. No new randomised trials were identified for inclusion
25 February 2012	New search has been performed	The discussion has been updated with two additional case series
24 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Dr Yee Cheun Chan wrote the [Background](#), [Results](#) and [Discussion](#).

Dr Yee Cheun Chan and Dr Yew Loong Lo independently examined all references retrieved by the search to select those meeting the inclusion criteria.

Dr Edwin SY Chan wrote the [Methods](#).

DECLARATIONS OF INTEREST

There are no potential conflicts of interest for any of the authors.

SOURCES OF SUPPORT

Internal sources

- National University Hospital, Singapore.
- National Neuroscience Institute, Singapore.
- Singapore Clinical Research Institute, Singapore.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We searched only the Cochrane Neuromuscular Trials Register, MEDLINE (January 1966 to the present), Embase (January 1980 to the present), www.controlled-trials.com, ICTRP and www.clinicaltrials.gov. We contacted authors of relevant publications and other experts in order to obtain additional references, unpublished trials, and ongoing trials. Omitted resources — Science Citation Index, BIOSIS, Web of Science Proceedings and International Pharmaceutical Abstracts — were considered unlikely to yield relevant studies. We made minor revisions to the analysis section of the Methods to comply with current Cochrane standards and stated how we would resolve any disagreements regarding study selection. Two review authors independently assessed Risk of bias (CYC and LYL).

INDEX TERMS

Medical Subject Headings (MeSH)

Diabetic Neuropathies [*drug therapy]; Immunotherapy [*methods]; Injections, Intravenous; Methylprednisolone [*administration & dosage]; Neuroprotective Agents [*administration & dosage]

MeSH check words

Humans