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Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis (Review)

Gordon PA, Winer JB, Hoogendijk JE, Choy EHS

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[Intervention Review]

Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis

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ABSTRACT

Background

Idiopathic inflammatory myopathies are chronic diseases with significant mortality and morbidity. Whilst immunosuppressive and immunomodulatory therapies are frequently used, the optimal therapeutic regimen remains unclear. This is an update of a review first published in 2005.

Objectives

To assess the effects of immunosuppressants and immunomodulatory treatments for dermatomyositis and polymyositis.

Search methods

We searched the Cochrane Neuromuscular Disease Group Specialized Register (August 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 3 2011), MEDLINE (January 1966 to August 2011), EMBASE (January 1980 to August 2011) and clinicaltrials.gov (August 2011). We checked the bibliographies of identified trials and wrote to disease experts.

Selection criteria

We included all randomised controlled trials (RCTs) or quasi-RCTs involving participants with probable or definite dermatomyositis and polymyositis as defined by the criteria of Bohan and Peter, or definite, probable or mild/early by the criteria of Dalakas. In participants without a classical rash of dermatomyositis, inclusion body myositis should have been excluded by muscle biopsy. We considered any immunosuppressant or immunomodulatory treatment. The two primary outcomes were the change in a function or disability scale measured as the proportion of participants improving one grade, two grades etc, predefined based on the scales used in the studies after at least six months, and a 15% or greater improvement in muscle strength compared with baseline after at least six months. Other outcomes were: the International Myositis Assessment and Clinical Studies Group (IMACS) definition of improvement, number of relapses and time to relapse, remission and time-to-remission, cumulative corticosteroid dose and serious adverse effects.

Data collection and analysis

Two authors independently selected papers, extracted data and assessed risk of bias in included studies. They collected adverse event data from the included studies.

Main results

The review authors identified 14 relevant RCTs. They excluded four trials.

Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis (Review)

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The 10 included studies, four of which have been added in this update, included a total of 258 participants. Six studies compared an immunosuppressant or immunomodulator with placebo control, and four studies compared two immunosuppressant regimes with each other. Most of the studies were small (the largest had 62 participants) and many of the reports contained insufficient information to assess risk of bias.

Amongst the six studies comparing immunosuppressant with placebo, one study, investigating intravenous immunoglobulin (IVIg), showed statistically significant improvement in scores of muscle strength in the IVIg group over three months. Another study investigating etanercept showed some evidence of a longer median time to relapse in the etanercept group, a secondary outcome in this review, but no improvement in other assessed outcomes. The other four randomised placebo-controlled trials assessed either plasma exchange and leukapheresis, eculizumab, infliximab or azathioprine against placebo and all produced negative results.

Three of the four studies comparing two immunosuppressant regimes (azathioprine with methotrexate, ciclosporin with methotrexate, and intramuscular methotrexate with oral methotrexate plus azathioprine) showed no statistically significant difference in efficacy between the treatment regimes. The fourth study comparing pulsed oral dexamethasone with daily oral prednisolone and found that the dexamethasone regime had a shorter median time to relapse but fewer side effects.

Immunosuppressants were associated with significant side effects.

Authors' conclusions

This systematic review highlights the lack of high quality RCTs that assess the efficacy and toxicity of immunosuppressants in inflammatory myositis.

PLAIN LANGUAGE SUMMARY

Drugs that suppress or modify the immune system for dermatomyositis and polymyositis

Dermatomyositis and polymyositis are long-term inflammatory muscle diseases, causing muscle weakness and disability. For some reason, the body's immune system turns against its own muscles in an autoimmune response. Corticosteroids are the principal treatment but due to side effects, there is a need for additional treatment with drugs that suppress the immune system (immunosuppressants) or modify it (immunomodulatory therapies) to improve patient outcomes. For this review, an update of a review first published in 2005, we found ten randomised trials available, involving 258 participants.

Amongst the six studies comparing immunosuppressant with placebo, one study, investigating intravenous immunoglobulin (IVIg), showed statistically significant improvement in scores of muscle strength in the IVIg group over three months. Another study investigating etanercept showed some evidence of a longer median time to relapse in the etanercept group, a secondary outcome in this review, but no improvement in other assessed outcomes. The other four randomised placebo-controlled trials assessed either plasma exchange and leukapheresis, eculizumab, infliximab or azathioprine against placebo and all produced negative results.

Three of the four studies comparing two immunosuppressant regimes (azathioprine with methotrexate, ciclosporin with methotrexate, and intramuscular methotrexate with oral methotrexate plus azathioprine) showed no statistically significant difference in efficacy between the treatment regimes. The fourth study comparing pulsed oral dexamethasone with daily oral prednisolone and found that the dexamethasone regime had a shorter median time to relapse but fewer side effects.

Most of the studies were small (the largest had 62 participants) and many of the reports contained insufficient information to assess risk of bias. Immunosuppressants were associated with significant side effects. The small number of RCTs of immunosuppressants and immunomodulatory therapies are inadequate to decide whether these agents are beneficial in dermatomyositis and polymyositis. Two small trials, one of IVIg in dermatomyositis, the other of etanercept in dermatomyositis suggested that they are beneficial. More RCTs are needed.

BACKGROUND

The inflammatory myopathies include recognised causes of muscle inflammation such as those due to infection by bacteria, viruses and parasites. Idiopathic inflammatory myopathies refer to diseases in which muscle inflammation occurs without a recognised infective cause and these include dermatomyositis and polymyositis. Such diseases are thought to result from an auto-immune process. Dermatomyositis and polymyositis are characterised by chronic inflammation of skeletal muscle which can result in persisting muscle weakness with significant disability (Dalakas 1991; Dalakas 2001). They may both occur in association with gastrointestinal, pulmonary and cardiac dysfunction, while only dermatomyositis has skin involvement. The prevalence of idiopathic inflammatory myositis is approximately 11 per 100,000 (Ahlgren 1993). As idiopathic inflammatory myositis is uncommon, optimal therapy has not been adequately defined (Choy 2002).

Corticosteroids are the principal treatment. Both high- and low-dose corticosteroid regimes are used. In many people, long-term high dose corticosteroids are necessary to control disease and, in a few people, myositis may be refractory to steroid treatment. Therefore, many people with an idiopathic inflammatory myopathy suffer from the side effects of corticosteroids. The mortality and morbidity of inflammatory myositis remains high despite such treatment (Carpenter 1977; Joffe 1993; Riddoch 1975). Thus, there is a frequent need to use additional treatment both to improve the disease response and to reduce the side effects of corticosteroids.

Immunosuppressive agents, especially azathioprine, methotrexate, mycophenolate mofetil and ciclosporin, are commonly used in autoimmune diseases as well as in transplant rejection and chronic inflammatory diseases. They are usually employed as second-line therapy to corticosteroids for disease refractory to steroid treatment alone. They can also be used as adjuvants to steroid treatment to allow reduction in the dosage of corticosteroids and thereby decrease the risk of long-term complications. While these treatments are in use for dermatomyositis and polymyositis, the optimal therapeutic regimen remains unclear (Choy 2002). Biological agents, in particular the anti-TNF agents and the B-cell depleting agent rituximab, are also presently being assessed as potential therapeutic agents in the inflammatory myopathies.

An alternative approach to improving the treatment of dermatomyositis and polymyositis is the use of immunomodulatory therapy. This includes interferon, intravenous immunoglobulin (IVIg) and plasma exchange which have proven efficacy in various autoimmune disorders. They are gaining attention as possible second-line treatment for polymyositis and dermatomyositis (Choy 2002; Dalakas 2001).

This is an update of a Cochrane review first published in 2005.

OBJECTIVES

To assess the effects of immunosuppressants and immunomodulatory treatments for dermatomyositis and polymyositis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs (trials in which allocation is not strictly random but is based, for example, on case record number or date of birth).

Types of participants

People with probable or definite dermatomyositis and polymyositis as defined by the criteria of Bohan and Peter (Bohan 1975 a; Bohan 1975 b) (Table 1) or definite, probable or mild/early by the criteria of Dalakas (Dalakas 1991) (Table 2). In participants without a classical rash of dermatomyositis, inclusion body myositis should have been excluded by muscle biopsy. If no diagnostic criteria were cited, all the assessors would have judged the quality of evidence for correct diagnosis. The study was included in the review only if the assessors agreed that the participants had probable or definite dermatomyositis or polymyositis.

Types of interventions

Any immunosuppressant or immunomodulatory treatment including corticosteroids, azathioprine, methotrexate, ciclosporin, chlorambucil, cyclophosphamide, IVIg, interferon and plasma exchange in dermatomyositis and polymyositis, compared with placebo, no treatment or another immunosuppressant or immunomodulatory treatment.

Types of outcome measures

Primary outcomes

1. Change in a function or disability scale after at least six months, measured as the proportion of participants improving one grade, two grades etc, predefined based on the scales used in the studies after at least six months. In order to harmonise results we planned to try to convert the results from all studies to either the disability scale that is used in most studies or to one which seemed to us most appropriate.
2. A 15% or greater improvement in muscle strength compared with baseline after at least six months.

Secondary outcomes

1. Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement (DOI) after at least six months. The definitions of improvement use six core set measures among five domains (Oddis 2005; Rider 2004). These core set measures are: the physician global disease activity, parent/patient global disease activity, muscle strength (manual muscle testing (MMT)), physical function assessment, laboratory assessment and extramuscular disease complications. Improvement is defined as occurring if three of any six core set measures improve by 20%, with no more than two worsening by 25% (measures that worsen cannot include manual muscle strength).
2. Number of relapses and time to relapse.
3. Remission and time-to-remission (remission is modified Rankin score of 0 or 1) (Van Swieten 1988) after at least six months.
4. Cumulative corticosteroid dose after at least six months.

5. Serious adverse effects as defined by any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

In this update we included 'Summary of findings' tables showing our primary outcomes and the first of our secondary outcomes. 'Summary of findings' tables in future updates of the review will include serious adverse events.

Search methods for identification of studies

We searched the Cochrane Neuromuscular Disease Group Specialized Register (August 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 3 2011), MEDLINE (January 1966 to August 2011), EMBASE (January 1980 to August 2011) and clinicaltrials.gov (August 2011) for articles including the terms 'corticosteroids', 'anti-metabolites' or 'azathioprine' or 'mercaptopurine' or 'methotrexate' or 'ciclosporin' or 'cyclosporin' or 'chlorambucil' or 'cyclophosphamide' or 'immunoglobulin' or 'interferon', 'gamma globulin' or 'plasma exchange' or 'plasmapheresis' or 'immunosuppressant' or 'immunosuppression' and 'dermatomyositis' or 'polymyositis' or 'inflammatory myositis' or 'myositis' and 'randomised controlled trial'. We searched clinicaltrials.gov (completed studies as of August 2011) for completed studies using the terms 'Myositis', 'polymyositis' and 'dermatomyositis'. We undertook a manual search using the bibliographies of trials identified. We also wrote to known disease experts and authors of trials that we discovered, asking them for more information about their trials and whether they knew of trials other than those which we identified.

Electronic database strategies

For detailed search strategies please see: [Appendix 1](#) (CENTRAL), [Appendix 2](#) (MEDLINE), [Appendix 3](#) (EMBASE) and [Appendix 4](#) (Clinicaltrials.gov).

Data collection and analysis

Selection of studies

For the previous version of the review, two review authors (EC and JH) independently selected trials and four authors independently assessed each study.

For the update two review authors (JW and PG) independently selected trials from the Cochrane Neuromuscular Disease Group Specialized Register (August 2011), the Cochrane Central Register of Controlled trials (CENTRAL) (August 2011), clinicaltrials.gov (August 2011), MEDLINE (January 1966 to August 2011) and EMBASE (1980 to August 2011).

Two review authors (JH and PG) independently assessed each study except one, in which JH was an author, which JW and PG independently assessed. The review authors recorded methodological criteria and the results of each study on data extraction forms.

Assessment of risk of bias in included studies

Two review authors (JH and PG) independently assessed the risk of bias for each trial using the domain based 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of*

Interventions 5.1.0 ([Higgins 2011](#)). In one trial JH was an author and therefore PG and JW independently assessed the risk of bias in this study.

We assessed the risk of bias as high, low or unclear based on the following questions, each representing a domain.

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a high risk of bias?

We then used the results to create the 'Risk of bias' tables presented in this review. Where the two review authors (JH and PG or PG and JW) could not agree on an domain, this was settled by a third author (JW or JH).

Data synthesis

If sufficient data had been available, we would have performed meta-analysis using the Cochrane statistical software, Review Manager 5.1 (RevMan) ([RevMan 2011](#)). We would have expressed results as risk ratios (RR) and risk differences (RD) with 95% confidence intervals (CI) for dichotomous outcomes and mean difference (MD) and 95% CI for continuous outcomes. We would have carried out tests for homogeneity. If there had been evidence of heterogeneity, we would have performed sensitivity analysis and excluded trials of lowest quality.

Subgroup analysis and investigation of heterogeneity

We would have analysed the following subgroups when possible.

1. Younger (up to 18 years of age) versus older.
2. Reason for failure of initial treatment (corticosteroids) in case of second-line intervention: inadequate response versus unacceptable side effects.
3. Diagnostic subgroups: polymyositis versus dermatomyositis versus myositis associated with other connective tissue disease versus myositis in the presence of cancer.
4. Myositis-specific autoantibodies: participants with autoantibodies versus participants without autoantibodies ([Bunch 1980](#)).

Sensitivity analysis

We would have carried out sensitivity analysis to assess the effect of using different diagnostic criteria on outcome: probable and definite versus definite only ([Bohan 1975 a](#); [Bohan 1975 b](#)) versus [Dalakas 1991](#) versus non-specified.

RESULTS

Description of studies

The number of papers found by the new, current strategies are: MEDLINE 774; EMBASE 1880; Cochrane Neuromuscular Disease Group Specialized Register 30 (14 new papers); CENTRAL 43; and clinicaltrials.gov 77. From the searches we identified fourteen potentially relevant RCTs ([Bunch 1980](#); [Bunch 1981](#); [Chung 2007](#);

Coyle 2008; Dalakas 1993; Donovan 1995; Fries 1973; Miller 1992; Miller 2002; Muscle Study Group 2011; Takada 2002; Vencovsky 2000; Van de Vlekkert 2010; Villalba 1998). Ten are full publications in peer reviewed journals, four are only published as abstracts (Coyle 2008; Donovan 1995; Miller 2002; Takada 2002). Two of the studies included authors who were also authors of this review (Miller 2002 (JW) and Van de Vlekkert 2010 (JH)). We excluded four trials (see [Characteristics of excluded studies](#)). We excluded one as it was an open unblinded follow-up of another study included in this review, and one because the agent being investigated was not felt to be immunosuppressive or immunomodulatory. We excluded the third because we could not confirm that the participants had polymyositis on the basis of the inclusion criteria. We excluded the fourth study as there was no evidence of randomisation or blinding.

The characteristics of the ten selected studies are listed in [Characteristics of included studies](#).

We identified 10 ongoing studies, which are described in [Characteristics of ongoing studies](#).

Study designs

Six studies compared immunosuppressant or immunomodulatory therapy with placebo (Bunch 1980; Coyle 2008; Dalakas 1993; Miller 1992; Muscle Study Group 2011; Takada 2002), four trials compared one immunosuppressant regime with another: one compared ciclosporin with methotrexate (Vencovsky 2000), one methotrexate with azathioprine (Miller 2002), one oral daily prednisolone with pulsed oral dexamethasone (Van de Vlekkert 2010) and the fourth trial compared intravenous methotrexate with oral methotrexate plus azathioprine (Villalba 1998). Three trials were cross-over studies (Coyle 2008; Dalakas 1993; Villalba 1998).

Participants

All trials recruited adults over 18 years of age. Six trials included participants with either polymyositis or dermatomyositis (Coyle 2008; Miller 1992; Miller 2002; Vencovsky 2000; Villalba 1998; Van de Vlekkert 2010), one trial studied polymyositis participants only (Bunch 1980) while the other three only included dermatomyositis participants (Dalakas 1993; Muscle Study Group 2011; Takada 2002). The Bohan and Peter diagnostic criteria (Bohan 1975 a; Bohan 1975 b) were the most frequently used. Muscle biopsies were performed in five studies (Bunch 1980; Coyle 2008; Dalakas 1993; Miller 1992; Vencovsky 2000). Three of the six trials that included participants with polymyositis specifically stated exclusion of inclusion body myositis (Miller 1992; Vencovsky 2000; Villalba 1998). A fourth, reported in abstract, is known to have excluded inclusion body myositis (Miller 2002). A fifth excluded participants who had three or more three rimmed vacuoles per 1000 muscle fibers on muscle biopsy (Van de Vlekkert 2010).

Interventions

The interventions studied included the following.

- Monthly infusions of 2 g/kg of immunoglobulin or placebo for three months (Dalakas 1993).
- Plasma exchange, leukapheresis or sham apheresis with twelve treatments given over a one month period (Miller 1992).
- Azathioprine 2 mg/kg/day or placebo for three months in addition to 60 mg of prednisolone daily (Bunch 1980).

- Prednisolone and either low-dose methotrexate (15 mg weekly) or azathioprine (2.5 mg/kg daily) for one year (Miller 2002).
- Methotrexate 7.5 to 15 mg (mostly 10 mg) orally weekly or ciclosporin 3.0 to 3.5 mg/kg/day for at least six months (Vencovsky 2000).
- Oral methotrexate up to 25 mg weekly with azathioprine 150 mg daily for six months or intravenous methotrexate 500 mg/m² every two weeks for 12 treatments each with leucovorin rescue (50 mg/m² every six hours for four doses) (Villalba 1998).
- Infliximab 5 mg/kg at weeks 0, 2, 6 and 14 or placebo (Coyle 2008).
- Eculizumab (a humanised monoclonal antibody to C5 that inhibits cleavage of C5) 8 mg/kg weekly for five weeks then two-weekly for a further two doses or placebo (Takada 2002).
- Oral dexamethasone pulse therapy or oral daily prednisolone (Van de Vlekkert 2010).
- Etanercept (50mg subcutaneously weekly) or placebo for 52 weeks (Muscle Study Group 2011).

Outcomes

Function or disability was assessed in eight trials using the modified Convery Assessment Scale (Miller 1992; Villalba 1998), the modified Rankin scale (Van de Vlekkert 2010), the Health Assessment Questionnaire (HAQ) (Muscle Study Group 2011), the Short Form 36 Health Survey (SF-36) (Van de Vlekkert 2010), ad hoc scales (Dalakas 1993; Vencovsky 2000), time to arise from a chair and time to walk 30 feet (Muscle Study Group 2011), the Neuromuscular Symptom Score (NSS) (Dalakas 1993; Van de Vlekkert 2010), the individualised neuromuscular quality of life questionnaire (Muscle Study Group 2011) or timed walk (Miller 2002).

Improvement in MMT by 15% or more was used as a defined outcome in one study (Coyle 2008) and could be inferred from another (Dalakas 1993).

Assessment of muscle strength was done by MMT in eight of the selected trials. Two used the standard six point MRC scale, (Miller 1992; Villalba 1998), one the five point MRC scale (Van de Vlekkert 2010) and two expanded MRC scales, one an eight point scale (Dalakas 1993) and one an expanded 13 point scale (Muscle Study Group 2011). One study used a non-standard scale (with 0 being normal and -4 being no movement) (Bunch 1980). Two, published in abstract form only, did not define the MMT scale used (Coyle 2008; Takada 2002). The studies also varied in the number of muscle groups assessed. One used 26 muscle groups (Muscle Study Group 2011), two used 18 muscle groups (Bunch 1980; Dalakas 1993), two used 16 muscle groups (Miller 1992; Villalba 1998) but one of these did not specify the muscle groups used (Miller 1992) and one used 15 muscle groups (Van de Vlekkert 2010). Two published in abstract form only did not include the number of muscle groups used (Coyle 2008; Takada 2002).

In the majority of studies the MMT results were expressed as a sum score, this being the addition of all the scores from all the muscles tested, and maximum sum scores were therefore 80 (Miller 1992; Villalba 1998), 90 (Dalakas 1993), and 140 (Van de Vlekkert 2010). The maximum sum score for one non-standard strength scale was not given (Bunch 1980) and another quoted a maximum score of 160 (Coyle 2008). One study reported the mean manual muscle strength of all the muscles tested (Muscle Study Group 2011). One trial assessed muscle endurance using repetitive testing with a 1 kg

weight on a range of muscle groups that were stated. The maximum score in this test was 56 but it was not stated how this score was obtained (Vencovsky 2000). One trial used myometry of nine muscle groups and hand grip measurements to assess muscle strength (Miller 2002).

The IMACS definition of improvement was used as an outcome in two studies (Coyle 2008; Muscle Study Group 2011), in a modified form in one case (Muscle Study Group 2011).

Two studies assessed time to relapse or treatment failure as an outcome (Muscle Study Group 2011; Van de Vlekkert 2010).

The number of participants in remission and time-to-remission was an outcome measure in one study, which compared

dexamethasone therapy to prednisolone therapy (Van de Vlekkert 2010).

Cumulative steroid dose was an outcome measure in one 52-week study comparing etanercept to placebo (Muscle Study Group 2011).

Risk of bias in included studies

Two trials were open label studies (Vencovsky 2000; Villalba 1998). One study had a randomised period followed by an open label cross-over period which were not reported separately (Coyle 2008). One study included the SF-36 in the protocol; however, in the abstract the trial authors did not report the result (Takada 2002). Due to limited information many of the 'Risk of bias' domains for the studies were reported as 'unclear' (see 'Risk of bias' tables in the section [Characteristics of included studies](#) and [Figure 1](#)).

Figure 1. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bunch 1980	?	?	+	?	-	?
Coyle 2008	?	?	+	?	+	+
Dalakas 1993	?	+	+	+	?	+
Miller 1992	?	?	+	+	?	+
Miller 2002	?	?	?	?	?	?
Muscle Study Group 2011	?	?	?	+	?	+
Takada 2002	?	?	?	?	-	?
Van de Vlekkert 2010	+	+	?	?	+	+
Vencovsky 2000	+	-	-	+	+	+
Villalba 1998	?	-	-	+	+	?

Effects of interventions

Primary outcome measure

Change in function or disability scale at six months

IVIg

In [Dalakas 1993](#) (15 participants), although an activities of daily living (ADL) score was assessed, the results in the two groups were not reported systematically and statistical comparison between the two groups was not reported. A significant improvement in the NSS (measured in 13 participants) was reported for IVIg (44.1 (SD 8.2) pretreatment and 51.4 (SD 6.0) at three months) but not for the placebo group (45.9 (SD 9.0) pretreatment and 45.7 (SD 11.3) at three months). The NSS is a score based on 20 activities, each scored from zero to three, where three signifies no impairment and zero severe impairment.

Azathioprine

One azathioprine trial did not have functional measures as an outcome ([Bunch 1980](#)). In another trial (28 participants), the abstract stated there was no significant difference between azathioprine and low dose methotrexate using timed walk as the outcome measure (data not available for analysis) ([Miller 2002](#)). In a trial which included participants on azathioprine and methotrexate, ADL score was used as an outcome but the results were only reported in participants who improved according to the trial definition ([Villalba 1998](#)).

Plasma exchange or apheresis

In one study the ADL scale measured after just one month of plasma exchange, leukopheresis or placebo was reported as not showing any significant change ([Miller 1992](#), 39 participants, data not supplied).

Methotrexate

In [Vencovsky 2000](#) (36 participants), significant improvement at 6 months in a composite score of muscle endurance and function (maximum score 56) was found in those taking methotrexate, from 24.1 (SD 14.9) to 40 (SD 9.3). Subgroup analysis showed that dermatomyositis and polymyositis participants showed similar changes in the composite score. There was also significant improvement over six months in the 'clinical assessment' score, a composite score of disease manifestations and function, from 12.0 (SD 6.7) to 5.6 (SD 4.6), and the global patient's assessment, the patient's subjective scoring of disability from 0 to 10, from 4.7 (SD 2.0) to 7.3 (SD 2.3).

The comparative arm was those treated with ciclosporin, with no statistical difference noted at six months between methotrexate and ciclosporin for the composite score of muscle endurance and function (MD 6.80, 95% CI -1.65 to 15.25) ([Analysis 5.1](#)), the 'clinical assessment' score (MD 1.90, 95% CI -1.83 to 5.63) ([Analysis 5.2](#)) or the global patient's assessment (MD 0.30, 95% CI -1.20 to 1.80) ([Analysis 5.3](#)).

In [Villalba 1998](#), which compared a combination of oral azathioprine and methotrexate to intravenous methotrexate, activities of daily living score was used as an outcome but the results were only reported in participants who improved according to the trial definition.

Ciclosporin

In [Vencovsky 2000](#) (36 participants), significant improvement in a composite score of muscle endurance and function (maximum score was 56) was found in those taking ciclosporin, from 30.5 (SD 12.8) to 39.6 (SD 14.6) at six months. There was also significant improvement over six months in the 'clinical assessment' score, a composite score of disease manifestations and function, from 11.3 (SD 5.5) to 6.8 (SD 5.1), and the global patient's assessment, the patient's subjective scoring of disability from 0 to 10, from 4.5 (SD 2.0) to 6.8 (SD 2.4).

The comparative arm was those treated with methotrexate, with no statistical difference seen between methotrexate and ciclosporin at 6 months for the composite score of muscle endurance and function (MD 6.20, 95% CI -2.25 to 14.65) ([Analysis 5.1](#)), the 'clinical assessment' score (MD 1.90, 95% CI -1.83 to 5.630) ([Analysis 5.2](#)) or the global patient's assessment (MD 0.30, 95% CI -1.20 to 1.80) ([Analysis 5.3](#)).

Infliximab

Beyond the IMACS definitions of improvement, change in function or disability scale was not reported in this study ([Coyle 2008](#)).

Etanercept

In a 52-week pilot study of etanercept compared to placebo (16 participants), no statistically significant differences between treatment groups were found for time to walk 30 feet (s) (MD 1.10, 95% CI -6.57 to 8.77) ([Analysis 7.6](#)), time to rise from a chair (MD 1.17, 95% CI -1.37 to 3.71) ([Analysis 7.7](#)), HAQ (MD -0.02, 95% CI -0.55 to 0.51) ([Analysis 7.1](#)), individualized Neuromuscular Quality of Life (INQoL) (MD -5.40, 95% CI -14.19 to 3.39) ([Analysis 7.9](#)) or physical component summary of the SF-36 at 52 weeks (MD 6.4, 95% CI 1.98 to 10.81) ([Analysis 7.10](#)) ([Muscle Study Group 2011](#)).

Ecuzumab

In a pilot study of ecuzumab compared to placebo, the SF-36 was included in the study protocol but not reported in the published abstract ([Takada 2002](#)).

Dexamethasone

In a study comparing pulsed oral dexamethasone to oral daily prednisolone (62 participants), the NSS showed no significant differences between the two groups at 18 months (MD -5.00, 95% CI -11.48 to 1.48) ([Analysis 8.1](#)) ([Van de Vlekkert 2010](#)). We decided not to impute a correlation to calculate the SD of the difference between groups for change from baseline scores as the difference in the means at follow-up was almost the same as at baseline. The physical function component of the SF-36 was also reported as showing no significant differences between the two groups at 18 months (full data not supplied).

15% or greater improvement in muscle strength at six months

Only four trials measured muscle strength at six months or more, using MMT in three ([Villalba 1998](#); [Van de Vlekkert 2010](#); [Muscle Study Group 2011](#)) and limited to hand grip in another ([Miller 2002](#)); the proportion of participants having a 15% improvement in muscle strength was not an outcome in any of these studies. Only one study used the outcome 15% or greater improvement in muscle strength ([Coyle 2008](#)) but this study assessed it at 16 weeks rather than six months.

IVIg

The only trial of IVIg (15 participants) measured muscle strength after just three months (Dalakas 1993). It found a statistically significant improvement in scores of muscle strength (maximum score 90) from 76.6 to 84.6 in the IVIg group but no change in the placebo group. The MD in improvement in muscle strength between the active and placebo group was 9.50 (95% CI 4.33 to 14.67). Using data derived from the figures in the paper, two of the eight participants treated with IVIg achieved $\geq 15\%$ improvement in muscle strength at three months compared to none of the seven participants in the placebo group (RR 4.44, 95% CI 0.25 to 79.42) (Analysis 1.1).

Azathioprine

In a trial of 16 participants with polymyositis, after three months of treatment, muscle strength (maximum score 0, minimum -140) increased by 6.5 (SD 23.5) in the azathioprine group compared with 1.1 (SD 12.6) in the placebo group (Bunch 1980). The MD in improvement in muscle strength between the azathioprine group and the placebo group was 5.40 (95% CI -13.08 to 23.88) (Analysis 2.1). However, the difference was not statistically significant. In another trial of 28 participants, using change in hand held myometry readings as the primary outcome, the authors reported that azathioprine had equivalent efficacy to methotrexate (Miller 2002), although no specific data were given in the abstract. In a third trial, data on muscle strength were only given in those who improved according to the trial definition (Villalba 1998).

Plasma exchange or leukapheresis

The trial of plasma exchange or leukapheresis versus placebo with 39 participants lasted only one month. During this time the RR of muscle strength improvement was not significantly different, being 1.0 (95% CI 0.3 to 3.37) in the active compared with the placebo treatment of the group (Miller 1992) (Analysis 3.1).

Methotrexate

One trial (28 participants) the investigators reported that hand grip strength after one year did not improve any more with oral methotrexate than with azathioprine (Miller 2002). In a trial of oral methotrexate and azathioprine versus intravenous methotrexate including 30 participants (Villalba 1998), the authors reported no significant difference in muscle strength (maximum score 80) between the two groups at six months ($P = 0.50$, data not supplied).

Ciclosporin

Muscle strength was not tested for this intervention (Vencovsky 2000).

Infliximab

In a cross-over study that was unblinded at 16 weeks (when participants on placebo were moved to the active arm), three of the 12 participants achieved a 15% or greater improvement in muscle strength after 16 weeks therapy with infliximab 5 mg/kg compared to none of the six participants during placebo therapy (RR 3.77, 95% CI 0.23 to 63.05) (Analysis 4.1). This difference was not statistically significant (Coyle 2008).

Etanercept

In a 52-week randomised, double-blind, placebo-controlled trial involving 16 participants, there was no significant difference in the improvement in muscle strength as assessed by MMT (MD 0.06, 95% CI -0.15 to 0.27) and quantitative myometry utilizing maximum voluntary isometric contraction testing (MVICT) (MD 0.67, 95% CI -0.30 to 2.78) between the treatment groups at 52 weeks. Our primary outcome, a 15% improvement in muscle strength, is a component of the IMACS DOI, but was not reported as individual item in this study (Muscle Study Group 2011).

Eculizumab

In a pilot study, MMT improved by an average of 6% in the actively treated arm (10 participants) after nine weeks of therapy compared to an average of 26% in those who received placebo (three participants) (Takada 2002). These data were from an abstract provided by the manufacturer. No raw data were available for analysis.

Dexamethasone

In an 18-month placebo-controlled, double-blind, randomised trial (62 participants), the mean MMT scores (maximum 140) were 136 (SD 5) in the dexamethasone group and 135 (SD 6) in the prednisolone group at 18 months (Van de Vlekkert 2010).

Secondary outcome measures

Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement

Only two studies assessed this outcome (Coyle 2008; Muscle Study Group 2011).

In one, which compared infliximab therapy to placebo, seven out of 12 participants improved by the IMACS definition after 16 weeks of therapy with infliximab compared to two out of six participants treated with placebo (RR 1.75, 95% CI 0.51 to 5.98) (Analysis 4.2) (Coyle 2008).

The second, comparing etanercept to placebo, used a modified form of the IMACS DOI in that the average percent of predicted normal MVICT score in addition to the MMT score was used for muscle strength testing (Muscle Study Group 2011). At 24 weeks nine of the 11 participants in the etanercept group achieved this definition of improvement compared to two of the five placebo-treated participants (RR 2.05, 95% CI 0.67 to 6.20) (Analysis 7.3). At 52 weeks, six of the 11 participants in the etanercept group achieved this definition of improvement compared to three of the five placebo-treated participants (RR 0.91, 95% CI 0.37 to 2.23) (Analysis 7.4). There was no significant difference between the groups at either of these time points.

Number of relapses and time to relapse

Only two studies assessed time to relapse or treatment failure as an outcome (Muscle Study Group 2011; Van de Vlekkert 2010).

One study compared dexamethasone to prednisolone (Van de Vlekkert 2010). Relapse was defined as 1. a decrease in MRC sum score by four points or more (maximum score 140), or 2. a reduction in the Rankin score by one or more, or 3. a greater than two-fold increase in serum creatine kinase associated with a reduction in strength or function. At 18 months, 14 of the 30 (47%) dexamethasone-treated participants had relapsed compared to 12

of the 32 (38%) prednisolone-treated participants (RR 1.24, 95% CI 0.69 to 2.24) ([Analysis 8.3](#)). Median time to relapse was 44 weeks (standard error (SE) 4.7) in the dexamethasone group compare to 60 (SE 2.9) in the prednisolone treated group (log rank test $P = 0.03$).

The other study compared etanercept to placebo ([Muscle Study Group 2011](#)). Treatment failure was said to have occurred if the study physicians felt it necessary to increase the participant's prednisolone and/or change to another agent, or if any one of the following five criteria were fulfilled: 1. reduction in the physician global disease activity assessment visual analogue scale by 2 cm or more; 2. worsening of MMT composite score by 20% or more; 3. worsening of oropharyngeal muscle weakness sufficient to compromise nutrition or cause a risk of aspiration; 4. 20% worsening of forced vital capacity or diffusion capacity; 5. no improvement in muscle strength after 12 weeks.

Six of 11 participants in the etanercept arm were treatment failures. All five participants receiving placebo were treatment failures (RR 0.59, 95% CI 0.33 to 1.05) ([Analysis 7.8](#)). Median time to treatment failure was 148 days in the placebo arm versus 358 days in the etanercept arm ($P = 0.0002$).

Number of participants in remission, and time-to-remission after at least six months

This was an outcome measure in one study, which compared dexamethasone therapy to prednisolone therapy ([Van de Vlekkert 2010](#)), and defined remission as a Rankin score of zero or one. At 18 months, five of 30 (17%) dexamethasone-treated participants and nine of 32 (28%) prednisolone-treated participants were in remission (RR 0.59, 95% CI 0.22 to 1.57) ([Analysis 8.2](#)). Mean time to remission was 58.8 (SE 5.1) weeks in the dexamethasone-treated group and 58.8 (SE 4.6) weeks in the prednisolone-treated group (log-rank test $P = 0.73$).

Cumulative corticosteroid dose after at least six months

This was an outcome measure in one study comparing etanercept to placebo ([Muscle Study Group 2011](#)), although the data were not presented in the paper, they were published on the clinicaltrials.gov website. The mean (SD) cumulative prednisolone dose in g over the one year study period was 5.90709 (3.48285) in the etanercept group and 9.91765 (4.76209) in the placebo group (MD -4.01, 95% CI -8.66 to 0.64) ([Analysis 7.5](#), no significant difference). The median prednisolone dose from weeks 25 to 52 was significantly higher in the placebo group (median 29.2 mg/day, range 9.9 to 62.6 mg/day) than the etanercept group (median 1.2 mg/day, range 0.0 to 31.1 mg/day) ($P = 0.02$).

Serious adverse effects

IVIg

In the study of IVIg for dermatomyositis no serious adverse events were reported ([Dalakas 1993](#)). In two participants a severe headache occurred with each infusion, requiring treatment with narcotics.

Azathioprine

In the study of azathioprine in polymyositis ([Bunch 1980](#)) only 16 of 23 participants completed the study. The other participants failed to complete the study either because they were lost to follow-up (three), failed to respond to treatment (one on placebo) or experienced adverse effects (three). Two of the three

subjects withdrawn from the study due to adverse effects were on azathioprine with one having severe nausea and vomiting and the other developing pneumonitis after one month of treatment. One subject on placebo developed acute diverticulitis and needed surgery. A further subject on azathioprine developed significant leukopenia at the end of the study but this was judged to be unrelated to the study as she was later found to have cyclic neutropenia. Azathioprine was also part of the oral regime in another trial ([Villalba 1998](#)) (see under methotrexate).

Plasma exchange or apheresis

Adverse events on apheresis were common in the study comparing plasma exchange, leukapheresis and sham apheresis ([Miller 1992](#)). Nine out of 39 participants required placement of a central venous catheter to maintain venous access. Three participants had major vasovagal episodes. Two participants had clinically important citrate reactions; and one participant receiving sham treatments required red cell transfusion for an apheresis-related decline in haemoglobin. In the plasma exchange group, one participant developed acute transient respiratory distress and one developed herpes zoster.

Methotrexate

Four out of 17 participants receiving oral methotrexate withdrew prematurely from one trial ([Vencovsky 2000](#)) because of pancytopenia, gut perforation, acute alveolitis or withdrawal of consent after suffering petechiae. Seven participants had minor adverse events including hypertension and rash which were not sufficient to stop their treatment. Assessment of the adverse effects of methotrexate in another trial ([Villalba 1998](#)) is complicated by the fact that oral methotrexate was given in combination with azathioprine and by the cross-over study design. A total of 28 participants had oral combination therapy (13 of whom had crossed over from the intravenous methotrexate arm). Of these, six had their oral treatment curtailed due to gastrointestinal side effects, and there was one fatality due to *Pneumocystis carinii* pneumonia. A total of 26 participants had intravenous methotrexate (11 having had prior oral treatment) of whom four had adverse events including gastrointestinal intolerance, abscesses, pseudomonas skin infection and legionella pneumonia. Liver enzyme elevations, infections and gastrointestinal intolerance were common side effects with both oral and intravenous methotrexate ([Villalba 1998](#)).

Ciclosporin

In one study two out of 19 subjects taking ciclosporin were withdrawn prematurely due to side effects which were creatinine elevation (one participant) and pneumonia (one participant); a third participant was withdrawn due to the adverse event of non-compliance ([Vencovsky 2000](#)). A further five had minor side effects including hypertension (three participants), bronchitis (one) and bronchopneumonia (one), that did not necessitate withdrawal from the trial ([Vencovsky 2000](#)).

Infliximab

Two undisclosed severe adverse events, reported as unrelated to infliximab, occurred in this study. In addition, one participant experienced an infusion reaction and an undisclosed number of mild adverse events occurred ([Coyle 2008](#)).

Etanercept

In a small study of 16 participants with dermatomyositis, six severe adverse events were reported in the etanercept group and three in the placebo group ([Muscle Study Group 2011](#)). In the etanercept group, the six serious adverse events occurred in three participants, comprising pregnancy and miscarriage in a partner; hospitalization for a urinary tract infection and fever of unknown origin; postherpetic neuralgia and two admissions for psychosis. Two participants in the etanercept group developed positive antinuclear antibodies compared to one of the placebo group ([Muscle Study Group 2011](#)). Five participants in the etanercept-treated group compared to one in the placebo group had worsening of their skin disease.

Eculizumab

In a pilot study of eculizumab compared to placebo the numbers of adverse events was not significantly different between the two groups. The nature of these adverse events was not disclosed. There were no serious adverse events in either group ([Takada 2002](#)).

Because the eight trials used different interventions and variable outcome measures, no meta-analysis was possible.

Dexamethasone

In a study comparing pulsed oral dexamethasone to oral daily prednisolone, there was a high rate of discontinuation of both treatments: 21 out of 30 in the dexamethasone group and 17 out of 32 in the prednisolone group ([Van de Vlekkert 2010](#)). The main reasons for discontinuation were relapse at less than six months, no improvement and serious side effects. The dexamethasone-treated participants had fewer side effects in total, with 22 (79%) suffering any side effect in the dexamethasone group compared to 29 (97%) in the prednisolone-treated group. The prednisolone group had a greater incidence of mood changes, diabetes mellitus, mean weight gain of more than 5 kg, cushingoid features, skin thinning, gastric symptoms, impaired wound healing, hair loss, infections, acne, hirsutism, hypertension, cataract formation and striae. One adverse event occurred with greater frequency in the dexamethasone group, renal crisis, which occurred in two participants, both in the dexamethasone group.

Subgroup analyses

Although we intended to analyse subgroups, this proved impossible. All the studies examined adult participants, therefore the effect of immunosuppressants on participants under the age of 18 could not be assessed. Participants with and without autoantibodies were not separated into different subgroups when analysing response to treatment. Reason for failed response to corticosteroids was rarely reported and subsequent analyses did not separate participants with inadequate response to corticosteroids versus those who had unacceptable side effects.

Comparison with excluded studies as sensitivity analysis

In contrast to the selected studies, the excluded studies predominantly reported positive results.

[Bunch 1981](#) reported one- and three-year follow-up data from the 1980 RCT comparing azathioprine with placebo discussed above ([Bunch 1980](#)). Muscle strength was not reported but the improvement in functional disability (graded from one to six, one being normal, six unable to walk without assistance) in the

azathioprine group (from 4.5 (SD 0.9) to 2.1 (SD 0.6)) was greater than that achieved in the prednisolone only group (from 4 (SD 0.8) to 3 (SD 0.6)). Mean change was 2.4 (SD 1.1) and 1 (SD 0.6) respectively.

[Chung](#) and colleagues reported a double-blind, randomised, placebo-controlled trial of creatine supplements in participants with established dermatomyositis or polymyositis undergoing a home exercise programme ([Chung 2007](#)). There was a significantly greater reduction in the primary outcome, the percentage change in the aggregate functional performance time, in the creatine arm ($P = 0.029$) at six months ([Chung 2007](#)). The aggregate functional performance time consisted of four timed functional activities: a 50 foot timed walk; the 'get up and go test'; a 19-step stair ascent test; and a 19-step stair descent test. Muscle strength was reported for individual muscle groups and only showed a significant difference between the two groups at six months, favouring the creatine-treated arm in four of the ten muscle groups assessed.

[Fries 1973](#) reported a randomised open-label study comparing 16 weeks of cyclophosphamide therapy with high dose oral prednisolone. The cyclophosphamide dose was titrated to maintain a white cell count of 3500 to 4000 cells/cu mm, this group received no prednisolone. The actual cyclophosphamide dose given averaged 125 mg daily. Where initial white counts permitted, participants in the cyclophosphamide group also received an initial infusion of nitrogen mustard at a dose of 0.4 mg/kg. The prednisolone group were commenced on a dose of 1 mg/kg or greater. Only eight polymyositis subjects were included, with five receiving initial cyclophosphamide therapy and three receiving prednisolone therapy. The trial authors stated that the muscle enzyme and sedimentation rates normalised in the prednisolone group but not the cyclophosphamide group, with a difference that was significant at the five per cent level. Although not stated, as the initial treatment period was 16 weeks it is likely that these data refer to this time period.

[Donov 1995](#) performed a trial of plasmapheresis in 30 children with juvenile dermatomyositis. There was no evidence of randomisation or blinding in the abstract. Four participants received sham plasmapheresis and 26 active therapy. The therapeutic regime consisted of plasmapheresis with a subsequent methylprednisolone dose one to three times a week. Therapy duration varied from one to 10 weeks. No improvement was seen in the sham plasmapheresis subjects but complete remission seen in 24 participants in the active arm with 'considerably decreased' disease activity in the other two cases. No definitions of complete remission or objective measures of disease activity were given.

DISCUSSION

This systematic review highlights the lack of high quality RCTs that assess the efficacy and toxicity of immunosuppressants in inflammatory myositis. Ten trials were included in the review with only one agent, IVIg demonstrating statistically significant superior efficacy against control, and a second agent, etanercept showing a possible steroid-sparing effect. Therefore, we have to conclude that there is insufficient evidence from available RCTs to confirm the value of immunosuppressants in inflammatory myositis. For 'Summary of findings' tables see [Table 3](#); [Table 4](#); [Table 5](#); [Table 6](#); [Table 7](#); [Table 8](#); [Table 9](#); [Table 10](#); [Table 11](#); and [Table 12](#).

This conclusion appears to contradict the experience of many clinicians. However, the lack of good evidence is not the same as no evidence. The lack of RCTs in inflammatory myositis is typical of the problem faced by evidence-based medicine. Conducting high quality RCTs in rare diseases is extremely difficult. Yet without data from high quality RCTs, it is impossible for clinicians to assess the benefit/risk ratio of immunosuppressants in myositis accurately. The trial of plasma exchange and leukapheresis is a good example of where a treatment is ineffective but has significant side effects. Indeed, this review found that immunosuppressants are associated with significant side effects. Clearly, it is important for physicians and participants to appreciate the precise benefit and risk of immunosuppressants in inflammatory myositis. Participants with inflammatory myositis are managed by different specialists: neurologists, rheumatologists, dermatologists or general physicians. Since high quality RCTs require sufficient sample sizes to deliver the necessary statistical power, individual clinicians rarely have a sufficient number of potential participants under their care to conduct trials. Therefore, multicentre trials with collaboration between all these specialists are the only means to study this rare disease. In recent years new collaborative efforts such as the International Myositis Assessment and Clinical Studies Group (IMACS), the European Myositis Network (EUMYONET) and the United Kingdom Myositis Network (UK MYONET) have formed to foster such collaboration.

Another major obstacle in evidence-based medicine in inflammatory myositis has been the lack of international consensus on outcome measures and how data should be presented in publications. However, in recent years the International Myositis Assessment and Clinical Studies Group (IMACS) has developed international multidisciplinary outcome measures (Isenberg 2004; Oddis 2005; Rider 2004). These include the 'definitions of improvement' which comprise six core set measures among five domains (Oddis 2005; Rider 2004). These core set measures are: the physician global disease activity, parent/patient global disease activity, muscle strength (MMT), physical function assessment, laboratory assessment and extramuscular disease complications. Improvement is defined as occurring if three of any six core set measures improve by 20%, with no more than two worsening by 25% (measures that worsen cannot include manual muscle strength).

Most of the studies included in this review used the Bohan and Peters diagnostic criteria (Bohan 1975 a; Bohan 1975 b) which were published well over thirty years ago. An international workshop on

clinical trials in inflammatory myositis highlighted the deficiency of the Bohan and Peters criteria in the diagnosis of polymyositis (Hoogendijk 2004). Many of these participants in fact had diagnoses other than polymyositis, especially inclusion body myositis and occasionally dystrophies with associated inflammatory features.

In the absence of adequate RCTs to address the question of which immunosuppressant treatment might be best to use in these inflammatory myopathies, it would be reasonable to look at any non-randomised trials that might help. However, Van de Vlekkert 2004 undertook a MEDLINE and EMBASE search from 1966 to 2001 for French, German, or English reports of treatment in dermatomyositis and polymyositis. They found 92 eligible papers describing a total of 915 participants (92 of whom were duplicated) in 74 single case reports and 18 case series. These reports were reviewed for 10 standards that were thought important to allow any reader to recognise their own participant, copy the treatment and have some idea of the treatment effect. The authors concluded that the majority of the reports were of dubious quality and thus a meaningful systematic review of case reports was unrealistic.

AUTHORS' CONCLUSIONS

Implications for practice

The small number of randomised trials of immunosuppressants and immunomodulatory therapies are inadequate to decide whether these agents are beneficial in dermatomyositis and polymyositis. Two small trials in dermatomyositis one of intravenous immunoglobulin and one of etanercept suggest that these agents may be beneficial.

Implications for research

More research is needed to investigate the efficacy of immunosuppressant and immunomodulatory agents in dermatomyositis and polymyositis.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bunch 1980

Methods	Double-blind placebo-controlled trial
Participants	23 participants with previously untreated polymyositis, but only the 16 participants completing the study were included in final analysis Age in years (SD) of 16 completers: azathioprine group, 38.3 (11.8); placebo group, 40.9 (10.6) Sex of 16 completers: azathioprine group, 5 females, 3 males; placebo group, 2 males, 6 females Mean disease duration (SD) of completers: azathioprine group, 8.6 (6) months, placebo group, 9.6 (9) months Established criteria not quoted but inclusion criteria should satisfy the Bowan and Peter criteria for definitive polymyositis
Interventions	60 mg of prednisolone per day plus either azathioprine (2 mg/kg/day) or placebo for 3 months
Outcomes	MMT, CK, muscle biopsy after 3 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methodology for producing random sequence not reported
Allocation concealment (selection bias)	Unclear risk	Methods for concealing allocation sequence not described beyond the study being double-blind, placebo-controlled
Blinding (performance bias and detection bias)	Low risk	Double-blinded study with placebo medication for control group

Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis (Review)

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Bunch 1980 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Significant attrition: 7 participants, of whom 3 were lost to follow up, 4 withdrew due to side-effects, failure of therapy or intercurrent illness
Selective reporting (reporting bias)	High risk	7 participants who failed to complete the study were excluded from the final analysis
Other bias	Unclear risk	Not clear

Coyle 2008

Methods	16-week randomised, double-blind, placebo-controlled trial with subsequent open label cross-over of placebo participants to active arm and active participants to dose escalation	
Participants	11 participants with polymyositis and 1 with dermatomyositis Age in years (SD): 45.4 (10.9) Sex: 11 female and 1 male Mean disease duration (SD): 5.6 (4.0) years Probable or definite refractory dermatomyositis or polymyositis by Bohan and Peter criteria Previously failed or had intolerance to immunosuppressive therapy. Baseline MMT score 80 to 120 (normal 160). Stable prednisolone (≤ 0.5 mg/kg/day) and immunosuppressive dose for at least 4 weeks	
Interventions	Active arm: infliximab 5 mg/kg at weeks 0, 2, 6 and 14. Non-responders based on IMACS criteria then increased to open label infliximab 7.5 mg/kg at weeks 22, 30 and 38 Placebo arm: placebo at weeks 0, 2, 6 and 14. Non-responders based on IMACS criteria then given infliximab 5 mg/kg at weeks 16, 18, 22, 30 and 38	
Outcomes	$\geq 15\%$ MMT improvement from baseline Improvement as defined by IMACS	
Notes	Data from the open label and double-blind sections of the study presented together	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methodology for producing random sequence not reported in abstract
Allocation concealment (selection bias)	Unclear risk	Insufficient detail reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded period lasted 16 weeks, then open follow-up
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attritions and exclusions not reported in abstract

Coyle 2008 (Continued)

Selective reporting (re-reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence to suggest other bias

Dalakas 1993

Methods	Double-blind RCT
Participants	<p>15 participants with dermatomyositis: 8 in IVIg group, 7 in placebo group</p> <p>Age in years: mean 36, range 18 to 55 years</p> <p>Sex: 10 females, 5 males</p> <p>Mean disease duration: IVIg group 3.9 years, placebo group 3.8 years</p> <p>No classification criteria used but participants quoted to have all had a diagnostic muscle biopsy, rash and progressive muscle weakness</p> <p>Participants had dermatomyositis that "had become unresponsive or poorly responsive to high-dose prednisolone or therapeutic doses of another immunosuppressant (methotrexate, azathioprine or cyclophosphamide) given for at least four to six months." Nine participants were taking concomitant immunosuppressive agents (azathioprine (5), methotrexate (3) or cyclophosphamide (1)) during the study</p>
Interventions	IVIg (2 g/kg) or placebo per month for 3 months
Outcomes	MMT, NSS, ADL Score (based on Barthel index), CK, photographs of rashes, muscle biopsy after 3 months of treatment
Notes	IVIg was beneficial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block-randomisation used but further methodology on randomisation not provided
Allocation concealment (selection bias)	Low risk	Randomisation in pharmacy, code not broken until completion of the study
Blinding (performance bias and detection bias) All outcomes	Low risk	Medication covered by opaque plastic to hide medication from participants and investigators. Stated that no inadvertent disclosure of randomisation but that all but 1 participant correctly identified the therapy they were on
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results for all recruited participants reported, although no clear statement on attrition or exclusions made
Selective reporting (re-reporting bias)	Unclear risk	One of the secondary outcomes, ADL score was not reported systematically and statistical comparison between the two groups was not reported
Other bias	Low risk	No evidence to suggest other bias

Miller 1992

Methods	Double-blind RCT
Participants	<p>39 participants: 19 with polymyositis, 16 with dermatomyositis and 4 with overlap syndromes (42 originally recruited, 3 excluded from analysis: 2 on later muscle biopsy had IBM, 1 withdrew for personal reasons after 1 week of therapy)</p> <p>Plasma exchange group:</p> <ul style="list-style-type: none"> age in years (SD): 41.5(11.7) sex: 4 males, 9 females disease duration (SD): 3.1 (2.3) years <p>Leukapheresis group:</p> <ul style="list-style-type: none"> age in years (SD): 41.4(11.7) sex: 3 males, 10 females disease duration (SD): 3.9 (2.1) years <p>Sham apheresis group:</p> <ul style="list-style-type: none"> age in years (SD): 40.2 (10.9) sex: 4 males, 9 females disease duration (SD): 2.4 (1.3) years <p>Participants had had "an incomplete response to high-dose prednisone therapy (≥ 1mg per kilogram of body weight per day for at least one month), the need for a prednisone dose of at least 0.25 mg per kilogram per day, or the occurrence of unacceptable side effects during the administration of the dose of corticosteroid needed to control disease". "Twenty-nine of the patients had previously not responded to at least one adequate trial of cytotoxic therapy"</p> <p>Bohan and Peter criteria used</p>
Interventions	Plasma exchange, leukapheresis or sham apheresis 12 treatments over a 1-month period
Outcomes	MMT, ADL Score, CK at 1 month
Notes	No benefit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	During apheresis evaluators not present, cell separator device and attached tubing and component bags shielded from view
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants excluded from analysis. 1 withdrew after 1st week due to personal reasons. 2 excluded as later biopsy showed IBM
Selective reporting (reporting bias)	Unclear risk	2 outcomes described in the methods but other measures including change in CK and change in lymphocyte count reported in results

Miller 1992 (Continued)

Other bias	Low risk	No evidence to suggest other bias
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Miller 2002

Methods	Double-blind RCT
Participants	28 participants with polymyositis or dermatomyositis Data on age, sex and disease duration not given
Interventions	Prednisolone plus either azathioprine 2.5 mg per kg daily or methotrexate 15 mg weekly for 1 year
Outcomes	Muscle strength measured by hand held myometry, timed walks, final steroid dose and side effects
Notes	Equivalent efficacy but methotrexate was better tolerated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported in abstract
Allocation concealment (selection bias)	Unclear risk	Not reported in abstract
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details reported beyond study randomised, double-blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Muscle Study Group 2011

Methods	Randomised, double-blind, placebo-controlled trial
Participants	16 participants with adult dermatomyositis. Mean age in years (range): 43.63 (21 to 61) Sex:10 female and 6 male Definite dermatomyositis by Bohan and Peter criteria In active arm 3 newly diagnosed, treatment-naïve patients and 8 refractory patients with a mean baseline prednisone dosage of 45 mg/day. Mean disease duration 1.1 years, SD 0.8 In placebo arm, 2 newly diagnosed, treatment naïve patients and 3 refractory patients with a mean baseline prednisone dosage of 39 mg/day. Mean disease duration 2.2 years, SD 3.4

Muscle Study Group 2011 (Continued)

Interventions

New patients were started on prednisone 60 mg daily. Refractory patients remained their maintenance prednisolone dosage for 2 months or had the dose increased to 60 mg at the discretion of their treating physician

After treatment with prednisolone for 2 months, participants received etanercept 50 mg/week or placebo for 52 weeks. This was followed in all participants by tapering of the prednisolone over 24 weeks starting after first treatment with etanercept or placebo

Outcomes

Outcome Measures in clinicaltrials.gov summarised

Primary

Occurrence of at least one adverse event (at each visit during the 12 month study)

Tolerability (at any point between baseline (week 0) and the end of the study (week 52))

Average change in each of the following from baseline to week 52 (at baseline (week 0) and week 52): oral temperature, respiration rate, systolic BP, diastolic BP, pulse, body weight in kg

Frequency of subjects with treatment emergent, clinically significant, abnormal laboratory values from baseline to week 52 (at screening, baseline (week 0), weeks 4, 8, 12, 16, 20, 24, 32, 40, and 52) in the following: CK, alanine aminotransferase, gamma-glutamyl transpeptidase, aldolase, glucose, potassium, white blood cell count, haemoglobin, haematocrit, platelet counts, urine leukocyte values, urine protein laboratory values, urine glucose, urine ketone

Frequency of subjects with treatment emergent, clinically significant, abnormal serum 25-hydroxyvitamin D laboratory values from the screening visit to week 52 (screening visit and week 52)

Frequency of subjects with treatment emergent, clinically significant, abnormal antinuclear antibody test (ANA) values from the screening visit to week 52 (at screening, weeks 12, 24, 40, and 52)

Frequency of subjects with treatment emergent, clinically significant, abnormal monoclonal protein detection by serum protein electrophoresis from the screening visit to week 52 (screening visit, weeks 12, 24, 40, and 52)

Average cumulative dosage of prednisone over the 1 year study period (baseline until week 52)

Secondary

Average prednisone dosage after week 24 (from week 24 to 52)

Average daily dose of prednisone from baseline to week 52 (baseline through week 52)

'Other Pre-specified'

The number of participants who were classified as treatment failures (at any point during the 52 week study)

From baseline to week 52 (at baseline (week 0) and week 52):

- change in the average MMT Score
- average change in time to rise from a chair
- average change in time (s) to walk 30 feet
- average change in Z-score for DEXA of the femur
- average change in Z-score for DEXA of the lumbar spine
- average change in physician global activity assessment
- average change in patient global activity assessment score
- average change in Cutaneous Disease Activity and Severity Index (CDASI) score
- change in pruritis rating
- change in HAQ score
- forced vital capacity (FVC) average change in percent predicted
- average change in percent predicted forced expiratory volume in 1 s (FEV1)
- average change in percent predicted diffusion capacity (DLCO)

Serious adverse events

Other adverse events

Outcome measures in published paper

Primary

Adverse events

"Time from randomization to treatment failure"

"Average prednisolone dosage after week 24"

Secondary

Cumulative and average MMT scores

Composite maximum voluntary isometric contraction testing (MVICT) scores

Myositis Intention to Treat Activity Index (MITAX)

Muscle Study Group 2011 (Continued)

Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT)
 "Subject and physician assessments of global disease activity utilizing Likert and visual analogue scales (VAS)"
 "Time to arise from a chair and walk 30 feet"
 HAQ
 "A modified cutaneous disease activity score index"
 Patient VAS for pruritis
 "Relevant components of the MYOACT and MITAX"
 SF-36
 Individualized Neuromuscular Quality of Life Questionnaire
 IMACS-recommended definitions of improvement

Notes Initially designed to enrol 40 newly diagnosed patients. Some slight but not significant differences in results data between published study and results section on clinicaltrials.gov. Modified form of the IMACS DOI used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 participants withdrew from the study, one lost to follow up in the etanercept group, 1 due to lack of perceived effect in the placebo group
Selective reporting (reporting bias)	Unclear risk	Many of the numerous prespecified outcomes on the clinicaltrials.gov website are not reported in the paper. However, these results are readily available on the clinicaltrials.gov website. Notably average prednisone dosage after week 24, a secondary outcome on the clinicaltrials.gov website, is reported in the paper but the primary outcome, average cumulative dosage of prednisone over the 1 year study period, is not. Several of the outcomes reported in the published paper were not amongst the primary or secondary outcomes published on clinicaltrials.gov website. Some of these are reported in the results section of clinicaltrials.gov as pre-specified outcomes. Notably, the missing outcomes would be not be possible to measure retrospectively
Other bias	Low risk	The study appears to be free of other sources of bias

Takada 2002

Methods	Double-blind RCT
Participants	13 participants with dermatomyositis: 10 treated with eculizumab, 3 treated with placebo Data on age and sex not given Disease duration: ≥ 6 months

Takada 2002 (Continued)

Eligibility criteria required included: a MMT score ≤ 136 out of 170, "Patients with persistent disease (defined as active rash plus CK greater than or equal to 2 times ULN, or rapidly progressive disease, or response to steroids with inability to taper dose, or unacceptable side effects of steroids." Participants could be on a stable dose of methotrexate or azathioprine

Interventions	Eculizumab 8 mg/kg weekly for 5 doses then 2-weekly for a further 2 doses. For a total of 10 weeks therapy or placebo
Outcomes	Adverse events MMT score Muscle enzyme level MRI findings SF-36 Skin findings and skin biopsy

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported beyond study double-blind and placebo-controlled
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported beyond study double-blind and placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition reported
Selective reporting (reporting bias)	High risk	SF-36 assessed but not reported in published abstract
Other bias	Unclear risk	Insufficient information

Van de Vlekkert 2010

Methods	Double-blind RCT
Participants	62 adult participants with treatment-naive inflammatory myopathies (sporadic IBM excluded)
Interventions	28-day cycles of oral high-dose dexamethasone or daily high-dose prednisolone Dexamethasone: 6 cycles, 40 mg/day for 4 consecutive days at 28-day intervals

Van de Vlekkert 2010 (Continued)

Prednisolone: 70 mg/day starting dose (body weight < 70 kg) or 90 mg/day (body weight ≥ 70 kg) for 28 days. Then slow tapering for 44 or 52 weeks, depending on the starting dose. Dosage decreased every week by 5 mg every other day

Outcomes	Primary outcome measures	
	7-point composite score of 6 outcomes	
	(Time to) remission and relapse	
	Secondary outcome measures	
	Treatment failure	
	Adverse events	
	Serum CK activity	
	Rankin score (0 to 5)	
	MRC sum score	
	Presence and VAS for pain (0 to 100)	
	Dysphagia	
	Skin changes	
	Presence of arthralgia or Raynaud's	
	NSS (maximum score of 60)	
	SF-36	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by the pharmacist of one of the organising hospitals (University Medical Center Utrecht) with a computer-generated randomisation list, applying stratification by diagnosis."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed by the pharmacist of one of the organising hospitals (University Medical Center Utrecht)"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants, investigator and treating physician blinded to treatment and placebo used. However, reported in paper that 69% of participants guessed their allocation correctly and the first author guessed the allocation correctly in 68% of cases. Allocation unintentionally revealed in one participant
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants followed but 61% discontinued allocated medication before end of trial at 18 months. Some differences in the reasons for discontinuation between the groups
Selective reporting (reporting bias)	Low risk	No suggestion of selective reporting of outcomes
Other bias	Low risk	Stopped early due to rarity of patient group. Free from other problems

Vencovsky 2000

Methods	RCT
Participants	<p>20 participants with dermatomyositis and 16 with polymyositis Ciclosporin (n = 17); methotrexate (n = 19) Age in years (SD): ciclosporin group 42.6 (12), methotrexate group 38.4 (22.2) Sex: 23 females and 13 males Disease duration (SD): ciclosporin group 28 (35) months, methotrexate group 30 (72) months</p> <p>All participants fulfilled Bohan and Peter's definite criteria</p> <p>30 participants had newly diagnosed disease, 6 participants relapse of previously controlled disease. All participants had weakness on MMT of at least degree 3 in at least 2 muscle groups and "severe and active" disease as judged by a physician</p>
Interventions	Ciclosporin 3.0 to 3.5 mg/kg/day versus oral methotrexate 7.5 to 15 mg/weekly for 6 months. All participants were treated with prednisone at a dose 0.5 to 1.0 mg/kg/day
Outcomes	<p>Muscle endurance and functional test. Maximum score 56. Improvement defined as an increase of at least 6 compared to baseline, or if original score < 36, an increase to 42</p> <p>Clinical assessment: clinical composite score. Maximum score 33. Improvement defined as an increase of at least 40% compared to baseline</p> <p>Global patient's assessment, VAS 0 to 10. Improvement defined as an increase of 2 points or more compared to baseline</p> <p>Muscle MRI as study entry and 3 months</p> <p>Laboratory features including: CK, myoglobin, serum interleukin-1 receptor antagonist and c-reactive protein</p>
Notes	No statistically significant difference between the two groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using a sequence of numbers generated by a computer program
Allocation concealment (selection bias)	High risk	Open label trial design
Blinding (performance bias and detection bias) All outcomes	High risk	Open label trial design
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 participants, 4 in the methotrexate group and 3 in the ciclosporin group, discontinued the study due to side effects. Those who discontinued after the 12 week evaluation were included in the semiquantitative evaluation
Selective reporting (reporting bias)	Low risk	Assessments described in the methods were all reported in the results
Other bias	Low risk	No evidence to suggest other bias

Villalba 1998

Methods	Randomised, cross-over, open-label trial
Participants	<p>30 participants, 11 with dermatomyositis, 18 with polymyositis and 1 overlap with systemic lupus erythematosus</p> <p>IV methotrexate group: Age in years (SD): 40.1 (9.5) Sex: 12 females, 3 males Disease duration (SD): 34.9 (12.3) months</p> <p>Oral methotrexate and azathioprine group: Age in years (SD): 41.5 (15.4) Sex: 12 females and 3 males Disease duration (SD): 45.1 (45.9)</p> <p>Diagnosis of definite polymyositis or dermatomyositis as defined by Bohan and Peter</p> <p>Inclusion required weakness on MMT of at least 3/5 in at least two muscle groups, a functional deficit of at least 1 level in at least 1 area of ADL, refractory disease (persistent disease despite 1 mg/kg/day prednisone, inability to taper prednisone below 0.25 mg/kg/day or unacceptable side effects) and active disease requiring further immunosuppression as judged by the evaluating physician</p> <p>25 participants had had failed previous trials of methotrexate and/or azathioprine</p>
Interventions	IV methotrexate 500 mg/m ² every 2 weeks for 12 treatments followed by leucovorin rescue (50 mg/m ² every 6 hours for 4 doses) versus oral methotrexate plus azathioprine (up to 25 mg/week and 150 mg/day) for 6 months
Outcomes	<p>Primary outcome was 'improvement' as defined by a combine evaluation of strength assessed by MMT (maximum score 80) and function assessed by ADL score (maximum 91)</p> <p>Improvement if net increase of a least 1 grade of muscle strength in at least 2 muscle groups on MMT and an increase in at least 1 functional level in one or more areas of function</p> <p>Assessed at 3 and 6 months</p>
Notes	No statistically significant difference between the 2 treatments but trend favours combination therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants withdrawn from the study in each arm. One due to worsening respiratory symptoms and one at own request
Selective reporting (reporting bias)	Low risk	Outcomes reported as outlined in methods section

Villalba 1998 (Continued)

Other bias	Unclear risk	Not clear
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ADL: activities of daily living

BP: blood pressure

CK: creatine kinase

DEXA: dual-emission X-ray absorptiometry

IMACS: International Myositis Assessment and Clinical Studies Group

IBM: inclusion body myositis

IV: intravenous

IVIg: intravenous immunoglobulin

MMT: manual muscle testing

NSS: Neuromuscular Symptom Score

RCT: randomised controlled trial

SD: standard deviation

SF-36: Short Form-36 Health Survey

ULN: upper limit of normal

VAS: visual analog score

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bunch 1981	Follow-up study of RCT by Bunch et al. (Bunch 1980). Participants and observer not blinded to treatment
Chung 2007	Assessing creatine supplementation as a therapy for dermatomyositis and polymyositis. This supplement is not known to be immunosuppressive or immunomodulatory
Donov 1995	No evidence of randomisation or blinding
Fries 1973	Participants could not be confirmed to have polymyositis on the basis of the inclusion criteria

Characteristics of ongoing studies [ordered by study ID]

ISRCTN40085050

Trial name or title	Second line agents in myositis (SELAM trial)
Methods	Randomised, double-blind, placebo-controlled trial
Participants	90 participants with inflammatory myositis fulfilling the Bohan and Peter criteria, on corticosteroids with active disease
Interventions	<p>Participants will be randomised into 4 therapy arms:</p> <ul style="list-style-type: none"> ciclosporin (1 to 10 mg/kg/day) and placebo ciclosporin (1 to 10 mg/kg/day) and methotrexate (7.5 to 25 mg/week) placebo and methotrexate (7.5 to 25mg/week) placebo and placebo <p>Treatments given for 56 weeks</p>
Outcomes	<p>Primary outcome measures</p> <p>MMT by standard MMT (modified MRC) of 16 muscle groups</p>

Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis (Review)

ISRCTN40085050 (Continued)

Timed 30 m walk

Secondary outcome measures

Modified Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS)

Generic health status measured by the SF-36

The acute phase response measured by Westergren erythrocyte sedimentation rate

Continuing muscle damage measured by plasma CK

The cumulative and change in oral steroid dosage

Adverse events

Starting date	2001
Contact information	Academic department of Rheumatology, GKT School of Medicine, London, UK
Notes	Study completed but not published. Preliminary data presented at the British Society for Rheumatology 2010 Annual Conference. ISRCTN40085050

NCT00001261

Trial name or title	Intravenous immunoglobulin (IVIg) for the treatment of inflammatory myopathies
Methods	Double-blind, randomised, placebo-controlled cross-over study in which participants will receive IVIg (2 gm/kg over two days each month) or placebo for 3 months and then will cross over to the alternate therapy for another period of 3 months
Participants	30 participants with dermatomyositis, polymyositis or inclusion body myositis, active disease and previous unsuccessful therapy with prednisolone and one immunosuppressive drug
Interventions	IVIg or placebo
Outcomes	Greater than 15% improvement in baseline muscle strength
Starting date	1999
Contact information	National Institutes of Health Clinical Center (CC)
Notes	Study completed according to clinicaltrials.gov website, last updated March 2008

NCT00035958

Trial name or title	Understanding the pathogenesis and treatment of childhood onset dermatomyositis
Methods	Randomised, open-label, multicentered trial comparing 3 treatments: oral prednisone, oral prednisone and methotrexate, and oral prednisone and etanercept. Treatment duration 24 months
Participants	75 participants with definite juvenile dermatomyositis

NCT00035958 (Continued)

Interventions	Oral prednisone, oral prednisone and methotrexate, or oral prednisone and etanercept
Outcomes	<p>Primary outcome measure</p> <p>Mean duration of steroid therapy and manual muscle strength</p> <p>Secondary outcome measures</p> <p>Disability in daily function and height and weight growth velocity (steroid toxicity measures)</p>
Starting date	2002
Contact information	Daniel J. Lovell, MD, MPH Children's Hospital Medical Center, Cincinnati
Notes	Study terminated 'Incorporating the recommendations of the NIH-formed DSMB in the study procedures would make the project budget over the limit for this funding mechanism.'

NCT00106184

Trial name or title	Rituximab for the treatment of refractory adult and juvenile dermatomyositis (DM) and adult polymyositis (PM)
Methods	<p>A randomised, double-blind, placebo-controlled delayed therapy trial</p> <p>Group A will receive rituximab 750 mg/m² body surface area up to a maximum dose of 1 g at weeks 0 and 1 and placebo at weeks 8 and 9</p> <p>Group B will receive placebo at weeks 0 and 1 and rituximab 750 mg/m² body surface area up to a maximum dose of 1 g at weeks 8 and 9</p>
Participants	<p>Participants with dermatomyositis, polymyositis or juvenile dermatomyositis (> 5 years old) and refractory disease</p> <p>Intolerance or inadequate response to therapy with corticosteroids plus at least 1 other immunosuppressive agent</p>
Interventions	<p>Rituximab 750 mg/m² body surface area up to a maximum dose of 1 g given at weeks 0 and 1 or weeks 8 and 9</p> <p>Placebo infusions given at weeks 0 and 1 or weeks 8 and 9</p>
Outcomes	<p>Primary outcome measure</p> <p>Comparison between the 2 groups of participants in their time to achieve improvement</p> <p>Secondary Outcome Measures</p> <p>Response rates (proportion of improved participants) between Groups A (rituximab-treated) and B (placebo-treated) at week 8</p> <p>20% improvement in MMT over baseline on 2 consecutive time points</p>
Starting date	March 2006
Contact information	National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Notes	Study completed but not published. Preliminary data presented at the American college of Rheumatology 2010 Annual Conference.

NCT00323960

Trial name or title	Five-year actively controlled clinical trial in new onset juvenile dermatomyositis
Methods	Randomised, open label, active control, parallel assignment study
Participants	Newly diagnosed and untreated children with probable or definite diagnosis of JDM according to the Bohan and Peter criteria, aged between 1 and 18 years
Interventions	Prednisolone, prednisolone plus ciclosporin (5 mg/kg in 2 oral doses daily) or prednisolone plus methotrexate (15 to 20 mg/m ² once per week)
Outcomes	<p>Primary outcome measure</p> <p>20% improvement in at least 3 core set variables with no more than 1 of the remaining variables (muscle strength excluded) worsened by > 30%.</p> <p>Secondary outcome measures</p> <p>Change over time in the individual components of the JDM core set of variables:</p> <ul style="list-style-type: none"> a) time to muscle enzymes normalisation; b) frequency of drop-out of suggested steroids use; c) frequency of drop-out for inefficacy of treatment.
Starting date	May 2006
Contact information	Nicolino Ruperto, MD, MPH 0039-010-382854 nicolaruperto@ospedale-gaslini.ge.it Simona Angioloni, B.A. 0039-010-393425 simonaangioloni@ospedale-gaslini.ge.it
Notes	Study currently recruiting according to clinicaltrials.gov website, last updated February 2011

NCT00335985

Trial name or title	Efficacy and safety study of GB-0998 for treatment of steroid-resistant polymyositis and dermatomyositis (PM/DM)
Methods	Randomised, double-blind, placebo-controlled study
Participants	Steroid-resistant polymyositis and dermatomyositis
Interventions	High-dose IVIg (400 mg of GB-0998/kg per day) or placebo daily for 5 successive days
Outcomes	<p>Primary outcome measure</p> <p>Change in MMT scores</p> <p>Secondary outcome measures</p> <p>Change in CK and total activity of daily living scores. Adverse events and laboratory tests</p> <p>'Time frame 8 weeks'</p>
Starting date	2006

NCT00335985 (Continued)

Contact information	Professor Nobuyuki Miyasaka, Tokyo Medical and Dental University
Notes	Study completed according to clinicaltrials.gov website, last updated July 2009

NCT00533091

Trial name or title	A phase 1B, randomised, double-blind, placebo-controlled, multicenter study to evaluate safety of multiple-dose, intravenously administered MEDI-545, a fully human anti interferon-alpha monoclonal antibody, in adult patients with dermatomyositis or polymyositis		
Methods	<p>Randomised, double-blind, placebo-controlled study</p> <p>40 participants with a positive gene signature randomised in a 3:1 ratio to initially receive MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) 2-weekly for 12 weeks or placebo. In each dose cohort, 6 participants to receive MEDI-545 and 2 participants placebo</p> <p>In addition, 8 participants with negative gene signature randomised in a 3:1 ratio to receive MEDI-545 (3.0 mg/kg) or placebo every 2 weeks for 12 weeks.</p> <p>Thereafter, participants initially randomised to MEDI-545 to receive the same dose of MEDI-545 every 2 weeks for 12 weeks and participants initially randomised to placebo to receive MEDI-545 every 2 weeks.</p>		
Participants	<p>40 adult participants with dermatomyositis or polymyositis and a positive gene signature</p> <p>8 adult participants with dermatomyositis or polymyositis and a negative gene signature</p>		
Interventions	MEDI-545 (0.3, 1.0, 3.0, or 10.0 mg/kg) via infusion 2-weekly, or placebo.		
Outcomes	<p>Primary outcome measures</p> <p>The primary endpoints of the study are safety and tolerability of multiple IV doses of MEDI-545 in adult participants with dermatomyositis or polymyositis</p> <p>Secondary outcome measures</p> <p>The secondary endpoints of the study are the PK and IM of multiple IV doses of MEDI-545</p> <p>The third endpoint of the study are the evaluations of disease activities</p>		
Starting date	April 2007		
Contact information	Mick G. Ribeiro	301-398-4202	ribeirom@medimmune.com
	Lisa Farace	301-398-4991	faracel@medimmune.com
Notes	Study completed according to clinicaltrials.gov website, last updated May 2011		

NCT00651040

Trial name or title	Combined treatment of methotrexate + glucocorticoids versus glucocorticoids alone in patients with polymyositis and dermatomyositis (Prometheus)		
Methods	Randomised, open-label, assessor-blind trial		

NCT00651040 (Continued)

Participants	50 participants with previously untreated polymyositis or dermatomyositis
Interventions	<p>Prednisolone at an initial dose of 1.0 mg/kg/day either alone or with methotrexate</p> <p>Methotrexate arm to receive methotrexate at an initial dose of 10 mg/wk escalating up to 20 to 25 mg/week according to clinical need with folic acid 10 mg given 24 hours after each methotrexate dose</p> <p>Treatment duration of 12 months with a further 12 month follow-up</p>
Outcomes	<p>Primary outcome measure</p> <p>Total dose of glucocorticoids administered between baseline and the end of treatment</p> <p>Secondary outcome measures</p> <p>Assessment of disease activity and damage, muscle strength and endurance, enzyme levels, glucocorticoid side-effects, dose, HAQ, SF-36, treatment failures</p>
Starting date	May 2008
Contact information	<p>Jiri Vencovsky, prof. MD. +420234075340 venc@revma.cz</p> <p>Jana Tomasova, MD. PhD. +420234075340 jtomasova@yahoo.com</p>
Notes	Study currently recruiting according to clinicaltrials.gov website, last verified July 2011

NCT01148810

Trial name or title	Efficacy and tolerability of BAF312 in patients with polymyositis and dermatomyositis
Methods	Randomised, double-blind, placebo-controlled trial of BAF312 or placebo for 12 weeks followed by a further 12 weeks where all participants receive BAF312
Participants	Polymyositis or dermatomyositis unresponsive to at least 3 months of therapy with corticosteroids with or without disease modifying antirheumatic drugs
Interventions	BAF312
Outcomes	IMACS core set measures
Starting date	2010
Contact information	Novartis Pharmaceuticals +41-61-324-1111
Notes	Study currently recruiting according to clinicaltrials.gov website, last verified April 2011

NCT01315938

Trial name or title	Abatacept treatment in polymyositis and dermatomyositis (ARTEMIS)
Methods	Randomised, single-blind (outcome assessor blinded), delayed treatment study

NCT01315938 (Continued)

Participants	20 participants with active dermatomyositis (10) or polymyositis (10) despite therapy with steroids and either methotrexate or azathioprine for at least 3 months
Interventions	Participants will be randomised to receive abatacept at time 0 then after 2, 4, 8, 12, 16 and 20 weeks, or to have this treatment delayed for 3 months
Outcomes	<p>Primary outcome:</p> <p>The number of responders, defined as improved according to the IMACs criteria, after treatment with abatacept for 6 months</p> <p>Secondary outcomes:</p> <p>The change in the individual components of the IMACS core set measures for disease activity at 3 and 6 months</p>
Starting date	January 2011
Contact information	<p>Ingrid E Lundberg, MD, PhD +46851770000 ext 6087 Ingrid.Lundberg@ki.se</p> <p>Jiri Vencovsky, MD, PhD +420224914469 venc@revma.cz</p> <p>Patrick Gordon, MBBS, PhD +44203 299 1735 patrick.gordon2@nhs.net</p>
Notes	Study currently recruiting

ADL: activities of daily living

CK: creatine kinase

HAQ: Health Assessment Questionnaire

IV: intravenous

MMT: manual muscle testing

SF-36: Short Form 36 Health Survey

DATA AND ANALYSES

Comparison 1. IVIg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in manual muscle strength by $\geq 15\%$ at 12 weeks	1	15	Risk Ratio (M-H, Fixed, 95% CI)	4.44 [0.25, 79.42]

Analysis 1.1. Comparison 1 IVIg versus placebo, Outcome 1 Improvement in manual muscle strength by $\geq 15\%$ at 12 weeks.

Study or subgroup	Favours IVIg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dalakas 1993	2/8	0/7		100%	4.44[0.25,79.42]
Total (95% CI)	8	7		100%	4.44[0.25,79.42]

Comparison 2. Azathioprine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in muscle strength	1	16	Mean Difference (IV, Fixed, 95% CI)	5.4 [-13.08, 23.88]

Analysis 2.1. Comparison 2 Azathioprine versus placebo, Outcome 1 Improvement in muscle strength.

Comparison 3. Plasma exchange or leukapheresis versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients who improved after treatment	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.37]

Analysis 3.1. Comparison 3 Plasma exchange or leukapheresis versus placebo, Outcome 1 Number of patients who improved after treatment.

Comparison 4. Infliximab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in manual muscle strength by $\geq 15\%$ at 16 weeks	1	18	Risk Ratio (M-H, Fixed, 95% CI)	3.77 [0.23, 63.05]
2 Improved by IMACS criteria at 16 weeks	1	18	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.51, 5.98]

Analysis 4.1. Comparison 4 Infliximab versus placebo, Outcome 1 Improvement in manual muscle strength by $\geq 15\%$ at 16 weeks.

Analysis 4.2. Comparison 4 Infliximab versus placebo, Outcome 2 Improved by IMACS criteria at 16 weeks.

Comparison 5. Ciclosporin versus methotrexate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in 'Muscle endurance with functional test' measurement at 6 months (maximum score 56)	1	36	Mean Difference (IV, Fixed, 95% CI)	6.80 [-1.65, 15.25]
2 Improvement in 'Clinical Assessment' score at 6 months (maximum score 33)	1	36	Mean Difference (IV, Fixed, 95% CI)	1.90 [-1.83, 5.63]
3 Improvement in global patient's assessment at 6 months (0 to 10)	1	36	Mean Difference (IV, Fixed, 95% CI)	0.30 [-1.20, 1.80]

Analysis 5.1. Comparison 5 Ciclosporin versus methotrexate, Outcome 1 Improvement in 'Muscle endurance with functional test' measurement at 6 months (maximum score 56).

Analysis 5.2. Comparison 5 Ciclosporin versus methotrexate, Outcome 2 Improvement in 'Clinical Assessment' score at 6 months (maximum score 33).

Analysis 5.3. Comparison 5 Ciclosporin versus methotrexate, Outcome 3 Improvement in global patient's assessment at 6 months (0 to 10).

Comparison 6. Oral methotrexate with azathioprine versus intravenous methotrexate with leucovorin rescue

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement as defined by 'combined evaluation of strength and function' tool	1	30	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.87, 8.15]

Analysis 6.1. Comparison 6 Oral methotrexate with azathioprine versus intravenous methotrexate with leucovorin rescue, Outcome 1 Improvement as defined by 'combined evaluation of strength and function' tool.

Comparison 7. Etanercept versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in Health Assessment Questionnaire score at 52 weeks	1	16	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.55, 0.51]
2 Mean change in Health Assessment Questionnaire score at 24 weeks	1	16	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.78, 0.58]
3 Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement at 24 weeks	1	16	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.67, 6.20]
4 Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement at 52 weeks	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.37, 2.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Cumulative dosage of prednisone over the one-year study period	1	16	Mean Difference (IV, Fixed, 95% CI)	-4.01 [-8.66, 0.64]
6 Average change in time (sec) to walk 30 feet comparing performance at baseline to week 52	1	16	Mean Difference (IV, Fixed, 95% CI)	1.10 [-6.57, 8.77]
7 Average change in time to rise from a chair from baseline to week 52	1	14	Mean Difference (IV, Fixed, 95% CI)	1.17 [-1.37, 3.71]
8 Treatment failure	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.33, 1.05]
9 Individualized Neuromuscular Quality of Life	1	16	Mean Difference (IV, Fixed, 95% CI)	-5.4 [-26.82, 16.02]
10 SF-36 Physical Component Summary Score	1	16	Mean Difference (IV, Fixed, 95% CI)	6.4 [-3.28, 16.08]

Analysis 7.1. Comparison 7 Etanercept versus placebo, Outcome 1 Mean change in Health Assessment Questionnaire score at 52 weeks.

Analysis 7.2. Comparison 7 Etanercept versus placebo, Outcome 2 Mean change in Health Assessment Questionnaire score at 24 weeks.

Analysis 7.3. Comparison 7 Etanercept versus placebo, Outcome 3 Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement at 24 weeks.

Analysis 7.4. Comparison 7 Etanercept versus placebo, Outcome 4 Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement at 52 weeks.

Analysis 7.5. Comparison 7 Etanercept versus placebo, Outcome 5 Cumulative dosage of prednisone over the one-year study period .

Analysis 7.6. Comparison 7 Etanercept versus placebo, Outcome 6 Average change in time (sec) to walk 30 feet comparing performance at baseline to week 52.

Analysis 7.7. Comparison 7 Etanercept versus placebo, Outcome 7 Average change in time to rise from a chair from baseline to week 52 .

Analysis 7.8. Comparison 7 Etanercept versus placebo, Outcome 8 Treatment failure.

Analysis 7.9. Comparison 7 Etanercept versus placebo, Outcome 9 Individualized Neuromuscular Quality of Life.

Analysis 7.10. Comparison 7 Etanercept versus placebo, Outcome 10 SF-36 Physical Component Summary Score.

Comparison 8. Pulse oral dexamethasone versus daily oral prednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neuromuscular Symptom Score	1	62	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-11.48, 1.48]
2 Remission	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.22, 1.57]
3 Relapse	1	62	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.69, 2.24]

Analysis 8.1. Comparison 8 Pulse oral dexamethasone versus daily oral prednisolone, Outcome 1 Neuromuscular Symptom Score.

Analysis 8.2. Comparison 8 Pulse oral dexamethasone versus daily oral prednisolone, Outcome 2 Remission.

Analysis 8.3. Comparison 8 Pulse oral dexamethasone versus daily oral prednisolone, Outcome 3 Relapse.

ADDITIONAL TABLES

Table 1. Bohan and Peter criteria

Features	Polymyositis	Dermatomyositis
1. Symmetrical proximal muscle weakness	Definite: all 1-4	Definite: 5 plus any 3 of 1-4
2. Muscle biopsy evidence of myositis	Probable: any 3 of 1-4	Probable: 5 plus any 2 of 1-4
3. Elevation in serum skeletal muscle enzymes	Possible: any 2 of 1-4	Possible: 5 plus any 1 of 1-4
4. Characteristic electromyographic pattern of myositis		
5. Typical rash of dermatomyositis		

Table 2. Dalakas criteria (PM: polymyositis; DM: dermatomyositis)

Features	Definite PM	Probable PM	Definite DM	Mild/early DM
Muscle strength	Myopathic muscle weakness	Myopathic muscle weakness	Myopathic muscle weakness	Seemingly normal strength
Electromyographic findings	Myopathic	Myopathic	Myopathic	Myopathic or non-specific
Muscle enzymes	Elevated (up to 50-fold)	Elevated (up to 50-fold)	Elevated (up to 50-fold) or normal	Elevated (up to 10-fold) or normal
Muscle-biopsy findings	Diagnostic for this type of inflammatory myopathy	Non-specific myopathy without signs of primary inflammation	Diagnostic	Non-specific or diagnostic
Rash or calcinosis	Absent	Absent	Present	Present

Table 3. Intravenous immunoglobulin (IVIg) versus placebo for dermatomyositis

IVIg versus placebo for dermatomyositis						
Patient or population: patients with dermatomyositis and polymyositis Settings: Intervention: IVIg versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	IVIg				
15% or greater improvement in muscle strength compared with baseline after at least six months	See comment	See comment	Not estimable	-	See comment	No data available, only one study of three months duration
Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement	See comment	See comment	Not estimable	-	See comment	Not measured
Change in function or disability scale at six months	See comment	See comment	Not estimable	-	See comment	Although an activities of daily living score was assessed, the results in the 2 groups were not reported systematically and statistical comparison between the 2 groups was not reported.

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

CI: confidence interval; IVIg: intravenous immunoglobulin

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.

Table 4. Azathioprine versus placebo for dermatomyositis and polymyositis

Azathioprine versus placebo for dermatomyositis and polymyositis						
Patient or population: patients with dermatomyositis and polymyositis Settings: Intervention: azathioprine						

Table 4. Azathioprine versus placebo for dermatomyositis and polymyositis (Continued)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Azathioprine				
15% or greater improvement in muscle strength compared with baseline after at least six months. - not measured	See comment	See comment	Not estimable	-	See comment	No data as study only lasted three months
Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Change in function or disability scale at six months - not measured	See comment	See comment	Not estimable	-	See comment	Not measured

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

CI: confidence interval

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.

Table 5. Azathioprine plus prednisolone versus methotrexate plus prednisolone

Azathioprine plus prednisolone compared with methotrexate plus prednisolone for polymyositis or dermatomyositis

Patient or population: patients with polymyositis or dermatomyositis

Settings:

Intervention: prednisolone plus either azathioprine 2.5 mg per kg daily

Comparison: prednisolone plus methotrexate 15 mg weekly for 1 year

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

Table 5. Azathioprine plus prednisolone versus methotrexate plus prednisolone (Continued)

	Low dose methotrex- ate	Azathio- prine				
15% or greater improvement in muscle strength compared with baseline after at least 6 months - not reported	See com- ment	See com- ment	Not es- timable	-	-	Hand-held my- ometry used but data not provid- ed
Achieving the International Myosi- tis Assessment and Clinical Studies Group (IMACS) definitions of improve- ment at 52 weeks - not measured	See com- ment	See com- ment	Not es- timable	-	-	Not measured
Change in function or disability scale at 6 months - not reported	See com- ment	See com- ment	Not es- timable	-	-	Timed walk was measured but data not avail- able

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

CI: confidence interval; **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.

Table 6. Plasma exchange or leukapheresis versus placebo for dermatomyositis and polymyositis

Plasma exchange or leukapheresis versus placebo for dermatomyositis and polymyositis						
Patient or population: patients with dermatomyositis and polymyositis						
Settings:						
Intervention: plasma exchange or leukapheresis versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Par- ticipants (studies)	Quality of the evi- dence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Plasma ex- change or leukapheresis				
15% or greater improvement in muscle strength compared with baseline after at least six months - not measured	See com- ment	See comment	Not es- timable	-	See com- ment	One study of only one month dura- tion.

Table 6. Plasma exchange or leukapheresis versus placebo for dermatomyositis and polymyositis (Continued)

Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Change in function or disability scale at six months ¹ - not measured	See comment	See comment	Not estimable	-	See comment	One study of only 1 month duration.

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

CI: confidence interval

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.

Table 7. Oral methotrexate with azathioprine versus intravenous methotrexate with leucovorin rescue for dermatomyositis and polymyositis

Oral methotrexate with azathioprine versus intravenous methotrexate with leucovorin rescue for dermatomyositis and polymyositis

Patient or population: patients with dermatomyositis and polymyositis

Settings:

Intervention: oral methotrexate with azathioprine

Comparison: intravenous methotrexate with leucovorin rescue

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intravenous methotrexate with leucovorin rescue	Oral methotrexate with azathioprine				
15% or greater improvement in muscle strength compared with baseline after at least six months - not reported	See comment	See comment	Not estimable	-	See comment	One study of 1 month's duration
Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) defin-	See comment	See comment	Not estimable	-	See comment	No data

Table 7. Oral methotrexate with azathioprine versus intravenous methotrexate with leucovorin rescue for dermatomyositis and polymyositis (Continued)
itions of improvement -
not measured

Change in function or disability scale at six months - not reported	See comment	See comment	Not estimable	-	See comment	No data available. Activities of daily living score was measured but the results were only presented in participants who improved according to the trial definition
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval

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.

Table 8. Methotrexate versus ciclosporin for dermatomyositis and polymyositis

Methotrexate versus ciclosporin for dermatomyositis and polymyositis

Patient or population: patients with dermatomyositis and polymyositis

Settings:

Intervention: methotrexate

Comparison: ciclosporin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Ciclosporin	Methotrexate				
15% or greater improvement in muscle strength compared with baseline after at least six months - not reported	See comment	See comment	Not estimable	-	See comment	Muscle strength data not available.
Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement - not measured	See comment	See comment	Not estimable	-	See comment	Not an outcome in this study
Change in function or disability scale at six months - not reported	See comment	See comment	Not estimable	-	See comment	Function measured but not reported separately

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Table 8. Methotrexate versus ciclosporin for dermatomyositis and polymyositis (Continued)

from composite score of 'muscle endurance with function'.

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

CI: confidence interval

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.

Table 9. Infliximab versus placebo for dermatomyositis and polymyositis

Infliximab versus placebo for dermatomyositis and polymyositis

Patient or population: patients with dermatomyositis and polymyositis

Settings:

Intervention: infliximab versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Infliximab				
15% or greater improvement in muscle strength compared with baseline after at least six months - not measured	See comment	See comment	Not estimable	-	See comment	No data
Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement Follow-up: 16 weeks	333 per 1000	1000 per 1000 (77 to 1000)	RR 3.77 (0.23 to 63.05)	18 (1 study)	⊕⊕⊕⊕ very low 1	-
Change in function or disability scale at six months - not measured	See comment	See comment	Not estimable	-	See comment	Not measured

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

CI: confidence interval; **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.

Table 9. Infliximab versus placebo for dermatomyositis and polymyositis (Continued)

Very low quality: We are very uncertain about the estimate.

¹ Extremely small numbers and includes open follow-up.

Table 10. Etanercept versus placebo
Etanercept versus placebo

Patient or population: patients with dermatomyositis, either 1. treatment naïve (prednisolone < 2 months) or 2. refractory to therapy with prednisolone > 2 months and either methotrexate (stable dose ≥1 month or more) or intravenous immunoglobulin ≥ 3 months

Settings:

Intervention: etanercept versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Etanercept				
15% or greater improvement in muscle strength compared with baseline after at least 6 months - not reported	See comment	See comment	Not estimable	-	See comment	Not an outcome in this study
Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement at 24 weeks	400 per 1000	820 per 1000 (268 to 1000)	RR 2.05 (0.67 to 6.2)	16 (1 study)	⊕⊕⊕⊕ moderate ¹	-
Change in function or disability score Various measures Follow-up: 24 weeks	See comment	See comment	Not estimable	16 (1 study)	See comment	No significant difference between control and etanercept in any measure of function or disability (final values) (see text)

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

CI: confidence interval; **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 Pilot study with small sample size of 16 participants. Wide 95% CI of RR (0.75 to 2.45).

Table 11. Eculizumab versus placebo for dermatomyositis and polymyositis

Eculizumab versus placebo for dermatomyositis and polymyositis						
Patient or population: patients with dermatomyositis and polymyositis Settings: Intervention: eculizumab versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Eculizumab				
15% or greater improvement in muscle strength compared with baseline after at least six months - not measured	See comment	See comment	Not estimable	-	See comment	Single study of only 9 weeks' duration.
Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement - not measured	See comment	See comment	Not estimable	-	See comment	Not an outcome in this study
Change in function or disability scale at six months - not measured	See comment	See comment	Not estimable	-	See comment	Single study of only 9 weeks' duration.
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: confidence interval</p>						
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>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.</p> <p>Very low quality: We are very uncertain about the estimate.</p>						

Table 12. Pulse oral dexamethasone versus daily oral prednisolone for dermatomyositis and polymyositis

Pulse oral dexamethasone versus daily oral prednisolone for dermatomyositis and polymyositis						
Patient or population: patients with dermatomyositis and polymyositis, non-specific myositis, myositis with a co-existing connective tissue disease or with cancer within 2 years before onset of myositis, disease of less than one year duration. On no more than 20 mg prednisolone and no other immunosuppressant or immunomodulatory therapy						
Settings:						
Intervention: pulse oral dexamethasone versus daily oral prednisolone						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

Table 12. Pulse oral dexamethasone versus daily oral prednisolone for dermatomyositis and polymyositis (Continued)

	Daily oral prednisolone	Pulse oral dexamethasone				
15% or greater improvement in muscle strength compared with baseline after at least 6 months - not reported	See comment	See comment	Not estimable	-	See comment	Not an outcome in this study
Achieving the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement at 52 weeks - not reported	See comment	See comment	Not estimable	-	See comment	Not an outcome in this study
Change in function or disability scale Neuromuscular Symptom Score Scale from: 0 to 60 Follow-up: 18 months	The mean function or disability scale score in the control group was 46 ¹	The mean function or disability scale score in the intervention groups was 5 lower (11.48 lower to 1.48 higher)	-	62 (1 study)	⊕⊕⊕⊕ moderate ²	-

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

CI: confidence interval

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 Mean final NSS in placebo group.

² Only one study of 62 participants with 61% discontinuing the study early.

APPENDICES

Appendix 1. CENTRAL search strategy

#1"ADRENAL CORTEX HORMONES" OR CORTICOSTEROID* OR ANTIMETABOLITES OR ANTI-METABOLITES

#2AZATHIOPRINE OR MERCAPTOPYRINE OR METHOTREXATE OR CICLOSPORIN* OR CYCLOSPORIN* OR CHLORAMBUCIL OR CYCLOPHOSPHAMIDE

#3IMMUNOGLOBULIN* OR INTERFERON* OR "GAMMA GLOBULIN"

#4"PLASMA EXCHANGE" OR PLASMAPHERESIS OR "IMMUNOSUPPRESSIVE AGENT*" OR ADJUVANTS NEXT IMMUNOLOGIC OR IMMUNOMODULAT*

#5(#1 OR #2 OR #3 OR #4)

#6DERMATOMYOSITIS OR POLYMYOSITIS OR MYOSITIS

#7(#5 AND #6)

Appendix 2. MEDLINE (OvidSP) search strategy

1 Adrenal Cortex Hormones/

2 corticosteroid\$.mp.

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3 anti-metabolites.mp.
 4 Antimetabolites/
 5 antimetabolites.mp.
 6 Azathioprine/
 7 azathioprine.mp.
 8 6-Mercaptopurine/
 9 Mercaptopurine.mp.
 10 Methotrexate/
 11 methotrexate.mp.
 12 ciclosporin.mp.
 13 Cyclosporine/
 14 cyclosporin.mp.
 15 Chlorambucil/
 16 chlorambucil.mp.
 17 Cyclophosphamide/
 18 cyclophosphamide.mp.
 19 Immunoglobulins/
 20 immunoglobulin\$.mp.
 21 Interferons/
 22 interferon\$.mp.
 23 gamma-Globulins/
 24 gamma Globulin\$.mp.
 25 Plasma Exchange/
 26 plasma exchange\$.mp.
 27 Plasmapheresis/
 28 Plasmapheresis.mp.
 29 Immunosuppressive Agents/
 30 immunosuppress\$.mp.
 31 Adjuvants, immunologic/
 32 immunomodulat\$.mp.
 33 or/1-30
 34 Dermatomyositis/
 35 dermatomyositis.mp.
 36 Polymyositis/
 37 polymyositis.mp.
 38 Myositis/
 39 myositis.mp.
 40 or/34-39
 41 33 and 40
 42 randomized controlled trial.pt.
 43 controlled clinical trial.pt.
 44 randomized controlled trials/
 45 random allocation/
 46 double-blind method/
 47 single-blind method/
 48 or/42-47
 49 animals/ not humans/
 50 48 not 49
 51 clinical trial.pt.
 52 exp clinical trial/
 53 (clin\$ adj25 trial\$).ti,ab.
 54 ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj25 (blind\$ or mask\$)).ti,ab.
 55 placebos/
 56 placebo\$.ti,ab.
 57 random\$.ti,ab.
 58 research design/
 59 or/51-58
 60 59 not 49
 61 60 not 50
 62 comparative study/
 63 exp evaluation studies/
 64 follow up studies/

65 prospective studies/
66 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
67 or/62-66
68 67 not 49
69 68 not (50 or 61)
70 50 or 61 or 69
71 41 and 70

Appendix 3. EMBASE (OvidSP) search strategy

1 Randomized Controlled Trial/
2 Clinical Trial/
3 Multicenter Study/
4 Controlled Study/
5 Crossover Procedure/
6 Double Blind Procedure/
7 Single Blind Procedure/
8 exp RANDOMIZATION/
9 Major Clinical Study/
10 PLACEBO/
11 Meta Analysis/
12 phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
13 (clin\$ adj25 trial\$).tw.
14 ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj25 (blind\$ or mask\$)).tw.
15 placebo\$.tw.
16 random\$.tw.
17 control\$.tw.
18 (meta?analys\$ or systematic review\$).tw.
19 (cross?over or factorial or sham? or dummy).tw.
20 ABAB design\$.tw.
21 or/1-20
22 human/
23 nonhuman/
24 22 or 23
25 21 not 24
26 21 and 22
27 25 or 26
28 exp Corticosteroid/
29 adrenal cortex hormone\$1.mp.
30 Antimetabolite/
31 (antimetabolites or anti-metabolites).mp.
32 Azathioprine/
33 azathioprine.mp.
34 Mercaptopurine/
35 mercaptopurine.mp.
36 METHOTREXATE/
37 methotrexate.mp.
38 Cyclosporin/
39 cyclosporin.mp.
40 CHLORAMBUCIL/
41 chlorambucil.mp.
42 ciclosporin.mp.
43 CYCLOPHOSPHAMIDE/
44 cyclophosphamide.mp.
45 Immunoglobulin/
46 immunoglobulin\$1.mp.
47 INTERFERON/
48 interferon\$1.mp.
49 gamma-globulin.mp. or Immunoglobulin/
50 plasma exchange.mp. or Plasmapheresis/
51 (plasma exchange or plasmapheresis).mp.
52 Immunosuppressive Agent/

53 immunosuppressive agent\$1.mp.
54 Immunological Adjuvant/
55 (immunologic adj1 adjuvant\$1).mp.
56 Immunomodulation/
57 immunomodulat\$.mp.
58 or/28-57
59 Dermatomyositis/
60 dermatomyositis.mp.
61 POLYMYOSITIS/
62 polymyositis.mp.
63 MYOSITIS/ or myositis.mp.
64 or/59-63
65 58 and 64
66 27 and 65

Appendix 4. clinicaltrials.gov search strategy

1. Dermatomyositis
2. Polymyositis
3. Myositis

WHAT'S NEW

Date	Event	Description
16 August 2016	Review declared as stable	This review is no longer being updated. It will be replaced by two new reviews. See Published notes .

HISTORY

Protocol first published: Issue 2, 2002
Review first published: Issue 3, 2005

Date	Event	Description
13 August 2012	Amended	Minor corrections to wording in abstract and objectives
7 March 2012	New citation required and conclusions have changed	New studies included with new interventions. Conclusions changed.
22 August 2011	New search has been performed	Searches were updated to August 2011 and four new trials were included. 'Risk of bias' and 'Summary of findings' tables were added. No new authors but change in order of listing.
29 May 2008	Amended	Converted to new review format.
10 March 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Ernest Choy drafted the original review, searched for trials, assessed methodological quality, extracted data and revised the review following peer review. Patrick Gordon drafted the updated review, searched for trials, assessed methodological quality, extracted data

and revised the updated review following peer and editorial review. Jessica Hoogendijk and John Winer searched for trials, assessed methodological quality and extracted data.

DECLARATIONS OF INTEREST

Professor Ernest Choy has received research grants, and served as member of advisory boards and speaker bureaus of Abbott Laboratories, Allergan, AstraZeneca, Boehringer Ingelheim, Chelsea Therapeutics, Chugai Pharma, Eli Lilly, Ferring Pharmaceutical, GSK, Jazz Pharmaceuticals, MedImmune, Merrimack Pharmaceutical, MSD, Pfizer, Pierre Fabre Medicament, Roche, Schering Plough, Synovate, UCB Celltech and Wyeth.

Dr Patrick Gordon's institution has received grants for three of the studies in this review. One was an excluded study ([Chung 2007](#)), funded by various non-commercial grant-giving bodies and two are ongoing studies, one funded by Bristol Myers Squibb and the Myositis Support Group ([NCT01315938](#)) and the other by the Arthritis Research Campaign (SELAM, [ISRCTN40085050](#)). Dr John Winer is a collaborator in the SELAM trial. Bristol Myers Squibb funded Dr Gordon's attendance at EULAR 2011 and 2012 (money paid to institution).

Dr Jessica Hoogendijk is co-author of a RCT in this review ([Van de Vlekkert 2010](#)). She has no other known conflicts of interest.

Dr John Winer's institution undertook an audit of IVIg side effects and received payment for travel and equipment from CSL Behring. He has been involved in an, as yet, unpublished trial of methotrexate and azathioprine for polymyositis and dermatomyositis ([Miller 2002](#)).

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other.

External sources

- No sources of support supplied

NOTES

This review is no longer being updated. It will be replaced by two Cochrane reviews, Biologics for dermatomyositis and polymyositis, and Immunosuppressant and immunomodulatory treatment other than biologics for dermatomyositis and polymyositis, planned for 2016 and 2017.

INDEX TERMS

Medical Subject Headings (MeSH)

*Leukapheresis; *Plasma Exchange; Blood Component Removal; Dermatomyositis [*therapy]; Immunoglobulins, Intravenous [therapeutic use]; Immunosuppressive Agents [adverse effects] [*therapeutic use]; Polymyositis [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans