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Immunosuppressive and immunomodulatory therapies for idiopathic inflammatory myopathies (Protocol)

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[Intervention Protocol]

Immunosuppressive and immunomodulatory therapies for idiopathic inflammatory myopathies

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

This protocol is for two separate reviews to assess the effects (benefits and harms) of immunosuppressant and immunomodulatory treatments for the idiopathic inflammatory myopathies.

Targeted treatments

To assess the effects (benefits and harms) of targeted immunosuppressant and immunomodulatory treatments for the idiopathic inflammatory myopathies: dermatomyositis (DM, including juvenile dermatomyositis, jDM), immune mediated necrotising myopathy (IMNM), anti-synthetase syndrome (ASS), overlap-myositis (OM) and polymyositis (PM). We will also include cancer-related myositis and amyopathic dermatomyositis.

Non-targeted treatments

To assess the effects (benefits and harms) of non-targeted immunosuppressant and immunomodulatory treatments for the idiopathic inflammatory myopathies: dermatomyositis (DM, including juvenile dermatomyositis, jDM), immune mediated necrotising myopathy (IMNM), anti-synthetase syndrome (ASS), overlap-myositis (OM) and polymyositis (PM). We will also include cancer-related myositis and amyopathic dermatomyositis.

BACKGROUND

Description of the condition

Idiopathic inflammatory myopathies (IIM) refer to diseases with auto-immune mediated inflammation of skeletal muscles without a recognised infective cause. The classification of IIMs remains the subject of debate (Schmidt 2018). For this review, we chose to use a comprehensive classification including dermatomyositis (DM, including juvenile dermatomyositis, jDM), immune-mediated necrotising myopathy (IMNM), anti-synthetase syndrome (ASS), overlap-myositis (OM) and polymyositis (PM). Polymyositis (PM) is a contested entity within the group of IIMs. It is the rarest form of myositis and is primarily considered a diagnosis of exclusion of all subsequent forms of myositis(Loarce-Martos 2020; Tanboon 2020). Cancer-related myositis (CAM), defined as the diagnosis of cancer within three years of the diagnosis of IIM, and amyopathic dermatomyositis will be included in this review**.**

Whilst inclusion body myositis (IBM) is often included within the classification of IIM, it remains disputed whether the primary pathology is inflammatory, and it is resistant to immunosuppressive therapy (Benveniste 2015). In view of this, a separate Cochrane Review on IBM is available (Rose 2015), and we have not included IBM within this review. Furthermore, we will not cover inflammatory myopathies as a result of systemic diseases (sarcoidosis, vasculitis), graft versus host myositis, immune checkpoint inhibitor-related myositis, focal myositis, or myositis in relation to eosinophilic fasciitis.

The prevalence of IIM is approximately 11 per 100,000 (Ahlstrom 1993; Meyer 2015). The incidence is estimated at 7.98 cases per million per year (range 1.16 to 19). For adults, the peak age of onset is between 30 and 50 years of age. IIMs occur more commonly in women than in men (ratio female:male 2:1), with the exception of IBM. The estimated annual incidence for children is 2.5 to 4.1 cases per million per year. The peak incidence for juvenile dermatomyositis is at the age of seven years.

DM, ASS, OM and PM are characterised by chronic inflammation of skeletal muscle (Dalakas 1991; Dalakas 2001), whereas IMNM is characterised histologically by muscle fibre necrosis and regeneration without a significant inflammatory cell infiltrate (Allenbach 2017). These diseases are thought to result from an auto-immune process and, consistent with this, in approximately 60% of cases an associated autoantibody is found (Betteridge 2019). Many of these antibodies (myositis-specific antibodies) are specific to IIM, whereas others (myositis-associated antibodies) also occur in other conditions. These antibodies can aid diagnosis, predict organ involvement and help assess prognosis (Mariampillai 2018; Rietveld 2019). The IIM may occur in association with a malignancy and can involve organs other than skeletal muscle with Raynaud's, joint, gastrointestinal, pulmonary and cardiac involvement. By definition, dermatomyositis has skin involvement. In amyopathic dermatomyositis, skin disease is found in the absence of muscle involvement.

IIMs are characterised by subacute progressive proximal, often symmetrical muscle weakness in a limb-girdle pattern. Due to muscle weakness, people with IIMs increasingly experience difficulties climbing stairs, rising from a chair, walking and running and lifting objects. Although few people recover completely after one disease episode, response to treatment is often incomplete and reduced activities of daily living and fatigue are common (Mecoli 2019).

Although IIMs account for the most common cause of acquired muscle diseases in adults, they are uncommon in general practice and optimal therapy has not been adequately defined.

Description of the intervention

This is a protocol for two reviews, one for targeted and the other for non-targeted immunosuppressive and immunomodulatory agents. We define targeted therapies as those directly targeting a recognised immunological pathway suspected to be involved in the pathogenesis of IIM.

Targeted drug therapies include biological therapies (e.g. B-cell depleting agents), Janus kinase inhibitors, complement inhibitors, and small molecules.

Non-targeted drug therapies include corticosteroids, intravenous or subcutaneous immunoglobulins, plasmapheresis, and conventional immunosuppressive agents (e.g. azathioprine, methotrexate, mycophenolate mofetil and calcineurin inhibitors).

How the intervention might work

Whilst the specific method of action varies between the different agents, they all modify or suppress the aberrant immune response in IIM.

Why it is important to do this review

This protocol has been developed from an earlier review of immunosuppressant and immunomodulatory treatments for dermatomyositis and polymyositis (Gordon 2012). An increasing number of trials in recent years have assessed targeted drug therapies including biologic agents. Following publication of the protocol, we will therefore split the earlier review into two separate reviews, one of targeted and the other of non-targeted treatments. We have chosen to include the conventional immunosuppressive agents (e.g. azathioprine, methotrexate, mycophenolate mofetil, and calcineurin inhibitors) in the review of non-targeted therapies, as they do not directly target a recognised pathway.

Changes to selection criteria and outcomes, and application of current Cochrane methodological standards have necessitated a new protocol.

OBJECTIVES

This protocol is for two separate reviews to assess the effects (benefits and harms) of immunosuppressant and immunomodulatory treatments for the idiopathic inflammatory myopathies.

Targeted treatments

To assess the effects (benefits and harms) of targeted immunosuppressant and immunomodulatory treatments for the idiopathic inflammatory myopathies: dermatomyositis (DM, including juvenile dermatomyositis, jDM), immune mediated necrotising myopathy (IMNM), anti-synthetase syndrome (ASS), overlap-myositis (OM) and polymyositis (PM). We will also include cancer-related myositis and amyopathic dermatomyositis.

Non-targeted treatments

To assess the effects (benefits and harms) of non-targeted immunosuppressant and immunomodulatory treatments for the idiopathic inflammatory myopathies: dermatomyositis (DM, including juvenile dermatomyositis, jDM), immune mediated necrotising myopathy (IMNM), anti-synthetase syndrome (ASS), overlap-myositis (OM) and polymyositis (PM). We will also include cancer-related myositis and amyopathic dermatomyositis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs are eligible (quasi-RCTs are trials in which allocation is not strictly random but is based, for example, on case record number or date of birth). We will include randomised cross-over trials. Cluster-randomised trials are very unlikely in this field and are not included. There will be no restrictions by language or publication status.

Types of participants

Eligible participants are adults and children with probable or definite dermatomyositis (DM, including juvenile dermatomyositis, JDM), immune-mediated necrotising myopathy (IMNM), anti-synthetase syndrome (ASS), overlap-myositis (OM) and polymyositis (PM) according to any of the following diagnostic criteria: Bohan and Peter (Bohan 1975a; Bohan 1975b) (Table 1), Dalakas (Dalakas 1991) (Table 2) European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria (Lundberg 2017), and the 119th (DM, IMNM, OM; Hoogendijk 2004), 224th (IMNM; Allenbach 2018) and 239th (DM; Mammen 2020) ENMC workshops. If no diagnostic criteria are cited, all the review authors will judge the quality of evidence for correct diagnosis. We will include a study in the review only if the review authors agree that the participants have probable or definite IIM. We will not include people with IBM, which is the topic of another Cochrane Review (Rose 2015). However, if only a small number, up to five per cent, of participants in a study are ineligible (e.g. they have an IBM diagnosis), we will include the study. We will otherwise include studies in people with a mixture of diagnoses only if they report separate data for participants eligible for this review.

Types of interventions

After publication of this protocol, we will create separate reviews for targeted and non-targeted treatments.

We will include treatment with immunosuppressant or immunomodulatory treatments used at any dosage, by any route, in any regimen and for any duration.

Targeted treatments

We will include any targeted immunosuppressant or immunomodulatory treatment including, but not restricted to, monoclonal antibodies, receptor fusion proteins, oligonucleotides, small molecule inhibitors such as Janus kinase inhibitors, cytokines, complement inhibitors in IIM, or other targeted treatments, compared with placebo, no treatment or another immunosuppressant or immunomodulatory treatment (targeted or non-targeted). We will also include interventions given in combination.

Non-targeted treatments

We will include non-targeted immunosuppressants and immunomodulatory treatments including, but not restricted to, corticosteroids, IVIg, plasmapheresis and conventional immunosuppressants, such as azathioprine, methotrexate, calcineurin inhibitors (e.g. ciclosporin, tacrolimus), cyclophosphamide, and mycophenolate, in IIM, compared with placebo, no treatment or another non-targeted immunosuppressant or immunomodulatory treatment. We will also include interventions given in combination.

We will include studies that compare targeted treatments with non-targeted treatments in the review of targeted treatments.

Types of outcome measures

We will not restrict eligibility to studies that report these specific outcomes, which are the outcomes of interest within the included trials, to avoid bias arising from selective reporting of findings.

We will report outcomes measured (other than adverse events) after at least three months and ideally at six months.

By preference, we will report the scales and measures below as they are validated for use in IIM. If during the review process we find studies that do not report these, but do use alternative measures that are validated for use in IIM, we will consider including the data in the review.

Primary outcomes

1. Achievement of a meaningful improvement in a validated function or disability scale; for adults our preferred scale is the Health Assessment Questionnaire (HAQ) (Ponyi 2005) and for children the Childhood Health Assessment Questionnaire (C-HAQ) (Feldman 1995; Huber 2001). We will define functional improvement as validated minimal clinical meaningful improvement for the scale used. Where these data are not available, we will report the overall change in score.
2. Achievement of a meaningful improvement in muscle strength compared with baseline, according to consensus criteria (likely to be ≥ 15%(Rider 2003) or ≥ 20% (Oddis 2005; Rider 2004). Where these data are not available we will report the overall change in score. If data using both thresholds are available for meta-analysis, we will present them in separate subgroups. By preference, we will use the Manual Muscle Test-8 (MMT8) score (adults or children; Rider 2010), otherwise the Medical Research Council sum score, or other validated score.

Secondary outcomes

1. Achievement of the International Myositis Assessment and Clinical Studies Group (IMACS) definitions of improvement (DOI). 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). If authors measure total improvement scores, i.e. use American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria, we will report the proportion achieving at least mild improvement (Aggarwal 2017). By preference, we will report IMACS DOI if a trial uses both measures, since this is likely to maximise the opportunity for pooling data. For children, we will report achievement of improvement defined by the Paediatric Rheumatology International Trials Organisation (PRINTO; Rider 2003; Rider 2011).

2. Cumulative corticosteroid dose.
3. Change in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) in adults or children (Tiao 2017; Yassaee 2010) is the preferred measure, or otherwise, another validated skin disease activity score for dermatomyositis.
4. 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.
5. Withdrawals for either lack of efficacy or adverse events.

For studies focussed on skin involvement only, we will consider the CDASI or another skin disease activity score as the primary outcome.

Search methods for identification of studies

Electronic searches

The Cochrane Neuromuscular Information Specialist (FS) will search the following databases.

- Cochrane Neuromuscular Specialised Register via Cochrane Register of Studies-Web (CRS-Web) (until search date; Appendix 1)
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library (until search date; Appendix 2)
- MEDLINE via Ovid SP (1946 — search date; Appendix 3)
- Embase via Ovid SP (1974 — search date; Appendix 4)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; Appendix 5)
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; Appendix 6)

We will search all databases from their inception to the present, and we will impose no restriction on the language of publication, date of publication, publication status, or document type.

Searching other resources

We will undertake a manual search using the bibliographies of trials and reviews identified. We will also write to known disease experts and authors of trials, asking them for more information about their trials and whether they know of trials other than those identified.

Data collection and analysis

Selection of studies

The Cochrane Neuromuscular Information Specialist (FS) will perform an initial screen of search results. Pairs of review authors (from NG, PG, NP and JR) will independently screen titles and abstracts of potential studies identified after initial screening and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve' using Covidence. We will retrieve full-text study reports, and pairs of review authors (from NG, PG, NP, JR, and SA) will independently screen the full text and identify studies for inclusion, and will identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Page 2021a), and 'Characteristics of excluded studies' table. Review authors will not screen abstracts or full-text of studies in which they have been involved.

If there are abstracts or trial registry entries but no published report for some studies, we will make efforts to find out whether the study was completed. We will include completed but unpublished studies if there is enough information to determine eligibility, although they may not contribute data.

Data extraction and management

We will use a data extraction form for study characteristics and outcome data that has been piloted on at least one study in the review. One review author (from among all listed authors) will extract study characteristics from included studies. A second review author (from among all listed authors) will spot-check study characteristics for accuracy against the trial report. We will extract the following study characteristics: study design and setting, participant characteristics (including disease severity and age), study eligibility criteria, details of the intervention(s) given, the outcomes assessed, the source of study funding and any conflicts of interest stated by the investigators. We will also examine relevant retraction statements and errata for information.

Pairs of review authors will independently extract outcome data from included studies (from NG, PG, JR, RB, FS, and SA). We will note in the 'Characteristics of included studies' table if a trial did not report outcome data in a usable way. We will resolve disagreements by consensus or by involving a third person. One review author will transfer data into Review Manager 5 (Review Manager 2020) or RevMan web (RevMan Web 2022). A second author (from RB, NG, PG, NP, JR, and SA) will check the outcome data entry.

When reports require translation, the translator will extract data directly using a data extraction form, or authors will extract data from the translation provided. Where possible, a review author will check numerical data in the translation against the study report.

If review authors are authors of an included study, other review authors (or if necessary a Cochrane Neuromuscular editor) will extract the data from that trial.

Assessment of risk of bias in included studies

Two review authors (from NG, PG, NP, JR, RB, or SA) will independently assess 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). A third author will arbitrate in the event of disagreement. If review authors

have themselves authored included studies, other review authors will independently assess the risk of bias in these studies.

We will assess the risk of bias as high, low or unclear for the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessors;
- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

We will assess design-specific sources of bias, such as those associated with cross-over design (carry-over, period effects, availability of only first-period data; Higgins 2021b), under other sources of bias.

Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table. We will provide a quote from the study report together with a justification for our judgement in the risk of bias table.

We will use the results to create the risk of bias tables presented in the review.

We will summarise the risk of bias judgements across different studies for each of the domains listed. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome. We will make summary assessments of the risk of bias for each important outcome (across domains) within and across studies (Higgins 2011), and take risk of bias assessments into account when judging the certainty of the evidence using the GRADE approach.

Measures of treatment effect

We will express results as a risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CI) for dichotomous outcomes and mean difference (MD) and 95% CI for continuous outcomes (Higgins 2021a).

For results across studies with continuous outcomes that are conceptually the same but measured in different ways, we will report a standardised mean difference (SMD) and 95% CI, ensuring that scales are pooled with a consistent direction of effect (Deeks 2021).

Unit of analysis issues

Where multiple trial arms are reported in a single trial, we will include only the arms eligible for this review, i.e. where participants receive our prespecified interventions, although we will describe all arms in the Characteristics of studies tables. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are to be included in the same meta-analysis, we will halve the control group to avoid double-counting participants (Higgins 2021b).

We will use the data from both arms of cross-over studies in meta-analyses if the authors describe a suitable washout period and the study has been correctly analysed (i.e. the study authors report summary statistics that take the within-subject study design into account, or this analysis is possible). Otherwise, we will use only first-period data, if available (Higgins 2021b).

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and attempt to obtain missing numerical outcome data (e.g. when a study is available as an abstract only). Where missing data are thought to introduce serious bias, we will take it into account in our GRADE assessment of study limitations.

We will calculate missing data from reported data to allow us to report the specified measures of treatment effect where possible, but do not plan to impute missing values.

Assessment of heterogeneity

If there is heterogeneity we will examine study characteristics for an explanation. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis.

We will use the rough guide to interpretation as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If we identify substantial unexplained heterogeneity we will report it and explore possible causes by prespecified subgroup analysis. We will avoid the use of absolute cut-off values, but interpret I^2in relation to the size and direction of effects and strength of evidence for heterogeneity (e.g. P value from the Chi-squared test, or CI for I^2) (Deeks 2021).

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases; however, it is unlikely that sufficient studies will be available (Page 2021b).

We will attempt to determine the status of any potentially eligible unpublished studies (e.g. where there is a trial registry entry or abstract but no full publication) by contact with the investigators. We will take unpublished studies into account in our assessment of publication bias for each comparison in the summary of findings tables.

Data synthesis

If sufficient data are available, we will perform meta-analysis using Review Manager 5 or RevMan Web (Review Manager 2020; RevMan Web 2022).

We will use a fixed-effect model and perform a sensitivity analysis with a random-effects model in the event of substantial heterogeneity, identified by methods described in the Assessment of heterogeneity section.

We will incorporate correctly analysed data from cross-over trials in analyses using the generic inverse variance (GIV) function in RevMan. If a cross-over trial has an inadequate washout period, we will use only the first-period data. For inappropriately reported

cross-over trials and dichotomous data from cross-over trials, we will seek guidance from a statistician.

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will pool all forms of IIM together in analyses. We will only combine different interventions in the same meta-analysis if they are the same class of drug or act on the same pathway. We will combine data for:

- comparisons of an intervention versus different inactive controls (e.g. placebo, no treatment, standard care) to maximise the possibility of meta-analysis.
- studies in adults and children (but perform subgroup analysis by age);
- subcutaneous and intravenous immunoglobulin.

We will perform a sensitivity analysis for studies at high risk of bias (including lack of blinding).

We will report results that cannot be included in meta-analyses (e.g. when interventions are too diverse, or when summary data are incompletely reported) in structured tables, organised by outcome domains, as described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2021).

We will undertake synthesis without meta-analysis (SWiM) for interventions where this is meaningful and data are sufficient to summarise effect estimates, combine P values, or vote count based on a direction of effect, but are insufficient for a meta-analysis.

We will take serious study limitations into consideration when assessing the certainty of the evidence for a given outcome but will not limit our primary analyses to studies at low risk of bias.

Targeted treatments

The review of targeted treatments will include comparisons of any of these interventions, alone or in combination with each other, or with non-targeted treatments:

- monoclonal antibodies;
- receptor fusion proteins;
- oligonucleotides;
- Janus kinase inhibitors;
- cytokines;
- complement inhibitors;
- other targeted treatments;

versus any of these comparators:

- placebo, no treatment, standard care;
- another immunosuppressant;
- another immunomodulatory treatment, whether targeted or non-targeted.

If any targeted treatment is given, whether as a combined intervention or as a comparator, we will include the evidence in this review.

Non-targeted treatments

The review of non-targeted treatments will include any of these treatments:

- corticosteroids;
- high dose immunoglobulin, intravenous or subcutaneous (in immunomodulatory but not replacement doses, e.g. in the region of 2 g/kg monthly IVIg);
- plasmapheresis
- azathioprine;
- methotrexate;
- calcineurin inhibitors, eg. ciclosporin, tacrolimus;
- cyclophosphamide;
- mycophenolate;

versus any of these comparators:

- placebo, no treatment, standard care;
- another non-targeted immunosuppressant or immunomodulatory treatment as above.

In this review, we will include non-targeted treatments given in combination with other non-targeted treatments but not with, or in comparison to, targeted treatments.

Subgroup analysis and investigation of heterogeneity

We will analyse the following subgroups when possible for each intervention and the primary outcomes.

1. Younger (up to 18 years of age) versus older.
2. Treatment-naive versus treatment-refractory disease (treatment-naive defined as never having received nonsteroid immunosuppressives; participants may have received corticosteroids).
3. Diagnostic subgroups: dermatomyositis (DM) juvenile dermatomyositis (jDM), immune mediated necrotising myopathy (IMNM), anti-synthetase syndrome (ASS), overlap-myositis (OM) and polymyositis (PM).
4. Myositis-specific autoantibodies: participants with autoantibodies versus participants without autoantibodies, and comparisons between different autoantibodies.

For improvement in muscle strength, we will present data dichotomised using different thresholds, for example ≥ 15% and ≥ 20%, in separate subgroups.

If there are sufficient studies to test for subgroup differences, we will use the formal statistical test in RevMan.

Sensitivity analysis

We will carry out sensitivity analyses as follows:

- to assess the effect of using different diagnostic criteria on outcomes, i.e. probable and definite versus definite only (Bohan 1975a; Bohan 1975b) versus Dalakas 1991 versus EULAR/ACR versus non-specified;
- with and without removal of trials at high risk of bias in any domain;
- comparing fixed-effect and random-effects models of meta-analysis;

- with and without data from unpublished sources.

Summary of findings and assessment of the certainty of the evidence

We will create summary of findings tables for any comparison for which data are available, but will prioritise the following for presentation in each review and include other comparisons for which data exist as Additional tables.

Targeted treatments

- Rituximab versus placebo, no treatment or standard care
- Abatacept versus placebo, no treatment or standard care
- Complement inhibitors versus placebo, no treatment or standard care

Non-targeted treatments

- Immunoglobulin versus placebo, no treatment or standard care
- Azathioprine versus placebo, no treatment or standard care
- Methotrexate versus placebo, no treatment or standard care

We will show the following outcomes in each table, measured (other than adverse events) after three months, and ideally at six months, as described in Types of outcome measures.

- Achievement of a meaningful improvement in a validated function or disability scale, for example the HAQ or in children C-HAQ. We will define functional improvement as validated minimal clinical meaningful improvement for the scale used. Where these data are not available, we will report the overall change in score.
- Achievement of a meaningful improvement in muscle strength compared with baseline according to consensus criteria.
- Achieving the IMACS DOI or, otherwise, achievement of mild improvement in Total Improvement Score (ACR/EULAR). In children, achievement of PRINTO definition of improvement.
- Cumulative corticosteroid dose.
- Change in the CDASI in adults or children, or other validated skin disease activity score for dermatomyositis.
- Serious adverse events (as defined in the Secondary outcomes).
- Withdrawals for either lack of efficacy or adverse events.

Two review authors (from RB, NG, PG, NP, JR, or SA) will independently perform GRADE assessments. We will resolve disagreements by discussion or consultation with other authors. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021), using GRADEpro software (GRADEpro GDT). We will downgrade the certainty of evidence once if a GRADE consideration is present to a serious degree and twice if very serious. We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will make comments to aid readers' understanding of the review where necessary. We will assess the certainty of the evidence for each outcome as high, moderate, low, or very low, downgrading RCT evidence from high for each.

ACKNOWLEDGEMENTS

The methods section of the review have been developed using text from a standard protocol adapted by Cochrane Neuromuscular from a template developed by Cochrane Airways. This is a new protocol for an update of Gordon 2012, with a revised scope.

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ADDITIONAL TABLES

Table 1. Bohan and Peter criteria

Features	Polymyositis	Dermatomyositis
1. Symmetrical proximal muscle weakness	Definite: all 1 to 4	Definite: 5 plus any 3 of 1 to 4

Table 1. Bohan and Peter criteria *(Continued)*

2. Muscle biopsy evidence of myositis	Probable: any 3 of 1 to 4	Probable: 5 plus any 2 of 1 to 4
3. Elevation in serum skeletal muscle enzymes	Possible: any 2 of 1 to 4	Possible: 5 plus any 1 of 1 to 4
4. Characteristic electromyographic pattern of myositis		
5. Typical rash of dermatomyositis		

Table 2. Dalakas criteria

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

PM: polymyositis; DM: dermatomyositis

APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register search strategy

1 MESH DESCRIPTOR Myositis AND INREGISTER 19

2 MESH DESCRIPTOR Polymyositis EXPLODE ALL AND INREGISTER 24

3 MESH DESCRIPTOR Dermatomyositis EXPLODE ALL AND INREGISTER 23

4 ((Musc* NEAR1 Infect*) or (Infect* NEAR1 Musc*) or (Musc* NEAR1 Inflammat*) or (Inflammat* NEAR1 Musc*) or (Inflammatory NEAR1 Myopath*) or Myositide* or Myositis or Dermatomyositis or Dermatopolymyositis or Polymyositis or Polymyositide? or (Necroti?ing NEAR1 Myopath*) or Anti?Synthetase Syndrome or Neuromyositis or Fibromyositis or Inomyositis):ti,ab AND INREGISTER 96

5 #1 OR #2 OR #3 OR #4 101

6 INCENTRAL AND INREGISTER 7221

7 #5 NOT #6 5

Appendix 2. CENTRAL search strategy

Date Run:27/11/2021 16:05:02

#1 [mh ^Myositis] or [mh Polymyositis] or [mh Dermatomyositis] or ((Musc* NEAR/1 Infect*) or (Infect* NEAR/1 Musc*) or (Musc* NEAR/1 Inflammat*) or (Inflammat* NEAR/1 Musc*) or (Inflammatory NEAR/1 Myopath*) or Myositide* or Myositis or Dermatomyositis or

Dermatopolymyositis or Polymyositis or Polymyositide? or (Necroti?ing NEAR/1 Myopath*) or Anti?Synthetase Syndrome or Neuromyositis or Fibromyositis or Inomyositis):ti,ab in Trials 809

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) ALL <1946 to November 24, 2021>

1 Myositis/ or exp Polymyositis/ or Dermatomyositis/ or ((Musc* adj Infect*) or (Infect* adj Musc*) or (Musc* adj Inflammat*) or (Inflammat* adj Musc*) or (Inflammatory adj Myopath*) or Myositide* or Myositis or Dermatomyositis or Dermatopolymyositis or Polymyositis or Polymyositide? or (Necroti?ing adj Myopath*) or Anti?Synthetase Syndrome or Neuromyositis or Fibromyositis or Inomyositis).ti,ab. (29026)

2 ((Randomized Controlled Trial or Controlled Clinical Trial).pt. or (Randomi?ed or Placebo or Randomly or Trial or Groups).ab. or Drug Therapy.fs.) not (exp Animals/ not Humans.sh.) (4526722)

3 1 and 2 (6773)

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1974 to 2021 Week 46>

1 Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or cross over or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention $1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers).ti,ab. or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (5570346)

2 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8758)

3 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or (randomi?ed controlled or control group$1).ti,ab.) (288287)

4 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (19113)

5 (Systematic review not (trial or study)).ti. (191167)

6 (nonrandom$ not random$).ti,ab. (17380)

7 ("Random field$" or (random cluster adj3 sampl$)).ti,ab. (3994)

8 (review.ab. and review.pt.) not trial.ti. (939739)

9 "we searched".ab. and (review.ti. or review.pt.) (38996)

10 ("update review" or (databases adj4 searched)).ab. (46509)

11 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1128199)

12 Animal experiment/ not (human experiment/ or human/) (2368121)

13 or/2-12 (3825742)

14 1 not 13 (4940930)

15 Myositis/ or exp Dermatomyositis/ or Polymyositis/ or Antisynthetase Syndrome/ or ((Musc* adj Infect*) or (Infect* adj Musc*) or (Musc* adj Inflammat*) or (Inflammat* adj Musc*) or (Inflammatory adj Myopath*) or Myositide* or Myositis or Dermatomyositis or Dermatopolymyositis or Polymyositis or Polymyositide? or (Necroti?ing adj Myopath*) or Anti?Synthetase Syndrome or Neuromyositis or Fibromyositis or Inomyositis).ti,ab. (44729)

16 14 and 15 (4809)

17 limit 16 to (conference abstracts or embase) (4533)

Appendix 5. ClinicalTrials.gov search strategy

Advanced Search

Condition or disease: Myositis OR Dermatomyositis OR Idiopathic Inflammatory Myopathies OR Immune-Mediated Necrotising Myopathy OR Juvenile Dermatomyositis OR Polymyositis

Study type: Interventional Studies (Clinical Trials)

Appendix 6. WHO ICTRP search strategy

Advanced Search

Myositis OR Dermatomyositis OR Idiopathic Inflammatory Myopathies OR Immune-Mediated Necrotising Myopathy OR Juvenile Dermatomyositis OR Polymyositis *in the Condition*

Recruitment status is: ALL

CONTRIBUTIONS OF AUTHORS

PG, JR and NG wrote the Background. All authors discussed and drafted the Methods. FS advised on the search and developed the search strategy. All authors checked and approved the final text.

DECLARATIONS OF INTEREST

JR: has no known conflicts of interest.

NG: declares clinical trial contracts to her institution from Izana Bioscience, Astra Zeneca, Eli Lilly, and Novartis. She has received honoraria for lectures and educational events from Abbvie, Celgene, Janssen, Eli Lilly, Novartis, and UCB. She has received support for conference attendance from Celgene, Janssen, Eli Lilly, and UCB and payment for Advisory Boards relating to treatment of psoriatic arthritis and axial spondyloarthropathy from Abbvie, Janssen, Novartis, and UCB. NG is a consultant physician involved in the care of patients with inflammatory myositis at the University Hospital Coventry & Warwickshire. The ARTEMIS study (of abatacept in myositis) was carried out as an investigator-initiated study funded by a grant from Bristol-Myers Squibb (BMS), the Myositis Support Group, and Börje Dahlin Foundation, Swedish Research Council GRANTK2014-52X-14045-14-3, Swedish Rheumatism Association, King Gustaf V 80-Year Foundation, and the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet. BMS provided the study drug. The presented work was initiated, conducted and performed independently of BMS.

NP: was a guest speaker at UCB-sponsored meetings: (Immunology Summits, Prague, 2012, 2013 & 2014, MACRO Meet the expert at the Academy of Rheumatology, Bologna 13 to 14 April 2012, GRAPPA Workshop, Milan 29 January 2016, and Rome 30 November 2017), Fininvest (Catania 2016), Aim Group (Reggio Emilia, 2018), I&C (Bologna, 2018), Alfa-Wassermann/Planning congressi sponsored meeting (Rhewind, Bologna, February 2016 and 2019). He has received royalties from Uptodate.com. He was an investigator for the Servier gevokizumab in myositis study (2014), the GlaxoSmithKline (GSK) sirukumab in giant cell arteritis (GCA) (2016), PI for the L'Agenzia Italiana del Farmaco (AIFA)-funded ToReMy (2017) study and for the FOREUM-funded GCA study (2018).

FS: no known conflicts of interest. He is the acting Information Specialist for Cochrane Neuromuscular.

RB: has no known conflicts of interest. She is Managing Editor of Cochrane Neuromuscular. She withdrew from an editorial role for this protocol upon joining the author team.

SSA: no known conflicts of interest. She works as a health professional.

PG: PG's institution has received funding for five studies relevant to this review. One was a study (Chung 2007), funded by various non-commercial grant-giving bodies, one study (ARTEMIS, NCT01315938) was funded in the UK by Bristol Myers Squibb and the Myositis Support Group and one by the Arthritis Research Campaign (SELAM, ISRCTN40085050). One study was a commercial trial funded by Corbus Pharmaceuticals. Inc (DETERMINE, NCT03813160), and one is ongoing, funded by Eli Lilly (MYOJAK, NCT04208464). PG's institution has received a grant from Corbus Pharmaceuticals. PG had or has control of or access to the institutional grants for the ARTEMIS, DETERMINE and MYOJAK trials and the Corbus Pharmaceuticals grant. He received personal payments for an Eli Lilly International Systemic Lupus Erythematosus Advisory Board in December 2020, a speaker's honorarium from UCB in 2021, and consultancy fees from Galapagos in 2023. He was funded to attend the EULAR e-congress in 2020 by AbbVie and has also been funded by other drug companies to attend meetings in the past. He was due to be an investigator for the study NCT02612857, a commercial trial funded by Idera Pharmaceuticals Inc, and was an author on an abstract presenting the protocol but had to withdraw from the study in 2017 due to personal illness.

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NOTES

This protocol has been developed from 'Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis' (Gordon 2012), which we have split into separate reviews of targeted therapies and non-targeted immunological treatments. The original review will be withdrawn when both new titles are published.