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Immunomodulators and immunosuppressants for progressive multiple sclerosis: a network meta-analysis (Protocol)

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[Intervention Protocol]

Immunomodulators and immunosuppressants for progressive multiple sclerosis: a network meta-analysis

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ABSTRACT

Objectives

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

We will perform a network meta-analysis to assess the relative effectiveness and safety of immunomodulatory and immunosuppressive treatments for people with multiple sclerosis in progressive forms of the condition.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is the most common immune-mediated, chronic inflammatory demyelinating disease of the central nervous system (CNS). In 85% of affected people the disease is characterised at onset by relapses followed by complete or partial recovery (relapsing-remitting phase). Relapses correspond to the clinical expression of focal inflammation and subsequent loss of the myelin sheath surrounding axons in the CNS. In a proportion of patients, increasing with time, the course turns into a secondary progressive phase (SPMS), typically 15 to 20 years from onset. In about 10% to 15% of people affected by MS the progressive course is not preceded by relapses (primary progressive MS (PPMS)). About 40% of people with PPMS or SPMS show relapses during the course of the disease. However, new activity becomes less frequent over time, while microglial activation and neurodegeneration become more relevant (Calabrese 2012).

A recent classification of MS clinical course (or 'phenotype') introduced the concepts of 'disease activity' and 'disease progression' (Lublin 2014). The former is based on the presence of clinical relapse or new or gadolinium-enhancing magnetic resonance imaging (MRI) lesions. Active forms of MS occur when the inflammatory process is ongoing, sometimes without corresponding clinical manifestations if the inflamed region of the CNS is clinically silent. Disease progression occurs when there is clinical evidence of disability worsening, independent of relapses, over a given period of time, in patients who are in a progressive phase of the disease (Lublin 2014). The current classification includes: (i) active or inactive relapsing MS (RMS), with or without worsening; (ii) active or inactive primary MS (PMS) or secondary progressive MS (SPMS), with or without progression; (iii) clinically isolated syndrome (CIS); and (iv) radiologically isolated syndrome (RIS). The definition of 'progressive-relapsing' MS was abandoned (Lublin 2014).

Furthermore, the concept of MS as a two-stage disease has been recently questioned by increasing evidence, both from MRI and pathological studies, of a complex interplay between inflammatory and subtle neurodegenerative processes (progression independent from relapse activity (PIRA)) even in the early stages of the disease (Giovannoni 2022). The identification of 'smouldering' progression in a consistent proportion of people with either active or inactive MS demands for a more thorough assessment to define progressive MS, with relevant implications for future trials (e.g. appropriate selection of patients in trials on anti-inflammatory drugs, evaluation of neuroprotective/neurorestorative agents).

MS represents a substantial health burden at a global level, since it affects young people during their productive life, the mean age of diagnosis being 32 years (Walton 2020). The global incidence and prevalence of MS are increasing. From 1990 to 2016 the age-standardised prevalence of MS increased by 10.4% (9.1 to 11.8). About 2.8 million people worldwide are affected by MS (35.9 per 100,000 population), a figure which has increased by about half-million since 2013. The global pooled incidence rate is 2.1 per 100,000 persons/year (GBD 2019; Walton 2020).

No current treatment is effective at stopping the natural course of MS towards progressive disability. Current MS treatments include disease-modifying treatments (DMTs) based on immune-modulating or immune-suppressing drugs, which are distinguished from symptomatic drugs for the treatment of specific symptoms of MS (e.g. urinary incontinence or retention, muscular spasms, painful sensitive symptoms). Providing effective and safe treatments for progressive MS (PMS) is particularly challenging due to incomplete understanding of the pathogenesis of progression. Moreover, while inflammation seem to provide a pivotal contribution to progression, other pathological changes - including cortical demyelination, axonal loss, and mitochondrial dysfunction - also seem to be important (Dutta 2014; Lassmann 2012) and may represent different therapeutic targets in PMS. Despite several new DMTs becoming available for the treatment of RMS and PMS in recent years, uncertainty remains regarding whether some of them may represent a preferable choice when starting pharmacological treatment, and which ones should be subsequently considered for the management of more advanced stages of the disease course (Reich 2018). Relatively few studies directly compare different DMTs or assess the sequential use of specific DMT combinations, therefore clinical practice guidelines on MS treatment usually do not recommend one DMT over the other. The variability of recommendations concerning specific drugs among different guidelines in part reflects differences in the decisions by regulatory drug agencies and local health policies (Ghezzi 2018).

A previous Cochrane Review and network meta-analysis of randomised clinical trials (RCT) (Filippini 2013) appraised the available evidence for the efficacy and safety of available DMTs compared to placebo and any other active drug in RMS and PMS. The authors concluded that, for the nine disease-modifying agents used in 18 trials including people with progressive MS, and the three trials including both relapsing and progressive forms, few studies were of high certainty and no drug was shown to be effective in preventing disability progression in people with MS by pairwise or network meta-analysis (Filippini 2013). The time elapsed since the search date of Filippini 2013 (February 2012) supports the need for an updated analysis, especially given the availability of more DMTs for progressive forms of MS.

Description of the intervention

Disease modifying treatments licensed for the treatment of RMS include the following drugs which will be considered in our review: beta-1a and beta-1b interferon (IFN), pegylated IFN beta-1a, mitoxantrone, glatiramer acetate, natalizumab, fingolimod, teriflunomide and leflunomide, dimethylfumarate and diroximel fumarate, alemtuzumab, laquinimod, intravenous (iv) immunoglobulins, steroids, ocrelizumab, cladribine, siponimod, ozanimod, ponesimod, ofatumumab, and daclizumab.

Interferon beta (IFNβ) was the first disease-modifying therapy available and approved in the US in 1993 to treat MS (Hu 2012; Kieseier 2011). Four IFNβ drugs are currently approved in the US and EU: subcutaneous (SC) IFNβ-1b, SC IFNβ-1a, intramuscular IFNβ-1a and, most recently, in 2014, SC peginterferon beta-1a. IFNβ-1b is also licensed in the US and EU for the treatment of active SPMS.

Glatiramer acetate is a synthetic amino acid copolymer, and one of the first approved DMTs for the treatment of relapsing-remitting MS (RRMS) in the US in 1996 (Aharoni 2014). Natalizumab was the first monoclonal antibody licensed for use in MS in 2004 in the US and in 2006 in the EU (Millard 2011). Since then, the monoclonal antibody

alemtuzumab has received approval by regulatory agencies for the treatment of RRMS (Kappos 2011; Lycke 2015). Two anti-CD20 monoclonal antibodies, ocrelizumab and ofatumumab, have been also approved. Ocrelizumab was approved as treatment for relapsing MS and PPMS (EMA 2018b; FDA 2017) and ofatumumab for relapsing MS and active SPMS (EMA 2021d).

Daclizumab is a monoclonal antibody licensed in 2016 for the treatment of RRMS, but due to safety concerns it was withdrawn worldwide from the market by its manufacturer in 2018 (EMA 2018a; FDA 2018).

Cladribine is a synthetic chlorinated deoxyadenosine analog approved for the treatment of RRMS in Russia and Australia in 2010, while in the EU and the US it was licensed in 2017 and 2019, respectively, for highly active RRMS and active SPMS (EMA 2017; FDA 2019a; Leist 2011).

Fingolimod is a non-selective modulator of a receptor involved in the sphingosine 1-phosphate pathway administered orally (Chun 2010). It was the first oral treatment approved for RMS in 2010 in the EU and US. More recently other compounds with similar mechanism of action were developed, in order to increase efficacy and improve safety, such as siponimod, approved in 2019 for active SPMS in the EU and also for RMS in the US (EMA 2020; FDA 2019b), as well as ozanimod and ponesimod, licensed in 2020 and 2021, respectively (EMA 2021a; EMA 2021b; FDA 2020; FDA 2021).

Two other oral drugs, both with a mainly immunomodulatory mode of action, are available for the treatment of RRMS: teriflunomide (Oh 2013), the active metabolite of leflunomide, inhibiting pyrimidine de novo synthesis, and dimethyl fumarate (Linker 2011), the methyl ester of fumaric acid, converted after administration into the active metabolite monomethyl fumarate. They were both approved for RRMS in the US in 2012 and in 2013, respectively. Recently, diroximel fumarate, a compound similar to dimethyl fumarate, was approved in 2019 in the US and EU for the treatment of RMS (EMA 2021c).

Laquinimod is an oral immunomodulator investigated in two phase 3 trials for the treatment of people with RRMS. Its use in treating people with RRMS was approved in Russia but not in the EU, since in 2014 the European Medicines Agency (EMA) refused authorisation (EMA 2014). Mitoxantrone was approved in 2000 in the US, EU and other countries for the treatment of people with RRMS and progressive MS (Fox 2004).

Given the limited efficacy of currently available DMTs in delaying the progression of RMS, many clinicians commonly prescribe immunosuppressant drugs with registered indications for conditions other than MS (mainly in rheumatological or autoimmune diseases, or in people undergoing transplant). As such, we decided to also include in our review the following interventions used in MS as off-label treatments: rituximab, azathioprine, iv immunoglobulins, methotrexate, cyclophosphamide, and long-term corticosteroids. Rituximab is an anti-CD20 monoclonal antibody similar to ocrelizumab and ofatumumab, commonly used to treat malignant blood cell neoplasms and several autoimmune diseases, such as rheumatoid arthritis, idiopathic thrombocytopenic purpura, and pemphigus vulgaris. Its efficacy and safety have also been studied in MS and in several countries, since rituximab is frequently prescribed off-label (Berntsson 2018; Brancati 2021; Laurson-Doube 2021).

Azathioprine is a purine analogue exerting its immunosuppressive action by affecting DNA replication through inhibition of the synthesis of nucleic acids. It has been used for the treatment of people with MS in many countries on the basis of favourable results reported by placebo-controlled RCTs (Laurson-Doube 2021). Intravenous immunoglobulins are considered in clinical practice for people with RRMS, although evidence on their efficacy in progressive forms is conflicting (Pöhlau 2007; Soelberg Sorensen 2008). Methotrexate, cyclophosphamide, long-term corticosteroids are systemic immunosuppressors. Methotrexate is a common treatment in autoimmune diseases. Since 1996 it has been used mainly in progressive forms of MS. Cyclophosphamide, a DNA-alkylating agent used for the treatment of people with autoimmune disorders, has been administered also to people with MS (Awad 2009). Long-term corticosteroids have been proposed for the treatment of patients with MS since 1961 with mixed results. They have been administered by different schedules as pulsed periodic high-dose methylprednisolone or oral continuous low-dose prednisolone (Ciccone 2008).

How the intervention might work

The pathophysiology of MS - chronic autoimmune disease of the CNS with inflammatory lesions, demyelination, axonal/neuronal damage, and metabolic changes - supports the use of immunosuppressive medications. Immunosuppressive or immunomodulatory effects are common to all treatments included in this review. Immunotherapies for MS belong to different pharmacological categories, have different modalities of administration (by intramuscular or subcutaneous injection, by infusion or by oral route), and variable metabolism characteristics. Although they all target the immune system, their effects vary as follows: (1) immunomodulation (IFNβ-1b, IFNβ-1a, glatiramer acetate, pegylated IFNβ-1a, iv immunoglobulins, dimethyl fumarate and diroximel fumarate, laquinimod); (2) systemic immunosuppression, inducing a reduction in the activation or efficacy of the immune system through cytostatic or cytotoxic effects (mitoxantrone, methotrexate, cyclophosphamide, long-term corticosteroids, cladribine, azathioprine, teriflunomide, and leflunomide); and (3) selective immunosuppression, as with monoclonal antibodies or biological agents directed towards specific antigenic targets (natalizumab, fingolimod, siponimod, ozanimod, ponesimod, alemtuzumab, ofatumumab, daclizumab, rituximab, and ocrelizumab). These aspects must be considered while assessing the risk of adverse events associated with the use of a drug, since safety is usually a consequence of the drug's main pharmacological effect (Compston 2002; Hauser 2020; Massacesi 2002; Meinl 2008).

Why it is important to do this review

Although there is general consensus that immunotherapies reduce the frequency of relapses in MS, the relative benefit of each DMT remains unclear. This uncertainty is in part due to the limited number of head-to-head trials, which provide the most rigorous and valid research evidence on the relative effectiveness and safety of different, competing treatments. The estimates from a network meta-analysis (NMA), by including both direct and indirect comparisons, may help to clarify uncertainties and provide valuable information to inform shared healthcare decisions by practitioners, policy makers, people with MS, and their families. Since the most recent Cochrane Review concerning MS with NMA (Tramacere 2015), new DMTs have been approved by regulatory

agencies, offering a broader spectrum of treatment options for people with PMS. Evidence of efficacy in chronic autoimmune conditions, relatively good tolerability, and reasonable cost has prompted the off-label use of several immunosuppressants and immunomodulators for the treatment of MS in many countries, particularly in settings with budget constraints (Zeineddine 2020). This is true not only for RMS, but also for progressive forms, for which therapeutic options have been very limited until recently. For this reason we decided to also include in the NMA drugs not approved by regulatory agencies.

OBJECTIVES

We will perform a network meta-analysis to assess the relative effectiveness and safety of immunomodulatory and immunosuppressive treatments for people with multiple sclerosis in progressive forms of the condition.

METHODS

Criteria for considering studies for this review

Types of studies

We will include individually randomised parallel controlled clinical trials (RCTs). We will not include non-randomised studies, cluster-randomised and cross-over trials, case reports and studies of within-group design, e.g. before-after (pre-post) studies with no control group or interrupted time series. We will consider studies published in abstract whenever sufficient information is available on study design, characteristics of participants, interventions, and outcomes. In all potentially eligible non-English language full-text articles the methods section will be translated for eligibility, and the full text translated for data extraction if the study is considered to be eligible. Studies with a follow-up of 12 months or longer will be included.

Types of participants

We will include adult participants (18 years or older) with a diagnosis of progressive multiple sclerosis (PMS) adopting any published diagnostic criteria, of either sex, who are treatment-naive or non-responsive to treatment with previous disease-modifying treatments (DMTs) regardless of degree of disability and disease duration. We will accept any definition of non-response reported in the included studies. We will consider both treatment-naive people with MS, as well as those switching from a previous different DMT, regardless of the reason for switching, method, or timing of the switching. Studies primarily focused on PMS but also including a subgroup of people with relapsing multiple sclerosis (RMS) will be considered only if the proportion of people with PMS is ≥ 80%. Studies on PMS including a mixed population with < 80% of people with PMS will be excluded. Evidence from studies including 80% to 99% of people with PMS will be considered for downgrading for indirectness while assessing the certainty of the evidence, according to GRADE methodology (Guyatt 2011). We assume that any patient who met the inclusion criteria was, in principle, equally likely to have been randomised to any of the eligible interventions.

Types of interventions

We will include any DMT used to treat people with MS (even if not licensed in any country). We will include regimens as defined in primary studies irrespective of their dose. The following treatments will be considered: alemtuzumab, azathioprine, cladribine, cyclophosphamide, daclizumab, dimethylfumarate, diroximel fumarate, fingolimod, fludarabine, glatiramer acetate, immunoglobulins, interferon beta 1-a and beta 1-b, interferon beta-1b (Betaferon), interferon beta-1a (Avonex, Rebif), laquinimod, leflunomide, methotrexate, minocycline, mitoxantrone, mycophenolate mofetil, natalizumab, ocrelizumab, ofatumumab, ozanimod, pegylated interferon beta-1a, ponesimod, rituximab, siponimod, corticosteroids, and teriflunomide.

We will include long-term corticosteroids (i.e. longer than 6 months) of any type of corticosteroid, continuous or intermittent, provided that they were not started for relapses (i.e. started more than 2 months after a relapse), whatever the administration route and dosage.

We assume that treatments are 'jointly randomisable' across trial participants (Salanti 2012).

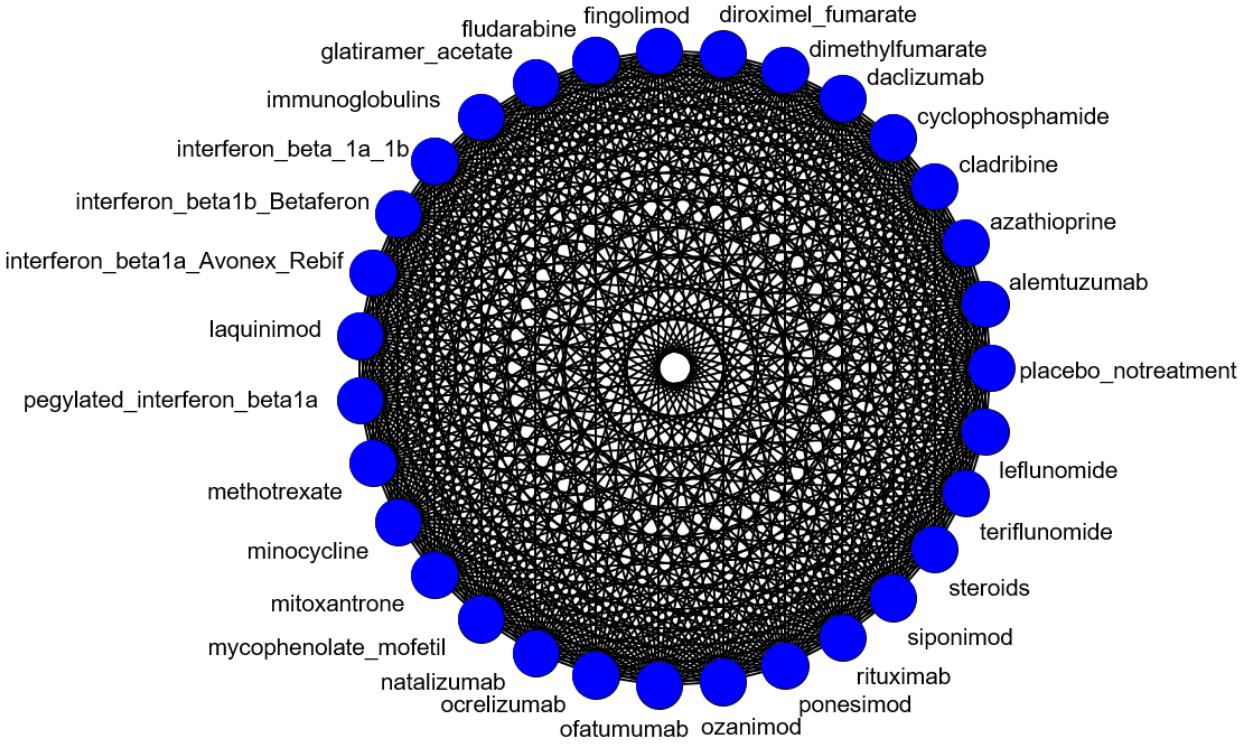
We will not include: combination treatments, trials in which a drug regimen was compared with a different regimen of the same drug without another active agent or placebo as a control arm, all non-pharmacological treatments, interventions with over-the-counter drugs.

Types of comparisons

We will consider placebo, no treatment, or another active agent. Studies comparing placebo and no treatment will be grouped in a single node in the network plot.

Figure 1 shows a network plot including all potential treatments and comparisons that we may expect to obtain.

Figure 1. Network plot.



Types of outcome measures

While defining the outcomes for our review, we searched the COMET core outcome set (COS) database (www.comet-initiative.org) and found the following COS covering the topic of pharmacological treatments in MS: one protocol of an ongoing COS project on DMTs in RCTs on RMS (Lucchetta 2020), one unpublished ongoing COS (S.O.S.MS Project 2020), one COS for clinical trials or clinical research on children with MS (Chitnis 2013), and one COS on MS therapeutic trials aimed at identifying the most important aspects of clinical evaluation, study design, and data analysis (Whitaker 1995).

We will estimate the relative effects of the competing interventions according to the following primary outcomes.

Primary outcomes

- **Disability:** number of participants with sustained disability worsening based on clinical follow-up visits at 24 and 36 months after randomisation. Worsening is defined as at least one increased point on the Expanded Disability Status Scale (EDSS) (Kurtzke 1983), or a 0.5-point increase if the baseline EDSS was greater than 5.5, confirmed during two consecutive clinical examinations separated by an interval of at least 6 months free from relapse, and carried out by the same physician. EDSS is an ordinal scale where 0 is normal, 3 indicates mild disability, 6 indicates care requirement, 7 indicates wheelchair use, and 10 indicates death. An advantage of the EDSS over other disability measures is its international acceptance, e.g. by the European Medicines Agency (EMA) (EMA 2015), as a primary end point in clinical trials. It is also widely used in trials, enabling cross-study comparisons (Meyer-Moock 2014).
- **Relapse:** number of participants with clinical relapse based on clinical follow-up visits at 12, 24, and 36 months after randomisation. Relapse is defined as the appearance of one or more new symptoms due to MS, or the deterioration of pre-existing symptoms, persisting more than 24 hours in the absence of fever, and preceded by a period of stability of at least 1 month (McDonald 2001).
- **Serious adverse events (SAEs):** number of participants with any (one or more) SAEs, defined according to the authors of the study. If sufficient information is available, we will specify individual SAEs.

Secondary outcomes

- **Cognitive decline**: will be assessed as a continuous outcome considering the variation in the score of the Symbol Digit Modalities Test (SDMT) (Benedict 2017) when available, or alternatively to the Paced Auditory Serial Addition Test (PASAT) (Gronwall 1977). Cognitive decline measured with other validated scales will be qualitatively described.
- **Quality-of-life impairment:** will be assessed as a continuous outcome considering the variation in the score of scales reporting quality-of-life impairment. Any available scale will be considered.
- **New or enlarging T2-weighted magnetic resonance imaging (MRI) lesions:** number of participants with new or enlarging T2-weighted MRI lesions at 12, 24, and 36 months after randomisation.
- **New gadolinium-enhancing positive T1-weighted MRI lesions:** number of participants with new gadolinium-enhancing T1-weighted MRI lesions at 12, 24, and 36 months after randomisation.

- **Treatment discontinuation due to adverse events:** number of patients who discontinued treatment due to adverse events, regardless of their severity.
- **Mortality:** overall number of MS-related deaths.

Search methods for identification of studies

An information specialist will design and conduct all searches.

Electronic searches

We will identify eligible study references through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue) - see Appendix 1 for search string.
- MEDLINE (PubMed) (January 2012 to date) - see Appendix 2 for search string.
- Embase (Embase.com) (January 2012 to date) - see Appendix 3 for search string.

We will not apply any search limitation with respect to study outcomes, methods of analysis, or language.

Searching other resources

To identify eligible studies prior to 2012, we will consult the identified studies in Filippini 2013, a prior Cochrane network meta-analysis review concerning immunomodulators and immunosuppressants for MS, whose search was performed February 2012.

We searched for ongoing studies on the following trial registries:

- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch). Search terms: progressive multiple sclerosis, filtered for "Phase 2" "Phase 3" trials.
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov). Search term: "progressive multiple sclerosis".

We checked reference lists of all included studies and any relevant systematic reviews identified for additional references to studies. We will examine any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

Study selection will be conducted by using the Rayyan platform (rayyan.ai) in accordance with the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Six review authors in pairs (Ben Ridley (BR), Elisa Baldin (EB), Francesco Nonino (FN), Guy Peryer (GP), Irene Tramacere (IT), Matteo Foschi (MF)) will independently screen the titles and abstracts. Potentially relevant articles will be acquired in full text and assessed for eligibility by the same six authors in pairs.

Data extraction and management

Two review authors (Silvia Minozzi (SM) and Marien Gonzalez-Lorenzo (MGL)) will independently extract data from the studies using a predefined data extraction form in an Excel spreadsheet and piloting the data extraction form on at least five studies in the review. Disagreements will be resolved by discussion. If necessary, a third author will be consulted (FN). Whenever data are available from peer reviewed journals as full publication as well as from trials registries (such as ClinicalTrials.gov or the WHO ICTRP platform), we will extract them from the former. We will extract results data from trials registries when these are the only available data.

Outcome data

We will extract from each included study the number of participants who:

- had relapses at 12, 24, and 36 months after randomisation;
- disability worsening at 24 and 36 months after randomisation;
- had at least one SAE at longest follow-up;
- had new or enlarging T2-weighted MRI lesions at 12, 24, and 36 months after randomisation;
- had new gadolinium-enhancing positive T1-weighted MRI lesions at 12, 24, and 36 months after randomisation;
- withdrew due to any adverse event at the end of follow-up;
- died due to MS at longest follow-up.

For continuous outcomes relative to the outcomes 'cognitive decline' and 'quality-of-life impairment' we will extract mean and standard deviation of the comparison groups, where possible. We will extract data at baseline, end point, and change score. We will use change score in case end point scores are not reported (da Costa 2013). We will extract data at the authors' defined timing points. When outcomes are not reported at our predefined time points, we will extract data as close as possible to that time point.

Data on potential effect modifiers

We will extract from each included study data on the following potential effect modifiers:

- diagnostic criteria (Poser or McDonald criteria);
- type of MS (active versus non-active);
- risk of bias.

Other data

From each included study we will extract data on the following additional information:

- study: first author or acronym, number of centres, year of publication, years that the study was conducted (recruitment and follow-up), publication (full-text publication, abstract publication, unpublished data);
- study design: inclusion criteria, number of randomised participants, number of participants in each arm, duration of follow-up, early termination of trial;
- participants: baseline mean age, gender distribution, diagnostic criteria, type of PMS: primary progressive (PPMS) or secondary progressive (SPMS), type of PMS activity: active or worsening or both, not active and stable or indeterminate, active or worsening or both when there is a lack of treatment response;
- interventions: route, dose, frequency, or duration of treatment;
- comparison(s): route, dose, frequency, or duration of treatment;
- funding source.

Assessment of risk of bias in included studies

We will assess the risk of bias of each included study using Cochrane criteria (Higgins 2017). These include: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, and selective outcome reporting.

Other potential risks of bias will include the role of the sponsor; we will judge a study as at high risk of bias if it is funded by industry, and it is stated that the funder was involved in data management, analysis and interpretation, in writing of the study report, or where it is reported that the funders approved the final version of the paper; we will judge studies as being at high risks of bias also if the first or last authors and authors who performed the statistical analysis were employed by industry.

We will judge incomplete outcome data at low risk of bias if numbers and causes of dropouts are balanced (i.e. in the absence of a significant difference) between arms. We will assess selective outcome reporting bias by comparing outcomes reported in the study protocol along with published outcome results. If a study protocol is not available, we will assign a judgement of unclear risk of bias. If the study protocol is available, but it is not dated prior to the start of the study, we will judge the study at high risk. We will consider a rating of high risk for selective reporting if the authors fail to report complete data for one or more outcomes (e.g., report the P value only or just state that the results were or were not statistically significant). We will explicitly judge the risk of bias of each study on each criterion and classified it as at low, high, or unclear risk of bias.

Two authors (SM, MGL) will assess the risk of bias of each study independently and will resolve any disagreement by discussion to reach consensus.

Measures of treatment effect

Relative treatment effects

For dichotomous outcomes (i.e. disability and relapses), we will report risk ratio (RR) and 95% confidence intervals (CIs). If the number of observed events had been small (less than 5% of sample per group), and if studies had balanced treatment groups, we will report the Peto odds ratio (OR) with 95% CI.
For continuous outcomes, we will calculate mean difference (MD) or standardised mean difference (SMD) if the same continuous outcome was measured with different metrics. To interpret SMD we will use the guiding principles (Schünemann 2013) of thresholds for small (SMD = ±0.2), moderate (SMD = ±0.5), and large effects (SMD = ±0.8). We will present results from network meta-analysis as summary relative effect sizes (RR, MD, or SMD) for each possible pair of treatments.

Relative treatment ranking

We will obtain a treatment hierarchy of the included interventions using the surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA will be expressed as the percentage and will represent the relative probability of a treatment to be among the best options without uncertainty (Salanti 2011).

Unit of analysis issues

We will not include cluster-randomised or cross-over trials to evaluate immunomodulator and immunosuppressant treatments for MS.

Studies with multiple treatment groups

In pairwise meta-analysis, we will consider the multi-arm studies as multiple independent two-arm studies. In network meta-analysis (NMA), we will account for the correlation between the effect sizes from multi-arm studies (Salanti 2012). For studies with multi-arm trials involving the same agent at different doses compared to a control treatment, we will convert the treatment arms into a single arm by merging the different doses, summing the number of events, and calculating the sample size.

Studies with multiple outcome scales

MS-specific scales (e.g. MSQOL-54, MSIS 29) will not be combined with non-MS-specific scales (e.g. SF-36 or EQ-5D index). If several scales are used in one RCT, we will select the scale that in the combination (via SMD) with the others across studies will provide lower heterogeneity.

Dealing with missing data

We will use data that reflect the intention-to-treat (ITT) analysis for each included outcome. Primary analysis will be performed considering the number of patients with the event in relation to the number of randomised subjects. In case of participants with missing data, primary analysis will be performed without any imputation. For adverse events we will use data of participants who received at least one dose of the study medication. If standard deviations are missing for continuous outcomes, we will calculate them according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Assessment of heterogeneity

Assessing clinical and methodological heterogeneity within and across comparisons of drugs

In each pairwise comparison, patient characteristics, treatments, and outcome definitions of included studies should be similar. We will produce descriptive statistics for studies and assess their similarity in each comparison. It is appropriate to use NMA if the assumption of transitivity can be defended, e.g. there is agreement between drug effects estimated directly and indirectly for a specific comparison. Transitivity holds when the distributions of the potential effect modifiers, like study and patient-level covariates, are balanced across all pairwise comparisons; in this case, direct and indirect evidence can be combined. This is why we will compare the distribution of the potential effect modifiers across the different pairwise comparisons (Cipriani 2013; Salanti 2012).

Assessment of reporting biases

For the primary outcomes, we will use a comparison-adjusted funnel plot for active treatments versus placebo to determine the possibility of small study-effects (Chaimani 2013; Peters 2008).

Data synthesis

First, we will conduct conventional pairwise meta-analyses with a random-effects model in RevMan Web (RevMan Web 2022) for each

outcome and comparisons with at least two studies (DerSimonian 1986). Then, we will perform NMA in a frequentist framework for each outcome with random-effects model using 'mvmeta' command in Stata 16, accounting for correlations induced by multi-arm studies (Salanti 2012; White 2011). NMA is a statistical method used to synthesise information from a network of trials addressing the same question but involving different interventions (Cipriani 2013). NMA combines direct and indirect evidence across a network of randomised trials into a single effect size, and under certain assumptions it can increase the precision in the estimates while randomisation is respected.

Whenever we cannot pool results from included studies quantitatively via pairwise or NMA, we will undertake narrative synthesis according to the Synthesis Without Meta-analysis (SWiM) reporting guideline (Brennan 2020).

Subgroup analysis and investigation of heterogeneity

Assessing and investigating statistical heterogeneity and incoherence

We will estimate heterogeneity variances for each pairwise comparison in standard pairwise meta-analyses and assess the presence of statistical heterogeneity by visually inspecting the forest plots, by looking at the Chi^2 and calculating the I^2 statistic (Higgins 2003). In NMA, we will assume a common estimate for heterogeneity variance across comparisons and base our assessment of statistical heterogeneity in the whole network on the magnitude of the common heterogeneity parameter (Rhodes 2015; Turner 2012). Statistical disagreement between direct and indirect effect sizes (incoherence) will be evaluated with local and global approaches (Higgins 2012). Locally, we will use the loop-specific approach, which calculates the difference between direct and indirect estimates in all closed loops in the network (Veroniki 2013). We will also apply the node splitting method, which separates evidence on a particular comparison into direct and indirect evidence (Higgins 2012). Globally, we will apply the 'design-by-treatment' approach (Higgins 2021).

Subgroup analyses

We will perform subgroup analyses for primary efficacy outcomes based on the type of MS (active or worsening or both PMS versus not active and stable or indeterminate PMS versus active or worsening or both PMS when there is a lack of treatment response).

Sensitivity analysis

We will perform the following sensitivity analyses for primary efficacy outcomes:

- including only trials with overall low risk of bias;
- excluding trials with a total sample size of fewer than 50 randomised participants.

Summary of findings and assessment of the certainty of the evidence

Assessment of certainty in the evidence of the retrieved RCTs for the NMA will be performed by means of the GRADE methodology, considering the following domains: risk of bias, inconsistency, indirectness, imprecision, incoherence, and publication bias. First, direct and indirect estimates of effect for the pairwise comparison will be presented, then the certainty of both of these estimates will be rated, the network estimate for the pairwise comparison will be presented, and finally the certainty of the network estimate will be rated, based on the ratings of the direct and indirect estimates and the assessment of coherence (i.e. extent of similarity of direct and indirect estimates) (Puhan 2014).

Since the results of this review and NMA will serve as evidence base for guidance on the use of DMTs in people with PMS, the certainty in the evidence will be assessed in a contextualised setting. This will imply predefining quantitative thresholds to determine the magnitude of each health effect (desirable or undesirable) measured by means of each outcome. Such magnitude will be defined according to the GRADE wording as 'trivial', 'small', 'moderate', and 'large'.

In order to determine their imprecision, and therefore decide if downgrading their level of certainty, point estimates of observed effects and their 95% CIs will be contextualised in relation to such predefined thresholds (Hultcrantz 2017). Thresholds between magnitudes of effect will be quantitatively expressed as Health State Utility Values (HSUV).

Evaluation of direct evidence from pairwise comparisons will be performed on the GRADEPro GDT platform (gdt.gradepro.org).

Summary of findings tables (SoF) for NMA will be developed manually presenting network geometry plots, estimates of effects, credible intervals, and certainty of the evidence according to the format suggested by the GRADE Working Group (Yepes-Nuñez 2019). One SoF will be developed for each outcome, including all interventions with estimates available from direct or indirect comparisons.

We will include an overall grading of the evidence for the following outcomes for the comparison with placebo as common comparators:

- proportion of people who experienced new relapses over 12 months;
- proportion of people who experienced new relapses over 24 months;
- proportion of people who experienced disability worsening over 24 months;
- proportion of participants with any (one or more) SAEs, defined according to the authors of the study.

If we are not able to perform the NMA, we will present results from simple pairwise estimates for each treatment versus placebo.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.
• Sign-off Editor (final editorial decision): Robert Boyle, Cochrane's Editorial Board.

• Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Anne-Marie Stephani, Cochrane Central Editorial Service.
• Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service.
• Copy Editor (copy editing and production): Luisa M Fernandez Mauleffinch, Copy Edit Support, Cochrane Central Production Service.

• Peer reviewers (provided comments and recommended an editorial decision): Paulus Rommer, Medical University of Vienna, Department of Neurology Vienna, Austria (clinical review); Mark S Freedman, University of Ottawa, Department of Medicine and the Ottawa Hospital Research Institute, Canada (clinical review); Kerry Dwan, Cochrane Methods Support Unit (methods review); and Jo Abbott (search review).

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APPENDICES

Appendix 1. Search strategy - CENTRAL

#	Query
#1	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only
#2	MeSH descriptor: [Demyelinating Diseases] this term only
#3	MeSH descriptor: [Multiple Sclerosis] explode all trees
#4	MeSH descriptor: [Myelitis, Transverse] explode all trees
#5	MeSH descriptor: [Optic Neuritis] explode all trees
#6	("clinically isolated" NEXT syndrome*):ti,ab
#7	(devic OR "devic s" OR devics):ti,ab
#8	(disseminated NEXT sclerosis*):ti,ab
#9	(demyelinating NEXT (disease* OR disorder*)):ti,ab
#10	((demyelinating OR necrotising OR necrotizing OR transverse) NEXT myelitis*):ti,ab
#11	multiple sclerosis:ti,ab OR MS:ti
#12	(neuropapilliti* OR ((optic OR retrobulbar) NEXT neuriti*)):ti,ab
#13	((neuromyelitis NEXT optica*) OR ("nmo spectrum" NEXT disorder*)):ti,ab
#14	{OR #1-#13}
#15	MeSH descriptor: [Adrenal Cortex Hormones] this term only and with qualifier(s): [therapeutic use - TU, adverse effects - AE]
#16	MeSH descriptor: [Alemtuzumab] explode all trees
#17	MeSH descriptor: [Azathioprine] explode all trees
#18	MeSH descriptor: [Cladribine] explode all trees
#19	MeSH descriptor: [Cyclophosphamide] explode all trees
#20	MeSH descriptor: [Daclizumab] explode all trees
#21	MeSH descriptor: [Dimethyl Fumarate] explode all trees
#22	MeSH descriptor: [Fingolimod Hydrochloride] explode all trees
#23	MeSH descriptor: [Glatiramer Acetate] explode all trees
#24	MeSH descriptor: [Immunoglobulins] this term only and with qualifier(s): [therapeutic use - TU, adverse effects - AE, drug effects - DE]

(Continued)

#25	MeSH descriptor: [Immunoglobulins, Intravenous] explode all trees
#26	MeSH descriptor: [Interferon-beta] explode all trees
#27	MeSH descriptor: [Interferon Type I] this term only
#28	MeSH descriptor: [Methotrexate] explode all trees
#29	MeSH descriptor: [Methylprednisolone] this term only
#30	MeSH descriptor: [Mitoxantrone] explode all trees
#31	MeSH descriptor: [Natalizumab] explode all trees
#32	MeSH descriptor: [Prednisolone] this term only
#33	MeSH descriptor: [Rituximab] explode all trees
#34	(("adrenal cortex" NEXT hormone*) OR corticoid*):ti,ab
#35	(corticosteroid* OR (cortico NEXT steroid*)):ti
#36	(alemtuzumab* OR campath* OR lemtrada*):ti,ab
#37	(avonex* OR rebif*):ti,ab
#38	(aubagio* OR teriflunomide*):ti,ab
#39	(azathioprine* OR azothioprine* OR imurel* OR imuran* OR immuran*):ti,ab
#40	(bafiertam* OR (monomethyl NEXT fumarate*) OR ("methyl hydrogen" NEXT fumarate*) OR methylhydrogenfumarate*):ti,ab
#41	((beta* NEAR/2 interferon*) OR fiblaferon* OR (fibroblast NEXT interferon*) OR IFNbeta* OR (IFN NEXT beta*)):ti,ab OR interferon*:ti
#42	(betaferon* OR betaseron* OR (beta NEXT seron*) OR extavia*):ti,ab
#43	(copaxone* OR "Cop 1" OR "copolymer 1" OR glatiramer* OR glatopa* OR "TV 5010" OR "TV5010"):ti,ab
#44	(cladribine* OR leustatin* OR mavenclad* OR movectro*):ti,ab
#45	(cyclophosphamide* OR cyclophosphane* OR cytophosphan* OR cytoxan* OR endoxan* OR neosar* OR procytox* OR sendoxan*):ti,ab
#46	(daclizumab* OR zinbryta* OR zenapax*):ti,ab
#47	(dimethylfumarate* OR (dimethyl NEXT fumarate*) OR "BG 00012" OR "BG00012" OR "BG12" OR (diroximel NEXT fumarate*) OR tecfidera* OR vumerity*):ti,ab
#48	(fingolimod* OR gilenya* OR gilenia* OR "FTY 720" OR "FTY720"):ti,ab
#49	(kesimpta* OR ofatumumab* OR "HUMAX CD20 2F2" OR "GSK 1841157" OR "GSK1841157"):ti,ab

(Continued)

#50	(immunoglobulin*):ti OR ((intravenous NEXT immunoglobulin*) OR (IV NEXT immunoglobulin*) OR IVIG):ti,ab
#51	(laquinimod* OR "ABR 215062" OR "ABR215062"):ti,ab
#52	(mayzent* OR siponimod* OR "BAF 312" OR "BAF312"):ti,ab
#53	(methotrexate* OR amethopterin* OR mexate*):ti,ab
#54	(methylprednisolone* OR metipred*):ti,ab
#55	(mitoxantrone* OR mitozantrone* OR ralenova* OR novantron* OR onkotrone*):ti,ab
#56	(natalizumab* OR tysabri* OR antegren*):ti,ab
#57	(ocrelizumab* OR ocrevus* OR "R 1594" OR "PR070769"):ti,ab
#58	(ozanimod* OR zeposia* OR "RPC1063"):ti,ab
#59	(peginterferon* OR (pegylated NEXT interferon*) OR plegridy* OR ("peg ifn" NEXT beta*)):ti,ab
#60	(prednisolone* OR predonine*):ti,ab
#61	(rituximab* OR rituxan* OR mabthera* OR "IDEC C2B8"):ti,ab
#62	{OR #15-#61}
#63	#14 AND #62
#64	#14 AND #62 in Trials

Appendix 2. Search strategy - MEDLINE (PubMed)

#	Query
1	("adverse effects" [Subheading]) AND "Multiple Sclerosis/drug therapy"[Majr]
2	"demyelinating autoimmune diseases, cns"[MeSH Terms:noexp]
3	"Demyelinating Diseases"[MeSH Terms:noexp]
4	"Multiple Sclerosis"[MeSH Terms]
5	"myelitis, transverse"[MeSH Terms]
6	"Optic Neuritis"[MeSH Terms]
7	"clinically isolated syndrome*"[Title/Abstract]
8	"devic"[Title/Abstract] OR "devic s"[Title/Abstract] OR "devics"[Title/Abstract]
9	"disseminated sclerosis*"[Title/Abstract]

(Continued)

10	"demyelinating disease*"[Title/Abstract] OR "demyelinating disorder*"[Title/Abstract]
11	"demyelinating myelitis*"[Title/Abstract] OR "necrotising myelitis*"[Title/Abstract] OR "necrotizing myelitis*"[Title/Abstract] OR "transverse myel*"[Title/Abstract]
12	"multiple sclerosis*"[Title/Abstract] OR "MS"[Title]
13	"neuropapilliti*"[Title/Abstract] OR "optic neuriti*"[Title/Abstract] OR "retrobulbar neuriti*"[Title/Abstract]
14	"neuromyelitis optica*"[Title/Abstract] OR "nmo spectrum disorder*"[Title/Abstract]
15	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16	("Adrenal Cortex Hormones/adverse effects"[Mesh:NoExp] OR "Adrenal Cortex Hormones/drug effects"[Mesh:NoExp] OR "Adrenal Cortex Hormones/drug therapy"[Mesh:NoExp] OR "Adrenal Cortex Hormones/therapeutic use"[Mesh:NoExp])
17	"Alemtuzumab"[MeSH Terms]
18	"Azathioprine"[MeSH Terms]
19	"Cladribine"[MeSH Terms]
20	"Cyclophosphamide"[MeSH Terms:noexp]
21	"Daclizumab"[MeSH Terms]
22	"Dimethyl Fumarate"[MeSH Terms]
23	"Fingolimod Hydrochloride"[MeSH Terms]
24	"Glatiramer Acetate"[MeSH Terms]
25	("Immunoglobulins/adverse effects"[Mesh:NoExp] OR "Immunoglobulins/drug effects"[Mesh:NoExp] OR "Immunoglobulins/therapeutic use"[Mesh:NoExp] OR "Immunoglobulins, Intravenous"[MeSH Terms])
26	"Interferon-beta"[MeSH Terms]
27	"Interferon Type I"[MeSH Terms:noexp]
28	"Methotrexate"[MeSH Terms]
29	"Methylprednisolone"[MeSH Terms:noexp]
30	"Mitoxantrone"[MeSH Terms]
31	"Natalizumab"[MeSH Terms]
32	"Prednisolone"[MeSH Terms:noexp]
33	"Rituximab"[MeSH Terms]
34	"adrenal cortex hormone*"[Title/Abstract] OR "corticosteroid*"[Title] OR "cortico steroid*"[Title] OR "corticoid*"[Title/Abstract]

(Continued)

35	"alemtuzumab*"[Title/Abstract] OR "campath*"[Title/Abstract] OR "lemtrada*"[Title/Abstract]
36	avonex*[Title/Abstract] OR rebif*[Title/Abstract]
37	"aubagio*"[Title/Abstract] OR "teriflunomide*"[Title/Abstract]
38	"azathioprine*"[Title/Abstract] OR "azothioprine*"[Title/Abstract] OR "imurel*"[Title/Abstract] OR "imuran*"[Title/Abstract] OR "immuran*"[Title/Abstract]
39	"bafiertam*"[Title/Abstract] OR "monomethyl fumarate*"[Title/Abstract] OR "methyl hydrogen fumarate*"[Title/Abstract] OR "methylhydrogenfumarate*"[Title/Abstract]
40	"beta interferon*"[Title/Abstract] OR "beta 1 interferon*"[Title/Abstract] OR "interferon beta*"[Title/Abstract] OR "fiblaferon*"[Title/Abstract] OR "fibroblast interferon*"[Title/Abstract] OR "IFNbeta*"[Title/Abstract] OR "IFN beta*"[Title/Abstract] OR "interferon*"[Title]
41	"betaferon*"[Title/Abstract] OR "betaseron*"[Title/Abstract] OR "beta seron*"[Title/Abstract] OR "extavia*"[Title/Abstract]
42	"copaxone*"[Title/Abstract] OR "Cop 1"[Title/Abstract] OR "copolymer 1"[Title/Abstract] OR "glatiramer*"[Title/Abstract] OR "glatopa*"[Title/Abstract] OR "TV 5010"[Title/Abstract] OR "TV5010"[Title/Abstract]
43	"cladribine*"[Title/Abstract] OR "leustatin*"[Title/Abstract] OR "mavenclad*"[Title/Abstract] OR "movectro*"[Title/Abstract]
44	"cyclophosphamide*"[Title/Abstract] OR "cyclophosphane*"[Title/Abstract] OR "cytophosphan*"[Title/Abstract] OR "cytoxan*"[Title/Abstract] OR "endoxan*"[Title/Abstract] OR "neosar*"[Title/Abstract] OR "procytox*"[Title/Abstract] OR "sendoxan*"[Title/Abstract]
45	"daclizumab*"[Title/Abstract] OR "zinbryta*"[Title/Abstract] OR "zenapax*"[Title/Abstract]
46	"dimethylfumarate"[Title/Abstract] OR "dimethyl fumarate*"[Title/Abstract] OR "BG 00012"[Title/Abstract] OR "BG00012"[Title/Abstract] OR "BG 12"[Title/Abstract] OR "diroximel fumarate*"[Title/Abstract] OR "tecfidera*"[Title/Abstract] OR "vumerity*"[Title/Abstract]
47	"fingolimod*"[Title/Abstract] OR "gilenya*"[Title/Abstract] OR "gilenia*"[Title/Abstract] OR "FTY 720"[Title/Abstract] OR "FTY720"[Title/Abstract]
48	"immunoglobulin*"[Title] OR "intravenous immunoglobulin*"[Title/Abstract] OR "IV immunoglobulin*"[Title/Abstract] OR "IVIG"[Title/Abstract]
49	"kesimpta*"[Title/Abstract] OR "ofatumumab*"[Title/Abstract] OR "HUMAX CD20 2F2"[Title/Abstract] OR "GSK 1841157"[Title/Abstract] OR "GSK1841157"[Title/Abstract]
50	"laquinimod*"[Title/Abstract] OR "ABR 215062"[Title/Abstract] OR "ABR215062"[Title/Abstract]
51	"mayzent*"[Title/Abstract] OR "siponimod*"[Title/Abstract] OR "BAF 312"[Title/Abstract] OR "BAF312"[Title/Abstract]
52	"methotrexate*"[Title/Abstract] OR "amethopterin*"[Title/Abstract] OR "mexate*"[Title/Abstract]
53	"methylprednisolone*"[Title/Abstract] OR "metipred*"[Title/Abstract]
54	"mitoxantrone*"[Title/Abstract] OR "mitozantrone*"[Title/Abstract] OR "ralenova*"[Title/Abstract] OR "novantron*"[Title/Abstract] OR "onkotrone*"[Title/Abstract]

(Continued)

55	"natalizumab*"[Title/Abstract] OR "tysabri*"[Title/Abstract] OR "antegren*"[Title/Abstract]
56	"ocrelizumab*"[Title/Abstract] OR "ocrevus*"[Title/Abstract] OR "R 1594"[Title/Abstract] OR "PR070769"[Title/Abstract]
57	"ozanimod*"[Title/Abstract] OR "zeposia*"[Title/Abstract] OR "RPC1063"[Title/Abstract]
58	"peginterferon*"[Title/Abstract] OR "pegylated interferon*"[Title/Abstract] OR "plegridy*"[Title/Abstract] OR "peg ifn beta*"[Title/Abstract]
59	"prednisolone*"[Title/Abstract] OR "predonine*"[Title/Abstract]
60	"rituximab*"[Title/Abstract] OR "rituxan*"[Title/Abstract] OR "mabthera*"[Title/Abstract] OR "IDEC C2B8"[Title/Abstract]
61	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60
62	#15 AND #61
63	#1 OR #62
64	randomized controlled trial [pt]
65	controlled clinical trial [pt]
66	randomized [tiab]
67	placebo [tiab]
68	"Clinical Trials as Topic"[Mesh:NoExp]
69	randomly [tiab]
70	trial [ti]
71	#64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70
72	animals [mh] NOT humans [mh]
73	#71 NOT #72
74	#63 AND #73

Appendix 3. Search strategy - Embase

1	'demyelinating disease'/de
2	'multiple sclerosis'/de
3	'optic neuritis'/de

(Continued)

4	'transverse myelitis'/exp
5	'clinically isolated syndrome*':ab,ti
6	devic:ab,ti OR 'devic s':ab.ti OR devics:ab,it
7	'disseminated sclerosis*':ab,ti
8	(demyelinating NEAR/1 (disease* OR disorder*)):ab,ti
9	((demyelinating OR necrotising OR necrotizing OR transverse) NEAR/1 myelitis*):ab,ti
10	'multiple sclerosis*':ab,ti OR 'MS':ti
11	neuropapilliti*:ab,ti OR ((optic OR retrobulbar) NEAR/1 neuriti*"):ab,ti
12	'neuromyelitis optica*':ab,ti OR 'nmo spectrum disorder*':ab,ti
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	'alemtuzumab'/de
15	'azathioprine'/de
16	'beta interferon'/exp
17	'cladribine'/de
18	'corticosteroid'/de/ae OR 'corticosteroid'/de/dt
19	'cyclophosphamide'/de/ae OR 'cyclophosphamide'/de/dt
20	'daclizumab'/de
21	'dimethyl fumarate'/de
22	'fingolimod'/de
23	'glatiramer'/de
24	'immunoglobulin'/de/ae or 'immunoglobulin'/de/dt or 'immunoglobulin'/de/iv
25	'methotrexate'/de/ae or 'methotrexate'/de/dt
26	'methylprednisolone'/de
27	'mitoxantrone'/de
28	'natalizumab'/de
29	'prednisolone'/de
30	'rituximab'/de
31	'adrenal cortex hormone*':ab,ti OR 'corticosteroid*':ti OR 'cortico steroid*':ti OR 'corticoid*':ab,ti

(Continued)

32	'alemtuzumab*':ab,ti OR 'campath*':ab,ti OR 'lemtrada*':ab,ti
33	avonex*:ab,ti OR rebif*:ab,ti
34	'aubagio*':ab,ti OR 'teriflunomide*':ab,ti
35	'azathioprine*':ab,ti OR 'azothioprine*':ab,ti OR 'imurel*':ab,ti OR 'imuran*':ab,ti OR 'immuran*':ab,ti
36	'bafiertam*':ab,ti OR 'monomethyl fumarate*':ab,ti OR 'methyl hydrogen fumarate*':ab,ti OR 'methylhydrogenfumarate*':ab,ti
37	'beta interferon*':ab,ti OR 'beta 1 interferon*':ab,ti OR 'interferon beta*':ab,ti OR 'fiblaferon*':ab,ti OR 'fibroblast interferon*':ab,ti OR 'IFNbeta*':ab,ti OR 'IFN beta*':ab,ti OR 'interferon':ti
38	'betaferon*':ab,ti OR 'betaseron*':ab,ti OR 'beta seron*':ab,ti OR 'extavia*':ab,ti
39	'copaxone*':ab,ti OR 'Cop 1':ab,ti OR 'copolymer 1':ab,ti OR 'glatiramer*':ab,ti OR 'glatopa*':ab,ti OR 'TV 5010':ab,ti OR 'TV5010':ab,ti
40	'cladribine*':ab,ti OR 'leustatin*':ab,ti OR 'mavenclad*':ab,ti OR 'movectro*':ab,ti
41	'cyclophosphamide*':ab,ti OR 'cyclophosphane*':ab,ti OR 'cytophosphan*':ab,ti OR 'cytoxan*':ab,ti OR 'endoxan*':ab,ti OR 'neosar*':ab,ti OR 'procytox*':ab,ti OR 'sendoxan*':ab,ti
42	'daclizumab*':ab,ti OR 'zinbryta*':ab,ti OR 'zenapax*':ab,ti
43	'dimethylfumarate*':ab,ti OR 'dimethyl fumarate*':ab,ti OR 'BG 00012':ab,ti OR 'BG00012':ab,ti OR 'BG 12':ab,ti OR 'diroximel fumarate*':ab,ti OR 'tecfidera*':ab,ti OR 'vumerity*':ab,ti
44	'fingolimod*':ab,ti OR 'gilenya*':ab,ti OR 'gilenia*':ab,ti OR 'FTY 720':ab,ti OR 'FTY720':ab,ti
45	'immunoglobulin*':ti OR 'intravenous immunoglobulin*':ab,ti OR "IV immunoglobulin*":ab,ti OR "IVIG":ab,ti
46	'kesimpta*':ab,ti OR 'ofatumumab*':ab,ti OR 'HUMAX CD20 2F2':ab,ti OR 'GSK 1841157':ab,ti OR 'GSK1841157':ab,ti
47	'laquinimod*':ab,ti OR 'ABR 215062':ab,ti OR 'ABR215062':ab,ti
48	'mayzent*':ab,ti OR 'siponimod*':ab,ti OR 'BAF 312':ab,ti OR 'BAF312':ab,ti
49	'methotrexate*':ab,ti OR 'amethopterin*':ab,ti OR 'mexate*':ab,ti
50	'methylprednisolone*':ab,ti OR 'metipred*':ab,ti
51	'mitoxantrone*':ab,ti OR 'mitozantrone*':ab,ti OR 'ralenova*':ab,ti OR 'novantron*':ab,ti OR 'onkotrone*':ab,ti
52	'natalizumab*':ab,ti OR 'tysabri*':ab,ti OR 'antegren*':ab,ti
53	'ocrelizumab*':ab,ti OR 'ocrevus*':ab,ti OR 'R 1594':ab,ti OR 'PR070769':ab,ti
54	'ozanimod*':ab,ti OR 'zeposia*':ab,ti OR 'RPC1063':ab,ti

(Continued)

55	'peginterferon*':ab,ti OR 'pegylated interferon*':ab,ti OR 'plegridy*':ab,ti OR 'peg ifn beta*':ab,ti
56	'prednisolone*':ab,ti OR 'predonine*':ab,ti
57	'rituximab*':ab,ti OR 'rituxan*':ab,ti OR 'mabthera*':ab,ti OR 'IDEC C2B8':ab,ti
58	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57
59	#13 AND #58
60	'randomized controlled trial'/de
61	'controlled clinical trial'/de
62	random*:ti,ab,tt
63	'randomization'/de
64	'intermethod comparison'/de
65	placebo:ti,ab,tt
66	(compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)
67	((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
68	(open NEXT/1 label):ti,ab,tt
69	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
70	'double blind procedure'/de
71	(parallel NEXT/1 group*):ti,ab,tt
72	(crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
73	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
74	(assigned:ti,ab,tt OR allocated:ti,ab,tt)
75	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt
76	(volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
77	'human experiment'/de
78	trial:ti,tt
79	#60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78

(Continued)

80	(((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))
81	('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))
82	('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))
83	('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))
84	(nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)
85	'random field*':ti,ab,tt
86	('random cluster' NEAR/4 sampl*):ti,ab,tt
87	(review:ab AND review:it) NOT trial:ti,tt
88	('we searched':ab AND (review:ti,tt OR review:it))
89	'update review':ab
90	(databases NEAR/5 searched):ab
91	((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)
92	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
93	#80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92
94	#77 NOT #93
95	#59 AND #94
95	([medline]/lim OR [pubmed-not-medline]/lim)
96	#95 NOT #96

WHAT'S NEW

Date	Event	Description
10 November 2022	Amended	Publishing an amendment to correct author order error.

HISTORY

Protocol first published: Issue 11, 2022

CONTRIBUTIONS OF AUTHORS

- Conception of the review: Francesco Nonino (FN), Silvia Minozzi (SM), Graziella Filippini (GF), Elisa Baldin (EB), Ben Ridley (BR).
- Design of the review: SM, Cinzia Del Giovane (CDG), FN, GF.
- Co-ordination of the review: FN, BR.
- Search and selection of studies for inclusion in the review: FN, Irene Tramacere (IT), EB, Matteo Foschi (MF), BR, Guy Peryer (GP).
- Collection of data for the review: SM, Marien Gonzalez-Lorenzo (MGL), BR, IT, FN.
- Assessment of the risk of bias in the included studies: SM, MGL.
- Analysis of data: CDG.
- Assessment of the certainty in the body of evidence: SM, MGL.
- Interpretation of data: FN, EB, GP, GF, MF.
- Writing of the review: FN, EB, CDG, BR, GF, GP, MF.

DECLARATIONS OF INTEREST

- Francesco Nonino (FN) declares no conflicts of interest.
- Elisa Baldin (EB) has worked as a health professional in an outpatient clinic of the Italian National Health System, has published opinions in a medical journal on other pharmaceuticals, and has received travel and meeting attendance support from Roche and Sanofi Genzyme.
- Ben Ridley (BR) declares no conflicts of interest.
- Guy Peryer (GP) has published opinions on the methodology of conducting interventions in the context of multiple sclerosis, has worked as an independent contractor with the Multiple Sclerosis Society, Bristol-Myers Squibb, and Multiple Sclerosis International Federation, as well as been involved in Data And Safety Monitoring with the National Institute for Health and Care Research.
- Silvia Minozzi (SM) declares no conflicts of interest.
- Matteo Foschi (MF) currently works as a health professional in a hospital of the Italian National Health System, has published opinions in a medical journal on other pharmaceuticals, and has received travel and meeting attendance support from Roche, Merck, Sanofi Genzyme, and Biogen.
- Graziella Filippini (GF) has been directly involved in a study that may meet the inclusion criteria for the review. In line with Cochrane's conflict of interest policy, GF was not involved in defining the overall inclusion and exclusion for the protocol and will not be involved in actions relating to their study when conducting the full review.
- Irene Tramacere (IT) has been directly involved in a study that may meet the inclusion criteria for the review. In line with Cochrane's conflict of interest policy, IT was not involved in defining the overall inclusion and exclusion for the protocol and will not be involved in actions relating to their study when conducting the full review.
- Cinzia Del Giovane (CDG) has received support from the Multiple Sclerosis International Federation.
- Marien Gonzalez-Lorenzo (MGL) declares no conflicts of interest.
- FN, GF, BR, and SM are Cochrane editors. They were not involved in the editorial process for this review.

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External sources

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