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[Intervention Protocol]

Treatment with disease modifying drugs for people with a first clinical attack suggestive of multiple sclerosis

Graziella Filippini[1], Marinella Clerico[2], Omid Beiki[3,4], Miriam Mattoscio[5], Federico Piazza[2], Cinzia Del Giovane[6], Sten Fredrikson[7], Irene Tramacere[8], Antonio Scalfari[9]

[1]Scientific Direction, Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy. [2]University of Turin, Division of Neurology, AOU San Luigi Gonzaga, Orbassano, Italy. [3]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. [4]Department of Epidemiology and Biostatistics, Kermanshah University of Medical Sciences, Kermanshah, Iran. [5]Department of Medicine, Division of Brain Sciences, Imperial College London, London, UK. [6]Italian Cochrane Centre, Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy. [7]Division of Neurology R54 - Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. [8]Neuroepidemiology Unit, Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy. [9]Department of Medicine, Division of Brian Sciences, Centre for Neuroscience, Wolfson Neuroscience Laboratories, Imperial College London, London, UK

Contact address: Graziella Filippini, Scientific Direction, Fondazione IRCCS, Istituto Neurologico Carlo Besta, via Celoria, 11, Milan, 20133, Italy. gfilippini@istituto-besta.it.

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ABSTRACT

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

- To estimate the benefit and safety of all DMDs that have been evaluated in all studies (randomised and non-randomised) for early treatment. We will employ novel, high-quality methods for systematic reviews and network meta-analysis in collaboration with the Cochrane Multiple Interventions Group.
- To evaluate the quality of the evidence provided by existing studies. We will consider the credibility of included studies and other characteristics of the evidence base as we characterise conclusions pertaining to high, low or very low quality of evidence.

We will undertake this review in accordance with the methods described by the template protocol published online and will use this template as we prepare the review.

BACKGROUND

Description of the condition

With the introduction of the 2001 McDonald criteria and their 2005 and 2010 revisions, multiple sclerosis (MS) could be diagnosed at the time of a first clinical attack with magnetic resonance imaging (MRI) of the brain and the whole spine (McDonald 2001; Polman 2005; Polman 2011). Opinion leaders have recommended early action as follows: "treating at first clinical attack may be the most effective strategy to manage disease progression" (Freedman 2014). Revised guidelines of the Association of British Neurologists (Scolding 2015) and NHS England (NHS England 2014) suggest that treatment should be advised for patients within 12 months of a first attack, if MRI establishes a diagnosis of MS according to 2010 McDonald criteria or predicts a high likelihood of recurrent attacks.

Once the decision is made for early treatment, patients and their healthcare providers need to select one of several disease-modifying drugs (DMDs). The benefit of starting early treatment with DMD has been demonstrated by some short-term trials that showed delay of recurrent attacks or fewer lesions in participants given interferons beta or glatiramer acetate compared with those given placebo (Comi 2001; Comi 2012). On the basis of these results, interferons beta and glatiramer acetate were approved by national regulatory agencies for treatment of a first attack (EMA 2015a). Guidelines of the Association of British Neurologists indicate that alemtuzumab and natalizumab are more efficient in preventing relapses. However, because of safety concerns, these guidelines recommend that these agents be given as second-line treatment, or as treatment for patients with rapidly evolving relapsing-remitting MS (RRMS); beta interferons, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod are recommended as first-line agents (the first therapy) (Scolding 2015). On the contrary, Australian and New Zealand guidelines suggest that all DMDs can be used as first-line treatment if the attending neurologist so judges (Broadley 2014).

No definitive evidence suggests that delayed recurrent clinical attacks or fewer MRI lesions over the two-year period reported in randomised trials translate into medium- or long-term benefit (Frischer 2009; Kinkel 2012), and large variability of long-term disability worsening has been reported even among people with frequent early relapses (Scalfari 2013).

We published a Cochrane review on benefit and acceptability of DMDs in people with RRMS. Evidence of moderate to high quality suggests that alemtuzumab, natalizumab and fingolimod when compared with placebo were associated with greater benefit for preventing clinical relapse, and evidence of moderate quality indicates that natalizumab was associated with greater benefit than placebo for preventing worsening of disability among all treatments evaluated (Tramacere 2015).

Description of the intervention

We will consider all DMDs that are used, approved or off-label, or are currently under marketing authorisation or investigation for people with a first clinical attack of MS. We will consider that all agents used or under investigation for RRMS could be given to people with a first attack complying with 2010 McDonald criteria.

- Approved for a first attack complying with 2010 McDonald criteria.
  - Beta interferons (Betaferon/Betaseron®; Extavia®; Rebif®; Avonex®) and glatiramer acetate (Copaxone®) (EMA 2015a; FDA 2012a; FDA 2012b; FDA 2013). These medications are administered subcutaneously, except for beta interferon 1a (Avonex®), which is administered via intramuscular injections.
- Approved for RRMS.
  - Natalizumab (Tysabri®) (EMA 2006; FDA 2006), administered by intravenous infusion at a dose of 300 mg every four weeks.
  - Fingolimod (Gilenya®) (EMA 2011; FDA 2010), given at an oral dose of 0.5 mg once daily.
  - Teriflunomide (Aubagio®) (EMA 2013a; FDA 2012), given at an oral dose of 7 or 14 mg once daily.
  - Dimethyl fumarate (Tecfidera®) (EMA 2014a; FDA 2013), given at an oral dose of 240 mg twice daily.
  - Alemtuzumab (Lemtrada®) (EMA 2013b; FDA 2014a), administered intravenously in two annual treatment courses - the first at a dose of 12 mg daily on five consecutive days (60 mg total dose), and the second, 12 months later, on three consecutive days (36 mg total dose).
  - Daclizumab (Zinbryta®), administered by subcutaneous or intravenous injections and approved by the European Medicines Agency (EMA) (EMA 2016). The review process of the Food and Drug Administration(FDA) (Biogen 2015b) is ongoing.
  - Peginterferon beta-1a (Plegridy®) (EMA 2014b; FDA 2014b), given by subcutaneous injection at a dose of 125 micrograms every 14 days.
  - Cladribine (Movectro®), approved in Russia and Australia in 2010 (Murphy 2010) but refused by the EMA (EMA 2015b) and the FDA in 2011 because of a suspected increase in cancer risk. This has not been confirmed by results of a meta-analysis of trials (Pakpoor 2015). Cladribine was investigated in two trials (Giovannoni 2010; Leist 2014).
  - Mitoxantrone (Novantrone®), approved in 2000 in the USA (FDA 2000), Europe and other countries for RRMS and progressive MS, administered as a short intravenous infusion every three months. Safety issues of concern for people treated with mitoxantrone include cardiotoxicity and acute leukaemia.
- Used off-label.
  - Azathioprine (Imuran®), used for the treatment of MS in many countries on the basis of placebo-controlled randomised controlled trials (RCTs) published more than two decades ago. However, since interferons beta were approved, azathioprine is no longer recommended as first-line therapy (Goodin 2002). It is taken daily orally as a 2 or 3 mg/kg tablet.
  - Intravenous immunoglobulins used for people with severe and frequent relapses, for whom other treatments were contraindicated (Scolding 2015)
  - Rituximab (Rituxan® or Mabthera®), evaluated in one trial (Hauser 2008). Study authors found beneficial effects on clinical and MRI-visualised disease activity that was maintained over 48 weeks. The drug is administered intravenously.
- Currently under marketing authorisation or investigation.

- Laquinimod (Nerventra®), evaluated in two trials for RRMS at an oral dose of 0.6 mg daily (Comi 2012; Vollmer 2014). The drug received a negative opinion from the EMA (EMA 2014c). Additional studies of laquinimod in RRMS are ongoing (Active Biotech 2014).
- Ocrelizumab is under development for treatment of patients with RRMS, and clinical trials are ongoing (Hauser 2015; Kappos 2011; Montalban 2015). It is administered by intravenous infusion every 24 weeks.

How the intervention might work

Immunosuppressive or immunomodulatory effects are common to all treatments included in the review.

- Approved.
  - Beta interferons are naturally occurring cytokines that possess antiviral activity and a wide range of anti-inflammatory properties. Recombinant beta interferons are believed to directly increase expression and concentration of anti-inflammatory agents, while downregulating expression of pro-inflammatory cytokines (Kieseier 2011).
  - Glatiramer acetate exerts an immunomodulatory action by inducing tolerance or anergy of myelin-reactive lymphocytes (Schmied 2003). Glatiramer acetate may promote neuroprotective repair processes (Aharoni 2014).
  - Natalizumab is a humanised monoclonal antibody directed against the alfa4 integrin. This integrin is essential in the process by which lymphocytes gain access to the brain by allowing cells to penetrate the blood-brain barrier. Natalizumab binds alfa4β1 and alfa4β7 integrin on the surface of circulating T lymphocytes, preventing interaction with cellular adhesion molecules that facilitate extravasation and migration from the circulation to the central nervous system (CNS) (Millard 2011).
  - Fingolimod is a sphingosine-1-phosphate (S1P) receptor modulator that prevents lymphocyte egress from lymphoid tissues, thereby reducing autoaggressive lymphocyte infiltration into the CNS. S1P receptors are also expressed by many CNS cell types and have been shown to influence cell proliferation, morphology and migration. Fingolimod crosses the blood–brain barrier and therefore may have direct CNS effects (Chun 2010).
  - Teriflunomide acts as an inhibitor of dihydroorotate dehydrogenase (DHODH), a mitochondrial enzyme involved in pyrimidine synthesis for DNA replication in rapidly proliferating cells. The drug reduces T lymphocyte and B lymphocyte activation and proliferation, and may attenuate the inflammatory response to autoantigens in MS. However, the exact mechanism of action for teriflunomide is not fully understood. Some observations suggest that the drug may have immunological effects outside of its ability to inhibit pyrimidine synthesis in rapidly proliferating cells (Claussen 2012; Oh 2013).
  - Dimethyl fumarate derives from fumaric acid, promotes anti-inflammatory activity and can inhibit expression of pro-inflammatory cytokines and adhesion molecules. Actions of neuroprotective and myelin-protective mechanisms have been proposed (Linker 2011; Wilms 2010).
  - Alemtuzumab is a monoclonal antibody to CD52 on the cell surface of lymphocytes and monocytes. Its effects are thought to be mediated by extended B and T lymphocyte depletion followed by a distinctive pattern of T and B cell repopulation that begins within weeks of treatment and leads to a rebalanced immune system, including an increased percentage of regulatory and memory T cells. Effects of alemtuzumab persisted after it was cleared from the circulation (Lycke 2015).
  - Daclizumab is a monoclonal antibody to the interleukin-2 receptor CD25 that is expressed on immune cells. The exact mechanism is not well understood. Daclizumab interrupts interleukin-2-mediated cell activation, thereby preventing expansion of autoreactive T lymphocytes and inhibiting survival of activated T cells (Wuest 2011).
  - Pegylated interferon beta-1a (PEG-IFN) is the drug obtained by PEGylation of IFN beta-1a (Avonex®) (i.e. joining of a polyethylene glycol group (PEG) molecule to the IFN beta-1a molecule). PEGylation has been applied to increase IFN stability, solubility and half-life, and to reduce dosing frequency (Hu 2012).
  - Cladribine is a chemotherapeutic drug approved for treatment of patients with hairy-cell leukaemia, a subtype of chronic lymphoid leukaemia. Short courses of cladribine induce prolonged lymphopenia by selectively interfering with DNA synthesis and repair in T and B lymphocytes lasting months to years (Leist 2011).
  - Mitoxantrone is a cytotoxic drug that intercalates with DNA and inhibits both DNA and RNA synthesis, thus reducing the number of lymphocytes (Fox 2004).
- Used off-label.
  - Azathioprine is a cytotoxic immunosuppressive drug that acts as a prodrug for mercaptopurine, inhibiting an enzyme required for DNA synthesis. Thus it most strongly affects proliferating cells, such as T cells and B cells of the immune system (Tiede 2003).
  - Intravenous immunoglobulins may improve remyelination of demyelinated axons through mediation of cytokines. However, their mechanism of action in MS remains unclear (Stangel 1999).
  - Rituximab is a monoclonal antibody to CD20 expressed on pre-B and mature B cells; it acts by depleting these cells in the circulation and the CNS. Although MS was traditionally considered a T cell-mediated disease, accumulating evidence suggests that B cells may play a role (Lycke 2015; Naismith 2010).
- Currently under marketing authorisation or investigation.
  - Laquinimod may have an immunomodulatory effect on the peripheral and central nervous systems. This drug modulates the function of various myeloid antigen-presenting cell populations, which thendownregulate pro-inflammatory T cell responses. Furthermore, data indicate that laquinimod acts directly on resident cells within the CNS to reduce demyelination and axonal damage. However, exactly how the drug works remains unknown (Varrin-Doyer 2014).
  - Ocrelizumab is a recombinant monoclonal antibody designed to selectively target CD20 B lymphocytes that are implicated in the pathogenesis of MS. Like rituximab, ocrelizumab depletes CD20 B cells, but it increases antibody-dependent cell-mediated cytotoxicity effects and reduces complement-dependent cytotoxicity effects compared with rituximab (Kappos 2011).

Why it is important to do this review

Uncertainty

Many treatment options are available, and patients and their clinicians may choose to start with a drug of moderate efficacy and general safety or with a drug of high efficacy and a complex safety profile. Consequently, a comprehensive appreciation of the benefits and risks of all treatment approaches is urgently needed (Scolding 2015; Wingerchuk 2014). Some evidence from individual studies shows the effects of various DMDs. Interferons and glatiramer acetate are indicated by the FDA and the EMA for treatment of people who have experienced a first attack and are at high risk of recurrent attacks. Other immunotherapies have been reported to delay recurrent attacks, but their benefit in terms of disability remains unclear, and various national guideline bodies have provided conflicting information about effects of these treatments and their use as first-line or second-line therapy (see Description of the condition). This uncertainty results from several factors, including intermediate outcomes and short follow-up periods in the clinical trials included in published systematic reviews. Immunotherapies administered early in the disease can delay intermediate outcomes (i.e. short-term relapses), but their effect on relapses poorly correlates with prevention of disability (Frischer 2009; Kinkel 2012; Scalfari 2013). Therefore an effect on disability cannot be claimed solely on the basis of relapse prevention (EMA 2015a). Safety outcomes have not been investigated extensively primarily because most evidence has been derived from short-term randomised trials that have low power to investigate rare adverse events.

Patients and their doctors must be given information about the relative benefit and safety of the various treatment options if they are to make informed decisions. Various DMDs have been shown to have different benefit/acceptability profiles. Differences in benefit are as important to consider as differences in safety. For example, local injection site reactions and flu-like symptoms have emerged as the main adverse effects of interferons beta, and cardiotoxicity and acute leukaemia as major safety issues of concern for mitoxantrone. An increasing body of non-randomised studies published in the scientific literature have reported on rare adverse events and have provided accumulating evidence. Investigators have described fatal cases of progressive multi-focal leucoencephalopathy (PML) in patients treated with natalizumab (EMA 2006), fingolimod (EMA 2011) and dimethyl fumarate (EMA 2014a). The few adverse events mentioned here are described in the large body of data on known and supposed drug-related adverse events provided in the literature. Researchers must identify, systematically collect and synthesise this information to provide a summary of existing scientific evidence that will assist healthcare providers and patients in making treatment decisions.

Relevance

In July 2014, the Cochrane Multiple Sclerosis Group launched a 'Priority Setting Survey' and invited consumers and MS societies to answer a questionnaire identifying priority research questions considered to have the most relevant impact for all stakeholders. The question - "Early onset of treatment may avoid disease progression?" - was one of the most frequently reported by patients and family members. The question - "Does early treatment with aggressive disease modifying drugs improve the prognosis for people with MS?" - addresses one of the top 10 MS priorities reported by the James Lind Alliance in collaboration with the UK MS Society 2012. This study aims to answer these two questions by comparing all DMDs with placebo and going a step farther; it also plans to provide an assessment of the relative effects of each drug compared with one other along with a ranking of treatments according to benefit and safety. The significance of this project is underlined by the fact that evaluation of disease modifying drugs for people with a first clinical episode has been identified as a priority and is featured in the Cochrane Priority Review List 2015/16.

Most published reviews have compared a single treatment versus placebo and have made inferences about benefits and safety. This information is unlikely to be useful in practice, as people with MS have several treatment options. Network meta-analysis (NMA), an extension of the traditional pairwise meta-analysis, collates information from studies comparing different treatments to form a 'network of interventions', providing information about the relative effects of all interventions included in the network, even those not directly compared in any trial. NMA can provide a hierarchy of treatments ordered by efficacy and safety.

None of the existing comparative effectiveness reviews have specifically targeted DMD in early treatment. As the number of patients who choose to start treatment soon after diagnosis increases, it is important for healthcare providers to know the relative benefit and safety of the various treatment options in this particular setting. Another important limitation of existing reviews is that all include randomised controlled trials. Although this study design is theoretically associated with low risk of bias when treatment efficacy is estimated, it has several shortcomings. First, randomised trials do not provide patient follow-up for a long period; consequently, this design is not appropriate when rare safety outcomes are of interest. Second, randomised trials are typically undertaken in highly selected conditions and do not represent real-world settings. Consequently, the generalisability of findings is doubtful. For these reasons, interest in including non-randomised studies in the decision-making process is growing (Faria 2015), and innovative methods have been developed for combining data obtained through different study designs (Schmitz 2013; Verde 2015). Overall, we believe that despite the wealth of information and the plethora of studies and reviews on treatments for MS, uncertainty surrounds the relative ranking of DMDs when treatment starts early. In particular, the issue of safety is less well studied, as evidence from non-randomised studies that provide useful information on adverse events has not been systematically considered.

We believe that having access to high-quality health information is a relevant component of good decision making and helps people take control of their health. Our certainty comes from the results of our previous studies, in which people with MS and their family members told us that they want access to high-quality information about MS from sources they can trust (Colombo 2014).

Potential to change or influence clinical practice or health policy

The review will provide critical information necessary in making informed healthcare decisions for people with MS, their caring neurologists and their family members who are looking for information about evidence of treatment outcomes. Note that marked variability in treatment decisions has been reported, likely as the result of physician preference and opinion (Palace 2013).

We hope that the results of this review will be understandable and useful for patients and clinicians who seek to make more informed treatment choices. Note that DMDs for MS are expensive, and that their use has significant economic implications for the healthcare system. Moreover, these treatments are 'aggressive' and are often associated with high risk of serious adverse events or side effects, which indirectly further increases treatment costs. Identifying treatment that offers a better benefit and safety profile, with particular attention to safety, may help to reduce indirect costs.

We will ensure that review results will be understandable, relevant and useful for people with MS, healthcare professionals, MS societies, policy makers, guidelines developers and existing and potential research funders. To this end, we will prepare lay summaries that will be disseminated online. Results of this review will also guide those who are entitled to make regulatory decisions and will inform those who have the responsibility of planning a future research agenda, such as funding of future studies in MS. We believe that having access to high-quality health information is an important component of good decision making and helps people take control of their health. Our certainty comes from the results of studies previously undertaken by the Cochrane Multiple Sclerosis Group, wherein people with MS and their family members told us that they want access to high-quality information about MS provided by sources they can trust (Colombo 2014; Colombo 2016; Hill 2012; Synnot 2014).

OBJECTIVES

- To estimate the benefit and safety of all DMDs that have been evaluated in all studies (randomised and non-randomised) for early treatment. We will employ novel, high-quality methods for systematic reviews and network meta-analysis in collaboration with the Cochrane Multiple Interventions Group.
- To evaluate the quality of the evidence provided by existing studies. We will consider the credibility of included studies and other characteristics of the evidence base as we characterise conclusions pertaining to high, low or very low quality of evidence.

We will undertake this review in accordance with the methods described by the template protocol published online and will use this template as we prepare the review.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs and non-randomised studies (NRSs) (open-label extension studies (OLEs), controlled clinical trials (CCTs), concurrent and historical cohort studies (CHs) and population-based registries). Inclusion of NRSs is supported by the need to provide evidence of long-term benefit and safety outcomes that cannot be studied in short-term randomised trials. We will base our inclusion criteria for NRSs on those reported in the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011).

Open-label extension studies follow on from RCTs. At the end of the double-blind phase of the RCT, participants are invited to carry on with, or convert to, the active treatment for an additional study period, during which all participants know they are being treated with the active drug and no participants receive placebo. Early-treatment cohorts and delayed-treatment cohorts are compared. Participants and outcome assessors are kept unaware of the initial treatment allocation throughout the open-label phase of the study.

A study is classified as a CCT when study author(s) do not state explicitly that the study was randomised. The classification CCT is also applied to quasi-randomised studies when the method of allocation is known but is not considered strictly random. Examples of quasi-random methods of assignment include alternation, date of birth and medical record number.

A concurrent cohort study is a follow-up study that compares outcomes between participants who have received an intervention and those who have not. Participants are studied during the same (concurrent) period, either prospectively or, more commonly, retrospectively. The historical cohort study is a variation on the traditional cohort study wherein the outcome from a new intervention is established for participants studied during one period and is compared with outcomes of those who did not receive the intervention during a previous period (i.e. participants are not studied concurrently). Common sources of cohort studies in MS include registries and large-scale clinical databases.

We will include RCTs and NRSs with follow-up of at least one year.

We will exclude non-comparative studies (e.g. within-participant comparisons).

Types of participants

We will consider for inclusion adults (18 years of age or older) with a first clinical attack according to the McDonald criteria (McDonald 2001; Polman 2005; Polman 2011) (i.e. one attack; objective clinical evidence of two lesions or one attack; objective clinical evidence of one lesion (clinically isolated syndrome)). We will accept the definition of a first clinical attack as reported by the authors of primary studies. We will include participants with optic neuritis, isolated brainstem or cerebellar syndrome or spinal cord or other clinical syndrome as a first attack, and we will include monofocal or multi-focal first attacks.

Types of interventions

Alemtuzumab, azathioprine, cladribine, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, immunoglobulins, interferon beta-1b, subcutaneous interferon beta-1a, intramuscular interferon beta-1a, laquinimod, mitoxantrone, natalizumab, ocrelizumab, pegylated interferon beta-1a, rituximab and teriflunomide as monotherapy compared with placebo or another active agent. We will include regimens irrespective of their dose and will assume that treatments are 'jointly randomiseable' across trial participants (Salanti 2012).

We will exclude combination treatments; trials in which a drug regimen was compared with different regimens of the same drug without another active agent or placebo as a control arm; all non-pharmacological treatments; and interventions consisting of over-the-counter drugs.

Types of outcome measures

Primary outcomes

Primary benefit outcomes

- Disability worsening defined as the proportion of participants who experienced confirmed disability worsening at 24 or 36 months, or at the end of the study. Disability worsening is defined as a sustained increase in Expanded Disability Status Scale (EDSS) score by at least 1 point, or by 0.5 point if the baseline EDSS was greater than or equal to 5.5 during a period when the patient had no relapses. The EDSS score quantifies disability on the basis of assessment of neurological function and ability to walk. Scores range from 0 (no neurological abnormality) to 10 (death from multiple sclerosis) (Kurtzke 1983).
- Relapses defined as the proportion of participants who experienced new relapses over 12, 24 or 36 months, or at the end of the study. A relapse is defined as newly developed or recently worsened symptoms of neurological dysfunction that last for at least 24 hoursand occur in the absence of fever or other acute diseases and are separated in time from any previous episode by more than 30 days. We will also accept a more stringent 48-hour criterion. A relapse can resolve partially or completely (McDonald 2001; Polman 2005).

Primary safety outcomes

- Proportion of participants with at least one serious adverse event (SAE) during the study.
- Proportion of participants who withdrew from the study because of adverse events (AEs).

Secondary outcomes

- Proportion of participants who discontinued treatment for any reason during the study.

Search methods for identification of studies

We will apply no language restrictions to the search.

Electronic searches

The Trials Search Co-ordinator will search the Trials Register of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group, which, among other sources, includes trials from the following.

- Cochrane Central Register of Controlled Trials (CENTRAL) (2016, most recent issue).
- MEDLINE (PubMed) (1966 to date).
- EMBASE (EMBASE.com) (1974 to date).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost) (1981 to date).
- Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to date).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch).

Information on the Trials Register or the Review Group and details of the search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group module.

We have listed in Appendix 1 the keywords that we will use to search for trials for this review.

We will perform an expanded search to identify articles on non-randomised clinical trials in the following databases: MEDLINE (Appendix 2) and EMBASE (Appendix 3).

Searching other resources

- We will handsearch the reference lists of all retrieved articles, texts and other reviews on the topic.
- We will contact study authors and researchers active in this field to ask for additional data, if necessary.
- We will search FDA and EMA reports on all of the treatments included in this review.

Data collection and analysis

Selection of studies

We will use the search strategy described above to obtain titles and abstracts of studies that may be relevant to the review. Two teams of three review authors each (MC, MM and AS; OB, FP and GF) will assess titles and abstracts to identify relevant studies for inclusion. We will note studies and reviews that might include relevant data and will obtain the full text of these studies when necessary to confirm inclusion. We will include all completed RCTs, OLEs, CCTs, CHs and registries meeting the inclusion criteria listed above. We will link multiple publications of the same study as companion reports, but we will exclude true duplicates. We will resolve discrepancies in judgement by discussion between review authors.

Data extraction and management

The three review authors on each team will independently extract data using an Excel sheet that will be piloted on two articles. Review authors will resolve disagreements on extractions by discussion.

Outcome data

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

- had relapses or worsening of disability at 12, 24 or 36 months, or at the end of the study;
- discontinued treatment for any reason during the study;
- withdrew because of any AE during the study; and
- had reported at least one SAE during the study.

We will extract arm-level data when possible and will extract effect sizes when not possible. When timing of outcome measures was not reported at selected time points, we will extract data as close as possible to that time point. When the number of withdrawals was not reported or was unclear in the primary study, we will rely on reports from the FDA or EMA, or we will ask the trial author to supply data.

Data on potential effect modifiers in RCTs

We will extract from each included RCT data on the following potential effect modifiers.

- Participants: age, baseline MRI eligibility criteria, monofocal or multi-focal first attack, proportion of participants treated with steroids at the first attack.
- Outcomes: definitions of relapse and disability worsening.
- Interventions: dose, frequency or duration of treatment.
- Risk of bias for each outcome: allocation concealment, blinding of participants and outcome assessors, incomplete outcome data.
- Study years (realisation).

Data on potential confounders in NRSs

- Differences between treated and untreated individuals at treatment start: age, disease duration, EDSS score, previous treatments.
- Type of analysis done to account for confounding (e.g. baseline confounding at the OLE phase, switch to other treatment during the OLE phase).

Assessment of risk of bias in included studies

RCTs

We will evaluate the risk of bias (RoB) of each included study using the tools of The Cochrane Collaboration for RCTs (Higgins 2011). These include random sequence generation, allocation concealment, blinding of personnel, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, evidence of major baseline imbalance and role of the sponsor. We will explicitly judge the RoB on each criterion as 'low', 'high' or 'unclear'. We will judge complete outcome data as having low RoB when numbers and causes of dropouts were balanced (i.e. in the absence of a significant difference) between arms. We will assess selective outcome reporting bias by comparing outcomes intended to be analysed using the published study protocol along with published study results. To summarise the quality of the evidence, we will consider allocation concealment, blinding of outcome assessors and incomplete outcome data to classify each study as having low RoB when all three criteria are judged as having low RoB; high RoB when at least one criterion is judged as having high RoB; unclear RoB when all three criteria are judged as having unclear RoB; and moderate RoB in remaining cases. Allocation concealment and blinding of outcome assessor are not expected to vary in importance across the two primary benefit outcomes (disability worsening and relapses), but incomplete outcome data might vary, and in that case we will summarise the RoB of each RCT by considering the two outcomes separately.

We will assess RoB for AEs by considering specific factors that may have a large influence on AE data. We will evaluate methods of monitoring and detecting AEs in each primary study: Did researchers actively monitor for AEs (low risk of bias), or did they simply provide spontaneous reporting of AEs that arose (high risk of bias)? Did study authors define AEs according to an accepted international classification and report the number of SAEs? (Singh 2011) We will report RoB for AEs in an additional table called 'Assessment of adverse events monitoring'.

The first team (MC, MM and AS) will independently assess the RoB of each RCT and will resolve disagreements by discussion to reach consensus.

Non-randomised studies (NRSs)

We will evaluate the RoB of each included study using the ROBINS-I tool for NRS (Sterne 2014) to provide the corresponding RoB (i.e. low/moderate/serious/critical/no information for each of the seven ROBINS-I domains including confounding, selection of participants into the study, classification of interventions, departures from intended interventions, missing data, measurement of outcomes and selection of reported results). We will provide the overall RoB judgement on the basis of four key domains: confounding, selection of participants, missing data and measurement of outcomes (i.e. blinding of outcome assessors). We will base the overall RoB judgement on the four key domains: low RoB if the study is judged to be at low RoB for all four key domains; moderate RoB if the study is judged to be at low or moderate RoB for all four domains; serious RoB if the study is judged to be at serious RoB for at least one of the four domains; critical if the study is judged to be at critical RoB for at least one of the four domains; and no information if no clear indication shows that the study is at serious or critical RoB and information for one or more of the four domains is lacking.

Other potential RoB, including that for AEs, is the same as in RCTs. The second team of review authors (OB, FP and GF) will independently assess RoB for each NRS and will resolve disagreements by discussion to reach consensus.

Measures of treatment effect

We will estimate treatment effects from each study using risk ratios (RRs) for binary data. We will also estimate hazard ratios or cumulative probability at the end of follow-up on the basis of Kaplan-Meier for each arm, or the crude probability (%) as the number of people with disability worsening and the number of randomised participants in each arm. We will estimate, through pairwise meta-analysis, treatment effects of competing interventions by using RRs with 95% confidence intervals (95% CIs) for each outcome at each time point. We will present results from network meta-analysis as summary relative effect sizes (RRs) for each possible pair of treatments.

Unit of analysis issues

Cluster and cross-over trials have not been carried out to evaluate DMDs for MS. We will perform separate analyses for participants who had relapses at 12, 24 or 36 months, or at the end of the study, and disability worsening at 24 or 36 months, or at the end of the study.

For multi-arm trials, intervention groups will be all those that can be included in a pairwise comparison of intervention groups, which, if investigated alone, would meet the inclusion criteria. For example, if a study compares 'interferon beta versus natalizumab versus interferon beta plus natalizumab', only one comparison ('interferon beta vs natalizumab') addresses the review objective, and no comparison involving combination therapy does this. However, if the study compares 'interferon beta-1b versus interferon beta-1a (Rebif) versus interferon beta-1a (Avonex)', all three treatment groups are relevant to the review. In this case, we will treat the multi-arm studies as multiple independent two-arm studies in pairwise meta-analysis; we will account for the correlation between effect sizes from multi-arm studies in the network meta-analysis. We will convert multi-arm trials involving the same drug at different doses compared with a control treatment

to a single arm by merging doses and summing the number of events and the sample size.

Dealing with missing data

To assess the effect of missing outcome data, we will analyse data according to a likely scenario (i.e. we will assume that both treated and control group participants who contributed to missing outcome data had an unfavourable outcome (relapse or disability worsening)).

Assessment of heterogeneity

To assess clinical heterogeneity within pairwise treatment comparisons, we will use data on potential effect modifiers in RCTs and data on potential confounders in NRSs and will compare them for each pair of interventions.

The transitivity assumption underlying NMA claims that treatment effects for A versus B estimated directly (in A vs B studies) or indirectly (by combining A vs C and B vs C studies) are in agreement. Transitivity holds when the distributions of potential effect modifiers are balanced across all pairwise comparisons (Salanti 2012); in such cases, direct and indirect evidence can be combined. We will compare the distribution of potential effect modifiers across different pairwise comparisons to assess transitivity across treatment comparisons (Cipriani 2013). If transitivity is deemed defendable, we will consider an NMA appropriate to synthesise the data.

Assessment of reporting biases

We will evaluate the possibility of reporting bias by using a contour-enhanced funnel plot for active interventions versus placebo. The plot indicates areas of statistical significance and helps to distinguish reporting bias from other possible reasons for funnel plot asymmetry (Chaimani 2013; Peters 2008).

Data synthesis

We will first perform standard pairwise meta-analyses using a random-effects model for every treatment comparison with at least two studies. Then, we will perform NMA in a frequentist context by using a random-effects model. We will present the results of NMA by using league tables and forest plots (Chaimani 2013).

To present trade-offs between benefit and safety, we will use two-dimensional plots. For each active intervention, we will present its average benefit for relapses and disability worsening versus its safety.

We will conduct the pairwise meta-analysis in Review Manager (RevMan 2016), and the NMA in STATA v13.

Subgroup analysis and investigation of heterogeneity

We will estimate different heterogeneity variances for each pairwise comparison evaluated in standard pairwise meta-analyses, and we will assess the presence of statistical heterogeneity by visually inspecting the forest plots and by calculating the I^2 statistic (Higgins 2003). In NMA, we will assume a common estimate for the heterogeneity variance across comparisons and will base the assessment of statistical heterogeneity in the entire network on the magnitude of the common heterogeneity parameter (Rhodes 2015; Turner 2012).

We will evaluate statistical disagreements between direct and indirect effect sizes (inconsistency) by using the 'design-by-treatment' Q-statistic (Higgins 2012). We will conduct all analyses in STATA v13 (White 2011). In the presence of moderate heterogeneity and/or inconsistency, we will explore the impact of potential study and patient-level co-variates using network meta-regression and subgroup analysis. Potential sources of heterogeneity and inconsistency include baseline mean age, monofocal or multifocal first attack, definitions of relapse and disability worsening, dose, frequency or duration of treatment, calendar year of study realisation and risk of bias.

Sensitivity analysis

We do not anticipate performing a sensitivity analysis.

'Summary of findings' table

We will present the main results of the review in a 'Summary of findings' (SoF) table. We will present a judgement about the credibility of evidence, inspired by the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) method (Puhan 2014; Salanti 2014), for three patient-important outcomes: relapses, disability worsening and proportion of participants with at least one SAE. We will transform risk ratios to absolute treatment effects.

REFERENCES

Additional references

Active Biotech 2014

Active Biotech. Teva and Active Biotech remain committed to the development of NERVENTRA® (laquinimod) for multiple sclerosis following the negative opinion from the EMA's CHMP. http://www.activebiotech.com/press-releases-1?pressurl=http://cws.huginonline.com/A/1002/PR/201401/1756936.xml. (accessed 13 April 2016).

Aharoni 2014

Aharoni R. Immunomodulation neuroprotection and remyelination. The fundamental therapeutic effects of glatiramer acetate: a critical review. *Journal of Autoimmunity* 2014;**54**:81-92.

Biogen 2015b

Biogen. FDA accepts biologics license application for ZINBRYTA (Daclizumab High-Yield Process) for treatment of MS. Biogen, 29 Apr 2015. http://biogen.newshq.businesswire.com/press-release/corporate/fda-accepts-biologics-license-application-zinbryta-daclizumab-high-yield-pro (accessed 13 April 2016).

Broadley 2014

Broadley SA, Barnett MH, Boggild M, Brew BJ, Butzkueven H, Heard R, et al. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective: part 3 treatment practicalities and recommendations. MS Neurology Group of the Australian and New Zealand Association of Neurologists. *Journal of Clinical Neuroscience* 2014;**21**(11):1857-65.

Chaimani 2013

Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in Stata. *PLoS One* 2013;**8**(10):e76654.

Chun 2010

Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. *Clinical Neuropharmacology* 2010;**33**(2):91-101.

Cipriani 2013

Cipriani A, Higgins JPT, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Annals of Internal Medicine* 2013;**159**(2):130-7.

Claussen 2012

Claussen MC, Korn T. Immune mechanisms of new therapeutic strategies in MS: teriflunomide. *Clinical Immunology* 2012;**142**:49-56.

Colombo 2014

Colombo C, Mosconi P, Confalonieri P, Baroni I, Traversa S, Hill SJ, et al. Web search behavior and information needs of people with multiple sclerosis: focus group study and analysis of online postings. *Interactive Journal of Medical Research* 2014;**3**(3):e12.

Colombo 2016

Colombo C, Filippini G, Synnot A, Hill S, Guglielmino R, Traversa S, et al. Development and assessment of a website presenting evidence-based information for people with multiple sclerosis: the IN-DEEP project. *BMC Neurology* 2016;**16**(1):30.

Comi 2001

Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernández O, et al. Early Treatment of Multiple Sclerosis Study Group. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet* 2001;**357**:1576-82.

Comi 2012

Comi G, Jeffery D, Kappos L, Montalban X, Boyko A, Rocca MA, et al. Placebo-controlled trial of oral laquinimod for multiple sclerosis. *New England Journal Medicine* 2012;**366**(11):1000-9.

EMA 2006

European Medicines Agency. Committee for proprietary medicinal products European public assessment report: Tysabri. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000603/wapp/Post-authorisation/human_wapp_000166.jsp&mid=WC0b01ac058001d128 (accessed June 2015).

EMA 2011

European Medicines Agency. Committee for proprietary medicinal products European public assessment report: Gilenya. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002202/human_med_001433.jsp&mid=WC0b01ac058001d124 (accessed June 2015).

EMA 2013a

European Medicines Agency. Committee for proprietary medicinal products European public assessment report: Aubagio. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002514/human_med_001645.jsp&mid=WC0b01ac058001d124 (accessed 13 April 2016).

EMA 2013b

European Medicines Agency. Committee for proprietary medicinal products European public assessment report: Lemtrada. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003718/human_med_001678.jsp&mid=WC0b01ac058001d124 (accessed 13 April 2016).

EMA 2014a

European Medicines Agency. Committee for proprietary medicinal products European public assessment report: Tecfidera. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002601/human_med_001657.jsp&mid=WC0b01ac058001d124 (accessed 13 April 2016).

EMA 2014b

European Medicines Agency. Committee for proprietary medicinal products European public assessment report: Plegridy. http://www.ema.europa.eu/docs/en˙GB/document˙library/EPAR-Summary˙for˙the˙public/human/002827/WC500170305.pdf (accessed 13 April 2016).

EMA 2014c

European Medicines Agency. Refusal of the marketing authorisation for Nerventra (laquinimod). http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002546/WC500160120.pdf (accessed 13 April 2016).

EMA 2015a

European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/771815/2011, Rev. 2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500185161.pdf (accessed 13 April 2016).

EMA 2015b

European Medicines Agency. Refusal of the marketing authorization for Movectro (cladribine): outcome of re-examination. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/001197/WC500101072.pdf (accessed 13 April 2016).

EMA 2016

EMA. Marketing authorisation for the medicinal product Zinbryta. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003862/smops/Positive/human_smop_000970.jsp&mid=WC0b01ac058001d127 (accessed 30 April 2016).

Faria 2015

Faria R, Hernandez Alava M, Manca A, Wailoo AJ. Nice Dsu technical support document 17: the use of observational data to inform estimates of treatment effectiveness in technology appraisal: methods for comparative individual patient data. http://www.nicedsu.org.uk/TSD17%20-%20DSU%20Observational%20data%20FINAL.pdf (accessed 9 May 2016).

FDA 2000

U.S. Food, Drug Administration. Mitoxantrone (Novantrone) Product Approval Information - Licensing Action 2000. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=MITOXANTRONE%20HYDROCHLORIDE (accessed 13 April 2016).

FDA 2006

U.S. Food, Drug Administration. FDA approves resumed marketing of Tysabri under a special distribution program. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108662.htm (accessed 13 April 2016).

FDA 2010

U.S. Food, Drug Administration. Gilenya (Fingolimod) Product Approval Information 2010. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=022527&DrugName=GILENY (accessed 13 April 2016).

FDA 2012

U.S. Food, Drug Administration. Aubagio (Teriflunomide) Product Approval Information 2012. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails (accessed 13 April 2016).

FDA 2012a

U.S. Food, Drug Administration. AVONEX® (interferon beta-1a) intramuscular injection. Prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103628s5191lbl.pdf (accessed 13 April 2016).

FDA 2012b

U.S. Food, Drug Administration. Betaseron® (interferon beta-1b). Prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103471s5063s5067s5079s5088s5120s5124s5136s5138lbl.pdf (accessed 13 April 2016).

FDA 2013

U.S. Food, Drug Administration. COPAXONE® (glatiramer acetate injection) solution for subcutaneous injection. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020622s087lbl.pdf (accessed 13 April 2016).

FDA 2014a

U.S. Food, Drug Administration. Alemtuzumab (Lemtrada) Product Approval Information. Licensing action 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103948s5139lbl.pdf (accessed 13 April 2016).

FDA 2014b

U.S. Food, Drug Administration. Peginterferon beta-1a (Plegridy) Product Approval Information. Licensing action 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125499lbl.pdf (accessed 13 April 2016).

Fox 2004

Fox E. Mechanism of action of mitoxantrone. *Neurology* 2004;**12**:15-8.

Freedman 2014

Freedman MS, Comi G, De Stefano N, Barkhof F, Polman CH, Uitdehaag BM, et al. Moving toward earlier treatment of multiple sclerosis: findings from a decade of clinical trials and implications for clinical practice. *Multiple Sclerosis and Related Disorders* 2014;**3**(2):147-55.

Frischer 2009

Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. *Brain* 2009;**132**:1175-89.

Giovannoni 2010

Giovannoni G, Comi G, Cook S. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *New England Journal Medicine* 2010;**362**:416-26.

Goodin 2002

Goodin DS, Frohman EM, Garmany GP Jr, HalperJ, Likosky WH, Lublin FD, et al. Disease modifying therapies in multiple sclerosis: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002;**58**(2):169-78.

Hauser 2008

Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *New England Journal Medicine* 2008;**358**:676–88.

Hauser 2015

Hauser SL, Comi GC, Hartung HP, Selmaj K, Traboulsee A, Bar-Or A, et al. Efficacy and safety of ocrelizumab in relapsing multiple sclerosis - results of the interferon-beta-1a-controlled, double-blind, Phase III OPERA I and II studies. ECTRIMS Online Library. 2015; Vol. 116634.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Higgins 2012

Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**:98-110.

Hill 2012

Hill S, Filippini G, Synnot A, Summers M, Beecher D, Colombo C, et al. Presenting evidence-based health information for people with multiple sclerosis: the IN-DEEP project protocol. *BMC Medical Informatics and Decision Making* 2012;**12**:20.

Hu 2012

Hu X, Miller L, Richman S, Hitchman S, Glick G, Liu S, et al. A novel PEGylated interferon beta-1a for multiple sclerosis: safety, pharmacology, and biology. *Journal of Clinical Pharmacology* 2012;**52**:798-808.

Kappos 2011

Kappos L, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, Yin M, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet* 2011;**378**(9805):1779-87.

Kieseier 2011

Kieseier BC. The mechanism of action of interferon-β in relapsing multiple sclerosis. *CNS Drugs* 2011;**25**:491-502.

Kinkel 2012

Kinkel RP, Dontchev M, Kollman C, Skaramagas TT, O'Connor PW, Simon JH, et al. Association between immediate initiation of intramuscular interferon beta-1a at the time of a clinically isolated syndrome and long term outcomes: a 10-year follow-up of the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance. *Archives of Neurology* 2012;**69**:183-90.

Kurtzke 1983

Kurtzke J. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983;**33**:1444-52.

Leist 2011

Leist TP, Weissert R. Cladribine: mode of action and implications for treatment of multiple sclerosis. *Clinical Neuropharmacology* 2011;**34**:28-35.

Leist 2014

Leist TP, Comi G, Cree BA, Coyle P, Freedman M, Hartung HP, et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. *Lancet Neurology* 2014;**13**(3):257–67.

Linker 2011

Linker RA, Lee DH, Ryan S, van Dam AM, Conrad R, Bista P, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. *Brain* 2011;**134**:678-92.

Lycke 2015

Lycke J. Monoclonal antibody therapies for the treatment of relapsing-remitting multiple sclerosis: differentiating mechanisms and clinical outcomes. *Therapeutic Advances in Neurological Disorders* 2015;**8**(6):274-93.

McDonald 2001

McDonald W, Compston A, Edan G, Goodkin D, Hartung H, Lublin F, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. *Annals of Neurology* 2001;**50**(1):121–7.

Millard 2011

Millard M, Odde S, Neamati N. Integrin targeted therapeutics. *Theranostics* 2011;**1**:154-88. [DOI: 10.7150/thno/v01p0154]

Montalban 2015

Montalban X, Hemmer B, Rammohan K, Giovannoni G, de Seze J, Bar-Or A, et al. Efficacy and safety of ocrelizumab in primary progressive multiple sclerosis - results of the placebo-controlled, double-blind, Phase III ORATORIO study. ECTRIMS Online Library. 2015; Vol. 116701.

Murphy 2010

Murphy JA, Harris JA, Crannage AJ. Potential short-term use of oral cladribine in treatment of relapsing-remitting multiple sclerosis. *Neuropsychiatric Disease and Treatment* 2010;**6**:619-25.

Naismith 2010

Naismith R, Piccio L, Lyons J, Lauber J, Tutlam N, Parks B, et al. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. *Neurology* 2010;**74**(23):1860–7.

NHS England 2014

NHS England Clinical Reference Group for Neurosciences. Clinical commissioning policy: disease modifying therapies for patients with multiple sclerosis (MS). http://www.england.nhs.uk/wp-content/uploads/2013/10/d04-p-b.pdf (accessed 13 April 2016). [http://www.england.nhs.uk/wp-content/uploads/2013/10/d04-p-b.pdf]

Oh 2013

Oh J, O'Connor PW. An update of teriflunomide for treatment of multiple sclerosis. *Therapeutics and Clinical Risk Management* 2013;**9**:177-90.

Pakpoor 2015

Pakpoor J, Disanto G, Altmann DR, Pavitt S, Turner BP, Marta M, et al. No evidence for higher risk of cancer in patients with multiple sclerosis taking cladribine. *Neurology Neuroimmunology & Neuroinflammation* 2015;**2**(6):e158.

Palace 2013

Palace J. Partnership and consent in MS treatment choice. *Journal of the Neurological Sciences* 2013;**335**:5-8.

Peters 2008

Peters J, Sutton A, Jones D, Abrams K, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *Journal of Clinical Epidemiology* 2008;**61**(10):991-6.

Polman 2005

Polman C, Reingold S, Edan G, Filippi M, Hartung H, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald criteria'. *Annals of Neurology* 2005;**58**:840–6.

Polman 2011

Polman C, Reingold S, Banwell B, Clanet M, Cohen J, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals Neurology* 2011;**69**(2):292-302.

Puhan 2014

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;**349**:g5630.

Reeves 2011

Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

RevMan 2016 [Computer program]

Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2016.

Rhodes 2015

Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *Journal of Clinical Epidemiology* 2015;**68**(1):52-60.

Salanti 2012

Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* 2012;**3**(2):80.

Salanti 2014

Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;**9**:e99682.

Scalfari 2013

Scalfari A, Neuhaus A, Daumer M, Deluca G, Muraro P, Ebers G. Early relapses, onset of progression, and late outcome in multiple sclerosis. *JAMA Neurology* 2013;**70**(2):214-22.

Schmied 2003

Schmied M, Duda PW, Krieger JI, Trollmo C, Hafler DA. In vitro evidence that subcutaneous administration of glatiramer acetate induces hyporesponsive T cells in patients with multiple sclerosis. *Clinical Immunology* 2003;**106**:163–74.

Schmitz 2013

Schmitz S, Adams R, Walsh C. Incorporating data from various trial designs into a mixed treatment comparison model. *Statistics in Medicine* 2013;**32**(17):2935-49.

Scolding 2015

Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Practical Neurology* 2015;**15**(4):273-9.

Singh 2011

Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, MacDonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD008794]

Stangel 1999

Stangel M, Toyka K, Gold R. Mechanisms of high-dose intravenous immunoglobulins in demyelinating diseases. *Archives of Neurology* 1999;**56**(6):661–3.

Sterne 2014

Sterne JAC, Higgins JPT, Reeves BC, on behalf of the Development Group for ACROBAT-NRSI. A Cochrane risk of bias assessment tool for non-randomized studies of interventions (ACROBAT-NRSI). Version 1.0.0, 24 September 2014. https://sites.google.com/site/riskofbiastool//home/resources (accessed 13 April 2016).

Synnot 2014

Synnot AJ, Hill SJ, Garner KA, Summers MP, Filippini G, Osborne RH, et al. Online health information seeking: how people with multiple sclerosis find, assess and integrate treatment information to manage their health. *Health Expectations* 2016;**19**(3):727-37.

Tiede 2003

Tiede I, Fritz G, Strand S, Poppe D, Dvorsky R, Strand D, et al. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. *Journal of Clinical Investigation* 2003;**111**:1133–45.

Tramacere 2015

Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD011381]

Turner 2012

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal o f Epidemiology* 2012;**41**(3):818-27.

Varrin-Doyer 2014

Varrin-Doyer M, Zamvil SS, Schulze-Topphoff U. Laquinimod, an up-and-coming immunomodulatory agent for treatment of multiple sclerosis. *Experimental Neurology* 2014;**262**:66-71.

Verde 2015

Verde PE, Ohmann C. Combining randomized and non-randomized evidence in clinical research: a review of methods and applications. *Research Synthesis Methods* 2015;**6**:45-62.

Vollmer 2014

Vollmer TL, Sorensen PS, Selmaj K, Zipp F, Havrdova E, Cohen JA, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. *Journal of Neurology* 2014;**261**(4):773-83.

White 2011

White IR. Multivariate random-effects meta-regression: updates to mvmeta. *Stata Journal* 2011;**11**(2):255-70.

Wilms 2010

Wilms H, Sievers J, Rickert U, Rostami-Yazdi M, MrowietzU, Lucius R. Dimethyl fumarate inhibits microglial and astrocytic inflammation by suppressing the synthesis of nitric oxide, IL-1beta, TNF-alpha and IL-6 in an in-vitro model of brain inflammation. *Journal of Neuroinflammation* 2010;**7**:30.

Wingerchuk 2014

Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. *Mayo Clinic Proceedings* 2014;**89**:225-40.

Wuest 2011

Wuest SC, Edwan JH, Martin JF, Han S, Perry JS, Cartagena CM, et al. A role for interleukin-2 trans-presentation in dendritic cell-mediated T cell activation in humans, as revealed by daclizumab therapy. *Nature Medicine* 2011;**17**(5):604-9.

APPENDICES

Appendix 1. Keywords

clinically isolated syndrome* OR first demyelinating event* OR first demyelinating episode OR first demyelinating attack OR First event OR first episode OR first clinical episode OR single clinical episodes OR first demyelinating event* OR clinically isolated syndrome*

Appendix 2. MEDLINE

((((((((((((((((((("clinically isolated syndrome*"[Title/Abstract]) OR cis"[Title/Abstract]) OR "first demyelinating event*"[Title/Abstract]) OR "first demyelinating episode"[Title/Abstract]) OR "first demyelinating attack"[Title/Abstract]) OR First event[Title/Abstract]) OR "first episode"[Title/Abstract] OR "first clinical episode"[Title/Abstract] OR "single clinical episodes"[Title/Abstract])))))) OR first demyelinating event*[Text Word]) OR clinically isolated syndrome*[Text Word]))

AND

((((((((((("Multiple Sclerosis"[Mesh:noexp]) OR ("Multiple Sclerosis/diagnosis"[Mesh:noexp] OR "Multiple Sclerosis/therapy"[Mesh:noexp])))) OR ("multiple sclerosis"[Title/Abstract]) OR "optic neuritis"[Title/Abstract]) OR "optic neuritis"[Title/Abstract])))) OR "early multiple sclerosis"[Title/Abstract]) OR "early stage multiple sclerosis"[Title/Abstract] OR conversion to multiple sclerosis[Title/Abstract])))) OR early stage multiple sclerosis[Text Word]) OR conversion to multiple sclerosis[Text Word])

Appendix 3. EMBASE

#27 **#13** AND **#26**

#26 **#14** OR **#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25**

#25 **multiple** AND **sclerosis** NEAR/5 **treatment***

#24 **conversion** NEAR/5 **multiple** AND **sclerosis**

#23 **conversion** NEXT/5 **multiple** AND **sclerosis**

#22 **multiple** AND **sclerosis** NEAR/5 **early** AND **stage**

#21 **multiple** AND **sclerosis** NEAR/5 **early**

#20 **'early stage multiple sclerosis'**:ab,ti

#19 **'early multiple sclerosis'**:ab,ti

#18 **'optic neuritis'**:ab,ti

#17 **optic** AND **'neuritis'**/exp

#16 **'multiple sclerosis'**:ab,ti

#15 **multiple** AND **'sclerosis'**/exp

#14 **multiple** AND **'sclerosis'**/mj

#13 **#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12**

#12 **single** AND **clinical** AND **episode***:ab,ti

#11 **'single clinical episode'**:ab,ti

#10 **clinically** AND **isolated** AND **syndrome** NEAR/5 **first** AND **attack**

#9 **clinically** AND **isolated** AND **syndrome** NEAR/5 **first** AND **attack***

#8 **clinically** AND **isolated** AND **syndrome** NEAR/5 **first** AND **episode**

#7 **clinically** AND **isolated** AND **syndrome** NEAR/5 **first** AND **event***

#6 **first** AND **demylinating** AND **attack***:ab,ti

#5 **first** AND **demylinating** AND **episode**:ab,ti

#4 **first** AND **demylinating** AND **event***:ab,ti

#3 **clinically** AND **isolated** AND **syndrome*** NEAR/5 **cis**

#2 **'clinically isolated syndromes'**:ab,ti

#1 **'clinically isolated syndrome'**:ab,ti

CONTRIBUTIONS OF AUTHORS

Concept development - GF, MC, OB, SF, AS.

Title registration - All.

Drafting of protocol - GF, IT.

Editing of protocol - All.

DECLARATIONS OF INTEREST

GF - none. As Co-ordinating Editor, Dr. Filippini was excluded from the editorial process to ensure separation of the review author from the editorial process. This includes all editorial decisions and related activities (e.g. sign-off for publication).

MC - received personal compensation from Merck, Biogen, Novartis and Genzyme for serving on advisory boards and for providing expert testimony as well as for travel/ accommodations/meeting expenses. Dr. Clerico's institution received some grants for research projects from Merck.

OB - none.

MM - received financial support for travel/accommodations/meeting expenses from Biogen Idec, Novartis, Genzyme and Teva. This had no bearing on, and did not influence, what has been written in the submitted work.

FP - none.

CDG - none.

SF - received honoraria for consultancy, educational activities and/or lectures from Allergan, Bayer, Biogen, Genzyme, Merck, Novartis, Sanofi and Teva.

IT - none.

AS - none.

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INDEX TERMS

Medical Subject Headings (MeSH)

Adjuvants, Immunologic [adverse effects] [*therapeutic use]; Cladribine [adverse effects] [therapeutic use]; Cohort Studies; Crotonates [adverse effects] [therapeutic use]; Disease Progression; Glatiramer Acetate [adverse effects] [therapeutic use]; Immunosuppressive Agents [adverse effects] [*therapeutic use]; Interferon beta-1a [adverse effects] [therapeutic use]; Multiple Sclerosis [*drug therapy]; Publication Bias; Randomized Controlled Trials as Topic; Recurrence; Time Factors; Toluidines [adverse effects] [therapeutic use]

MeSH check words

Humans