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TABLE OF CONTENTS

[Intervention Protocol]

Rituximab for people with multiple sclerosis

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ABSTRACT

Objectives

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

The main objective is to assess the benefits and harms of rituximab compared to placebo or another DMT for people with multiple sclerosis.

Specific comparisons include:

- rituximab compared with placebo or other DMTs as first choice treatment for relapsing forms of MS;
- rituximab when switching from another DMT compared with placebo or other DMTs for relapsing forms of MS;
- rituximab compared with placebo or other DMTs as first choice treatment for progressive forms of MS; and
- rituximab when switching from another DMT compared with placebo or other DMTs for progressive forms of MS.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system. The global prevalence of MS is estimated at 36 per 100,000 people, which means there are 2.8 million adults living with MS in the world (MSIF 2020). MS is present in all regions of the world, but prevalence is noticeably higher in Europe and the Americas (MSIF 2020). There are at least twice as many females (69%) with MS as there are males (31%) (MSIF 2020). MS can occur at any age, but the average age at which MS is diagnosed from from 30 to 33 years (MSIF 2020). MS is the most common neurological cause of disability for young adults (MSIF 2020).

MS is pathologically characterised by inflammation, demyelination, and axonal and neuronal loss. Clinically, it is characterised by recurrent relapses and worsening disability. In 1996, the clinical course of MS was classified as relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MS (PRMS) (Lublin 1996). These forms of MS were used to design trials of interventions over two decades. An updated classification of MS forms was produced in 2013 (Lublin 2014). The concept of disease activity was added, based on the presence of clinical relapse or new magnetic resonance imaging (MRI) lesions in the brain. The new classification included: (i) active or inactive relapsing MS, with or without worsening; and (ii) active or inactive primary or secondary progressive disease, with or without progression. Two new forms were also added: clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS). PRMS was no longer used in the updated classification (Lublin 2014). Worldwide, 85% of people with MS are initially diagnosed with RRMS and 12% with progressive MS. The remaining 3% are given an unknown disease type on diagnosis (MSIF 2020).

Description of the intervention

Rituximab is a chimeric monoclonal antibody and is approved for the treatment of adults with B cell non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's granulomatosis), microscopic polyarteritis and pemphigus vulgaris (FDA 2020a). Neurologists have used rituximab off-label to treat neuromyelitis optica (Damato 2016), myasthenia gravis (Banerjee 2018), autoimmune encephalitis (Nepal 2020), autoimmune neuropathies and myopathies (Fasano 2017), and multiple sclerosis (European Commission 2017; Sarsour 2020). This drug is marketed by Genentech-Biogen in the US under the brand name Rituxan, and by Roche in Europe under the brand name MabThera.

Rituximab is administered by intravenous infusion at single doses of 500 mg or 1000 mg, two weeks apart. The maintenance dose is 500 mg or 1000 mg every six to 12 months. The alternative induction dose, or in cases of disease breakthrough, is 375 mg/m^2 every week for four weeks. However, a treatment protocol has not yet been established; induction and maintenance doses may change based on the type of MS, MRI lesion load, clinical response and CD19 or C20 cell counts. The summary of product characteristics states that rituximab should be administered under the close supervision of an experienced physician. Serum rituximab's half-life is reported to be 76.3 hours (Maloney 1997).

The most frequently observed short-term adverse events in people receiving rituximab are infusion-related reactions (Caldito 2020; FDA 2020a). The majority of these reactions occur during the first infusion or within 24 hours of the infusion. The final report of the Rheumatoid Arthritis Global Clinical Trial Program, based on over 11 years' follow-up, reported that rituximab remained well tolerated over time and for multiple courses (van Vollenhoven 2015). Under long-term therapy with B-cell-depleting drugs, and with alternative immunomodulatory agents for MS, immunoglobulin deficiency syndromes can occur that may be associated with severe infections (Caldito 2020; Hallberg 2019; Luna 2020; Tsao 2019; van Vollenhoven 2015). Hepatitis B virus (HBV) reactivation following chemotherapy that includes rituximab has been reported in people who have either had hepatitis B or are a carrier of HBV (Evens 2011; Pourcher 2020). Progressive multifocal leucoencephalopathy (PML), a rare but serious brain infection caused by a virus, can occur in rituximab-treated people with hematologic malignancies or with autoimmune diseases. The majority of people with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant (FDA 2020a). People with autoimmune diseases diagnosed with PML had prior or concurrent immunosuppressive therapy (Berger 2018; FDA 2020a). Most cases of PML were diagnosed within 12 months of their last infusion of rituximab (FDA 2020a). Rituximab is listed as having "no or very low risk for PML" by Yukitake 2018. Cardiac and vascular events (hypotension, hypertension, arrhythmias and angina) have been reported with rituximab (Caldito 2020). Two registry studies in Sweden showed no evidence of an increased risk of cancer with rituximab use, either in 3585 people with rheumatic disease (Wadstrom 2017), or using evidence from 4187 people with MS (Alping 2020). However, the results of the Caldito 2020 study showed an association between malignant melanoma and breast cancer with rituximab use. The authors of those studies suggested that these findings warrant further evaluation in the context of cancer epidemiology. Most of the available data relating to rituximab and pregnancy suggests that the majority of pregnancies occurred more than 12 months after the woman's last rituximab treatment. No increased rates of deformities have been observed so far (Chakravarty 2011; Das 2018; Kümpfel 2019; Smith 2020).

Several national and international guidelines on the use of DMTs have been produced since the 2013 classification of MS forms. Common to all guidelines is a moderate or low level of evidence available to assign strength to treatment recommendations, because there were few studies that directly compared different DMTs or assessed the sequential use of specific DMT combinations (Table 1). Recommendations vary among guidelines concerning specific drugs, reflecting — among other things — the differences in regulatory agencies' recommendations and different regional or local health policies. For example, azathioprine is approved in Germany (DGN 2020) and the American guideline (Rae-Grant 2018) contains a specific recommendation on the off-label use of azathioprine for people who, for financial or geographical reasons, do not have access to approved DMTs. The European guideline does not include off-label recommendations (Montalban 2018), as regulations on this topic vary broadly between different European countries. For example, the use of rituximab in the clinical setting has increased rapidly within Sweden for treating relapsing MS, since under existing Swedish free right to prescription provisions, the treating hospital, rather than the pharmaceutical company,

assumes responsibility and the liabilities associated with off-label rituximab use (Spelman 2018). The data from the national Swedish MS registry showed an increasing prescription rate of rituximab in relation to other DMTs during the years 2011 to 2016 for the nation of Sweden. In June 2017, the proportion of patients starting rituximab treatment among all patients who initiated a DMT treatment was as high as 53.3% (Berntsson 2018). This rapid escalation was secondary to both a perceived effectiveness advantage and a marked reduction in the overall costs of treatment, relative to interferons or new DMTs (Salzer 2016; Spelman 2018). Rituximab is recommended by the Middle East and North Africa Committee (MENACTRIMS) Consensus as an off-label treatment for highly active MS and as an escalation therapy for all levels of MS activity in special populations, such as refugees, or in countries where other appropriate options are not available (Yamout 2020) (Table 1).

In recent years, there has been a rapidly-evolving change in definitions of MS forms. The Food and Drug Administration (FDA) approved oral siponimod (FDA 2019a) and oral ozanimod (FDA 2020b) for CIS, RRMS and active SPMS (aSPMS), and approved oral cladribine for RRMS and aSPMS (FDA 2019b). These FDA approvals allowed people with SPMS to be treated with DMTs for the first time.

How the intervention might work

The inflammation in the central nervous system in MS stems from complex interactions between T cells and antigen-presenting cells, such as B cells and myeloid cells (macrophages, dendritic cells and microglia) (Comi 2021; Zhong 2020). The pro-inflammatory role of B cells in MS involves antigen presentation to activate pathogenic T cells and macrophages, production of pro-inflammatory cytokines, formation and maintenance of ectopic lymphoid organs in the central nervous system (Greenfield 2018; Hauser 2015; Sabatino 2019). B cells are highly selective for antigens bound to their cell receptor (BCR) (Greenfield 2018). The antigen-BCR complex is internalised and processed, its constituent peptides are then complexed with the major histocompatibility complex (MHC) class II molecules, and the antigen-MHC complex is transported to the cell surface where it can activate T cells (Th1 and Th17) by involvement of the T cell receptor and costimulatory molecules (Batista 2009). In MS, priming of T cells is caused by autoreactive B cells that demonstrate higher levels of antigen-presenting activity compared to B cells of healthy controls or individuals with other neuroinflammatory diseases (Jelcic 2018; Mathias 2017). The binding of autoantigen to BCR also causes aberrant B cells to produce pro-inflammatory and regulatory cytokines. B cells of people with MS cultured in vitro have been found to secrete higher levels of pro-inflammatory cytokines and lower levels of regulatory cytokines (Bar-Or 2010; Duddy 2007). In the milieu of pro-inflammatory cytokines, chemokines and lymphotoxin signalling, B cells support the development of ectopic B-cell follicles that have been detected in the meninges of people with secondary progressive MS (Serafini 2004).

Rituximab binds selectively to the CD20 antigen expressed on the surface of pre-B cells, mature and memory B cells and some plasmablasts, but not B cell progenitors (pro-B cells) and differentiated plasma cells, i.e. B cells that do not express CD20 (Greenfield 2018; St Clair 2010). Therefore, administration of rituximab causes selective loss of circulating and tissue-based B cells that are responsible for antigen presentation and cytokine production, without affecting B cell reconstitution or pre-existing humoral immunity. Mechanisms of B cell lysis include primarily complement-dependent cytotoxicity (CDC) but also antibody-dependent cellular cytotoxicity (ADCC) (Greenfield 2018).

Rituximab was detectable in the serum of people three to six months after completion of treatment (FDA 2020a). Following intravenous administration of rituximab, B lymphocytes typically remain depleted in peripheral blood for six to nine months (Greenfield 2018; Roll 2006). In non-blood tissues, including the central nervous system, the extent and duration of depletion is not fully known but is likely to be partial, to depend on the dose, and to be modulated by individual factors such as genetic background (Greenfield 2018).

Why it is important to do this review

Rituximab is not officially approved for the treatment of MS, but its off-label use for relapsing form of MS is widely used in high- medium- and low-income countries (Bourdette 2016). Several published observational data have strengthened the evidence for its effectiveness and safety in MS, and reported a discontinuation rate that is lower than that of other DMTs (Granqvist 2018; Salzer 2016). The identification of benefits and harms of rituximab for both relapsing MS and progressive forms of MS, including switching drug regimens, increases this review's importance and novelty for implementing cost-effective treatments that target advancing disability.

Given that the period of patent protection of rituximab has expired, it is extremely unlikely that a registration trial of this treatment for MS will ever been undertaken (Greenfield 2018). Therefore, evidence on benefit and harms of rituximab for MS will not be provided by randomised trials. Considering that rituximab is widely used as off-label treatment in people with MS, we have a duty to people with MS, practitioners and policy makers to do our best to provide these groups with a summary of available evidence that includes non-randomised studies, albeit qualified with a certainty assessment (Reeves 2019).

Ocrelizumab, an anti-CD20 monoclonal antibody similar to rituximab, has been approved as a treatment for primary progressive and relapsing MS, but ocrelizumab is not available in low-income countries due to prohibitive costs. Rituximab is a relatively inexpensive treatment, cheaper than any other approved disease-modifying drugs for MS, and it is a feasible option in resource-limited settings (Mathew 2020). With increasing incidence and prevalence of multiple sclerosis globally, especially in low and middle-income countries, it is essential to ensure that people with MS have timely access to safe and effective treatments (Lancet Neurology 2019).

OBJECTIVES

The main objective is to assess the benefits and harms of rituximab compared to placebo or another DMT for people with multiple sclerosis.

Specific comparisons include:

- rituximab compared with placebo or other DMTs as first choice treatment for relapsing forms of MS;

- rituximab when switching from another DMT compared with placebo or other DMTs for relapsing forms of MS;
- rituximab compared with placebo or other DMTs as first choice treatment for progressive forms of MS; and
- rituximab when switching from another DMT compared with placebo or other DMTs for progressive forms of MS.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel randomised controlled trials (RCTs) and controlled non-randomised studies of interventions (NRSIs) of between-group design, i.e. open-label extension (OLE) studies, controlled clinical trials, controlled cohort studies, regression discontinuity designs, case-control studies and registries. There are two main justifications for including NRSIs in the review. First, to provide evidence of the effects (benefit and harm) of rituximab for which only a small number of RCTs is available. Second, to address long-term outcomes and different populations that are typical of real-world practice. We will exclude studies of within-group design, e.g. before-after (pre-post) studies with no control group, interrupted time series and case reports.

We will not apply any limitation with respect to study outcomes, the length of follow-up or methods of analysis. We will include full-text publications, results published in non-commercial trial registries (e.g. ClinicalTrials.gov record) and abstracts if sufficient information is available on study design, characteristics of participants, interventions and outcomes.

Types of participants

We will include adult participants (18 years or older), of either gender, who are treatment-naive or non-responsive to their current DMT. We will accept any definition of non-response that was used in the included studies because the criteria for treatment failure, either using clinical or imaging criteria, are still not agreed upon and different criteria are used in clinical routine practice. Diagnostic criteria for MS are the Poser criteria (Poser 1983), and the McDonald criteria and its revisions (McDonald 2001; Polman 2005; Polman 2011; Thompson 2018). We will include all types of MS, i.e. relapsing MS, secondary progressive MS and primary progressive MS, regardless of disease duration and disability degree according to the Expanded Disability Status Scale (EDSS) (Kurtzke 1983).

Types of interventions

The intervention of interest is rituximab, as monotherapy or in combination treatments, irrespective of doses, timing, and frequency of treatment. We will include combination treatments only if they were used in all the comparison groups. We will include studies comparing rituximab with placebo or with approved DMTs, interferon, peg interferon, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, cladribine, alemtuzumab, daclizumab, or ocrelizumab. We will include studies that assessed switching to rituximab from another DMT compared to placebo or any other DMT, independently of the reason for switching, method or the time when the switch was made.

Types of outcome measures

We will include short- and long-term outcomes reported in the included studies.

Primary outcomes

- Disability: number of participants with sustained disability worsening based on clinical follow-up visits. Worsening is defined as at least a 1-point increase on the EDSS (Kurtzke 1983), or a 0.5-point increase if the baseline EDSS score was more than 5.5, confirmed during two consecutive clinical examinations separated by an interval of at least six months free of attacks and carried out by the same physician. EDSS is an ordinal scale, where a score of zero is no disability, three indicates mild disability, a score of six cane requirement, seven wheelchair use, and 10 is death from MS. An advantage of the EDSS over other disability measures is its international acceptance, e.g. by the European Medicines Agency (EMA) as a primary endpoint in clinical trials (EMA 2015), and its broad use in trials that enables cross-study comparisons (Meyer-Moock 2014).
- Relapse: number of participants with clinical relapse, based on clinical follow-up visits. '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 one month (McDonald 2001).
- Serious adverse events (SAEs): number of participants with SAEs, as defined by the authors of the study. If an insufficient number of studies report the total number of SAEs and person-years, we plan to use the number of participants with at least one SAE as defined in the study.

Secondary outcomes

- Annualised relapse rate (ARR): mean number of new relapses per participant, adjusted for the duration of follow-up to annualise it. ARR is a frequently-reported clinical outcome in trials on RRMS.
- Cognitive decline: number of participants with cognitive worsening, assessed according to validated neurocognitive batteries for MS, e.g. the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Benedict 2020; Langdon 2012).
- Quality of life impairment: number of participants reporting quality of life impairment, assessed according to validated measures, e.g. the Multiple Sclerosis Quality of Life-54 tool (MSQOL-54), which is a multidimensional health-related quality of life measure (Vickrey 1995). MSQOL-54 includes the generic Short-Form 36-item quality of life instrument, supplemented with 18 MS-specific items that were based on expert opinion and literature review. There is no single overall score for MSQOL-54. Two summary scores, physical health and mental health, can be derived from a weighted combination of scale scores (scale scores range from 0 to 100 and a higher scale score indicates improved quality of life).
- Number of participants with new or enlarging T2-weighted MRI lesions. A T2 MRI image provides information about the total number of lesions. T2 lesions appear as bright spots on the scan which indicate areas where the myelin sheath has been damaged or destroyed.

- Number of participants with new gadolinium-enhancing positive T1-weighted MRI lesions. A T1 MRI image provides information about current disease activity by highlighting areas of active inflammation.
- Number of participants who discontinued treatment due to adverse events.
- Number of participants with grade 3 and grade 4 adverse events (US Department of Health and Human Services 2017).
- Number of participants with long-term adverse events: common infections, opportunistic infections, hypogammaglobulinemia, cardiovascular events (hypotension, hypertension, arrhythmias and angina), HBV reactivation, cancer, death.
- Number of participants with short-term adverse events: infusion-related reactions.

Search methods for identification of studies

We will not apply any language restrictions to the search.

Electronic searches

We designed search strategies for electronic databases according to methods suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019). The Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System group's Information Specialist peer-reviewed them. We will search all potential relevant trials registries in detail to detect ongoing as well as completed studies, but not yet published studies.

We will search the following databases and sources.

Databases of medical literature

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (latest issue) (Appendix 1)
- MEDLINE (PubMed) (1966 to date) (Appendix 2)
- EMBASE (Embase.com) (1974 to date) (Appendix 3)
- CINAHL (EBSCOhost) (1981 to date)

Trials registries and registry platforms to identify ongoing studies and results of completed studies

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch)
- US National Institutes of Health clinical trial register (www.clinicaltrials.gov)
- European Union Clinical Trials Register (www.clinicaltrialsregister.eu)

Searching other resources

We will review the references of any RCTs and NRSIs identified, review articles, and textbooks. We will contact study investigators to request missing data.

Data collection and analysis

Selection of studies

We will use the search strategy described in the 'Search methods for identification of studies' section to obtain titles and abstracts of studies. Two review authors (DH and GF) will independently screen the titles and abstracts and discard studies that are not applicable; however, they will initially retain studies and reviews that might include relevant data or information on trials. Two review authors (DH and GF) will independently assess the retrieved abstracts and, when necessary, the full-text articles to determine which studies satisfy the inclusion criteria. The two review authors will compare multiple reports of the same study and use the most comprehensive report. They will link together multiple publications as companion reports, but exclude true duplicates. DH and GF will resolve discrepancies in judgement by discussion, and will report excluded studies and their reasons for exclusion in the 'Characteristics of excluded studies' table. We will report included studies in the 'Characteristics of included studies'. We will create a PRISMA flow chart reporting the selection process (Moher 2009).

Data extraction and management

Two review authors (DH and GF) will independently extract data using a predefined data extraction form in an Excel spreadsheet. They will resolve any disagreements by discussion. When necessary data are unavailable from the study report, we will try to obtain them through correspondence with the study authors.

Outcome data

We will extract the following data from each included study:

- number of participants who had a sustained disability worsening based on clinical follow-up visits;
- number of participants who had clinical relapses based on clinical follow-up visits;
- number who withdrew due to any adverse event; and
- measures and results of all important outcomes that were reported in the included studies.

We will extract the authors' definition and measure used in the study to assess each reported outcome. For continuous outcomes we will extract mean and standard deviation of the comparison groups, where possible. We will extract arm-level data when possible. When arm-level data are not available we will extract effect sizes. We will extract data at the authors' defined time points.

Other data

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

- study: first author or acronym; number of centres and location; study setting; year of publication; years that the study was conducted (recruitment and follow-up); publication (full-text publication, abstract publication, unpublished data);
- study design (RCT or NRSI); inclusion and exclusion criteria; number of randomised participants; withdrawals; early termination of trial;
- participants: age; sex; diagnostic criteria; type and duration of MS; important baseline data (EDSS score, percentage of participants with previous use of DMTs; MRI lesions);
- interventions: first choice or switching intervention, comparison, concomitant medications, duration of follow-up;
- conflict of interests of study authors; and
- funding of the study.

One review author (GF) will transfer data into the Review Manager Web software (Review Manager Web).

Assessment of risk of bias in included studies

For the scope of this review, we will assess the effect of assignment to the intervention ('intention-to-treat effect') for the primary and secondary beneficial outcomes, and for treatment discontinuation due to adverse events. For the numbers of participants with SAEs and further adverse events, we will assess the effect of adhering to the intervention ('per protocol effect').

Randomised controlled trials

Two reviews authors (DH and GF) will independently assess the risk of bias for each study result using the Cochrane criteria that include: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessor, incomplete outcome data, selective outcome reporting and other bias (Higgins 2017). We will assess both primary and secondary outcomes. We will judge the risk of bias of each outcome and classify it as being at 'low', 'high', or 'unclear' risk of bias. We will judge incomplete outcome data to be at low risk of bias when numbers and causes of dropouts are balanced between arms (i.e. in the absence of a significant difference) and appear to be unrelated to the outcome. We will assess selective outcome reporting bias by comparing outcomes reported in the study protocol against published outcome results. We will resolve any disagreements between the review authors by discussion.

Controlled non-randomised studies of interventions

Three reviews authors (DH, JK, GF) will independently assess the risk of bias using the Risk Of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool (Sterne 2016). Based on the inclusion and exclusion criteria for this review, we will define our generic target trial as rituximab versus placebo or versus other DMTs for the treatment of people with MS. Therefore, we will use the ROBINS-I analogue of starting experimental intervention versus starting control intervention to evaluate risk of bias.

The ROBINS-I tool includes the following bias domains: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of reported result. We will assign an overall risk of bias to each outcome based on the worst assessment across all bias domains using the recommended levels (low, moderate, serious or critical risk of bias, or no information) (Sterne 2016). We will resolve any disagreements between the review authors by discussion.

Baseline confounding by indication is likely to be the most frequent confounder in NRSIs that meet the inclusion criteria. For example, participants with high pretreatment MS activity are likely to be treated with a highly efficacious drug (e.g. fingolimod, natalizumab) whereas participants with low pretreatment MS activity are likely to be treated with a less powerful drug (e.g. interferon beta or glatiramer acetate). A cohort study comparing two or more DMTs for MS should control for baseline age, sex, MS duration, relapse within the previous year, EDSS score, MRI activity and proportion of participants previously treated with DMTs. All these variables are prognostic for the outcomes included in the review, and are also likely to influence choice of treatment. In some NRSIs, particularly those based on registries (i.e. routinely collected data), participants might have been observed for different follow-up periods due to differences in drug licensing and availability across different geographical and historical cohorts (Trojano 2017). This different follow-up period could confound the results, particularly regarding long-term outcomes. For each NRSI, we will record whether the study controlled for these important confounding domains and used an analysis method to reduce confounding.

Adverse events

We will assess adverse events according to methods suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Peryer 2020). We will extract data on the prespecified adverse events and the total number of withdrawals due to adverse events, along with any other adverse effects found in the included studies. We will evaluate each study's methods for monitoring and detecting adverse events by consideration of two questions: firstly, did researchers actively monitor for adverse events, or did they simply provide spontaneous reporting of adverse events that arose? Secondly, did study authors define serious adverse events according to an accepted international classification and report the number of serious adverse events? We will report answers to these questions in a table 'Assessment of adverse events monitoring, definition and reporting of serious adverse events'. We will use the resulting answers to assess the 'indirectness' GRADE domain.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

Randomised controlled trials

If available, we will extract and report hazard ratios (HRs) with 95% confidence intervals (95% CIs) for time-to-event outcomes (time to disability worsening, time to relapse and time to treatment discontinuation). For continuous outcomes (ARR, cognitive decline and quality of life), we will calculate the mean difference (MD), or the standardised mean difference (SMD) for the same continuous outcome measured with different metrics. We will back-calculate any results that we generate with an SMD based on scales that most closely reflect the outcome measure of interest to the review (as listed under Types of outcome measures). For dichotomous outcomes, we will report the risk ratio (RR) with a 95% CI. If the number of observed events is small (less than 5% of sample per group) and studies have balanced treatment groups, we will report the Peto odds ratio (OR) with 95% CI.

Controlled non-randomised studies of interventions

For time-to-event outcomes, if available, we will extract and report HRs with 95% CIs from statistical analyses adjusted for baseline difference (such as regression models). For dichotomous outcomes, if available, we will extract and report RRs with 95% CIs from statistical analyses adjusted for baseline differences (such as regression models). For continuous variables, if available, we will extract and report the difference between groups of the change from baseline, or the difference in score post intervention, derived from a statistical analysis adjusted for baseline differences (such as regression models, mixed models or hierarchical models).

Unit of analysis issues

Cluster-randomised trials and cross-over trials are not relevant to DMTs for multiple sclerosis.

Studies with multiple treatment groups

For multi-arm trials, the intervention groups of relevance will be all those that could be included in a pairwise comparison of intervention groups which, if investigated alone, would have met the criteria for including studies in the review. For example, if we identify a study comparing 'rituximab versus glatiramer acetate versus rituximab plus glatiramer acetate', we would only use one comparison ('rituximab versus glatiramer acetate'), since it addresses the review's objective. Thus, data from the 'rituximab plus glatiramer' treatment group is not relevant to the review. However, if the study compares 'rituximab versus glatiramer versus fingolimod', all three pairwise comparisons of interventions are relevant to the review. In this case, we will treat multi-arm studies as multiple independent two-arm studies. For 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 participants who had the event and calculating the merged sample size. For continuous outcomes, we will combine means and standard deviations using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Dealing with missing data

We will use data that reflect the intention-to-treat analysis (the effect of assignment) for each included outcome with the exception of adverse events, for which we will assess the risk of bias in relation to the effect of adherence (per protocol effect). We will attempt to retrieve missing data from study authors. In order to assess the effect of missing outcome data where not reported or provided, we will assume that treated and control group participants who are missing both had an unfavourable outcome. 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

We will quantify statistical heterogeneity using the I^2 statistic (Higgins 2003). We will interpret it using the following guide: I^2 statistic > 30% signifies moderate heterogeneity, I^2 statistic > 75% signifies considerable heterogeneity; Deeks 2019). When the I^2 statistic value is over 75%, we will explore possible reasons for this through subgroup and sensitivity analyses.

Assessment of reporting biases

Reporting bias

As specified in the Types of studies section, we will include results that are published in non-commercial trial registries. This is to ensure that we capture completed studies that have not been published elsewhere, in order to minimise or determine publication bias. We will include studies irrespective of their publication status, as recommended in *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2019). We will evaluate potential publication bias by means of funnel plots for meta-analyses involving at least 10 studies (Page 2019).

Selective non-reporting bias

We expect that most of the included NRSIs will not have an available protocol, and that even protocols for RCTs may lack an analysis plan. Therefore, we decided that if a study appears to be carried out appropriately and the authors are known and trustworthy, we will see if there is correspondence between the outcome measurements and analyses described in the Methods section of the published paper and those reported in the Results section.

Data synthesis

We will conduct an initial qualitative comparison of all the included studies to examine whether pooling of results (meta-analysis) will be reasonable. This will take into account differences in study populations, inclusion and exclusion criteria, interventions and outcome assessment. We will pool the results from included studies that report any of the outcomes of interest in meta-analyses. If we cannot perform meta-analyses, we will present the results from all included studies in tables and comment on the results as a narrative.

We will conduct separate analyses for RCTs and NRSIs. We will conduct separate analyses for relapsing and progressive forms of MS, and for 'first treatment' (treatment naive) and 'when switching from other DMTs' types of intervention. We will use the Review Manager Web software for analyses (Review Manager Web).

We will use a random-effects model for all analyses because we assume that the studies are not all estimating the same intervention effect, and are estimating intervention effects that follow a distribution across studies (DerSimonian 1986). For continuous outcomes, we will calculate MD or SMD, if the outcome is measured on different assessment scales (such as QOL), with 95% CIs. For dichotomous outcomes, we will use the Mantel-Haenszel method to calculate between-study variance. We will combine HRs and continuous outcomes using the inverse-variance method. If a meta-analysis is feasible for NRSIs, we plan to analyse the different types of studies separately. We plan to only analyse outcomes with adjusted effect estimates if these were adjusted for the same factors using the inverse-variance method, as recommended in Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2019).

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses of the following characteristics:

- participants: active or inactive relapsing MS
- participants: active or inactive primary or secondary progressive MS
- treatment comparison: placebo or each individual DMT

We will use the tests for interaction to test for differences between subgroup results.

Sensitivity analysis

We will assess the impact of studies that have results for critical and important outcomes that we judge to be at high or critical risk of bias, by removing them from the analysis. We will use the sensitivity analyses to inform the downgrading decisions relating to risk of bias. We will consider different assumptions relating to missing outcome as the basis for sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

We will present the main results of the review in 'Summary of findings' tables, according to recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of*

Interventions (Schünemann 2020). For the included NRSIs we will follow GRADE guidance 18, starting from high-certainty evidence with the opportunity to downgrade by three points for critical risk of bias (Schünemann 2019). For time-to-event outcomes we will calculate absolute effects at specific time points, as recommended in GRADE guidance 27 (Skoetz 2020). We will express the findings and certainty of the evidence as suggested in the informative statement guidance (Santesso 2020).

We plan to present four 'Summary of findings' tables addressing the following comparisons in relapsing or progressive MS.

- Rituximab as a first choice compared with other DMTs for relapsing MS
- Rituximab when switching from another DMT compared with other DMTs for relapsing MS
- Rituximab as a first choice compared with other DMTs for progressive MS
- Rituximab when switching from another DMT compared with other DMTs for progressive MS

We plan to assess the certainty of the evidence for the following main outcomes.

- Number of participants with sustained disability worsening
- Number of participants with clinical relapses
- Number of participant reporting impairment in quality of life
- Number of participants with SAEs
- Number of participants with common infections
- Number of participants with cancer
- Number of deaths

For any outcome which has both RCT and NRSI data, we will present the result with the higher grade of certainty in the 'Summary of findings' table.

In the 'Summary of findings' tables, we will prioritise long-term outcomes if they are available, otherwise we will include short-term outcomes. We will assess the certainty of evidence for each outcome considering the risk of bias, indirectness, inconsistency, imprecision of effect estimates, and risk of publication bias. Using GRADEpro GDT software (GRADEpro GDT), we will assign one of four levels of certainty of evidence: high, moderate, low, or very low.

We will include the following additional comparisons in the additional tables' section.

- Rituximab as a first choice compared with placebo for relapsing MS
- Rituximab when switching from another DMT compared with placebo for relapsing MS
- Rituximab as a first choice compared with placebo for progressive MS
- Rituximab when switching from another DMT compared with placebo for progressive MS

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ADDITIONAL TABLES

Table 1. Treatment guidelines for multiple sclerosis

	European ECTRIMS/EAN Guideline (Montalban 2018)	**American academy of neurology (AAN) practice guideline** (Rae-Grant 2018)	**Brazilian Consensus** (Marques 2018)	**The Middle East and North Africa Committee (MENACTRIMS) Consensus** (Yamout 2020)
Question 1	In people with CIS, what is the benefit of starting treatment with a DMT compared to no treatment?	In people with CIS, are DMTs superior to placebo in decreasing the risk of conversion to MS?	In people with CIS, are DMTs efficacious in preventing conversion to MS?	Should people with CIS be treated with DMTs?
Recommendation	Offer interferon or glatiramer acetate to people with CIS and an abnormal MRI with lesions suggestive of MS who do not fulfil criteria for MS.	a) Clinicians may recommend at least annual MRI for the first 5 years and follow-up rather than initiating DMT in people with CIS who have not had relapses in the preceding 2 years, and do not have active new MRI lesions on recent imaging. b) After discussing the risks and benefits, clinicians should prescribe DMT to people with CIS and 2 or more brain lesions characteristic of MS who decide they want this therapy.	It seems reasonable to start DMTs only in people with high-risk CIS[a] as well as to choose safer drugs. Efficacy in CIS has been demonstrated with the beta interferons, cladribine, glatiramer acetate, and teriflunomide. Since no direct comparison between these is available, any of these drugs are deemed appropriate	If the overall clinical and radiological picture is suggestive of MS, people with CIS and high MRI lesion load (> 9 T2 lesions), or with severe relapses with incomplete recovery, or both, should be treated.

Table 1. Treatment guidelines for multiple sclerosis *(Continued)*

			for the treatment of high-risk CIS[a].	
Quality of evidence	Strong	a) Level C: "may" b) Level B: "should"	Not reported	Not reported
Question 2	In people with RRMS, what is the benefit of treating with a DMT compared to no treatment or another DMT?	In people with RRMS, are DMTs superior to placebo or other DMTs in preventing relapse at 2 years, reducing MRI new disease activity, and preventing disease progression?	In people with relapsing MS, are DMTs efficacious in reducing relapses, MRI disease activity and disability?	Should people with RRMS be treated with DMTs?
Recommendation	a) Offer early treatment with DMTs to people with active RRMS[b] b) For active RRMS, choosing between the wide range of available DMTs, from the modestly effective to the highly efficacious, depends on individual characteristics and comorbidities, disease severity or activity, drug safety profile, and accessibility of the drug, in discussion with the person with active RRMS.	Clinicians should a) offer DMTs to people with RRMS with recent clinical relapses or MRI activity b) prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS[b] Clinicians may c) recommend azathioprine or cladribine for people with RRMS who do not have access to approved DMTs.	a) It would seem reasonable to start treatment with interferons, glatiramer acetate, pegylated interferon beta, dimethyl fumarate, or teriflunomide, (good safety profile and more easily available, including in the Brazilian public health system). b) Consider alemtuzumab, cladribine, fingolimod, natalizumab, and ocrelizumab for people with highly active relapsing MS[c].	a) In treatment-naive patients, interferons, glatiramer acetate, teriflunomide and dimethyl fumarate can be initiated. b) In people with highly active disease[d] fingolimod, siponimod, natalizumab, ocrelizumab, or cladribine may be initiated. c) In people with rapidly evolving aggressive disease[e] natalizumab, ocrelizumab or alemtuzumab are recommended after careful risk stratification. d) Rituximab can be used off label for highly active disease and rapidly evolving aggressive disease in special populations such as refugees, or in countries where other appropriate options are not available.
Quality of evidence	a) Strong b) Consensus statement	a, b) Level B: "should" c) Level C: "may"	Not reported	Not reported
Question 3	In people with active SPMS, what is the benefit of treating with a DMT compared to no	In people with SPMS, are DMTs efficacious?	In people with non-active SPMS, are DMTs efficacious?	Should people with SPMS be treated with DMTs?

Table 1. Treatment guidelines for multiple sclerosis *(Continued)*

	treatment or another DMT?			
Recommendation	Consider treatment with interferons, mitoxantrone, ocrelizumab or cladribine for people with active SPMS.	a) Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS[b]. b) Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses or MRI activity and have not been ambulatory (EDSS 7 or greater) for at least 2 years.	a) Not prescribing a DMT is an acceptable choice in people with SPMS who no longer present relapses. b) In cases of rapidly-progressive disease, cyclophosphamide, mitoxantrone, and autologous hematopoietic stem cell transplantation may be used as off-label treatments.	a) Consider treatment with ocrelizumab or siponimod in people with active SPMS, age ≤ 60 years and EDSS ≤ 6.5 (i.e. not wheelchair bound). b) In people with rapidly progressive SPMS not responding to ocrelizumab or siponimod or who have no access to these medications, cyclophosphamide, methotrexate, or mycophenolate may be warranted.
Quality of evidence	Weak	a) Level B: "should" b) Level C: "may"	Not reported	Not reported
Question 4	In people with PPMS, what is the benefit of treating with a DMT compared to no treatment?	In people with PPMS, are DMTs superior to placebo or other DMTs as measured by relapse rate or disease progression?	In people with PPMS, are DMTs efficacious in delaying the progression of disability?	Should people with PPMS be treated with DMTs?
Recommendation	Consider treatment with ocrelizumab for people with PPMS.	Clinicians should offer ocrelizumab to people with PPMS.	Ocrelizumab should be the treatment of choice for people with PPMS, after consideration of the expected benefits and potential risks on a case-by-case basis.	Consider treatment with ocrelizumab for people with PPMS, age ≤ 55 years, EDSS ≤ 6.5 (i.e. not wheelchair bound) and disease duration ≤ 10 to 15 years.
Quality of evidence	Weak	Level B: "should"	Not reported	Not reported
Question 5	a) In people with RRMS treated with interferon or glatiramer acetate and evidence of disease activity at 6 or 12 months, what is the benefit of switching to more efficacious drugs? b) In people with relapsing MS who stop taking a highly efficacious drug,	In people with RRMS who experience disease activity while on a DMT, is changing to a different DMT superior to continuing the present DMT in terms of relapse and MRI disease activity?	When to consider DMT switching in people with RRMS?	When to consider DMT switching in people with RRMS?

Table 1. Treatment guidelines for multiple sclerosis *(Continued)*

	what is the benefit of further treatment?			
Recommendation	a) Offer a more efficacious drug to people treated with interferon or glatiramer acetate who show evidence of disease activity. b) Consider starting another highly efficacious drug, taking into account disease activity, half-life and biological activity of the previous drug, and the potential for rebound (particularly with natalizumab).	a) Clinicians should discuss switching from one DMT to another in people with MS treated long enough for the treatment to take full effect when they experience ≥ 1 relapse, ≥ 2 new MRI lesions, or increased disability, over a 1-year period of using a DMT. b) Clinicians should evaluate the degree of disease activity, adherence, AE profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use.	a) If the management of highly active MS[c] with potent DMTs has achieved a satisfactory response and stability for several years, it would be acceptable (though not mandatory) to consider switching to a lower potency DMT. b) If a person with relapsing MS fails to achieve satisfactory responses, presents intolerance or safety concerns with interferons, dimethyl fumarate, glatiramer acetate, pegylated interferon, teriflunomide, a switch to alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab should be considered.	a) In people with moderately active disease and suboptimal response[f] to interferons, dimethyl fumarate, glatiramer acetate, teriflunomide, treatment escalation to fingolimod, siponimod, natalizumab, ocrelizumab or cladribine should be considered. b) Rituximab can be used off label as an escalation therapy for all levels of MS activity, in special populations such as refugees, or in countries where other appropriate options are not available. c) In people with evidence of suboptimal response to any of the second line medications, off-label cyclophosphamide, autologous hematopoietic stem cell transplantation, or mitoxantrone should be considered.
Quality of evidence	a) Strong b) Consensus statement	a, b) Level B: “should”	Not reported	Not reported
Question 6	Not reported	In people with RRMS who experience adverse events while on a DMT, is switching necessary?	Not reported	Not reported
Recommendation		Clinicians should: a) discuss a change to non-injectable or less frequently injectable DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs; b) discuss a medication switch with people with MS for whom adverse		

Table 1. Treatment guidelines for multiple sclerosis *(Continued)*

	events negatively influence adherence; c) discuss switching DMT or reducing dosage or frequency when there are serious infections or persistent laboratory abnormalities; d) discuss switching to a DMT with a lower risk of progressive multifocal leucoencephalopathy with people with MS taking natalizumab who are or become antibody–positive to John Cunningham (JCV) virus, while on therapy; e) discuss switching to an alternate DMT for people with MS who develop a malignancy while using azathioprine, methotrexate, mycophenolate, cyclophosphamide, fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate; f) switch DMTs in people with MS who have persistent natalizumab antibodies.
Quality of evidence	a, b, c, d, e, f) Level B: "should"

[a]High risk CIS defined by one or more typical MRI T2 lesion(s), provided both the clinical presentation and MRI lesion(s) are suggestive of central nervous system demyelination and not attributable to other diseases.
[b]Active RRMS or highly active MS defined by clinical relapses or MRI activity (active lesions–contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually) or both.
[c]Highly active MS defined as: (i) at least two disabling relapses with incomplete resolution and at least one contrast-enhancing lesion or significant increase in T2 lesion load in the previous year in treatment-naive patients; or (ii) breakthrough disease activity in the previous year, under an adequate course of at least one DMT (in the absence of intolerance or non-adherence), presenting with at least one relapse in the previous year while on therapy and at least nine MRI T2 lesions or at least one contrast-enhancing lesion.
[d]Highly active disease defined as: (i) at least two relapses in the previous year; (ii) relapse severity; (iii) incomplete recovery; (iv) at least 10 MRI T2 lesions; (v) multiple contrast enhancing lesions.
[e]Rapidly evolving aggressive disease defined as the presence of at least two disabling relapses with incomplete recovery in the previous year and at least 10 MRI T2 lesions.
[f]Suboptimal response to chronic DMTs should be considered after one year of treatment in people with at least one relapse or disability progression or both, or at least two active MRI lesions (Gd+ or new T2W or both) after one year of adequate treatment and using as baseline an MRI performed six months after treatment initiation.
Abbreviations
AE: adverse events; CIS: clinically isolated syndrome; DMT: disease-modifying treatments; ECTRIMS/EAN: European Committee of Treatment of Research in Multiple Sclerosis and European Academy
of Neurology; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; MS: multiple sclerosis; PPMS: primary progressive MS; RRMS: relapsing-remitting MS; SPMS: secondary progressive MS; T2: T2 lesions; T2W: T2-weighted lesions.

APPENDICES

Appendix 1. Search strategy CENTRAL

((mabthera OR rituximab OR rituxan OR (monoclonal NEAR antibod*) OR (MeSH descriptor, Antibodies, Monoclonal, this term only in MeSH products)) AND ((MeSH descriptor, multiple sclerosis, demyelinating diseases, this term only in MeSH products) OR MS)

Appendix 2. Search strategy MEDLINE (PubMed)

1. "Rituximab"[Mesh]
2. "IDEC C2B8"[All Fields]
3. Rituxan[All Fields]
4. rituximab[All Fields]
5. mabthera[All Fields]
6. "anti cd20"[All Fields]
7. immunotherap*
8. monoclonal antibod*[all fields]
9. "Immunotherapy"[Mesh:NoExp]
10. "Antibodies,Monoclonal"[Mesh:NoExp]
11. 1/10 OR
12. "Demyelinating Diseases"[Mesh:NoExp]
13. "Demyelinating Autoimmune Diseases, CNS" [Mesh:NoExp]
14. Demyelinating Diseases*[all fields]
15. Demyelinating Disorder*[all fields]
16. "Multiple Sclerosis"[Mesh]
17. "Multiple Sclerosis, Chronic Progressive"[Mesh]
18. "Multiple Sclerosis, Relapsing-Remitting"[Mesh]
19. "Multiple sclerosis"[all fields]
20. 12/19 OR
21. 11 AND 20

Appendix 3. Search strategy Embase

1. 'multiple sclerosis'/exp OR 'demyelinating disease'/de
2. ((demyelinating NEAR/3 disorder*):ti,ab,kw) OR ((demyelinating NEAR/3 disease*):ti,ab,kw) OR 'first demyelinating':ti,ab,kw OR cis:ti,ab,kw OR (('clinically isolated' NEAR/2 'syndrome*'):ti,ab,kw)
3. 1 OR 2
4. rituximab:ti,ab,kw OR 'idec c2b8':ti,ab,kw OR rituxan:ti,ab,kw OR mabthera:ti,ab,kw OR 'anti cd20':ti,ab,kw OR immunotherap*:ti,ab,kw OR ((monoclonal NEAR/2 antibod*):ti,ab,kw)
5. 'rituximab'/exp OR 'immunotherapy'/de OR 'monoclonal antibody'/de
6. 4 OR 5
7. 3 AND 6

WHAT'S NEW

Date	Event	Description
18 February 2021	Amended	Republishing the protocol, broken links in Appendix 2 fixed

HISTORY

Protocol first published: Issue 2, 2021

CONTRIBUTIONS OF AUTHORS

GF wrote the protocol. JK, DH, and CDG provided comments on drafts of the protocol.

DECLARATIONS OF INTEREST

GF: none known

JK: none known

DH: none known

CDG: none known