Outcome measures for disease-modifying therapies in relapsing multiple sclerosis randomized clinical trials: a scoping review protocol

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ABSTRACT

Objective: The objective of the review is to explore randomized controlled trials on disease-modifying therapies for relapsing multiple sclerosis to identify and quantify the different outcome measures, instruments and definitions of efficacy, safety outcomes, health-related quality of life instruments and population subgroups.

Introduction: A wide range of therapies are available for relapsing multiple sclerosis, as well as a wide range of outcome measures and definitions, which can be explained by the absence of a core outcome set for this disease. Establishing a core outcome set is fundamental for guiding future studies as they improve the consistency and relevance of new findings and enable the results of trials to be compared and combined. These features are especially important for relapsing multiple sclerosis due to the limited number of head-to-head studies on this disease. Although many systematic reviews and meta-analyses have focused on the efficacy and safety of disease-modifying therapies in relapsing multiple sclerosis, none have had the specific objective of mapping outcome measures.

Inclusion criteria: This review will consider randomized controlled trials that explore populational subgroups, efficacy, safety outcomes, health-related quality of life instruments and their definitions in the context of disease-modifying therapies for adults with relapsing multiple sclerosis.

Methods: Electronic searches will be performed in PubMed, Scopus, the Cochrane Library, ClinicalTrials.gov, and *JBI Evidence Synthesis* with no time limit. Two researchers will independently select registries (screening and eligibility steps) and extract data on study characteristics, outcome measures, definitions and population subgroups. Data will be presented in graphical or tabular form, accompanied by a narrative summary.

Keywords antibodies, monoclonal, humanized; immunomodulation; multiple sclerosis, relapsing-remitting; treatment outcome

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Introduction

In 2013, approximately 2.3 to 2.5 million people were reported to have multiple sclerosis (MS).[1,2] Multiple sclerosis is a leading cause of morbidity and disability in young adults. It is classified into four major phenotypes, namely, clinically isolated syndrome, primary progressive MS, secondary progressive MS and, the most prevalent, relapsing multiple sclerosis (RMS). The latter group represents 80% to 85% of new cases of MS.[3-5]

Relapsing multiple sclerosis is characterized by symptomatic relapses at irregular intervals, interspersed with periods of remission in which there is total or partial recovery of the patient.[6] In order to reduce the frequency and severity of relapses, delay disease progression, decrease the number of lesions in the central nervous system and maintain patients' quality of life (QoL), RMS treatment should comprise disease-modifying therapies (DMTs), such as interferons, glatiramer, natalizumab, teriflunomide, ocrelizumab, alemtuzumab, fingolimod, dimethyl fumarate and cladribine. Numerous experimental

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and observational studies have evaluated DMTs through well-established outcome measures together with surrogate endpoints that consider new knowledge about the clinical, radiological, genetic, pathological and biological differences between patients, in addition to diagnostic advances and the potential for new DMTs.[7]

Due to the multiple proposed primary and secondary endpoints, the design of new studies, as well as decision-making – regulatory, resource allocation and clinical – has become more challenging. A further difficulty in the context of DMTs for RMS is the existence of a broad range of available therapies with few head-to-head comparisons.[8] Therefore, comparative critical analysis of these therapies depends on analyses of common outcomes provided by network meta-analyses (NMAs) and, ideally, common outcome definitions.

It is important to note that while the main MS complaints are sensory and motor symptoms, patients' QoL is also significantly affected by RMS.[1,2] Nevertheless, in an NMA that evaluated the efficacy, safety and health-related QoL (HRQoL) of DMT for RMS,[8] the authors found that HRQoL was generally poorly reported and different assessment tools were considered, including specific tools for MS (e.g. Hamburg QoL Questionnaire in MS, MS QoL-54 questionnaires, MS International QoL), EuroQoL-5 dimensions and Short Form-12 or Short Form-36 surveys considering different domains (physical or mental). Thus, pooling HRQoL in the meta-analysis of DMT for RMS can be difficult, considering the interpretability and usefulness of systematic reviews, as different instruments are being used to measure the same constructs.[9]

The heterogeneity in measuring and reporting outcomes may be explained by the absence of a "core outcome set" for RMS in adults. Thus, developing a set of core outcomes is paramount to guiding future studies. Indeed, this endeavor would improve the consistency and relevance of new findings and enable the results of trials to be compared and combined. According to the Core Outcome Measures in Effectiveness Trials (COMET) initiative, a core outcome set is an agreed minimum that should be selected, collected, measured and reported in all clinical trials of a condition or intervention. Different strategies can be used to reach a consensus, including systematic reviews, group discussions and structured surveys.[10]

An initial search of the Cochrane Database of Systematic Reviews, *JBI Database of Systematic Reviews and Implementation Reports* (JBISRIR), Campbell Collaboration Online Library and PROSPERO in May 2019 revealed that although there are many systematic reviews and meta-analyses on the efficacy and safety of DMTs in RMS, none had the specific objective of mapping outcome measures.[8,11-15] Additionally, Lavery *et al.* conducted a non-systematic review where they defined and discussed the efficacy of primary and secondary outcome measures reported for 19 phase III clinical trials, the most recent of which was published in 2012.[7] This review provided an outstanding clinical perspective, but had a major limitation in the lack of a comprehensive search and systematic data summary. Therefore, we aim to conduct a scoping review of randomized controlled trials (RCTs; at least phase II), including post hoc and extension analyses, to identify and quantify the different outcome measures, instruments and definitions of efficacy, safety outcomes, HRQoL instruments and population subgroups. Given the broader inclusion and comprehensive search criteria, this updated scoping review will potentially include more than 200 studies and 150 outcome measures. Additionally, comparisons between outcome measures and subgroup populations and their definitions will help clarify potential discrepancies between studies, providing a basis for future structured surveys (i.e. the Delphi technique), including multiple stakeholder experts in the treatment of RMS.

Thus, the objective of this scoping review is to explore existing RCTs related to DMTs in RMS, and to identify and quantify the different outcome measures, instruments and definitions of efficacy, safety outcomes, HRQoL instruments and population subgroups.

Review questions

Three main questions will be addressed in this review:

i) What efficacy, safety outcome measures and HRQoL instruments are reported in RCTs that assess DMTs in RMS patients?
ii) What outcome definitions are reported in RCTs that assess DMTs in RMS patients?
iii) What population subgroups are reported in RCTs that assess DMTs in RMS patients?

Inclusion criteria

Participants

This review will consider studies that include participants aged 18 years or older with a diagnosis of RMS, regardless of the diagnostic criteria, sex, degree of disability or duration of disease.

Concept

This review will consider studies that explore population subgroups (e.g. sex, age, degree of disability) and report outcomes about the efficacy, safety and HRQoL of DMTs for RMS. Safety outcomes of interest include those that are non-specific (e.g. death, serious adverse events) to the detriment of specific ones (e.g. nausea, lymphopenia). Additionally, the scoping review will consider the definition of each outcome measure as well as potential differences in the reporting of these outcome measures, as many studies include specific analyses that relate to the same measure (e.g. number of relapses per patient, patients with at least one relapse, patients free from relapse).

Context

This review will consider studies regardless of their location, country or setting. Only studies that evaluated DMTs in monotherapy (i.e. use of a single DMT to treat RMS) rather than combinations will be included.

Types of studies

This scoping review will employ a quantitative study design for inclusion, specifically randomized controlled trials (phase II or higher, and including post-hoc and extension analyses), with the objective of evaluating the efficacy, safety and HRQoL of DMTs for RMS. Equivalence and non-Roman alphabet languages studies (e.g. Arabic, Chinese, Russian) will be excluded. There will be no date restrictions.

Methods

The proposed scoping review will be conducted in accordance with JBI methodology for scoping reviews.[16,17]

Search strategy

The search strategy will aim to locate both published and unpublished RCTs. An initial limited search of PubMed and Scopus was undertaken to identify articles on the topic. The text words in the titles and abstracts of relevant articles, together with the index terms used to describe the articles, were used to develop a full search strategy for PubMed, which includes MEDLINE and PubMed Central databases, Scopus, Cochrane Library and ClinicalTrials.gov (see Appendix I). This search strategy, including all identified keywords and index terms, will be adapted for each of the included information sources. In addition, the reference lists of all articles included in the review, as well as systematic reviews recovered in the Cochrane Library and *JBI Evidence Synthesis*, will be screened to identify any additional papers.

Information sources

The information sources will be: PubMed, Scopus, Cochrane Library, ClinicalTrials.gov and *JBI Evidence Synthesis*, as well as the reference lists of included articles.

Study selection

Following the search, all identified records will be collated and uploaded into EndNote X7.2.1 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers against the inclusion criteria for the review. Potentially relevant papers will be retrieved in full, and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia). The full text of selected articles will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for the exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or by a third reviewer. The results of the search will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[18]

Data extraction

Data will be extracted from all papers included in the scoping review by two independent reviewers using a data extraction tool developed by the reviewers in Microsoft Excel or Microsoft Word (Redmond, Washington, USA). The extracted data will include

specific details about: i) baseline study characteristics (author names, year of publication, country, sample size, patient sex and age, disease duration, onset of symptoms, follow-up and timing measures, and evaluated DMTs); ii) methodological aspects (e.g. phase, post hoc or extension analysis, national clinical trial number [NCT]); iii) reported clinical outcome measures (efficacy and safety), HRQoL instruments and definitions; and iv) population subgroups. A draft extraction tool is provided in Appendix II. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included paper. Modifications will be detailed in the full scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or by a third reviewer. Authors of papers will be contacted to request missing or additional data where required.

Data presentation

The extracted data will be presented in graphical or tabular form. Figures, tables and charts will be used, where appropriate. The tables and charts will report: i) distribution of studies by year, design, country, follow-up and funding source; ii) distribution of outcomes; iii) definitions of outcomes; iv) distribution of HRQoL instruments; and v) distribution of population subgroup analyses. A narrative summary will accompany the tabulated and/or charted results, focusing on outcome measures, instruments and population subgroups, along with their definitions. It will describe how the results relate to the objectives and questions of the review.

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Appendix I: Search strategy

PubMed (MEDLINE and PubMed Central)
Search conducted in November 2019

#1: (RRMS[TIAB] OR RMS[TIAB] OR ''Multiple Sclerosis, Relapsing-Remitting''[MH] OR (((''Multiple Sclerosis''[TIAB] OR ''Multiple Sclerosis''[MeSH]) AND (relaps*[TIAB] OR remitting[TIAB])))

#2: (natalizumab[MeSH] OR natalizumab[TIAB] OR alemtuzumab[TIAB] OR ''Interferon beta-1a''[MeSH] OR ''Interferon beta-1a''[TIAB] OR avonex[TIAB] OR rebif[TIAB] OR Interferon beta-1b[MeSH] OR ''Interferon beta-1b''[TIAB] OR betaferon[TIAB] OR extavia[TIAB] OR ''Fingolimod Hydrochloride''[MeSH] OR fingolimod[TIAB] OR ''Dimethyl Fumarate''[MeSH] OR ''dimethyl fumarate''[TIAB] OR ''Glatiramer Acetate''[MeSH] OR glatiramer[TIAB] OR ocrelizumab[TIAB] OR peginterferon[TIAB] OR teriflunomide[Supplementary Concept] OR teriflunomide[TIAB] OR cladribine[MeSH] OR cladribine[TIAB] OR Pixantrone[TIAB] OR ozanimod[TIAB] OR BAF312[TIAB] OR Siponimod[TIAB] OR amiselimod[TIAB] OR Abatacept[TIAB] OR GSK239512[TIAB] OR Clemastine[TIAB] OR Ofatumumab[TIAB] OR EK-12[TIAB] OR Vatelizumab[TIAB] OR RNS60[TIAB] OR VAY736[TIAB] OR TMP001[TIAB] OR INT131[TIAB] OR GSK239512[TIAB] OR MT-1303[TIAB] OR GNbAC1[TIAB] OR M2951[TIAB] OR Flupirtine[TIAB] OR ''ALKS 8700''[TIAB] OR NT-KO-003[TIAB] OR Ublituximab[TIAB] OR Plovamer[TIAB] OR AIN457[TIAB] OR Ponesimod[TIAB] OR ACT-128800[TIAB] OR RPC1063[TIAB] OR Atacicept[TIAB] OR BIIB033[TIAB] OR opicinumab[TIAB] OR ATX-MS-1467[TIAB])

#3: (((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]))

#4: (letter[PT] OR editorial[PT] OR historical article[PT])

#5: (animals[MH:noexp] NOT (animals[MH:noexp] AND humans[MH]))

Search: #1 AND #2 AND #3 NOT #4 NOT #5 (records retrieved = 3189)

Appendix II: Data extraction instrument

Sheets in Microsoft Excel, with the following columns:
Identification
Study
Number of clinical trials
Year
Countries (# centers)
Study type
Acronym
Time point (months)
Follow-up time (months)
Type of multiple sclerosis and other important condition
Evaluated alternatives
Participants (# women)
Age, years (mean [standard deviation - SD])
Baseline Expanded Disability Status Scale (mean [SD])
Disease duration, years (mean [SD])
Time since symptom onset, years (mean [SD])
Previous disease modifying therapy (%)
Funding
Outcomes measures
Health related quality of life (HRQoL) instruments
Domain of HRQoL instruments
Population subgroups
Legend for abbreviations

Document in Microsoft Word, with:

Definitions of outcomes.