ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis

X. Montalban[a], R. Gold[b], A. J. Thompson[c], S. Otero-Romero[a,d], M. P. Amato[e], D. Chandraratna[f], M. Clanet[g], G. Comi[h], T. Derfuss[i], F. Fazekas[j], H. P. Hartung[k], E. Havrdova[l], B. Hemmer[m,n], L. Kappos[o], R. Liblau[p], C. Lubetzki[q], E. Marcus[r], D. H. Miller[s], T. Olsson[t], S. Pilling[r], K. Selmaj[u], A. Siva[v], P. S. Sorensen[w], M. P. Sormani[x], C. Thalheim[y], H. Wiendl[z] and F. Zipp[aa]

[a]*Multiple Sclerosis Centre of Catalonia (Cemcat), Department of Neurology-Neuroimmunology, Vall d'Hebron University Hospital, Barcelona, Spain;* [b]*Department of Neurology, Ruhr University, St Josef-Hospital, Bochum, Germany;* [c]*Department of Brain Repair and Rehabilitation, Faculty of Brain Sciences, University College London Institute of Neurology, London, UK;* [d]*Preventive Medicine and Epidemiology Department, Vall d'Hebron University Hospital, Barcelona, Spain;* [e]*Department NEUROFARBA, Section Neurosciences, University of Florence, Florence, Italy;* [f]*Multiple Sclerosis International Federation, London, UK;* [g]*Department of Neurology, Toulouse University Hospital, Toulouse, France;* [h]*Neurological Department, Institute of Experimental Neurology (INSPE), Scientific Institute Hospital San Raffaele, University Vita-Salute San Raffaele, Milan, Italy;* [i]*Departments of Neurology and Biomedicine, University Hospital Basel, Basel, Switzerland;* [j]*Department of Neurology, Medical University of Graz, Graz, Austria;* [k]*Department of Neurology, Medical Faculty, Multiple Sclerosis, Heinrich-Heine-University, Düsseldorf, Germany;* [l]*Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic;* [m]*Department of Neurology, Klinikum Rechts der Isar, Technische Universität München, Munich;* [n]*Munich Cluster for Systems Neurology (SyNergy), Munich, Germany;* [o]*University Hospital Basel, Basel, Switzerland;* [p]*INSERM UMR U1043 – CNRS U5282, Centre de Physiopathologie de Toulouse Purpan, Université de Toulouse, UPS, Toulouse;* [q]*ICM-GHU Pitié-Salpêtrière, Sorbonne Universités UPMC Univ Paris 06, UMR_S 1127, Paris, France;* [r]*Centre for Outcomes Research and Effectiveness (CORE), Research Department of Clinical, Educational and Health Psychology, University College London, London;* [s]*NMR Research Unit, Queen Square Multiple Sclerosis Centre, University College London (UCL) Institute of Neurology, London, UK;* [t]*Neuroimmunology Unit, Centre for Molecular Medicine, L8:04, Karolinska University Hospital (Solna), Stockholm, Sweden;* [u]*Department of Neurology, Medical University of Lodz, Lodz, Poland;* [v]*Clinical Neuroimmunology Unit and MS Clinic, Department of Neurology, Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey;* [w]*Danish Multiple Sclerosis Centre, Department of Neurology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark;* [x]*Biostatistics Unit, University of Genoa, Genoa, Italy;* [y]*European Multiple Sclerosis Platform (EMSP), Schaerbeek/Brussels, Belgium;* [z]*Department of Neurology, University of Münster, Münster; and* [aa]*Department of Neurology, Focus Program Translational Neuroscience (FTN) and Immunology (FZI), Rhine-Main Neuroscience Network (rmn2), University Medical Centre of the Johannes Gutenberg University Mainz, Mainz, Germany*

Keywords:
demyelinating, disease-modifying treatment, diseases, GRADE methodology, guideline, multiple sclerosis, neurological disorders, research methods

Received 22 November 2017
Accepted 27 November 2017

Background and purpose: Multiple sclerosis (MS) is a complex disease with new drugs becoming available in the past years. There is therefore a need for a reference tool compiling current data to aid professionals in treatment decisions. The objective was to develop an evidence-based clinical practice guideline for the pharmacological treatment of people with MS.

Methods: This guideline has been developed using the GRADE methodology and following the updated EAN recommendations for guideline development. Clinical questions were formulated in PICO format (patient, intervention, comparator, outcome) and outcomes were prioritized according to their relevance to clinical practice. Literature searches up to December 2016 were performed and the evidence is presented narratively and, when possible, combined in a

Correspondence: For ECTRIMS: X. Montalban, Multiple Sclerosis Centre of Catalonia (Cemcat), Department of Neurology-Neuroimmunology, Vall d'Hebron University Hospital, Pg. Vall d'Hebron, 119-129, 08035 Barcelona, Spain (tel.: +34 93 2746202; fax: +34 93 2746084; e-mail: xavier.montalban@cem-cat.org) and for EAN: R. Gold, Department of Neurology, Ruhr University, St Josef-Hospital, Gudrunstr. 56, 44791 Bochum, Germany (tel.: +49-234-509244; fax: +49-234-5092414; e-mail: ralf.gold@rub.de).

This is a Continuing Medical Education article, and can be found with corresponding questions on the EAN website, LEARN section https://www.ean.org/CME.2714.0.html. Certificates for correctly answered questions will be issued by EAN directly, you simply have to be logged-in. With positive results, EAN recommends accreditation of 1 hour of CME, which may be claimed with the national body in charge of CME accreditation. This paper is being simultaneously published in *European Journal of Neurology* and *Multiple Sclerosis Journal*.

[Correction added on 13 February 2018, after online and print publication: (a) The abstract has been updated and a conclusion section in now included; (b) Recommendation 4 and 7 has been amended, and an additional recommendation has been added after the latter].

EUROPEAN JOURNAL OF NEUROLOGY

European Journal of Neurology 2018, **25:** 215–237

doi:10.1111/ene.13536

meta-analysis. The quality of evidence was rated into four categories – very high, high, low and very low – according to the risk of bias. The recommendations with assigned strength (strong, weak) were formulated based on the quality of evidence and the risk–benefit balance. Consensus between the panelists was reached by use of the modified nominal group technique.

Results: A total of 10 questions have been agreed, encompassing treatment efficacy, response criteria, strategies to address suboptimal response and safety concerns and treatment strategies in MS and pregnancy. The guideline takes into account all disease-modifying drugs approved by the European Medicine Agency at the time of publication. A total of 21 recommendations were agreed by the guideline working group members after three rounds of consensus.

Conclusion: The present guideline, which includes descriptions of the evidence together with recommendations, will enable homogeneity of treatment decisions across Europe.

Background and scope

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that is characterized by inflammation, demyelination and degenerative changes. MS usually begins between the ages of 20 and 40 and affects two to three times as many women as men; it also constitutes the most frequent cause of non-traumatic disability in the young adult population [1]. The incidence of MS varies across regions, with rates as high as 8–10 new cases per 100 000 in high latitudinal regions [2,3]. Current estimates suggest that over 700 000 people are affected in Europe, with over 2.5 million cases worldwide [4], which represent a significant burden in terms of impact on quality of life, societal costs and personal expenses [5,6]. Most patients (85%–90%) have a relapsing course from onset that is characterized by relapses and remissions of neurological symptoms associated with areas of CNS inflammation, and over the course of two decades more than half of untreated patients transition to a phase of gradual worsening independent of acute attacks [7,8]. Progressive forms of MS can be present as the initial disease course (primary progressive MS) in approximately 10%–15% of patients [9,10].

There is no curative treatment available for MS, and the current therapeutic strategy is aimed at reducing the risk of relapses and potentially disability progression. The treatment era for MS began in 1993, when the first interferon became available, and recent years have seen a large expansion in the therapeutic options for MS, with 11 disease-modifying therapies approved by the European Medicine Agency (EMA) in both injectable and oral formulations by the beginning of 2017 [11]. The growing armamentarium of therapies brings new opportunities for individualized therapy where patients and providers must balance considerations around efficacy, side effects and potential harm in a shared-decision process. However, the variety of mechanisms of action, monitoring requirements and risk profiles together with the existing knowledge gaps make individualized medicine a complex task [12,13]. There is still controversy about the relative efficacy of the drugs available, who should receive therapy and the optimum time to start. The heterogeneity of MS together with the changes in the diagnostic criteria over the years [14–17] and the recent redefinition of the clinical subtypes [18] hamper direct comparisons across studies for different drugs. Moreover, despite the identification of several prognostic factors [19–21], there is no accepted consensus definition that allows physicians to classify patients into high risk and low risk groups in order to prioritize treatment strategies.

A number of evidence-based guidelines and technology appraisal documents have been produced over the past 5 years [22–25] but there is no comprehensive document that incorporates recently approved drugs to help clinicians and patients in the decision-making process for those aspects that raise specific difficulties when facing everyday clinical practice. These are questions such as how to select the initial therapy and choose subsequent therapies; how best to monitor treatment response; when to switch or discontinue treatment; and how to manage therapy in special situations such as pregnancy. In this context, the European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) have joined forces to provide up-to-date, evidence-based recommendations for the treatment of patients with MS to assist physicians, patients, healthcare providers and health policy makers in Europe and worldwide in the decision-making process.

This guideline focuses on disease-modifying treatment for the adult population with MS, including all

immunomodulatory and immunosuppressive drugs authorized by the EMA. It does not include recommendations concerning combination therapies or new active agents in the final stages of clinical evaluation that are not approved by the EMA at the time of publication. Nevertheless, the available evidence regarding these drugs has been analysed, and a regular update of the document is planned in order to incorporate new drugs in the recommendations as soon as they are approved. This guideline does not include treatments usually considered complementary and/or alternative medicine or aspects of symptomatic treatment and/or treatment of relapses.

Patients with clinically isolated syndrome (CIS) who do not fulfil the current MS 2010 diagnostic criteria and patients with confirmed MS have been considered, distinguishing between the different clinical subtypes of MS using previous and recent classification criteria [18,26]. Guidance relating to paediatric MS is not included in this guideline and can be found in recent documents [27–30].

The document is a joint venture of ECTRIMS and EAN and, as such, the recommendations have been drawn up considering its European scope, including both the outpatient and in-hospital setting, but it does not address specific organizational issues, management models or country-specific regulations required to implement the recommendations. Users of these guidelines should adapt the recommendations to be consistent with their local regulations and/or team capacities, infrastructure and cost–benefit strategies.

Guideline questions

The guideline task force, on the basis of its extensive expertise in the field, has prioritized the key aspects to be covered in the guideline. These aspects are as follows: early treatment in CIS patients, treatment in patients with established disease (both relapsing and progressive), monitoring of treatment response, treatment strategies in the case of inadequate treatment response, treatment discontinuation and/or switch, as well as treatment in special situations such as pregnancy.

To address the previous topics, 10 questions have been formulated and classified into the following two types: those involving a specific therapeutic intervention, formulated following the PICO framework (patients, intervention, comparator, outcome); and those covering aspects of clinical management, formulated considering population, management aspects and outcome.

An explicit list of outcomes for each question was proposed by the guideline chairs and circulated to the rest of the working group who were invited to rate their relative importance for clinical decision-making and add new outcomes if needed. The outcome prioritization was performed via a two-round consensus exercise using a nine-point Likert scale and grouped into three categories (1–3, outcome of low importance; 4–6, outcome important but not critical for decision-making; 7–9, outcome critical for decision-making). Only outcomes graded as critical or important according to expert opinion were analysed.

Therapeutic intervention questions

1 In patients with CIS (regardless of whether they fulfil criteria of definite MS [15]), what is the benefit of starting treatment with a disease-modifying drug (DMD) compared to no treatment?

2 In patients with relapsing–remitting MS and secondary progressive MS, what is the benefit of treating with a DMD compared to no treatment/another DMD?

3 In patients with primary progressive MS, what is the benefit of treating with a DMD compared to no treatment?

Clinical management questions

4 In patients with relapsing MS treated with DMDs, does the presence of early disease activity [relapses and/or disability progression and/or magnetic resonance imaging (MRI) activity at 6 months/12 months] predict an increased risk of future disability?

5 In MS patients treated with DMDs, should a follow-up MRI be performed within a pre-specified time frame to monitor treatment response and safety?

6 In patients with relapsing MS treated with interferon or glatiramer acetate and with evidence of early disease activity (relapses and/or disability progression and/or MRI activity at 6/12 months), what is the benefit of switching between interferon and glatiramer acetate versus moving to more efficacious drugs?

7 In patients with relapsing MS who stop taking a highly efficacious drug, is there a risk of return and/or rebound of their disease activity (increased risk of relapses, disability progression and/or MRI activity)?

8 In patients with relapsing MS who stop taking a highly efficacious drug, what is the benefit of further treatment?

9 In patients with relapsing MS treated with DMDs who remain stable over a long time period, what is the benefit of continuing treatment compared to stopping?

10 In women with MS treated with DMDs who wish to become pregnant or who have an unplanned pregnancy, what should the therapeutic approach be?

Methodology

This guideline was developed in accordance with the recommendations of the GRADE (Grading of

Recommendations Assessment, Development and Evaluation) Working Group [31] and in line with the 2015 practical recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces [32].

Search strategy

Searches were performed following a predefined review protocol (Appendix S1) and conducted in the following databases: the Cochrane Central Register of Controlled Trials (Central), Excerpta Medica Database (Embase), Medical Literature Analysis and Retrieval System Online (MEDLINE)/MEDLINE In-Process, and Psychological Information Database (PsycINFO). All search terms for each search are listed in Appendix S2.

Titles and abstracts of identified studies were screened for inclusion against agreed criteria. Eligibility criteria for therapeutic intervention questions included systematic reviews (SRs), randomized controlled trials (RCTs) with at least 1 year follow-up (48 weeks acceptable) and long-term extensions on included RCTs. Studies on paediatric populations, studies evaluating combinations of drugs, unlicensed doses, those published in non-English language and those with <10 participants per arm were excluded. For clinical management questions, SRs, RCTs and observational studies were included. Exclusion criteria varied between the different clinical management questions and details can be found in Appendix S1.

All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility at the time they were entered into a study database (standardized template created in Microsoft Excel). The full-text papers were screened by two reviewers using the inclusion criteria for reference. Study characteristics, aspects of methodological quality and outcome data were extracted from all eligible studies using an Excel-based form and Review Manager Version 5.3 (Cochrane Collaboration, London, UK, 2014).

Quality appraisal and data synthesis

The quality appraisal process was conducted depending on the study design using available standardized tools. For the evidence coming from RCTs, the quality of individual studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [33]. For cohort studies, the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I; Cochrane Bias Methods Group) [34] was used, whereas for before and after studies, the Quality Assessment of Before–After (Pre–Post) Studies with No Control Group tool developed by the National Heart, Lung, and Blood Institute and the Research Triangle Institute International was used. SRs were assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool. For RCTs, meta-analysis using a random-effects model was used to combine results from similar studies using Review Manager Version 5.3. Where application of this analysis was not possible, a narrative synthesis was used. Observational studies were analysed separately from the RCTs and synthesized narratively. Dichotomous outcomes were analysed as relative risks (RR; also called a risk ratio), and continuous outcomes were analysed using the mean difference (MD) with the associated 95% confidence interval (CI).

Grading the quality of the evidence

The process for grading the quality of the evidence followed two different approaches according to the type of question.

Therapeutic intervention

For questions about the effectiveness of interventions, the GRADE approach was used to assess the quality of evidence for each outcome [35] taking into account the following items: study design, risk of bias, inconsistency, indirectness and imprecision. GRADE evidence profiles, including both the quality of the evidence and the results of the evidence synthesis for each 'critical and important' outcome, were created using GRADEprofiler (GRADEpro) software (Version 3.6).

Clinical management

For the clinical management questions, the risk of bias was assessed using different tools depending on study design as detailed previously, and this information was presented narratively and in summary tables.

Method for reaching consensus

The panel formulated practice recommendations on the basis of the quality of the evidence and the balance between health benefits and harms for both therapeutic and clinical management questions. Consensus was reached by use of the modified nominal group technique following a two-stage process [36]. In the first stage, participants received a summary of the available evidence and its quality as detailed previously, an overview of the modified nominal group technique, and a ranking Excel sheet containing the proposed list of statements and instructions on its use. The proposed list of statements and their assigned strength (strong, weak) was initially drafted by the guideline chairs during a face-to-face meeting with

participation of the methodologists in charge of the evidence analysis. For those aspects for which there was not sufficient evidence to support a formal recommendation, consensus statements were formulated.

The panel members were asked to indicate their agreement with the set of statements by taking into account the available evidence and their expertise and to provide written comment on their reason for any disagreement and possible modifications. The statements were rated on a nine-point Likert scale and grouped into three categories (1–3, inappropriate strategy; 4–6, uncertain; 7–9, appropriate strategy). In the second stage, panellists met during a face-to-face consensus meeting, and anonymized distributions of responses to each statement were presented to all members, together with the additional comments and a ranking of statements. Those statements with less than 80% agreement were redrafted, and a second round of voting using show of hands was conducted. If agreement of 80% or above was achieved, then the re-rated statements were adopted [37]. Those statements that could not be approved during the face-to-face meeting due to time limitations were evaluated in a third round via e-mail.

Results

Efficacy of DMDs

Review question 1: In patients with CIS (regardless of whether they fulfil the criteria of definite MS [15]) what is the benefit of starting treatment with a DMD compared to no treatment?

An electronic database search was performed for questions 1–3 simultaneously and identified 4416 records. Of these, 4266 studies were excluded based on their title/abstract and 150 studies were subjected to a full-text appraisal. Information about the excluded studies can be found in Appendix S3. Five trials [38–42] and their extensions [43–48] met the eligibility criteria for question number 1. They were all placebo-controlled trials testing interferon, glatiramer acetate and teriflunomide. Sample sizes of the pivotal trials varied from 383 to 618 participants (mean 493), with a follow-up ranging from 104 to 156 weeks (mean 125 weeks). All trials included participants who had not received any prior disease-modifying therapy before study entry, and the mean Expanded Disability Status Scale (EDSS) scores at baseline ranged from 1 to 1.67 (mean 1.42). Further details about the characteristics of the included studies can be found in Appendix S4, Tables S1–S5.

Three trials [38,40,41] (n = 1368) comparing interferon with placebo showed a longer time to conversion to clinically definite MS (CDMS) at 2 years [high quality meta-analysis, two trials [38,41], n = 808; hazard ratio (HR) 0.49, 95% CI 0.38–0.64] and a reduced number of participants converting to CDMS at follow-ups ranging from 2 to 3 years (moderate quality meta-analysis, two trials [38,40], n = 723; RR 0.71, 95% CI 0.61–0.82). Treatment with interferon also showed a benefit in the number of participants free from new or newly enlarging T2 lesions and gadolinium (GAD) enhanced lesions but MRI results could not be combined into meta-analyses due to the variability of MRI outcomes reported across the three trials. The interferon group resulted in a higher but not significant discontinuation risk for any reason (moderate quality meta-analysis, three trials [38,40,41], n = 1193; RR 1.11, 95% CI 0.80–1.54) and a higher discontinuation risk due to side effects (low quality meta-analysis, two trials [40,41], n = 810; RR 2.17, 95% CI 0.16–28.82). In the extension studies, patients on placebo were offered interferon. The early-intervention group showed a greater time to conversion to CDMS than the delayed-treatment group at 3 years' follow-up [47], and this difference was maintained at 5 [45,48], 8 [46] and 11 years' follow-up [44].

There is only one available trial of glatiramer acetate compared with placebo (n = 481) in CIS patients showing a delayed conversion to CDMS at 3 years (moderate quality; HR 0.55, 95% CI 0.40–0.76), with a higher number of discontinuations in the glatiramer acetate group for any reason (moderate quality; RR 1.66, 95% CI 1.02–2.69) and due to side effects (moderate quality; RR 3.43, 95% CI 1.14–10.26) [39]. According to a single extension study, there was a beneficial effect of early treatment with glatiramer acetate on the time to CDMS, the number of new or newly enlarging T2 lesions, the number of GAD lesions and brain volume change, with no significant differences in adverse events at 5 years' follow-up [43].

According to a single placebo-controlled trial (n = 413), treatment of CIS patients with teriflunomide resulted in a delayed time to conversion to CDMS (low quality; HR 0.57, 95% CI 0.38–0.87) and a reduced number of participants converting to CDMS at 2 years' follow-up (low quality; RR 0.64, 95% CI 0.44–0.92). MRI outcomes showed a lower number of GAD lesions (low quality; MD = −0.56, 95% CI −1.04 to −0.08) and a beneficial effect on the change in T2 lesion volume (low quality; MD = −0.07, 95% CI −0.18 to 0.03), with no difference between groups in brain atrophy. The study reported a higher number of non-significant discontinuations in the placebo group for any reason (RR 0.83, 95% CI 0.60–1.15) and due to side effects (RR 0.91, 95% CI 0.49–1.70) [42]. GRADE tables and forest plots are presented in Appendix S5 and

Appendix S6. Further details about the safety issues of these drugs are shown in Appendix S7.

Review question 2: In patients with relapsing–remitting MS and secondary progressive MS, what is the benefit of treating with a DMD compared to no treatment/another DMD?

Thirty-three RCTs met the eligibility criteria for question number 2 and, of these, 28 RCTs included patients with relapsing–remitting forms of MS (some of which included patients with and without progression) and five RCTs were restricted to patients with secondary progressive MS.

Relapsing–remitting MS. The trials on relapsing–remitting MS comprised 16 placebo-controlled trials, including interferon, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab and daclizumab, and 12 head to head trials involving many of these agents and including alemtuzamab. Sample sizes ranged from 75 to 2244 participants (mean 879), and the length of study follow-up ranged from 48 to 260 weeks (mean 98 weeks). Overall, participants were predominantly female (mean of means 70%) in their late 30s (mean of means 36 years) who had been diagnosed with MS for an average of 5.3 years (range 1.1–10.6 years). Twenty-two studies reported the number of participants who had received any DMD prior to study entry, which was 0% in five studies, 100% in one study, and ranged from 7.6% to 75% in the remaining 16 studies (mean of means 32%). At baseline, the EDSS scores ranged from 1.9 to 2.9 (mean of means 2.5), and the number of relapses in the previous year ranged from 1 to 1.8 (mean of means 1.4). Further details about the characteristics of the included studies can be found in Appendix S4, Tables S6–S25.

All the evaluated drugs showed a significant treatment effect compared with placebo. Interferon resulted in a lower annualized relapse rate at follow-up ranging from 48 to 104 weeks (moderate quality meta-analysis, two trials [49,50], $n = 1909$; MD = −0.10, 95% CI −0.16 to −0.04) and a beneficial effect on the number of participants free from relapse at 48 weeks' follow-up (moderate quality evidence; RR 1.15, 95% CI 1.08–1.23) [49] and at 104 weeks' follow-up (low quality meta-analysis, three trials [51–53], $n = 960$; RR 1.73, 95% CI 1.35–2.21). Interferon had an impact on disability worsening confirmed at 3 months over 48 weeks' follow-up (low quality evidence, $n = 1012$; RR 0.61, 95% CI 0.39–0.93) [49] and on disability worsening confirmed at 6 months over 2 years' follow-up (low quality evidence meta-analysis, two trials [50,53], $n = 1069$, $k = 2$; RR 0.71, 95% CI 0.51–0.98). Interferon also showed an impact on MRI parameters, according to moderate quality evidence, with fewer new or newly enlarging T2 lesions (MD = −7.30, 95% CI −8.85 to −5.75) [49] and a change in brain volume at 48 weeks' follow-up (MD = −0.10, 95% CI −0.20 to 0.00) [49] and at 2 years' follow-up (MD = −0.11, 95% CI −0.28 to 0.06) [50]. Similarly, low quality evidence suggested a larger proportion of participants free from T2 active lesions (RR 2.80, 95% CI 1.69–4.63) and free from combined unique active lesions (RR 2.97, 95% CI 1.49–5.92) at 2 years [52]. The evidence suggested an increased risk of trial discontinuation due to side effects and for any reason in the interferon group compared with the placebo group at 48 weeks' [49] and at 2 years' follow-up (low quality evidence meta-analysis, three trials [50,52,53], $n = 1630$; RR 1.72, 95% CI 1.04–2.86).

Extension studies available for four of the interferon pivotal trials concluded that the early-intervention group had a lower annualized relapse rate and fewer new or newly enlarging T2 lesions at 2 and 4 years' follow-up [54,55], as well as a lower proportion of participants with disability worsening at 2 and 8 years' follow-up [55,56]. At 16 years' follow-up, there was little difference between the early- and delayed-treatment groups in the number of participants reaching an EDSS score of 6 and those converting to secondary progressive MS [57]. Further details about the study outcomes can be found in Appendix S8.

Three trials ($n = 3217$) compared glatiramer acetate with placebo with length of follow-up ranging from 52 to 104 weeks [58–60]. Glatiramer acetate resulted in a lower annualized relapse rate at follow-ups ranging from 52 to 96 weeks (moderate quality evidence meta-analysis of two trials [58,60], $n = 2117$; MD = −0.14, 95% CI −0.21 to −0.06) and a higher proportion of participants free from relapse at follow-ups ranging from 1 to 2 years (moderate quality evidence meta-analysis of three trials [58–60], $n = 2360$; RR 1.17, 95% CI 1.10–1.24). There was a non-statistically significant evidence effect on disability at 96–104 weeks' follow-up (low quality evidence meta-analysis of two trials [58,59], $n = 964$; RR 0.86, 95% CI 0.66–1.11) and 128 weeks' follow-up (low quality evidence meta-analysis of two trials [58,59], $n = 964$; RR 0.79, 95% CI 0.52–1.20). Glatiramer acetate resulted in a lower number of cumulative GAD lesions (MD = −0.73, 95% CI −1.15 to −0.31) and cumulative new or newly enlarging T2 lesions at 6 and 12 months' follow-up [58,60] as well as a beneficial (but non-statistically significant) effect on the percentage change in brain volume at 1 year, according to high quality evidence (MD = −0.06, 95% CI −0.19 to 0.06) [60]. According to the only available extension study, there was little difference between groups

in the proportion of participants discontinuing the trial for any reason during the extension phase. The early-treatment group had a higher proportion of injection site reactions (2.4% vs. 0.9%) [61].

Two trials compared teriflunomide with placebo with length of follow-up ranging from 104 to 108 weeks [62,63]. According to a moderate quality evidence meta-analysis of the two trials (n = 1479), teriflunomide reduced the risk of relapses (RR 1.25, 95% CI 1.16–1.36), resulted in a decreased annualized relapse rate (MD = −0.18, 95% CI −0.24 to −0.11) and reduced disability worsening compared with that associated with placebo (RR 0.76, 95% CI 0.62–0.93) at 48–108 weeks' follow-up. Only one of the trials reported MRI data that showed a beneficial effect on the mean number of GAD lesions (MD = −1.07, 95% CI −1.40 to −0.74) and on the number of patients free from enhanced lesions (moderate quality evidence; RR 1.62, 95% CI 1.39–1.87) [63]. In the single extension study available, there was little difference up to 9 years' follow-up between the early- and delayed-treatment groups for the annualized relapse rate and a lower proportion of participants with disability worsening in the early-treatment group [64].

Two trials (n = 2667) compared dimethyl fumarate with placebo with length of follow-up ranging from 96 to 104 weeks [58,65]. A moderate quality meta-analysis of both trials (n = 1479) showed a beneficial effect of dimethyl fumarate at 2 years' follow-up on the number of participants free from relapses (RR 1.28, 95% CI 1.14–1.43), the annualized relapse rate (MD = −0.19, 95% CI −0.25 to −0.13), the risk of disability worsening (RR 0.66; 95% CI 0.51–0.85) and the presence of new or newly enlarging T2 lesions (MD = −13.36, 95% CI −16.63 to −10.9) and GAD lesions (MD = −1.64, 95% CI −2.17 to −1.10). One extension study reported outcomes at 5 years with the previous trials combined, where participants receiving placebo were re-randomized to one of the two doses of dimethyl fumarate. The results indicated little difference between the early- and delayed-treatment groups for the annualized relapse rate during the extension phase and a lower proportion of participants with disability worsening in the early-treatment group [66].

Two trials compared fingolimod with placebo with 104 weeks' follow-up [67,68]. According to a meta-analysis of the two trials (n = 2355), moderate quality evidence showed that fingolimod was associated with a larger proportion of participants free from relapse (RR 1.44, 95% CI 1.28–1.63), a lower annualized relapse rate (MD = −0.21, 95% CI −0.25 to −0.16), lower risk of disability worsening (RR 0.71, 95% CI 0.56–0.90) and a trend in favour of fingolimod for all MRI outcomes. The extension studies available for both trials show a beneficial effect in the early-treatment group compared with the delayed-treatment group with a lower annualized relapse rate, a higher proportion of participants free from disability worsening and a beneficial effect of early fingolimod on the number of new T2 lesions, GAD lesions and the percentage change in brain volume at 4–6 years' and 4.5 years' follow-up [69].

One trial (n = 942) compared natalizumab with placebo for 104 weeks [70]. High quality evidence from a single trial indicated a higher number of participants free from relapse (RR 1.59, 95% CI 1.40–1.81), a lower annualized relapse rate (MD = −0.50, 95% CI −0.63 to −0.37), fewer GAD lesions (RR −1.10, 95% CI −1.54 to −0.66) and new or newly enlarging T2 lesions (RR −9.10, 95% CI −10.98 to −7.22) in the natalizumab group. Moderate quality evidence suggested a beneficial effect on the number of participants with disability worsening (RR 0.59, 95% CI 0.46–0.75).

One trial (n = 621) compared daclizumab with placebo for 52 weeks [71] and indicated a lower annualized relapse rate (high quality evidence; MD = −0.25, 95% CI −0.37 to −0.13), a higher proportion of patients free from relapse (high quality evidence; RR 1.25, 95% CI 1.11–1.42) and a lower mean number of GAD lesions (moderate quality evidence; MD = −1.10, 95% CI −1.45 to −0.75) and new or newly enlarging T2 lesions in the daclizumab group. Low quality evidence from the same trial indicated a reduced risk of disability worsening (RR 0.43, 95% CI 0.22–0.85). In the extension study, the participants receiving placebo were re-randomized at 2 years post-randomization of the SELECT trial to receive 150 or 300 mg of daclizumab, whilst those already receiving the investigational drug were re-randomized to continue with their present dose or undergo a 20-week wash-out and subsequent re-initiation of the drug [72]. The results indicated a lower annualized relapse rate and fewer new T2 lesions in the continuous, wash-out and re-initiation groups than in the delayed-treatment group at 2 years' follow-up.

One trial (n = 1326) compared cladribine with placebo for 96 weeks [73]. High quality evidence from a single trial indicated a higher number of participants free from relapse (RR 1.31, 95% CI 1.20–1.42) and a lower annualized relapse rate (MD = −0.19, 95% CI −0.23 to −0.14) in the intervention group. The authors reported statistically significant reductions in GAD lesions, active T2 lesions and combined unique lesions in the intervention group compared with placebo (P < 0.0001).

Head to head comparisons. Head to head comparisons are available only for interferon, glatiramer acetate and natalizumab. Head to head comparisons between

glatiramer acetate and interferon are available from four trials [74–77], with the length of follow-up ranging from 52 to 104 weeks. There was no difference in the number of participants free from relapse at 2 years' follow-up (moderate quality evidence meta-analysis of three trials [74,76,77], $n = 2175$; RR 0.98, 95% CI 0.90–1.06) or disability worsening (RR 1.07, 95% CI 0.83–1.31), according to moderate quality evidence from a single trial [77]. At 2 years' follow-up, a low quality meta-analysis of the four trials ($n = 2341$) [74–77] indicated that fewer people in the glatiramer acetate group discontinued for any reason (RR 1.30, 95% CI 0.68−2.47) and due to side effects (RR 1.15, 95% CI 0.75–1.77) than in the interferon group, although the data were imprecise and the differences were not significant.

Teriflunomide, fingolimod and daclizumab were compared with interferon in single trials. There was a higher proportion of participants free from relapse in the interferon group ($n = 342$; RR 0.68, 95% CI 0.57–0.82) than in the teriflunomide group, with little difference between groups in the annualized relapse rate at 48 weeks' follow-up, according to low quality evidence [78]. Moderate quality evidence showed more participants free from relapse ($n = 1292$; RR 1.19, 95% CI 1.11–1.29), a lower annualized relapse rate (MD = −0.17, 95% CI −0.26 to −0.08) and fewer participants with disability worsening in the fingolimod group than in the placebo group at 1 year; however, the estimate was imprecise and not significant. MRI outcomes consistently favoured the fingolimod group [79]. Two extension studies at 2 [80] and 4.5 years [81] after the start of the original trial reported that early treatment showed a significant effect on the annualized relapse at 2 years with no significant differences for the annualized relapse or for disability worsening and little difference in the number of new T2 lesions, GAD lesions and percentage change in brain volume at 4.5 years' follow-up. Compared with interferon, daclizumab resulted in more participants free from relapse ($n = 1841$; RR 1.31, 95% CI 1.22–1.42), a lower annualized relapse rate (MD = −0.17, 95% CI −0.22 to −0.12), a reduced risk of disability worsening (RR 0.80, 95% CI 0.66–0.98) and a lower mean number of new or newly enlarging T2 lesions (MD = −5.20, 95% CI −6.30 to −4.10) at 144 weeks' follow-up, according to moderate quality evidence [82].

Three trials ($n = 1755$) compared alemtuzumab with interferon, with follow-ups ranging from 104 to 260 weeks [83–85]. There was a higher proportion of participants free from relapse (moderate quality evidence meta-analysis of three trials [83–85], $n = 1414$; RR 1.38, 95% CI 1.26–1.51) and a lower annualized relapse rate (moderate quality evidence meta-analysis of two trials [84,85], $n = 851$; MD = −0.25, 95% CI −0.33 to −0.18) in the alemtuzumab group at follow-ups ranging from 2 to 3 years. The effect on the annualized relapse in the alemtuzumab group (MD = −0.23, 95% CI −0.30 to −0.16) was maintained at 5 years according to low quality evidence from a single study [84]. Moreover, fewer participants in the alemtuzumab group had disability worsening at 2 to 3 years' follow-up (low quality evidence meta-analysis of three trials [83–85], $n = 1414$; RR 0.59, 95% CI 0.40–0.86) and at 5 years' follow-up (RR 0.43, 95% CI 0.24–0.78) [84]. Meta-analysis of the MRI data reported in two of the trials [84,85] showed a substantial and significant heterogeneity in the findings ($I^2 = 81\%$, $P = 0.02$) due to the different proportion of participants in the interferon group with new or newly enlarging T2 lesions. Considering each study individually, there was moderate evidence of a lower proportion of participants with a new or newly enlarging T2 in the alemtuzumab group, which was not statistically significant in one of the trials [83].

Two trials ($n = 1656$) compared ocrelizumab with interferon for 96 weeks [86]. The annualized relapse rate was significantly lower in participants receiving ocrelizumab than in those receiving interferon (high quality evidence, meta-analysis of two trials [86], $n = 1656$; MD = −0.13, 95% CI −0.18 to −0.08), and a higher proportion of participants with ocrelizumab showed disability improvement at the end of the trial when confirmed at 12 weeks (moderate quality evidence; RR 1.32, 95% CI 1.04–1.68) and at 24 weeks (moderate quality evidence; RR 1.35, 95% CI 1.02–1.79).

Secondary progressive MS. Considering specifically those trials addressing secondary progressive MS patients, five studies met the eligibility criteria (reported across seven papers) with sample sizes ranging from 194 to 939 participants and a 156-week follow-up for all trials. Overall, there was a higher proportion of women (58%) than men, the average age was 43 years, and the participants had been diagnosed with MS for approximately 13 years (range 10–14.7 years). At baseline, the EDSS scores ranged from 4.8 to 5.4 (mean of means 5.1). Interferon and mitoxantrone were the only DMDs studied. Further details about the characteristics of the included studies can be found in Appendix S4, Tables S26–S28.

Four trials ($n = 2646$) compared interferon with placebo [87–90]. At 3 years, there was a significant effect on disability worsening confirmed at 3 months (RR 0.78, 95% CI 0.66–0.92) [87] and a smaller effect on disability confirmed at 6 months (moderate quality evidence meta-analysis of three trials [87,89,90], $n = 1707$; RR 0.92, 95% CI 0.80−1.06). These studies reported a higher proportion of participants free from

combined unique active lesions in the interferon group than in the placebo group (meta-analysis of two trials [87,88], $n = 970$; RR 1.71, 95% CI 1.17–2.49). The only available extension study reported outcomes at 10 years after randomization in the core trial [91]. Patients who completed the core trial were offered interferon in an open-label extension for 18 months. Thereafter, treatment decisions were at the discretion of the treating physicians and the patient. Fewer participants in the early-treatment group (29%) had progressed to an EDSS score of 8 or higher than in the delayed-treatment group (36.4%).

One trial ($n = 194$) [92] compared mitoxantrone with placebo and reported a reduced risk of disability worsening (RR 0.38, 95% CI 0.15–0.99) at 104 weeks. A small non-randomized subgroup of participants in the trial underwent MRI scanning that showed no significant difference between the groups in the number of participants with positive GAD enhancement or in the number of GAD lesions at 1 or 2 years. The mean change from baseline of new T2-weighted lesions was significant at 2 years but not at 1 year.

GRADE tables and forest plots are presented in Appendix S5 and Appendix S6. Further details about the safety issues of these drugs are detailed in Appendix S7.

Review question 3: In patients with primary progressive MS, what is the benefit of treating with a DMD compared to no treatment?

Five RCTs met the eligibility criteria for this review (reported across six papers) [93–97], and all compared active drugs against placebo, with sample sizes ranging from 50 to 970 participants (mean 553) and a length of study follow-up ranging from 104 to 156 weeks. Overall, just over half of the participants were male, and the average age was 47 years. Participants had been diagnosed with primary progressive MS for an average of 6 years (range 2.9–11.4 years) and at baseline the EDSS scores ranged from 4.7 to 5.2 (mean of means 4.9). Further details about the characteristics of the included studies can be found in Appendix S4, Tables S29–S33.

Two available trials comparing interferon with placebo indicated little difference in the number of participants with disability worsening (confirmed at 3 months) at 2 years' follow-up (low quality evidence meta-analysis of two trials [93,95], $n = 108$; RR 0.97, 95% CI 0.62–1.52). In the single available extension study, patients who completed the core trial were eligible to enter the 5-year extension phase with no treatment [98]. There was no significant difference between early and delayed treatment in the proportion of participants with disability worsening, in their cognitive performance [as measured with the Paced Auditory Serial Addition Test (PASAT 3)] or in the change in T2 lesion volume. The authors reported a beneficial effect of early treatment on the change in brain parenchymal fraction.

Moderate quality evidence of a single trial of glatiramer acetate compared with placebo ($n = 2646$) suggested a non-significant effect on the number of participants with disability worsening (RR 0.87, 95% CI 0.75–1.02) and a longer time to disability worsening (HR 0.87, 95% CI 0.71–1.07) in the active treatment group at 156 weeks [97].

Moderate quality evidence of a single trial of fingolimod compared with placebo ($n = 970$) indicated little difference between groups in the proportion of participants with disability worsening [94].

Finally, a recently published trial ($n = 732$) compared ocrelizumab with placebo and showed high quality evidence of greater time to disability worsening in the ocrelizumab group than in the placebo group at 120 weeks' follow-up, when confirmed at 12 weeks (HR 0.76, 95% CI 0.59–0.98) and 24 weeks (HR 0.75, 95% CI 0.58–0.97). The authors also reported evidence of benefit with ocrelizumab compared with placebo for the volume of hyperintense lesions on T2-weighted images (HR 0.90, 95% CI 0.88–0.92) and change in brain volume at 120 weeks' follow-up (HR 17.5, 95% CI 3.2–29.3) [96].

GRADE tables and forest plots are presented in Appendix S5 and Appendix S6. Further details about the safety issues of these drugs are detailed in Appendix S7.

Quality assessment

All included studies in questions 1−3 were assessed for risk of bias. Sequence generation and allocation concealment were issues in most of the trials either because they were improperly conducted (causing high risk of bias) or because these issues were unclear according to the published information. Participants, personnel and outcome assessors were blind in most of the trials, with few exceptions that posed a high risk of bias [50,58,73,76,78,83–85,90]. When considering incomplete outcome data, a few trials had a high risk of bias due to missing data for more than 20% of the study sample or due to unequal drop-out between intervention groups [42,62,65,67,68,75,77,78,82,87–90,92,94,96,99]. Outcome assessor bias and selective outcome reporting were also a problem in some trials, either due to not meeting requirements with a high risk of bias [71,76,77,79] or because there was not enough information to make a judgement as no study protocols were available [51–53,59,75,93,95,97,99]. Appendix S5 gives further details on quality assessment.

Recommendations

Recommendation 1. The entire spectrum of DMDs should be prescribed only in centres with adequate infrastructure to provide:

1 proper monitoring of patients
2 comprehensive assessment
3 detection of side effects and capacity to address them promptly

[consensus statement]

Recommendation 2. Offer interferon or glatiramer acetate to patients with CIS and an abnormal MRI with lesions suggestive of MS who do not fulfil criteria for MS.

[strong]

Recommendation 3. Offer early treatment with DMDs in patients with active relapsing–remitting MS as defined by clinical relapses and/or MRI activity (active lesions, contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). This also includes CIS fulfilling current diagnostic criteria for MS.

[strong]

Recommendation 4. For active relapsing–remitting MS, choosing between the wide range of available drugs (interferon beta-1b, interferon beta-1a subcutaneously, intramuscularly, peginterferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, fingolimod, daclizumab, natalizumab, ocrelizumab and alemtuzumab) from the modestly effective to the highly efficacious will depend on the following factors, in discussion with the patient:

1 patient characteristics and comorbidities
2 disease severity/activity
3 drug safety profile
4 accessibility of the drug

[consensus statement]

Recommendation 5. Consider treatment with interferon beta-1a (subcutaneously) or interferon beta-1b in patients with active secondary progressive MS taking into account, in discussion with the patient, the dubious efficacy, as well as the safety and tolerability profile of these drugs.

[weak]

Recommendation 6. Consider treatment with mitoxantrone in patients with active secondary progressive MS taking into account, in discussion with the patient, the efficacy and specifically the safety and tolerability profile of this agent.

[weak]

Recommendation 7. Consider treatment with ocrelizumab or cladribine for patients with active secondary-progressive MS.

[weak]

Recommendation 8. Consider treatment with ocrelizumab for patients with primary-progressive MS.

[weak]

Recommendation 9. Always consult the Summary of Product Characteristics for dosage, special warnings and precautions for use, contraindications, and monitoring of side effects and potential harms.

[consensus statement]

Monitoring treatment response

Review question 4: In patients with relapsing MS treated with DMDs, does the presence of early disease activity (relapses and/or disability progression and/or MRI activity at 6 months/12 months) predict an increased risk of future disability?

One SR with a literature search up to 2014 met the inclusion criteria for this review [100]. An updated electronic database search from January 2014 to December 2016 identified 1653 records, and 1464 studies were excluded based on the title/abstract. After full-text appraisal of five studies, three met the eligibility criteria [101–103] and two were excluded [104,105]. An additional targeted electronic database search assessing the predictive value of early 'no evidence of disease activity' (NEDA) on disability progression (criterion was not included in the previous SR) identified 244 records, but only one study met the inclusion criteria [106] (Appendix S3).

The available SR [100] described the criteria used in the literature to define long-term (≥2 years from start of treatment) and short-term (≤2 years from treatment initiation) non-response to interferon or glatiramer acetate and examined the predictive value of short-term suboptimal response criteria (including EDSS score and/or an MRI parameter and/or relapse rate) for long-term non-response, at least 24 months after the start of treatment. Two additional studies not included in the previous SR used the Rio score and the modified Rio score at 1 year to predict responses at 3 [103] and 5 years [102] in MS patients treated with interferon beta for at least 1 year. Sormani *et al.* pooled data from nine European MS centres that evaluated response to treatment at 3 years or more [101]. The NEDA criterion was assessed yearly in a prospective cohort of CIS and relapsing–remitting MS patients to predict absence of disability worsening [106]. Further details about the study characteristics and assessed criteria can be found in Appendix S4, Tables S34–S36.

Overall, criteria that included MRI or MRI combined with clinical measures had a higher predictive value than clinical criteria alone. When considering

only MRI criteria, measures of new/newly enlarging T2 lesions outperformed those of GAD lesions. Of the 16 criteria evaluated in the SR by Rio & Ruiz-Pena [100] the following three were determined to have the best predictive value:

1 one or more new/newly enlarging T2 lesions
2 two or more new/newly enlarging T2 lesions
3 two or more criteria from the modified Rio score

The presence of one or more new/newly enlarging T2 lesions for predicting EDSS worsening at 4–4.8 years' follow-up resulted in a specificity of 70.2% and sensitivity of 85.5% for one or more lesions and a specificity of 83.6% and sensitivity of 62.4% for two or more lesions, according to a meta-analysis of two studies [104,107] (n = 764). The presence of two or more criteria from the modified Rio score had a specificity of 89.1% and sensitivity of 26.4% in predicting EDSS worsening at 4 years' follow-up, according to a meta-analysis of two studies [104,108] (n = 957). This result was confirmed in the study by Romero and colleagues [102]; however, in the study by Hyun *et al*. [103], the values for specificity and sensitivity appeared to be much higher. Rotstein 2015 [106] (n = 219) reported only the positive and negative predictive value of NEDA. The positive predictive value suggested that 71.7% of participants with NEDA at 1 year also had an absence of disability worsening at 7 years' follow-up. The authors reported only the lowest (40.7%) and highest (43.1%) negative predictive value of NEDA between years 2 and 6. Tables with descriptive results corresponding to this question are presented in Appendix S9.

Quality assessment

Using criteria from the AMSTAR tool, the SR was rated as low quality. This was due to the absence of reported information, namely the study characteristics of included studies, an excluded studies list and a quality assessment of included studies. The primary studies were assessed with the Cochrane tool ROBINS-I. All four studies were judged as having a moderate risk of bias. This was mainly due to a lack of information about missing data and potential confounding factors.

Review question 5: In MS patients treated with DMDs, should a follow-up MRI be performed in a pre-specified time scheme to monitor treatment response and safety?

No studies assessing the value of different MRI monitoring schemes for treatment response and safety were found. The use of MRI in the routine follow-up of patients with MS is, to date, less straightforward than in the diagnostic process. In the studies that assessed treatment response criteria (described in question 4), the MRI evaluation was performed at 6–12 months after treatment initiation and compared with a baseline MRI carried out at or prior to treatment onset.

Currently, there are several guidelines that aim to define the indications and frequency of MRI for monitoring the disease course in patients with an established diagnosis of MS [109,110]. Only the most recent guideline, developed by the MAGNIMS group, covers specific aspects regarding the use of MRI for monitoring treatment response and safety [111]. The Guideline Steering Committee has referred to the 'MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis for establishing disease prognosis and monitoring patients' to generate recommendations for this review question.

Recommendations

Recommendation 10. Consider combining MRI with clinical measures when evaluating disease evolution in treated patients.

[weak]

Recommendation 11. When monitoring treatment response in patients treated with DMDs, perform a standardized reference brain MRI usually within 6 months of treatment onset and compare it with a further brain MRI performed typically 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the following aspects:

1 the drug's mechanism of action (particularly the speed of action)
2 disease activity (including clinical and MRI measures)

[consensus statement]

Recommendation 12. When monitoring treatment response in patients treated with DMDs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method supplemented by GAD enhancing lesions for monitoring treatment response. Evaluation of these parameters requires:

1 high quality, standardized MRI scans
2 interpretation by highly qualified readers with experience in MS

[consensus statement]

Recommendation 13. When monitoring treatment safety in patients treated with DMDs, perform a standardized reference brain MRI:

1 every year in low risk progressive multifocal leukoencephalopathy (PML) patients
2 more frequent MRIs (on a 3–6 monthly basis) in high risk PML patients (JC virus positive, natalizumab treatment duration over 18 months)
3 in patients with high risk of PML who switch drugs, at the time that the current treatment is discontinued and after the new treatment is started

[consensus statement]

Treatment strategy if inadequate treatment response

Review question 6: In patients with relapsing MS treated with interferon or glatiramer acetate and evidence of early disease activity (relapses and/or disability progression and/or MRI activity at 6/12 months), what is the benefit of switching between interferon and glatiramer acetate versus moving to more efficacious drugs?
For review questions 6–8, the electronic database search identified 3856 records. Of these, 3853 studies were excluded based on their title/abstract and 82 studies were subjected to a full-text appraisal. After a full-text review and removal of duplicates, nine studies met the eligibility criteria for this review. Due to differences in study design and included populations, the results could not be meta-analysed and are reported narratively. Three of the studies were RCTs [85,112,113]; five were retrospective cohorts [114–118]; and one was a prospective cohort [119]. Before switching drugs, all participants had been receiving interferon beta-1a, interferon beta-1b or glatiramer acetate and were described as having had a treatment failure, although this term was not always defined [115,117] or was assessed subjectively by the neurologist [118]. Two studies included specific treatment failure definitions combining relapses (more than one or more than two) and sustained disability worsening (defined as increase in at least 0.5 points or increase in at least 1 point in the EDSS score compared with the year prior to therapy) [114,119]. In four studies, participants who switched drugs received fingolimod [112–116]; in two studies, participants switched to immunomodulators [118,119]; in one study, participants switched to natalizumab [117]; and in one trial, participants switched to alemtuzumab [85]. Further study characteristics are presented in Appendix S4, Tables S37 and S38.

All analysed studies were consistent in showing a benefit in switching to alemtuzumab, fingolimod or natalizumab compared with interferon or glatiramer acetate, depending on specific study comparators. Switching to alemtuzumab resulted in better outcomes in terms of relapses, with a lower annualized relapse rate (0.26 vs. 0.52; $P = 0.0002$) and a higher proportion of participants free from relapse (66% vs. 47%; $P < 0.0001$). Switching to alemtuzumab also resulted in a lower proportion of participants with disability worsening (13% vs. 20%; $P = 0.02$) and fewer participants with new or newly enlarging T2 lesions (46% vs. 68%; $P < 0.00001$) at 2 years after the switch, according to evidence with a moderate risk of bias [85]. Moreover, a larger proportion of participants in the interferon group dropped out of the study for any reason (8% vs. 32%; $P < 0.00001$) and due to side effects (3% vs. 7%, $P = 0.02$).

Switching to fingolimod resulted in a 61% reduction in the annualized relapse rate, a 46%–48% reduction in GAD lesion count and a 21%–27% reduction in new or newly enlarged T2 lesions at 52 weeks in a study with a low risk of bias [112]. Further evidence with a serious risk of bias reported a longer time to relapse (360 vs. 274 median days; $P = 0.006$) and a lower annualized relapse rate (0.19 vs. 0.51; $P = 0.0013$) in the group that switched to fingolimod at 51 weeks [114]. Finally, evidence from two studies with a moderate risk of bias showed consistent findings, with a greater time to relapse, a lower annualized relapse rate and a greater time to EDSS progression at 2 years after the switch [115,116]. All these studies reported consistent results of a higher proportion of participants discontinuing the study for any reason in the interferon/glatiramer acetate group than in the fingolimod group [113–116].

Switching to natalizumab resulted in a longer time to relapse and to disability worsening (HR 0.42, 95% CI 0.24–0.71; HR 0.38, 95% CI 0.20–0.71) at 2 years post-switch, according to evidence with a serious risk of bias [119]. The impact on annualized relapse rate, which held at 2, 3 and 4 years, was confirmed by a later study with a moderate risk of bias (annualized relapse rate of 0.20 vs. 0.58), but there was a disproportionately higher drop-out rate in the natalizumab group, which warrants caution when interpreting findings [118]. Other studies with a serious risk of bias could not confirm the positive results on the annualized relapse rate [117] or on time to disability worsening [118]. These studies reported little difference in the proportion of participants discontinuing due to adverse events (7% vs. 5.8%) [119] or a longer time to treatment discontinuation in the natalizumab group (HR 0.40, 95% CI 0.34–0.47) [118].

Quality assessment
Evidence obtained by RCTs was assessed for risk of bias using the Cochrane Risk of Bias tool. There was a low risk of bias for sequence generation, allocation concealment, attrition and selective outcome reporting for all included trials. In two of the trials, there was a high risk of performance and detection bias since all patients, providers and assessors were aware of treatment allocation [85,113], whereas in the third trial [112] the risk of bias was low since all participants, providers and assessors were blinded to treatment allocation. Appendix S4, Table S37, gives further details on the quality assessment.

The cohort studies were assessed using the Cochrane tool ROBINS-I; three were judged as

having a moderate risk of bias [115,116,118] and three as having a serious risk of bias [114,117,119]. The domain that most commonly had a high risk of bias was in the measurement of outcomes, as outcome assessors were not blinded to participant treatment. In two studies [114,117], the authors did not report all outcomes specified in the paper and were therefore at a high risk of bias for selective outcome reporting. Five out of the six cohort studies [114–116,118,119] used propensity score matching to account for potential confounders, and one of them [119] reported differences at baseline between participants who switched to a second-line drug and those who switched to a different first-line drug. Appendix S4, Table 38, gives further details on the quality assessment.

Recommendations

Recommendation 14. Offer a more efficacious drug to patients treated with interferon or glatiramer acetate who show evidence of disease activity assessed as recommended in questions 4 and 5 of this guideline.

[strong]

Recommendation 15. When deciding on which drug to switch to, in consultation with the patient, consider the following factors:

1 patient characteristics and comorbidities
2 drug safety profile
3 disease severity/activity

[consensus statement]

Treatment strategies if safety issues

Review question 7: In patients with relapsing MS who stop taking a highly efficacious drug, is there a risk of return and/or rebound of their disease activity (increased risk of relapses, disability progression and/or MRI activity)?

For review questions 6–8, the electronic database search identified 3853 records. Of these, 3771 studies were excluded based on their title/abstract and 82 studies were subjected to a full-text appraisal. After a full-text review and removal of duplicates, 19 studies met the eligibility criteria for this review. One study was an RCT [120]; 12 were prospective cohort studies [121–132]; and six were retrospective cohorts [133–138]. In 15 studies, participants were receiving natalizumab before discontinuing treatment due to safety issues, whereas in one study [127] participants were receiving fingolimod. The number of included participants ranged from 18 to 333 (mean 83). Treatment strategies after discontinuation of the drug varied and mainly included the following: no treatment, corticosteroids, interferon/glatiramer acetate and fingolimod. There was also great variation in the length of wash-out, which ranged from 1 month to 6 months. The mean/median number of natalizumab doses received prior to the switch ranged from 19 to 41. Further study characteristics are presented in Appendix S4, Table 39.

Rebound. Rebound was generally described as a return of disease activity beyond that seen in the pre-treatment period; however, there were differences in definitions across the included studies, ranging from the general 'change in the disease course with worsening of the disease activity beyond the pre-treatment levels' to the more specific 'increase in disease activity following natalizumab interruption defined as at least four T1 GAD lesions more than in pre-natalizumab scans'. Across 11 studies, two reported no evidence of rebound [123,135] and one reported no evidence of immune reconstitution inflammatory syndrome [128]. The proportion of participants showing evidence of rebound ranged, in most of the studies, from 9% to 12% [126,127,131,132,137], whereas other authors reported higher rebounds, including 14% [136], 21.2% [134] and 38.3% [138].

Relapse outcomes. At 24 weeks after natalizumab cessation, there was a significant reduction in the annualized relapse rate between the pre-natalizumab period and the post-natalizumab period (2 vs. 0.3; $P = 0.009$) [128] and a reduction in the mean number of relapses (1.1 vs. 0.07), although no P values were reported [120], according to fair quality evidence. At 52 weeks after natalizumab discontinuation, several studies of fair to poor quality reported a statistically significant reduction in the annualized relapse rate compared with that during the pre-natalizumab period [131,135,137,138] or described a reduction without statistical calculations [123,126]. However, other studies of fair quality reported no change in the annualized relapse rate and mean number of relapses between the two time periods [120,134].

Treatment after natalizumab varied across these studies. Patients treated with fingolimod approximately 3 months after natalizumab cessation showed a significantly reduced annualized relapse rate, whereas those who received no treatment showed a return to the same relapse rate observed in the pre-natalizumab period, according to fair quality evidence [133]. The length of wash-out prior to switching to fingolimod was described to have an impact on the proportion of participants relapsing, with 19.9% in wash-out up to 3 months, 31.1% for 3–6 months and 59.1% if wash-out was longer than 6 months [124]. In some studies [124,129,132,136], relapse was reported as a continuous outcome for the pre-natalizumab/fingolimod period and as a dichotomous outcome for the post-natalizumab/fingolimod period, so it was not possible to make a direct comparison between the two time periods.

Magnetic resonance imaging outcomes. Only six studies reported MRI outcomes in the pre-natalizumab and post-natalizumab period [121,123,126,128,131,138], and the results were less consistent than those for relapses. The presence of any new or enlarging T2-weighted lesion or any GAD lesion at 52 weeks after discontinuation was described in 48% of participants who had interrupted natalizumab, compared with 54% in the pre-natalizumab period [123]. Similarly, a small study (n = 23) reported a reduction in the proportion of participants who had an active MRI scan in the post-natalizumab period (30%) at 15 weeks compared with that during the pre-natalizumab period (70%) [121]. Various studies reported an increase in the mean number of GAD lesions in all participants as a group during the pre-natalizumab period compared to that during the post-natalizumab period [126,128,131,138].

Quality assessment

The study quality was assessed with the Quality Assessment of Before–After (Pre–Post) Studies with No Control Group tool developed by the National Heart, Lung, and Blood Institute and the Research Triangle Institute International. One study [123] was rated 'good'; 11 were rated 'fair', indicating some susceptibility to bias [120,121,124,126,128,129,131,134,135,137,138]; and four were rated 'poor', indicating a significant risk of bias [127,132,133,136]. The main reasons for the 'fair' and 'poor' ratings were a lack of outcome assessor blinding, a lack of definition of outcomes, no power calculations and no statistical analyses for the pre- and post-drug periods. Appendix S4, Table S39, gives further details on the quality assessment.

Review question 8: In patients with relapsing MS who stop taking a highly efficacious drug, what is the benefit of further treatment?

For review questions 6–8, the electronic database search identified 3853 records. Of these, 3771 studies were excluded based on their title/abstract and 82 studies were subjected to a full-text appraisal. After a full-text review and removal of duplicates, four studies met the eligibility criteria: three were prospective cohorts [131,139,140]; one was an RCT [141]; and participants in all the studies were receiving natalizumab before switching to other DMDs. The number of included participants ranged from 110 to 214 (mean 166), and the length of the follow-up post-switch ranged from 28 to 52 weeks (mean 44 weeks). Due to differences in study design and treatment groups post-switch, it was not possible to meta-analyse the data, and the results are reported narratively. Further details on the study characteristics are presented in Appendix S4, Table S40.

Evidence from a single RCT with a high risk of bias indicated that fewer participants who stayed on natalizumab had relapses (4%) compared to those who switched to placebo (17%) or to other therapies (20%) (interferon, glatiramer acetate, methylprednisolone) at 24 weeks post-switch. Similarly, in the natalizumab group, no participants had disease recurrence (one new GAD lesion of >0.8 cm^3 or two or more GAD lesions of any size), compared with 46% in the placebo group and 37% in the other therapies group [141]. Evidence from an observational study with a moderate risk of bias compared patients switching from natalizumab to fingolimod or to interferon/glatiramer acetate. The results showed a reduced risk of relapse (inter-rater reliability 0.52, 95% CI 0.37–0.74) and a lower proportion of patients showing disability worsening (11.4% vs. 22.5%) in the fingolimod group at 1 year post-switch, with no significant difference between groups in the time to disability worsening (HR 0.58, 95% CI 0.26–1.31) [140]. Additional evidence with a serious risk of bias indicated no significant difference between switching to fingolimod or switching to interferon/glatiramer acetate in the number of participants who were free from relapse [131]. Finally, switching from natalizumab to rituximab resulted in a reduced risk of relapse compared to that associated with switching to fingolimod (1.8% vs. 17.6%; HR 0.10, 95% CI 0.02–0.43) and a lower proportion of participants with contrast-enhancing lesions (1.4% vs. 24.2%; OR 0.05, 95% CI 0.0–0.22), according to evidence with a moderate risk of bias [139].

Quality assessment

According to the Cochrane tool ROBINS-I, two of the observational studies [139,140] were judged as having a moderate risk of bias, and the third one [131] was judged as having a serious risk of bias. All three observational cohort studies had a high risk of bias for outcome measurements, as outcome assessors were not blinded to participant treatment. There was no clear evidence of selection bias, and it was unclear how many participants dropped out of the studies. Only Alping *et al*. [139] and Iaffaldano *et al*. [140] used propensity score matching to account for potential confounders. The RCT [141] was judged as having a high risk of bias. There was a high risk of performance and detection bias since all patients, providers and assessors were aware of treatment allocation. There was an unclear risk of bias for missing outcome data, as the authors reported study drop-out only for 52 weeks' follow-up, and outcomes were reported only at 24 weeks. There was a low risk of bias for sequence generation and allocation concealment. Appendix S4, Table S40, gives further details on the quality assessment.

Recommendations

Recommendation 16. When treatment with a highly efficacious drug is stopped, either due to inefficacy or safety concerns, consider starting another highly efficacious drug. When starting the new drug, take into account the following factors:

1 disease activity (clinical and MRI), since the greater the activity the higher the urgency to start new treatment
2 half-life and biological activity of the previous drug
3 the potential for resumed disease activity or even rebound (particularly with natalizumab)

[consensus statement]

Recommendation 17. In treatment decisions, consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab.

[weak]

Long-term treatment

Review question 9: In patients with relapsing MS treated with a DMD who remain stable over a long time period, what is the benefit of continuing treatment compared to stopping?

The electronic database search for this question identified 3066 records. After removal of duplicates, 3014 studies were excluded based on their title/abstract. After a full-text review, one study was excluded, and only one prospective cohort study met the eligibility criteria [142]. It included patients treated with interferon or glatiramer acetate for at least 3 years without relapses for at least 5 years and compared those patients who stopped versus those who continued treatment using propensity score matching. At the study baseline, the mean age was 44 years, and the mean EDSS score was 3.5. The reason for treatment discontinuation was recorded only in 40% of the group (26.2% medication intolerance, 23.8% lack of improvement, 13% adverse event and 11% disease progression). There was little difference between the groups in the proportion of participants who relapsed (36% vs. 37.8%) and in the time to relapse (HR 1.07, 95% CI 0.84–1.37; $P = 0.584$), according to evidence with a moderate risk of bias. There was a longer time to disability progression in the group of participants who continued treatment than in those who discontinued (HR 1.47, 95% CI 1.18–1.84; $P = 0.001$) [142].

Quality assessment

According to the Cochrane tool ROBINS-I, the study was judged to have a moderate risk of bias overall. This was due to an unclear risk of attrition because the authors did not report whether any data were missing. There was a moderate risk of detection bias as it was not possible to blind treatment discontinuation.

Recommendations

Recommendation 18. Consider continuing a DMD if a patient is stable (clinically and on MRI) and shows no safety or tolerability issues.

[weak]

Treatment in special situations: pregnancy

Review question 10: In women with MS treated with DMDs who wish to start a pregnancy or who have an unplanned pregnancy, what should be the therapeutic approach?

For this question, an existing SR [143] was used to locate studies published prior to 2012, and eight studies met the eligibility criteria. These studies were supplemented by an electronic database search, which identified 808 records published between January 2012 and December 2016 and, of these, 787 studies were excluded based on their title/abstract and 21 studies were subjected to a full-text appraisal. After a full-text review and removal of duplicates, 14 studies met the eligibility criteria for this review, resulting in a total of 19 available studies. Due to differences in study design and included populations, it was not possible to meta-analyse any data, and the results are reported narratively. Further study characteristics are presented in Appendix S4, Table S41.

Several studies investigated the impact of exposure to interferon beta and/or glatiramer acetate [144–158], whilst fewer and more recent ones explored the effect of natalizumab [159–161], dimethyl fumarate [162], teriflunomide [163] and fingolimod [164]. In most studies, women were classified as being exposed to a disease modifying treatment (DMT) provided the last dose/injection of drug was administered after the last menstrual period before conception. Participants were recruited through patient registries, MS centres and clinical trials and from pharmaceutical companies' global pharmacovigilance databases. The number of included pregnancies ranged from 35 to 445 (mean 206).

Exposure to interferon and/or glatiramer acetate. Regarding exposure to interferon, a study with a moderate risk of bias indicated no significant difference between groups (exposed versus non-exposed) in the proportion of infants born with low birth weight (OR 1.14, 95% CI 0.41–3.15; $P = 0.803$) [165]. This was confirmed in two additional studies with a serious risk of bias [145,155]. For spontaneous abortion, evidence with a serious risk of bias due to low numbers indicated a higher proportion of women with spontaneous abortion in the exposed group [144,145,155,165]. The proportion of infants with congenital malformations

was higher in the exposed group (9% vs. 5%) [145] but was not confirmed in a later study showing a higher risk in the unexposed group (3.1% vs. 5.5%) [165]. These comparisons were based on a small number of participants and should be interpreted with caution. For glatiramer acetate, evidence with a moderate risk of bias (n = 246) indicated a higher number of spontaneous abortions in the exposed group than in the unexposed group (8.6% vs. 6.3%); however, congenital malformations were reported to be higher in the unexposed group (6.7% vs. 2.2%) [153]. Seven additional studies included women who were exposed to interferon or glatiramer acetate; in three of these studies, the exposure groups were combined [143,147,149], whereas in four they were separated, resulting in three armed studies [150–152,158]. There are inconsistent findings between the different studies regarding low birth weight, spontaneous abortion and congenital malformations. Further details of the study results are presented in Appendix S9, Table S4.

Exposure to natalizumab. One study with a serious risk of bias compared exposure to natalizumab with interferon or glatiramer acetate and suggested little difference between the groups in the proportion of infants born with low birth weight but a higher risk of spontaneous abortion in the group exposed to interferon or glatiramer acetate (21.1% vs. 17.4%) and a higher proportion of infants with congenital malformations in the group exposed to natalizumab (3.9% vs. 1.4%) [159]. Compared to women who were not exposed to DMDs, evidence with a serious risk of bias indicated a higher proportion of women experiencing a spontaneous abortion in those exposed to natalizumab but a higher proportion of infants born with a congenital malformation in the unexposed group [161]. Further details of the study results are presented in Appendix S9, Table S4.

Exposure to other disease-modifying treatments. Three studies with a serious risk of bias compared pregnancy outcomes in women who had unplanned conceptions whilst receiving dimethyl fumarate [162], fingolimod [164] and teriflunomide [163] during clinical trials with those who had received placebo. In both the fingolimod and teriflunomide studies [163,164], the placebo groups could not be considered as there were very few participants. Amongst the women receiving fingolimod, 24% experienced a spontaneous abortion, and 5% of live births resulted in infants with a congenital malformation. For the women exposed to teriflunomide, 18.8% had a spontaneous abortion, and out of 27 live births there were no malformations. The only study with a control group suggested a higher proportion of pregnancies resulting in spontaneous abortion in the placebo group (15.4%) than in the dimethyl-fumarate-exposed group (7.7%) [162]. Further details of study results are presented Appendix S9, Table S4.

Quality assessment

According to the Cochrane tool ROBINS-I, all cohort studies that included an exposed and unexposed group except four [153,154,158,165] were judged as having a serious risk of bias. Confounding and outcome measurement were the domains that most commonly had a high risk of bias, as outcome assessors may have been aware of participants' exposure to DMDs. The risk of selective outcome reporting could not be assessed because no study protocols were available. The classification of participants as exposed or unexposed was not a problem in several studies [149,150,153–155,158,159,161–165] as exposed status was clearly defined, and classification was unlikely to have been affected by knowledge of the outcomes as they were measured prospectively. However, in some studies, information used to define DMT exposure was recorded retrospectively after delivery and therefore infant outcomes may have biased recall of prior exposure. This issue resulted in a serious risk of bias [144,147,151,155] or a moderate risk of bias [145,152] in this domain. For the five cohort studies that included only an exposed group, three were rated as moderate quality [146,148,160] and two as poor quality [156,157] according to the National Institutes of Health Quality Assessment Tool for Before–After (Pre–Post) Studies with No Control Group.

Recommendations

Recommendation 19. Advise all women of childbearing potential that DMTs are not licensed during pregnancy, except glatiramer acetate 20 mg/ml.

[consensus statement]

Recommendation 20. For women planning a pregnancy, if there is a high risk of disease reactivation, consider using interferon or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered.

[weak]

Recommendation 21. For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who, despite this advice, still decide to become pregnant or have an unplanned pregnancy:

1. treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications
2. treatment with alemtuzumab could be an alternative therapeutic option for planned pregnancy in very

active cases, provided that a 4-month interval is strictly observed from the latest infusion until conception.
[weak]

Guideline update

The present guideline will be updated in 5 years. In the case of major changes in the evidence on the existing benefits and harms of included interventions or if new interventions become available this update could be approached earlier.

Disclosure of conflicts of interest

X. Montalban reports personal fees for consultancy and speaking from Actelion, Bayer, Biogen, Celgene, Hoffmann-La Roche, Merck, Novartis, Oryzon Genomics, Sanofi Genzyme, and Teva, outside the submitted work.

R. Gold reports personal fees from Biogen, Teva, Novartis, Sanofi Genzyme, Bayer Vital, Merck Serono and Roche, and grants from Biogen, Teva, Sanofi Genzyme and Novartis, outside the submitted work.

A. J. Thompson reports personal fees and other from MedDay, Novartis, Eisai, Biogen, and Teva, outside the submitted work; as Editorial Board member of *The Lancet Neurology*, he received free subscription; as Editor-in-Chief of *Multiple Sclerosis Journal*, he received honorarium from SAGE Publications; received support for travel as Chair of Scientific Advisory Board, International Progressive MS Alliance (PMSA), Member; National Multiple Sclerosis Society (USA), Research Programs Advisory Committee; Chair, International Medical and Scientific Board, and Board Member Multiple Sclerosis International Federation (MSIF); he received honoraria and support for travel for lecturing from EXCEMED, Academic CME and Remedica.

S. Otero reports personal fees and support for travel to meetings from Serono Foundation, outside the submitted work.

M. P. Amato reports grants from Biogen, Merck, Sanofi and Teva and personal fees for lecturing and advising from Bayer, Biogen, Roche, Sanofi Genzyme, Teva and Celgene, outside the submitted work.

G. Comi reports personal fees from Novartis, Teva, Sanofi Genzyme, Merck, Biogen, Roche, Almirall, Celgene, Forward Pharma, MedDay, EXCEMED, outside the submitted work.

T. Derfuss serves on scientific advisory boards/steering committees for Novartis, Merck Serono, Biogen, GeNeuro, Sanofi Genzyme, Mitsubishi Tanabe Pharma, Teva, Octapharma and Bayer Schering Pharma; has received funding for travel and/or speaker honoraria from Biogen, Novartis, Sanofi Genzyme, Merck Serono and Bayer Schering Pharma; and receives research support from Novartis, Biogen, the Swiss National Research Foundation, the European Union and the Swiss Multiple Sclerosis Society; reports grants from Biogen and Novartis, other from Biogen, Novartis, Sanofi Genzyme, Merck Serono, GeNeuro, Roche, Celgene, MedDay, outside the submitted work; his wife is an employee of Novartis and holds stock options.

F. Fazekas reports personal fees for consulting and lecturing and support for travel to meetings from Actelion, Biogen, Sanofi Genzyme, MedDay, Merck, Pfizer, Novartis, Teva Ratiopharm, Perceptive Informatics, outside the submitted work.

H. P. Hartung reports fees for serving on steering committees, data monitoring committees, adboards, speaking and support for travel to meetings from BayerHealthcare, Biogen, Sanofi Genzyme, GeNeuro, MedImmune, Merck, Novartis, Octapharma, Receptos, Roche, Teva, and personal fees for consulting from Opexa, outside the submitted work.

E. Havrdova received honoraria for speaking and consulting services from Actelion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi Genzyme and Teva. She has been supported by Czech Ministry of Education, project PROGRES Q27/LF1.

B. Hemmer reports grants from Chugai; personal fees and non-financial support from Bayer, Novartis, Biogen and Merck; grants, personal fees and non-financial support from Hoffman-La Roche, outside the submitted work.

L. Kappos reports grants received at his institution from Actelion, Bayer, Biogen, CSL Behring, df-mp, the European Union, Sanofi Genzyme, Merck, Mitsubishi Pharma, Novartis, Pfizer, Receptos/Celgene, Roche, Sanofi-Aventis, Santhera, Teva, UCB, Alkermes, Almirall, EXCEMED, GeNeuro SA, Vianex, Allergan, Roche Research Foundations, the Swiss Multiple Sclerosis Society, the Swiss National Research Foundation, and other from Neurostatus, outside the submitted work.

R. Liblau reports having received grants and honoraria for consultancy and speaking from Biogen, Diaccurate, Servier, Sanofi Genzyme, GlaxoSmithKline, and Novartis.

C. Lubetzki reports personal fees from Biogen, Sanofi Genzyme, Novartis, Roche, and other from Vertex, during the conduct of the study.

D. H. Miller reports grants from Biogen, personal fees from Mitsubishi Pharma Europe, Bayer Schering, and GlaxoSmithKline, grants and personal fees from Novartis, outside the submitted work.

T. Olsson reports grants and honoraria for lecturing from Biogen, Merck, Novartis, Roche and Sanofi Genzyme.

K. Selmaj reports personal fees from Roche during the conduct of the study; personal fees from Roche,

Receptos, Novartis, Biogen, Synthon, Teva, Sanofi Genzyme, outside the submitted work.

A. Siva reports receiving honoraria and consultation fees from Novartis, Genzyme, Bayer, Biogen Idec, Merck Serono; Genzyme, Teva and Roche; received travel and registration coverage for attending several national or international congresses or symposia, from Merck Serono, Biogen Idec/Gen Pharma of Turkey, Novartis, Teva; Genzyme and Roche outside the submitted work.

P. S. Sorensen reports grants and honoraria for consultancy and lecturing from Merck, Teva, Novartis, Sanofi Genzyme, Biogen, GlaxoSmithKline, MedDay, Forward Pharma, Teva and GlaxoSmithKline, outside the submitted work.

M. P. Sormani reports personal fees from Biogen, Novartis, Teva, Merck Serono, Roche, GeNeuro, Medday and Sanofi Genzyme, outside the submitted work.

C. Thalheim, in his capacity as consultant for EU health affairs, has received consultancy fees by Gruenenthal and by PharmaGenesis. In his capacity as Director External Affairs of the European MS Platform, he served in advisory boards and/or workshops by Biogen, Merck, Novartis, Sanofi Genzyme, Servier and Takeda. His employer, the European Multiple Sclerosis Platform, has received unrestricted project grants from Actelion, Almirall, Bayer, Biogen, icometrix, MedDay, Merck, Mylan, Novartis, Roche, Sanofi Genzyme, SCA, Servier, Synthon, Terumo and Teva.

H. Wiendl reports personal fees from AbbVie, Actelion, Alexion, Cognomed, Evgen Pharma, Hoffmann-La Roche, Gemeinnützige Hertie-Stiftung, IGES, MedDay Pharmaceuticals, Novartis Pharma AG, PeerVoice; Roche Pharma AG, Sanofi-Aventis, Swiss Multiple Sclerosis Society, Teva, and WebMD Global; grants from GlaxoSmithKline; grants and personal fees from Biogen GmbH, Genzyme – A Sanofi Company, Merck Serono GmbH, outside the submitted work.

F. Zipp reports grants from the German Research Foundation (DFG) and the German Federal Ministry of Education and Research (BMBF), personal fees from Octapharma, personal fees and travel support from Novartis, Merck, Biogen, Sanofi-Aventis and ONO, during the conduct of the study; grants from the DFG, BMBF and Progressive MS Alliance, personal fees and travel support from Biogen, ONO, Sanofi Genzyme, Sanofi-Aventis and Octapharma, grants, personal fees and travel support from Teva, Merck Serono, Novartis, Bayer Healthcare, outside the submitted work.

D. Chandraratna, M. Clanet, E. Marcus and S. Pilling declare no financial or other conflicts of interest. All ICMJE forms are available in Appendix S11.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Review protocols.
Appendix S2. Search strategies.
Appendix S3. Excluded studies.
Appendix S4. Characteristics of included studies.
Appendix S5. GRADE tables.
Appendix S6. Forest plots.
Appendix S7. Additional safety data.
Appendix S8. Results of the extension studies.
Appendix S9. Descriptive results tables.
Appendix S10. Results of the consensus process.
Appendix S11. ICMJE forms.

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000; **343:** 938–952.
2. Kingwell E, Zhu F, Marrie RA, *et al*. High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991−2010). *J Neurol* 2015; **262:** 2352–2363.
3. Grytten N, Aarseth JH, Lunde HM, Myhr KM. A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland County, Western Norway. *J Neurol Neurosurg Psychiatry* 2016; **87:** 100–105.
4. Browne P, Chandraratna D, Angood C, *et al*. Atlas of Multiple Sclerosis 2013: a growing global problem with widespread inequity. *Neurology* 2014; **83:** 1022–1024.
5. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. *Mult Scler* 2017; **23:** 179–191.
6. Stawowczyk E, Malinowski KP, Kawalec P, Mocko P. The indirect costs of multiple sclerosis: systematic review and meta-analysis. *Expert Rev Pharmacoecon Outcomes Res* 2015; **15:** 759–786.
7. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain* 2006; **129:** 606–616.
8. Weinshenker BG, Bass B, Rice GP, *et al*. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989; **112:** 133–146.
9. Miller DH, Leary SM. Primary-progressive multiple sclerosis. *Lancet Neurol* 2007; **6:** 903–912.
10. Thompson AJ, Polman CH, Miller DH, *et al*. Primary progressive multiple sclerosis. *Brain* 1997; **120:** 1085–1096.
11. European public assessment reports: European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=Diseases.Nervous+System+Diseases.Demyelinating+Diseases.Demyelinating+Autoimmune+Diseases%2C+CNS&treeNumber=&currentCategory=Multiple+Sclerosis&searchGenericType=generics (accessed 10/10/2017).

12. Winkelmann A, Loebermann M, Reisinger EC, Hartung HP, Zettl UK. Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat Rev Neurol* 2016; **12:** 217–233.
13. Subei AM, Ontaneda D. Risk mitigation strategies for adverse reactions associated with the disease-modifying drugs in multiple sclerosis. *CNS Drugs* 2015; **29:** 759–771.
14. McDonald WI, Compston A, Edan G, *et al*. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol* 2001; **50:** 121–127.
15. Polman CH, Reingold SC, Banwell B, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; **69:** 292–302.
16. Polman CH, Reingold SC, Edan G, *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald Criteria'. *Ann Neurol* 2005; **58:** 840–846.
17. Thompson AJ, Banwell BL, Barkhof F, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2017; https://doi.org/10.1016/S1474-4422(17)30470-2. [Epub ahead of print].
18. Lublin FD, Reingold SC, Cohen JA, *et al*. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; **83:** 278–286.
19. Tintore M, Rovira A, Rio J, *et al*. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain* 2015; **138:** 1863–1874.
20. Jokubaitis VG, Spelman T, Kalincik T, *et al*. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. *Ann Neurol* 2016; **80:** 89–100.
21. Degenhardt A, Ramagopalan SV, Scalfari A, Ebers GC. Clinical prognostic factors in multiple sclerosis: a natural history review. *Nat Rev Neurol* 2009; **5:** 672–682.
22. Broadley SA, Barnett MH, Boggild M, *et al*. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective: part 2 New and emerging therapies and their efficacy. MS Neurology Group of the Australian and New Zealand Association of Neurologists. *J Clin Neurosci* 2014; **21:** 1847–1856.
23. Correale J, Abad P, Alvarenga R, *et al*. Management of relapsing–remitting multiple sclerosis in Latin America: practical recommendations for treatment optimization. *J Neurol Sci* 2014; **339:** 196–206.
24. National Clinical Guideline Centre. National Institute for Health and Care Excellence: Clinical Guidelines. Multiple Sclerosis: Management of Multiple Sclerosis in Primary and Secondary Care. London: National Institute for Health and Care Excellence (UK) Copyright (c) National Clinical Guideline Centre, 2014.
25. Yamout B, Alroughani R, Al-Jumah M, *et al*. Consensus recommendations for the diagnosis and treatment of multiple sclerosis: the Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS). *Curr Med Res Opin* 2015; **31:** 1349–1361.
26. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* 1996; **46:** 907–911.
27. Chitnis T, Tenembaum S, Banwell B, *et al*. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. *Mult Scler* 2012; **18:** 116–127.
28. Wassmer E, Chitnis T, Pohl D, *et al*. International Pediatric MS Study Group Global Members Symposium report. *Neurology* 2016; **87**(9 Suppl. 2)**:** S110–S116.
29. Krupp LB, Tardieu M, Amato MP, *et al*. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* 2013; **19:** 1261–1267.
30. Tardieu M, Banwell B, Wolinsky JS, Pohl D, Krupp LB. Consensus definitions for pediatric MS and other demyelinating disorders in childhood. *Neurology* 2016; **87**(9 Suppl. 2)**:** S8–S11.
31. Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64:** 383–394.
32. Leone MA, Keindl M, Schapira AH, Deuschl G, Federico A. Practical recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces. *Eur J Neurol* 2015; **22:** 1505–1510.
33. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic review of Interventions*. The Cochrane Collaboration, 2008.
34. Sterne JA, Hernan MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355:** i4919.
35. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:** 924–926.
36. Rankin NM, McGregor D, Butow PN, *et al*. Adapting the nominal group technique for priority setting of evidence–practice gaps in implementation science. *BMC Med Res Methodol* 2016; **16:** 110.
37. Murphy MK, Black NA, Lamping DL, *et al*. Consensus development methods, and their use in clinical guideline development. *Health Technol Assess* 1998; **2:** i–iv, 1–88.
38. Comi G, De Stefano N, Freedman MS, *et al*. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. *Lancet Neurol* 2012; **11:** 33–41.
39. Comi G, Martinelli V, Rodegher M, *et al*. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **374:** 1503–1511.
40. Jacobs LD, Beck RW, Simon JH, *et al*. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med* 2000; **343:** 898–904.
41. Kappos L, Polman CH, Freedman MS, *et al*. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology* 2006; **67:** 1242–1249.
42. Miller AE, Wolinsky JS, Kappos L, *et al*. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; **13:** 977–986.
43. Comi G, Martinelli V, Rodegher M, *et al*. Effects of early treatment with glatiramer acetate in patients with

clinically isolated syndrome. *Mult Scler* 2013; **19:** 1074–1083.
44. Kappos L, Edan G, Freedman MS, *et al*. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. *Neurology* 2016; **87:** 978–987.
45. Kinkel RP, Kollman C, O'Connor P, *et al*. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. *Neurology* 2006; **66:** 678–684.
46. Edan G, Kappos L, Montalban X, *et al*. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. *J Neurol Neurosurg Psychiatry* 2014; **85:** 1183–1189.
47. Kappos L, Freedman MS, Polman CH, *et al*. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet* 2007; **370:** 389–397.
48. Kappos L, Freedman MS, Polman CH, *et al*. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. *Lancet Neurol* 2009; **8:** 987–997.
49. Calabresi PA, Kieseier BC, Arnold DL, *et al*. Pegylated interferon beta-1a for relapsing–remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol* 2014; **13:** 657–665.
50. Vollmer TL, Sorensen SP, Selmaj K, *et al*. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. *J Neurol* 2014; **261:** 773–783.
51. Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. *Neurology* 1993; **43:** 655–661.
52. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet* 1998; **352:** 1498–1504.
53. Jacobs LD, Cookfair DL, Rudick RA, *et al*. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol* 1996; **39:** 285–294.
54. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. *Neurology* 2001; **56:** 1628–1636.
55. Kieseier BC, Arnold DL, Balcer LJ, *et al*. Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. *Mult Scler* 2015; **21:** 1025–1035.
56. Kappos L, Traboulsee A, Constantinescu C, *et al*. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing–remitting MS. *Neurology* 2006; **67:** 944–953.
57. Ebers GC, Traboulsee A, Li D, *et al*. Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial. *J Neurol Neurosurg Psychiatry* 2010; **81:** 907–912.
58. Fox RJ, Miller DH, Phillips JT, *et al*. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; **367:** 1087–1097.
59. Johnson KP, Brooks BR, Cohen JA, *et al*. Copolymer 1 reduces relapse rate and improves disability in relapsing–remitting multiple sclerosis: results of a phase III multicenter, double- blind, placebo-controlled trial. *Neurology* 1995; **45:** 1268–1276.
60. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. Three times weekly glatiramer acetate in relapsing–remitting multiple sclerosis. *Ann Neurol* 2013; **73:** 705–713.
61. Johnson KP, Brooks BR, Ford CC, *et al*. Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. Copolymer 1 Multiple Sclerosis Study Group. *Mult Scler* 2000; **6:** 255–266.
62. Confavreux C, O'Connor P, Comi G, *et al*. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; **13:** 247–256.
63. O'Connor P, Wolinsky JS, Confavreux C, *et al*. Randomised trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011; **365:** 1293–1303.
64. O'Connor P, Comi G, Freedman MS, *et al*. Long-term safety and efficacy of teriflunomide: nine-year follow-up of the randomized TEMSO study. *Neurology* 2016; **86:** 920–930.
65. Gold R, Kappos L, Arnold DL, *et al*. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; **367:** 1098–1107.
66. Gold R, Arnold DL, Bar-Or A, *et al*. Long-term effects of delayed-release dimethyl fumarate in multiple sclerosis: interim analysis of ENDORSE, a randomized extension study. *Mult Scler* 2016; **23:** 253–265.
67. Calabresi PA, Radue EW, Goodin D, *et al*. Safety and efficacy of fingolimod in patients with relapsing–remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; **13:** 545–556.
68. Kappos L, Radue EW, O'Connor P, *et al*. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 387–401.
69. Kappos L, O'Connor P, Radue EW, *et al*. Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial. *Neurology* 2015; **84:** 1582–1591.
70. Polman CH, O'Connor PW, Havrdova E, *et al*. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 899–910.
71. Gold R, Giovannoni G, Selmaj K, *et al*. Daclizumab high-yield process in relapsing–remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet* 2013; **381:** 2167–2175.
72. Giovannoni G, Gold R, Selmaj K, *et al*. Daclizumab high-yield process in relapsing–remitting multiple sclerosis (SELECTION): a multicentre, randomised, double-blind extension trial. *Lancet Neurol* 2014; **13:** 472–481.
73. Giovannoni G, Comi G, Cook S, *et al*. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 416–426.
74. Cadavid D, Wolansky LJ, Skurnick J, *et al*. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology* 2009; **72:** 1976–1983.
75. Calabrese M, Bernardi V, Atzori M, *et al*. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing–remitting multiple sclerosis. *Mult Scler* 2012; **18:** 418–424.

76. Mikol DD, Barkhof F, Chang P, *et al*. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol* 2008; **7:** 903–914.
77. O'Connor P, Filippi M, Arnason B, *et al*. 250 μg or 500 μg interferon beta-1b versus 20 mg glatiramer acetate in relapsing–remitting multiple sclerosis: a prospective, randomised, multicentre study. *Lancet Neurol* 2009; **8:** 889–897.
78. Vermersch P, Czlonkowska A, Grimaldi LM, *et al*. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Mult Scler J* 2014; **20:** 705–716.
79. Cohen JA, Barkhof F, Comi G, *et al*. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 402–415.
80. Khatri B, Barkhof F, Comi G, *et al*. Comparison of fingolimod with interferon beta-1a in relapsing–remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. *Lancet Neurol* 2011; **10:** 520–529.
81. Cohen JA, Khatri B, Barkhof F, *et al*. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. *J Neurol Neurosurg Psychiatry* 2016; **87:** 468–475.
82. Kappos L, Wiendl H, Selmaj K, *et al*. Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2015; **373:** 1418–1428.
83. Cohen JA, Coles AJ, Arnold DL, *et al*. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing–remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; **380:** 1819–1828.
84. Coles AJ, Compston DA, Selmaj KW, *et al*. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008; **359:** 1786–1801.
85. Coles AJ, Twyman CL, Arnold DL, *et al*. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; **380:** 1829–1839.
86. Hauser SL, Bar-Or A, Comi G, *et al*. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017; **376:** 221–234.
87. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. *Lancet* 1998; **352:** 1491–1497.
88. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: clinical results. *Neurology* 2001; **56:** 1496–1504.
89. Andersen O, Elovaara I, Farkkila M, *et al*. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2004; **75:** 706–710.
90. Panitch H, Miller A, Paty D, Weinshenker B; North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology* 2004; **63:** 1788–1795.
91. Kuhle J, Hardmeier M, Disanto G, *et al*. A 10-year follow-up of the European multicenter trial of interferon beta-1b in secondary-progressive multiple sclerosis. *Mult Scler* 2016; **22:** 533–543.
92. Hartung HP, Gonsette R, Konig N, *et al*. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002; **360:** 2018–2025.
93. Leary SM, Miller DH, Stevenson VL, Brex PA, Chard DT, Thompson AJ. Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. *Neurology* 2003; **60:** 44–51.
94. Lublin F, Miller DH, Freedman MS, *et al*. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2016; **387:** 1075–1084.
95. Montalban X. Overview of European pilot study of interferon b-1b in primary progressive multiple sclerosis. *Mult Scler* 2004; **10**(3 suppl)**:** S62–S64.
96. Montalban X, Hauser SL, Kappos L, *et al*. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017; **376:** 209–220.
97. Wolinsky JS, Narayana PA, O'Connor P, *et al*. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. *Ann Neurol* 2007; **61:** 14–24.
98. Tur C, Montalban X, Tintore M, *et al*. Interferon beta-1b for the treatment of primary progressive multiple sclerosis: five-year clinical trial follow-up. *Arch Neurol* 2011; **68:** 1421–1427.
99. Evidence of interferon beta-1a dose response in relapsing–remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. *Neurology* 1999; **53:** 679–686.
100. Rio J, Ruiz-Pena JL. Short-term suboptimal response criteria for predicting long-term non-response to first-line disease modifying therapies in multiple sclerosis: a systematic review and meta-analysis. *J Neurol Sci* 2016; **361:** 158–167.
101. Sormani MP, Gasperini C, Romeo M, *et al*. Assessing response to interferon-beta in a multicenter dataset of patients with MS. *Neurology* 2016; **87:** 134–140.
102. Romeo M, Martinelli V, Rodegher M, *et al*. Validation of 1-year predictive score of long-term response to interferon-beta in everyday clinical practice multiple sclerosis patients. *Eur J Neurol* 2015; **22:** 973–980.
103. Hyun JW, Kim SH, Jeong IH, *et al*. Utility of the Rio score and modified Rio score in Korean patients with multiple sclerosis. *PLoS One* 2015; **10:** e0129243.
104. Prosperini L, Mancinelli CR, De Giglio L, De Angelis F, Barletta V, Pozzilli C. Interferon beta failure predicted by EMA criteria or isolated MRI activity in multiple sclerosis. *Mult Scler* 2014; **20:** 566–576.
105. Rio J, Rovira A, Blanco Y, *et al*. Response to treatment with interferon beta in patients with multiple sclerosis. Validation of the Rio score. *Rev Neurol* 2016; **63:** 145–150.
106. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of no evidence of disease activity in a

7-year longitudinal multiple sclerosis cohort. *JAMA Neurol* 2015; **72:** 152–158.
107. Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. *Eur J Neurol* 2009; **16:** 1202–1209.
108. Sormani MP, Rio J, Tintore M, *et al*. Scoring treatment response in patients with relapsing multiple sclerosis. *Mult Scler* 2013; **19:** 605–612.
109. Simon JH, Li D, Traboulsee A, *et al*. Standardized MR imaging protocol for multiple sclerosis: consortium of MS centers consensus guidelines. *AJNR Am J Neuroradiol* 2006; **27:** 455–461.
110. Cook SD, Dhib-Jalbut S, Dowling P, *et al*. Use of magnetic resonance imaging as well as clinical disease activity in the clinical classification of multiple sclerosis and assessment of its course: a report from an international CMSC consensus conference, March 5–7, 2010. *Int J MS Care* 2012; **14:** 105–114.
111. Wattjes MP, Rovira A, Miller D, *et al*. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis – establishing disease prognosis and monitoring patients. *Nat Rev Neurol* 2015; **11:** 597–606.
112. Cohen JA, Barkhof F, Comi G, *et al*. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. *J Neurol* 2013; **260:** 2023–2032.
113. Fox E, Edwards K, Burch G, *et al*. Outcomes of switching directly to oral fingolimod from injectable therapies: results of the randomized, open-label, multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis. *Mult Scler Relat Disord* 2014; **3:** 607–619.
114. Bergvall N, Makin C, Lahoz R, *et al*. Relapse rates in patients with multiple sclerosis switching from interferon to fingolimod or glatiramer acetate: a US claims database study. *PLoS One* 2014; **9:** e88472.
115. Braune S, Lang M, Bergmann A. Efficacy of fingolimod is superior to injectable disease modifying therapies in second-line therapy of relapsing remitting multiple sclerosis. *J Neurol* 2016; **263:** 327–333.
116. He A, Spelman T, Jokubaitis V, *et al*. Comparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. *JAMA Neurol* 2015; **72:** 405–413.
117. Rio J, Tintore M, Sastre-Garriga J, *et al*. Change in the clinical activity of multiple sclerosis after treatment switch for suboptimal response. *Eur J Neurol* 2012; **19:** 899–904.
118. Spelman T, Kalincik T, Zhang A, *et al*. Comparative efficacy of switching to natalizumab in active multiple sclerosis. *Ann Clin Transl Neurol* 2015; **2:** 373–387.
119. Prosperini L, Gianni C, Leonardi L, *et al*. Escalation to natalizumab or switching among immunomodulators in relapsing multiple sclerosis. *Mult Scler J* 2012; **18:** 64–71.
120. Weinstock-Guttman B, Hagemeier J, Kavak KS, *et al*. Randomised natalizumab discontinuation study: taper protocol may prevent disease reactivation. *J Neurol Neurosurg Psychiatry* 2016; **87:** 937–943.
121. Borriello G, Prosperini L, Mancinelli C, Gianni C, Fubelli F, Pozzilli C. Pulse monthly steroids during an elective interruption of natalizumab: a post-marketing study. *Eur J Neurol* 2012; **19:** 783–787.
122. Borriello G, Prosperini L, Marinelli F, Fubelli F, Pozzilli C. Observations during an elective interruption of natalizumab treatment: a post-marketing study. *Mult Scler J* 2011; **17:** 372–375.
123. Clerico M, Schiavetti I, De Mercanti SF, *et al*. Treatment of relapsing–remitting multiple sclerosis after 24 doses of natalizumab: evidence from an Italian spontaneous, prospective, and observational study (the TY-STOP study). *JAMA Neurol* 2014; **71:** 954–960.
124. Cohen M, Maillart E, Tourbah A, *et al*. Switching from natalizumab to fingolimod in multiple sclerosis: a French prospective study. *JAMA Neurol* 2014; **71:** 436–441.
125. Evangelopoulos ME, Koutoulidis V, Andreadou E, Evangelopoulos DS, Kilidireas C. Pulsed corticosteroid treatment in MS patients stabilizes disease activity following natalizumab withdrawal prior to switching to fingolimod. *Int J Neurosci* 2016; **126:** 1097–1102.
126. Gueguen A, Roux P, Deschamps R, *et al*. Abnormal inflammatory activity returns after natalizumab cessation in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2014; **85:** 1038–1040.
127. Hatcher SE, Waubant E, Nourbakhsh B, Crabtree-Hartman E, Graves JS. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. *JAMA Neurol* 2016; **73:** 790–794.
128. Magraner MJ, Coret F, Navarre A, *et al*. Pulsed steroids followed by glatiramer acetate to prevent inflammatory activity after cessation of natalizumab therapy: a prospective, 6-month observational study. *J Neurol* 2011; **258:** 1805–1811.
129. Miravalle A, Jensen R, Kinkel RP. Immune reconstitution inflammatory syndrome in patients with multiple sclerosis following cessation of natalizumab therapy. *Arch Neurol* 2011; **68:** 186–191.
130. Rossi S, Motta C, Studer V, *et al*. Treatment options to reduce disease activity after natalizumab: paradoxical effects of corticosteroids. *CNS Neurosci Ther* 2014; **20:** 748–753.
131. Sangalli F, Moiola L, Ferre L, *et al*. Long-term management of natalizumab discontinuation in a large monocentric cohort of multiple sclerosis patients. *Mult Scler Relat Disord* 2014; **3:** 520–526.
132. West TW, Cree BAC. Natalizumab dosage suspension: are we helping or hurting? *Ann Neurol* 2010; **68:** 395–399.
133. Havla J, Tackenberg B, Hellwig K, *et al*. Fingolimod reduces recurrence of disease activity after natalizumab withdrawal in multiple sclerosis. *J Neurol* 2013; **260:** 1382–1387.
134. Lo Re M, Capobianco M, Ragonese P, *et al*. Natalizumab discontinuation and treatment strategies in patients with multiple sclerosis (MS): a retrospective study from two Italian MS centers. *Neurol Ther* 2015; **4:** 147–157.
135. Melis M, Cocco E, Frau J, *et al*. Post-natalizumab clinical and radiological findings in a cohort of multiple sclerosis patients: 12-month follow-up. *Neurol Sci* 2014; **35:** 401–408.
136. Rinaldi F, Seppi D, Calabrese M, Perini P, Gallo P. Switching therapy from natalizumab to fingolimod in relapsing–remitting multiple sclerosis: clinical and magnetic resonance imaging findings. *Mult Scler* 2012; **18:** 1640–1643.
137. Salhofer-Polanyi S, Baumgartner A, Kraus J, Maida E, Schmied M, Leutmezer F. What to expect after

natalizumab cessation in a real-life setting. *Acta Neurol Scand* 2014; **130:** 97–102.
138. Vidal-Jordana A, Tintore M, Tur C, *et al*. Significant clinical worsening after natalizumab withdrawal: predictive factors. *Mult Scler* 2015; **21:** 780–785.
139. Alping P, Frisell T, Novakova L, *et al*. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Ann Neurol* 2016; **79:** 950–958.
140. Iaffaldano P, Lucisano G, Pozzilli C, *et al*. Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis. *Brain* 2015; **138:** 3275–3286.
141. Fox RJ, Cree BAC, De Seze J, *et al*. MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study. *Neurology* 2014; **82:** 1491–1498.
142. Kister I, Spelman T, Alroughani R, *et al*. Discontinuing disease-modifying therapy in MS after a prolonged relapse-free period: a propensity score-matched study. *J Neurol Neurosurg Psychiatry* 2016; **87:** 1133–1137.
143. Lu E, Wang BW, Guimond C, Synnes A, Sadovnick D, Tremlett H. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. *Neurology* 2012; **79:** 1130–1135.
144. Amato MP, Portaccio E, Ghezzi A, *et al*. Pregnancy and fetal outcomes after interferon-beta exposure in multiple sclerosis. *Neurology* 2010; **75:** 1794–1802.
145. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology* 2005; **65:** 807–811.
146. Coyle PK, Sinclair SM, Scheuerle AE, Thorp JM Jr, Albano JD, Rametta MJ. Final results from the Betaseron (interferon beta-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events. *BMJ Open* 2014; **4:** e004536.
147. De Las Heras V, De Andres C, Tellez N, *et al*. Pregnancy in multiple sclerosis patients treated with immunomodulators prior to or during part of the pregnancy: a descriptive study in the Spanish population. *Mult Scler* 2007; **13:** 981–984.
148. Fares J, Nassar AH, Gebeily S, Kobeissy F, Fares Y. Pregnancy outcomes in Lebanese women with multiple sclerosis (the LeMS study): a prospective multicentre study. *BMJ Open* 2016; **6:** e011210.
149. Fernandez Liguori N, Klajn D, Acion L, *et al*. Epidemiological characteristics of pregnancy, delivery, and birth outcome in women with multiple sclerosis in Argentina (EMEMAR study). *Mult Scler* 2009; **15:** 555–562.
150. Fragoso YD, Boggild M, MacIas-Islas MA, *et al*. The effects of long-term exposure to disease-modifying drugs during pregnancy in multiple sclerosis. *Clin Neurol Neurosurg* 2013; **115:** 154–159.
151. Giannini M, Portaccio E, Ghezzi A, *et al*. Pregnancy and fetal outcomes after glatiramer acetate exposure in patients with multiple sclerosis: a prospective observational multicentric study. *BMC Neurol* 2012; **12:** 124.
152. Hellwig K, Haghikia A, Rockhoff M, Gold R. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. *Ther Adv Neurol Disord* 2012; **5:** 247–253.
153. Herbstritt S, Langer-Gould A, Rockhoff M, *et al*. Glatiramer acetate during early pregnancy: a prospective cohort study. *Mult Scler* 2015; **22:** 810–816.
154. Lu E, Dahlgren L, Sadovnick AD, Sayao A, Synnes A, Tremlett H. Perinatal outcomes in women with multiple sclerosis exposed to disease-modifying drugs. *Mult Scler J* 2012; **18:** 460–467.
155. Patti F, Cavallaro T, Lo Fermo S, *et al*. Is *in utero* early-exposure to interferon beta a risk factor for pregnancy outcomes in multiple sclerosis? *J Neurol* 2008; **255:** 1250–1253.
156. Romero RS, Lunzmann C, Bugge J-P. Pregnancy outcomes in patients exposed to interferon beta-1b. *J Neurol Neurosurg Psychiatry* 2015; **86:** 587–589.
157. Shimizu Y, Makioka H, Harada N, Nakabayashi S, Saida T, Kira JI. Outcomes of pregnancy during interferon beta-1a therapy in Japanese patients with multiple sclerosis: interim results of a postmarketing surveillance study. *Clin Exp Neuroimmunol* 2015; **6:** 402–408.
158. Weber-Schoendorfer C, Schaefer C. Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study. *Mult Scler* 2009; **15:** 1037–1042.
159. Ebrahimi N, Herbstritt S, Gold R, Amezcua L, Koren G, Hellwig K. Pregnancy and fetal outcomes following natalizumab exposure in pregnancy. A prospective, controlled observational study. *Mult Scler* 2015; **21:** 198–205.
160. Friend S, Richman S, Bloomgren G, Cristiano LM, Wenten M. Evaluation of pregnancy outcomes from the Tysabri (natalizumab) pregnancy exposure registry: a global, observational, follow-up study. *BMC Neurol* 2016; **16:** 150.
161. Hellwig K, Haghikia A, Gold R. Pregnancy and natalizumab: results of an observational study in 35 accidental pregnancies during natalizumab treatment. *Mult Scler J* 2011; **17:** 958–963.
162. Gold R, Phillips JT, Havrdova E, *et al*. Delayed-release dimethyl fumarate and pregnancy: preclinical studies and pregnancy outcomes from clinical trials and postmarketing experience. *Neurol Ther* 2015; **4:** 93–104.
163. Kieseier BC, Benamor M. Pregnancy outcomes following maternal and paternal exposure to teriflunomide during treatment for relapsing–remitting multiple sclerosis. *Neurol Ther* 2014; **3:** 133–138.
164. Karlsson G, Francis G, Koren G, *et al*. Pregnancy outcomes in the clinical development program of fingolimod in multiple sclerosis. *Neurology* 2014; **82:** 674–680.
165. Thiel S, Langer-Gould A, Rockhoff M, *et al*. Interferon-beta exposure during first trimester is safe in women with multiple sclerosis – a prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry. *Mult Scler* 2015; **22:** 801–809.