Drug Class Review

Disease-modifying Drugs for Multiple Sclerosis

Final Update 3 Report

May 2016

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STRUCTURED ABSTRACT

Purpose. We compared the effectiveness and safety of disease-modifying drugs for the treatment of multiple sclerosis: alemtuzumab, dimethyl fumarate, fingolimod, terifunomide, glatiramer acetate, ocrelizumab, daclizumab High Yield Process (HYP), interferon beta-1a, and interferon beta-1b in a streamlined, comparative systematic review.

Data Sources. We searched Ovid MEDLINE® and the Cochrane Library and the Database of Abstracts of Reviews of Effects through January 2016. For additional data we also hand searched reference lists, government Web sites, and dossiers submitted by pharmaceutical companies.

Review Methods. Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project review methods.

Results. We identified 39 head-to-head trials, 6 observational studies, and 4 systematic reviews for inclusion in this review. Most of the evidence was in patients with relapsing-remitting multiple sclerosis (RRMS). In patients with RRMS we conducted a network meta-analysis, which included placebo-controlled trials, for risk of relapse (32 trials, N=18,576) and study withdrawal due to adverse events (33 trials, N=19,191). These analyses included two drugs not yet approved by the Food and Drug Administration for the treatment of multiple sclerosis (ocrelizumab and daclizumab HYP). Our network meta-analysis (NMA) provided low strength evidence that treatment with ocrelizumab 600 mg was associated with the lowest risk of relapse. However, these results must be interpreted with caution as there was limited or no evidence for many drug comparisons. Of the currently approved drugs for multiple sclerosis, our analysis suggests that treatment with alemtuzumab 12 mg is associated with the lowest risk of relapse and also the lowest rate of study withdrawals due to adverse events.

In patients with RRMS, there is head-to-head evidence that compared with interferon beta-1a 44 µg SC, treatment with alemtuzumab 12 mg (moderate strength evidence) or ocrelizumab 600 mg (low strength evidence) is associated with lower risk of relapse and less disability progression, while treatment with interferon beta-1a 44µgSC resulted in improved risk of relapse compared with teriflunomide 7 mg, but not teriflunomide 14 mg, although there were fewer study withdrawals due to adverse events with teriflunomide (low strength evidence). There was low strength evidence that treatment with daclizumab HYP 150 mg resulted in lower risk of relapse at week 144 and less disability progression at 24 weeks compared with interferon beta-1a 30µgIM but also increased study withdrawals due to adverse events compared with the same interferon. Compared with interferon beta-1a 30µgIM, treatment with fingolimod 0.5 mg resulted in lower rates of relapse (moderate strength of evidence) while ocrelizumab 600 mg was associated with similar risk of relapse (although annualized rates favored ocrelizumab; low strength evidence. Treatment with interferon beta-1a 44µgSC or interferon beta-1b 250µgSC also improved relapse-related outcomes compared with interferon beta-1a 30µgIM based on moderate strength evidence.

There is additional head-to-head evidence that treatment fingolimod 0.5µgcompared with interferon beta-1a 30µgIM is associated with similar rates of disability progression, and elevated alanine aminotransferase but lower rates of pyrexia, flu-like illness and myalgia. Head-to-head evidence also exists that treatment with dimethyl fumarate 240 mg and glatiramer acetate 20 mg

resulted in similar rates of relapse and disability progression but that dimethyl fumarate was associated with increased risk of any adverse event compared with glatiramer, although there was no difference in rates of serious adverse events based on low strength evidence. Comparisons between glatiramer 20 mg and the beta interferons found no evidence of a difference in relapse-related outcomes or in disability progression.

In patients with primary progressive multiple sclerosis, ocrelizumab 600 mg delayed disability progression compared with placebo based on moderate strength evidence, with no difference in serious adverse events. A good-quality systematic review pooling evidence across progressive multiple sclerosis phenotypes found very low strength evidence of lower relapse rates with interferon beta-1b than with placebo, but no other differences in efficacy between interferons or glatiramer and placebo (harms were not analyzed by population).

For patients with clinically isolated syndrome, we found no head-to-head evidence comparing included drugs. Indirect analysis of placebo-controlled trials provided low strength evidence of no statistically significant differences among interferons and teriflunomide in progression to multiple sclerosis. Withdrawals due to adverse events were more likely with teriflunomide 7 mg, glatiramer, or interferon beta-1b (Betaseron®), each compared with interferon beta-1a IM (Avonex®), and less likely with teriflunomide 14 mg than with glatiramer.

Conclusion. In drugs approved for multiple sclerosis, there is moderate evidence in patients with relapsing-remitting multiple sclerosis that alemtuzumab is associated with reduced relapse rates compared with interferon beta-1a 44µgSC, while fingolimod is associated with lower risk of relapse compared with interferon beta-1a 30µgIM, but both agents may also be associated with increased adverse events. There was low strength evidence that dimethyl fumarate is associated with increased adverse events compared with glatiramer but similar serious adverse events and adverse event withdrawals. Relapse rates were increased with teriflunomide 7 mg, but not 14 mg, versus interferon beta-1a 44µgSC but treatment with teriflunomide resulted in fewer study withdrawals due to adverse events. Our network meta-analysis and currently available trial results suggest that the two included, but unapproved, drugs (ocrelizumab and daclizumab HYP) may be promising additions to current treatments for multiple sclerosis in the future. However additional comparative research is needed for these two drugs, as well as for alemtuzumab, fingolimod, dimethyl fumarate, and teriflunomide in order to draw definitive conclusions regarding benefits and harms. Limited evidence was available for populations other than relapsing-remitting MS.

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EVIDENCE TABLES

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Shading indicates new information for Update 3.

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INTRODUCTION

Epidemiology. Multiple sclerosis is a chronic, autoimmune disease of the central nervous system affecting 2.3 million people worldwide.[1] Prevalence estimates in the United States range from 250,000 to 400,000 people.[2,3] Most patients are diagnosed between the ages of 20 and 50 years, with women affected more often than men. The highest prevalence of multiple sclerosis is found in Caucasian women, people of Northern European descent, and in those who live in northern latitudes. In a 2010 study, the US age-adjusted prevalence was 47.2, 86.3, and 109.5 per 100,000 for three large geographic areas in Texas, Missouri, and Ohio, respectively.[4]

Pathophysiology. Multiple sclerosis causes demyelination of neuronal axons that form lesions within the white matter of the central nervous system (cerebral white matter, brain stem, cerebellar tracts, optic nerves, or spinal cord) when viewed on magnetic resonance imaging (MRI). Demyelination may slow, or even block, axonal conduction,[5] and neuronal degeneration may occur.[5] Impaired neuronal conduction ultimately causes the neurological symptoms associated with multiple sclerosis.

Although more data are becoming available, the pathogenesis of multiple sclerosis remains elusive. Myelin-reactive T cells and B cells are present in multiple sclerosis.[6] Environmental factors, such as infectious agents, seem to facilitate the movement of these cells from the periphery, across the blood brain barrier, and into the central nervous system in those genetically susceptible to multiple sclerosis.[6] Antigen-presenting cells and T helper cells form a complex by binding to a self-antigen, such as myelin basic protein, via the major histocompatibility complex and T cell receptor, respectively.[6] Antigen presentation to these cells causes an enhanced immune response. Acute inflammatory, demyelinating plaques occur when myelin undergoes phagocytosis by macrophages when coated with antibodies for myelin basic protein and myelin oligodendrocyte glycoprotein.[5] In addition, cytotoxic T cells and pro-inflammatory cytokines may directly damage the myelin.[5]

Diagnosis. The 2010 McDonald Criteria[7] for diagnosis of multiple sclerosis combine evidence of attacks (acute demyelinating events) and central nervous system lesions on MRI. Different combinations of these criteria can support an MS diagnosis; for example, a clinical presentation of 2 or more attacks, as well as objective clinical evidence of 2 or more lesions, or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack, is adequate for diagnosis. Alternative criteria for diagnosis allow fewer attacks and/or lesions, but with evidence of dissemination in time or space.[7] A diagnosis of multiple sclerosis may also be made in a clinically isolated syndrome with presentation of a single attack and evidence of 1 or more lesions, with dissemination in both space and time.[7] To maintain specificity, criteria have become stricter, such that magnetic resonance imaging and dissemination in space and time are critical. Cerebrospinal fluid analysis may be needed to identify oligoclonal bands (or increased immunoglobulin G that are often present in multiple sclerosis.

Clinical course. Progression of multiple sclerosis is measured by the disability caused by the disease. The Expanded Disability Status Scale (EDSS) is a common measure of multiple sclerosis disability, and is a clinical outcome in many multiple sclerosis clinical trials.[8,9] The scale ranges from 0, defined by a normal neurological examination, to 10, defined as death due to multiple sclerosis.[8] An EDSS <6 indicates that the patient can walk without aid for limited

distances.[8] An EDSS ≥6 and <8 indicates that the patient is severely restricted in movement with aids or assistance.[8] An EDSS >8 indicates the person is restricted to bed, and use of arms and legs are severely restricted.[8]

Four main types of multiple sclerosis have been characterized: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing. About 85% of multiple sclerosis patients have relapsing-remitting multiple sclerosis at the onset of the disease, and about 10% have primary progressive multiple sclerosis.[6] Relapsing-remitting multiple sclerosis is characterized by well-defined acute relapses (attacks) of neurological symptoms, followed by full or partial recovery. Relapsing-remitting multiple sclerosis rarely progresses between relapses, although the patient may never fully recover after a relapse. In contrast, primary progressive multiple sclerosis progresses from the onset without acute attacks. Most patients with relapsing-remitting multiple sclerosis will eventually develop secondary progressive multiple sclerosis, which is a progressive form of the disease that may or may not have superimposed relapses. Progressive relapsing multiple sclerosis occurs in about 5% of the multiple sclerosis population and progresses from the onset with superimposed relapses of neurological symptoms followed by full or partial recovery.[6]

Treatment. The treatment of multiple sclerosis involves acute relapse treatment with corticosteroids, symptom management with appropriate agents, and disease modification with disease-modifying drugs. For example, when acute exacerbations occur (such as vision loss or loss of coordination), they are commonly treated with a short duration of high-dose oral or intravenous corticosteroid. If spasticity occurs, it can be addressed acutely with muscle relaxants. Therapy with disease-modifying drugs is designed to prevent relapses and progression of disability, rather than to treat specific symptoms or exacerbations of the disease. These agents modify the immune response that occurs in multiple sclerosis through various immunomodulatory or immunosuppressive effects. Table 1 summarizes the pharmacology, dosing, and indications of disease-modifying drugs for multiple sclerosis that are included in this review. Shaded drugs are new for Update 3 of this report.

Table 1. Pharmacology, indications, and dosing of disease-modifying drugs for multiple sclerosis

Agent	Dosage, route and frequency	Indication
Fingolimod Gilenya™	0.5 mg Orally once daily	Patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
Glatiramer Acetate Copaxone®, Glatopa™[a]	20 mg in 1 mL Subcutaneously once daily, 40mg in 1 mL subcutaneously three times weekly at least 48 hours apart	Treatment of relapsing forms of multiple sclerosis
Interferon beta-1a Avonex®	30 µg Intramuscularly once weekly	Treatment of patients with relapsing forms of MS to slow accumulation of physical disability and decrease frequency of clinical exacerbations. Effective in patients who experienced first clinical episode and have MRI features consistent with MS
Interferon beta-1a Rebif®	22 or 44 µ Subcutaneously three times weekly	Treatment of relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability
Interferon beta-1b Betaseron®, Extavia®	0.25 mg in 1 mL Subcutaneously every other day	Treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Effective in patients who experienced first clinical episode and have MRI features consistent with MS
Peginterferon beta-1a Plegridy™	125 µ Subcutaneously every 14 days	Treatment of relapsing forms of multiple sclerosis
Teriflunomide Aubagio®	7 mg or 14 mg Orally once daily	Treatment of relapsing forms of multiple sclerosis
Dimethyl fumarate Tecfidera®	Maintenance dose: 240 mg Orally twice daily	Treatment of relapsing forms of multiple sclerosis
Alemtuzumab Lemtrada™	Intravenous infusion for 2 treatment courses. First course: 12 mg/day for 5 days. Second course: 12 mg/day for 3 days 12 months after first treatment course	Treatment of relapsing forms of MS. Because of its safety profile, use should be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.
Daclizumab HYP Zinbryta™	NA	Submitted for approval to the FDA
Ocrelizumab[c]	NA	FDA granted Breakthrough Therapy designation for ocrelizumab in PPMS in February 2016.

Abbreviations: MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable; PPMS, primary-progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.
[a]Administered 20 mg in 1 ml once daily
[b]Biologics License Application (BLA) submitted 4/29/2015
[c]Not yet submitted for FDA approval (expected first half of 2016).

Drugs approved by the US Food and Drug administration for multiple sclerosis but not included in this review are mitoxantrone and natalizumab. Mitoxantrone is used to treat secondary progressive multiple sclerosis, and is rarely used. Natalizumab is not generally a first-line agent for RRMS. Both were excluded at DERP participants' request to reduce the size and cost of the report. Included approved drugs with studies administering higher than doses approved by the US Food and Drug Administration are fingolimod (1.25 mg), dimethyl fumarate (720 mg daily), and interferon beta-1b (0.5 mg). One included drug, alemtuzumab, was approved in 2001 to treat B-cell chronic lymphocytic leukemia with brand name Campath®, but used off-label to treat multiple sclerosis. In November 2014 alemtuzumab (brand name Lemtrada®) received

supplemental approval to treat relapsing forms of multiple sclerosis. This review also includes two investigational agents, one that has been submitted for approval to the FDA (daclizumab HYP) and one that has not yet been submitted but has been granted Breakthrough Therapy status for primary progressive MS (ocrelizumab).

Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A.

Scope and Key Questions

The purpose of this review is to compare the effectiveness and safety of different disease-modifying drugs for the treatment of multiple sclerosis. In the original report, placebo-controlled trials were included as part of the evidence base, along with head-to-head trials and systematic reviews. A streamlined approach was used the previous version of this review which focused on head-to-head studies. At the direction of the participating organizations, for Update #3 we have once more included evidence on placebo-controlled trials to allow indirect comparisons of included drugs, though we do not report comparisons to placebo unless no other evidence is available for a drug and/or population.

The Pacific Northwest Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis?
2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?
3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?
4. Do disease-modifying treatments for multiple sclerosis or a clinically isolated syndrome differ in harms?
5. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

METHODS

Inclusion Criteria

Populations

- Adult outpatients (age ≥18 years) with multiple sclerosis[10,11]
    - Relapsing-remitting multiple sclerosis

    - Secondary progressive multiple sclerosis
    - Primary progressive multiple sclerosis
    - Progressive relapsing multiple sclerosis
- Adult outpatients with a clinically isolated syndrome (also known as "first demyelinating event", first clinical attack suggestive of multiple sclerosis, or monosymptomatic presentation).[11]

Interventions (all formulations)

Interventions included in this review are fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, teriflunomide, dimethyl fumarate, alemtuzumab, daclizumab HYP, and ocrelizumab. All formulations are included in this review. Trade names, dosage form, and administration and information on indication can be found in Table 1.

Effectiveness Outcomes

Multiple sclerosis

- Disability
- Clinical exacerbation/relapse
- Quality of life
- Functional outcomes (e.g., wheel chair use, time lost from work)
- Persistence (discontinuation rates).

Clinically isolated syndrome

- Disability
- Clinical exacerbation/relapse of symptoms
- Quality of life
- Functional outcomes (e.g., wheel chair use, time lost from work)
- Persistence (discontinuation rates)
- Progression to multiple sclerosis diagnosis.

Note: Magnetic resonance imaging findings are not included, as they are intermediate or surrogate outcomes.

Harms

- Overall rate of adverse effects
- Withdrawals due to adverse effects or drug discontinuations due to adverse events
- Serious adverse events
- Specific adverse events (cardiovascular, hepatotoxicity, progressive multifocal leukoencephalopathy, secondary cancers, etc.).

Study Designs

1. For effectiveness and harms, head-to-head controlled clinical trials and good-quality comparative systematic reviews were included. Comparative observational studies with 2 concurrent arms of at least 100 patients each and duration ≥1 year are also included for evaluation of harms.
2. Placebo-controlled trials (PCT) were included for network meta-analysis in the absence of head-to-head trials and the PCT is the only information for a new drug or formulation.

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® (1946 – December Week 5 2015), the Cochrane Database of Systematic Reviews® (2005 to January 2016), and the Cochrane Central Register of Controlled Trials® (December 2015) using terms for included drugs, indications, and study designs (see Appendix B for complete search strategies). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the clinical trials registry for unpublished studies. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X7, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Two reviewers independently assessed titles and/or abstracts of citations identified from literature searches for inclusion, using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. Discrepancies in abstract or full-text review were resolved by consensus and if consensus was not able to be reached the discrepancies were resolved by a third reviewer. Results published *only* in abstract form were not included because inadequate details were available for quality assessment, however if we were provided with enough information to conduct quality assessment we did include the study. Additional results from fully published studies (e.g., relating to secondary outcome measures) found only in abstract form were included because the study quality could be assessed through the complete publication.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. Data were abstracted by 1 reviewer and checked by a second. Discrepancies were resolved by consensus. We recorded intention-to-treat results when reported. If true intent-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per-protocol results were reported, we calculated intent-to-treat results if the data for these calculations were available.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria of the Drug Effectiveness Review Project.[12] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups

at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intent-to-treat analysis. Trials that had fatal flaws were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid in that the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failing to meet *combinations* of items of the quality assessment checklist.

The criteria for observational studies of adverse events reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on predefined criteria, including a clear statement of the questions(s), inclusion criteria, methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence, as well as details provided about included studies. Again, these studies were categorized as good when all criteria were met.

Two reviewers independently assessed each study for quality and differences were resolved by consensus.

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[13] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy, and harms of disease-modifying drugs for multiple sclerosis. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus. Strength of evidence for all outcome measures that are limited to indirect evidence only is deemed insufficient or low strength of evidence. When there is both direct evidence and indirect evidence for an outcome, or only direct evidence available, strength of evidence may receive any of the grades defined in Table 2.

We chose outcomes related to relapse and disease progression. Magnetic resonance imaging findings were considered intermediate outcomes and were not assessed.

Table 2. Definitions of the grades of overall strength of evidence[14]

Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this**

Grade	Definition
	outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated 1 disease-modifying drug for multiple sclerosis against another provided *direct* evidence of comparative effectiveness and adverse event rates. Where possible, these data were the primary focus.

Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for which studies were homogeneous enough to provide a meaningful combined estimate. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and heterogeneity across studies in study design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively.

Random-effects models were used to estimate pooled effects.[15] The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[16,17] Meta-analysis was performed using Stats Direct (Cam code, United Kingdom) and the meta package in R,[18] and Stata 14 (StataCorp, College Station, TX).

Indirect meta-analyses were done in Update 1 to compare interventions for which there were no head-to-head comparisons and where there was a common comparator intervention across studies, using the Bucher, et al. method.[19] Indirect comparisons usually agree with direct comparisons, though large discrepancies have been reported in some cases.[20,21] In addition, indirect comparisons also result in less precise estimates of treatment effects compared with the same number of similarly sized head-to-head trials because methods for indirect analyses incorporate additional uncertainty from combining different sets of trials.[19,22] Because of this, in Update 1 we pursued an exploratory analysis combining the indirect and direct pooled estimates using a Bayesian approach. Data from indirect comparisons was synthesized with data from direct, head-to-head studies when possible. Using a Bayesian data analytical framework, effect size estimated from the indirect analysis was used as the prior probability distribution in a meta-analysis of the data from the direct head-to-head studies. Bayesian analysis was conducted using Open BUGS and the BRugs package in R.[18,23]

For Update 3, we conducted network meta-analyses (NMAs) of RCTs in patients with relapsing multiple sclerosis and separate NMAs in patients with CIS. We used Stata and a

frequentist approach with mvmeta command.[24] For these NMAs we included only approved drug doses and dosing schedules. When more than one dose of a drug was included, we did not combine drug doses but analyzed the doses separately. We also conducted subgroup analysis based on trial duration. In general, the longer the duration of the trial, the greater the risk of relapse in patients with relapsing MS. We examined the relapse rate in the placebo arms of trials, and also the relapse rates in the interferons and glatiramer arms. We also conducted a sensitivity analysis after removing two trials that demonstrated much larger than expected percentage of relapses in a short duration and two trials reporting fewer than expected relapses with a longer duration. Additionally, we conducted a sensitivity analysis removing all studies with estimated numbers of patients who relapsed (or were relapse-free) based on Kaplan-Meyer estimates as this method includes censoring of patients and is based on the product-limit method rather than actual numbers of patients who relapsed during a specific time period. We did not conduct further sensitivity analysis because a good-quality Cochrane systematic review of immunomodulators and immunosuppressants for RRMS conducted multiple subgroup and sensitivity analyses and did not find any differences based on patient or study characteristics.[25] When our results were not consistent with the Cochrane NMA[25] we point that out. Finally, we compared the results from the previous NMA of the interferons with the NMA new for this update.

Our NMA and Cochrane's NMA provide our "best guesses" for an effect estimate comparing two different treatment regimens when head-to-head evidence is sparse or lacking. In the absence of any head-to-head evidence, we consider the strength of the evidence to be low for those comparisons. In our NMA we included placebo-controlled trials, head-to-head trials and active controlled trials when the active control was one of our included drugs. We were limited in defining relapse to the way the trialists defined relapse which may not be identical across studies. We defined withdrawal due to adverse events as either withdrawal from the study due to adverse events or in the absence of that evidence, as discontinuation of the study drug due to adverse events. We utilized the actual number of relapses, rather than the annualized relapse rate, and the actual number of withdrawals due to adverse events, along with the total number of persons within each group as data for the NMA.

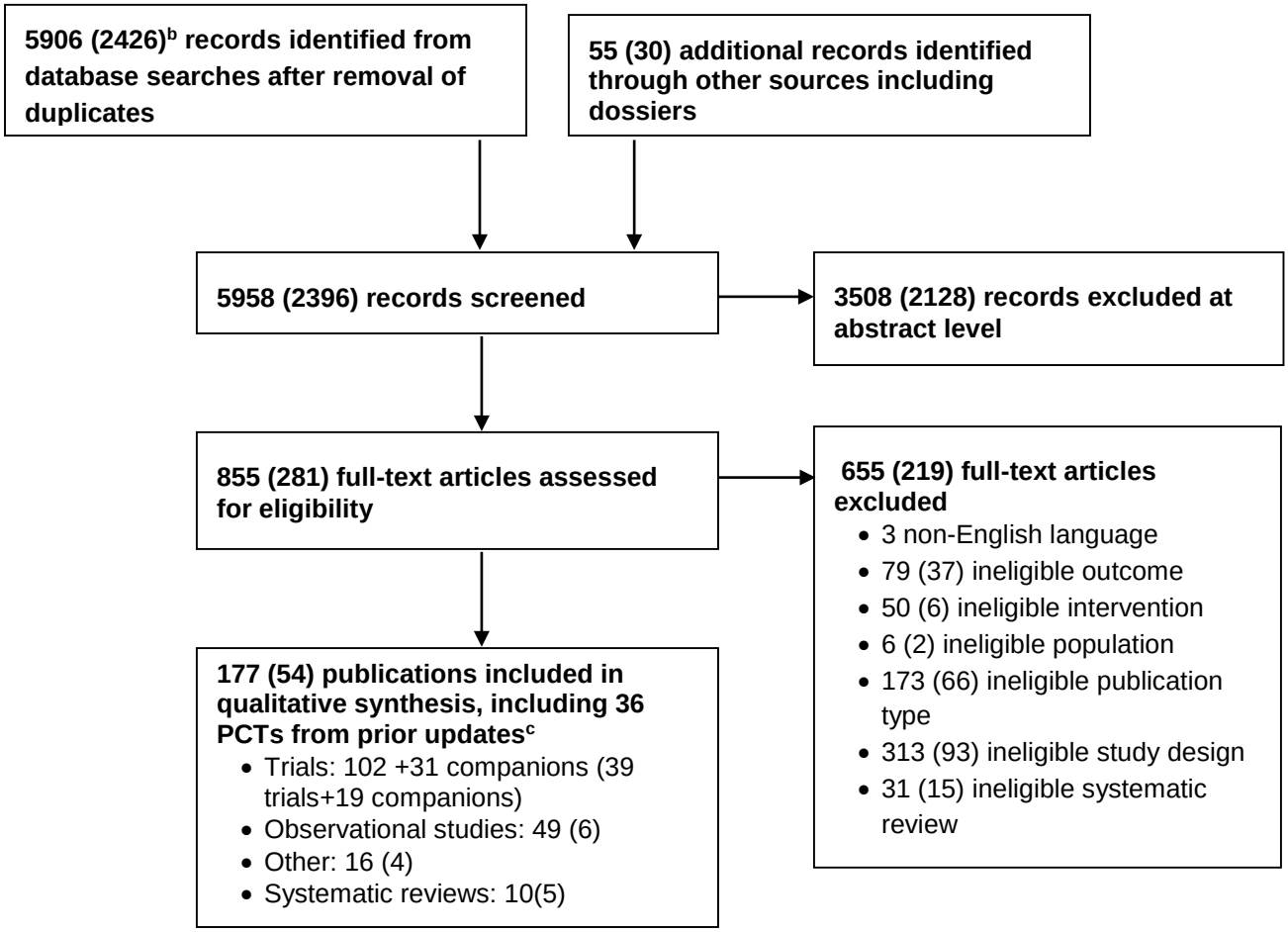
RESULTS

Overview

Literature searches identified a total of 5,906 citations from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and peer review comments. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 855 publications, 281 for Update 3. After re-applying the criteria for inclusion, we ultimately included 177 publications, 54 for Update 3, comprising 102 trials and 31 companions (39 trials and 19 companions for Update 3), 49 observational studies (6 for Update 3), 10 systematic reviews (5 for Update 3) and 16 other study designs (4 for Update 3) comprising pooled analyses, post-hoc analyses and medical and statistical reviews produced by the Center for Drug Evaluation and Research. See Appendix C for a list of excluded trials and reasons for exclusion at this stage. Figure 1 shows the flow of study selection. We received dossiers from 7 pharmaceutical manufacturers: Abbvie, Bayer, Biogen Idec, EMD Serono, Genentech/Roche, Novartis, and Teva Neuroscience Inc. Throughout the report we generally refer to the included drugs by their full name. At times we also included

brand names for the interferons in an effort to avoid confusing the drugs, which have differing doses and routes of administration.

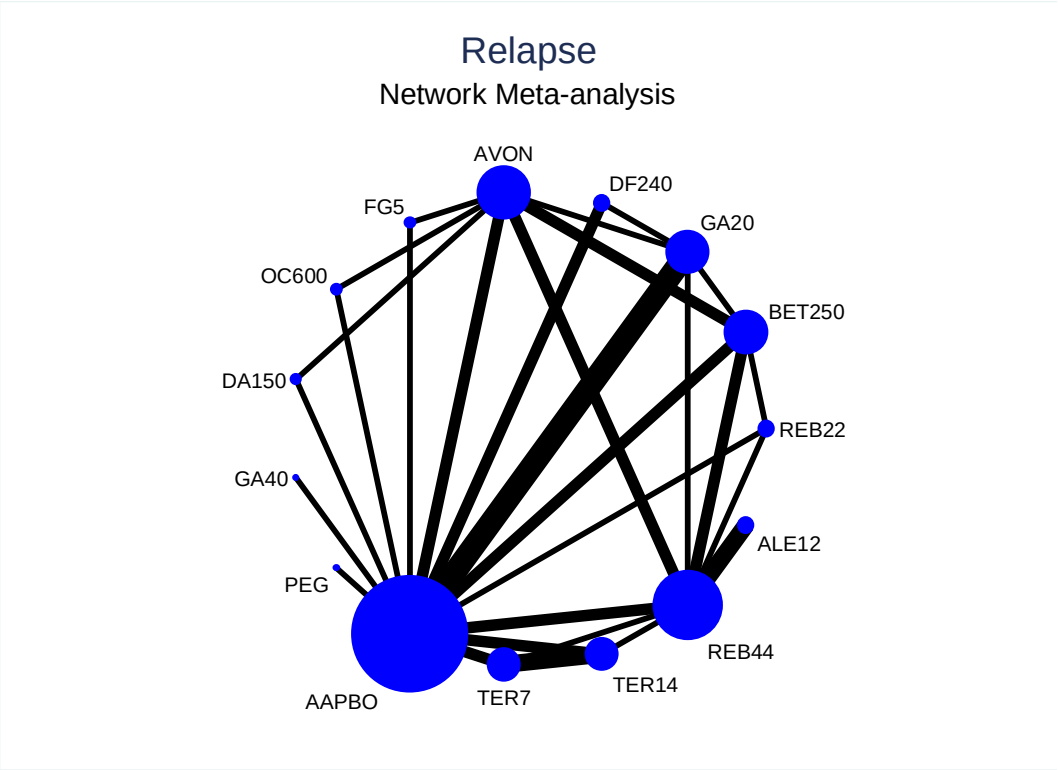
Figure 1. Results of literature search[a]



[a] The Drug Effectiveness Review Project uses a modified PRISMA flow diagram.[26]
[b] Numbers in parentheses indicate information new to Update 3.
[C] Placebo-controlled trials (PCTs) were evaluated for inclusion in the original report but were excluded in Update 2. We have included them in Update 3.

Network meta-analysis for risk of relapse consisted of 31 studies (N=18,088) shown below (Figure 2). The sizes of the circles reflect the number of studies with that treatment. The thicknesses of the lines reflect the number of studies with that comparison. The treatment arm that is most frequent in studies is placebo (AAPBO) and the most frequent comparison is glatiramer 20 mg with placebo. There were 105 total comparisons in the network for which 15% contained direct evidence. In the NMA ocrelizumab 600 mg was considered to have the highest probability of being the best treatment to prevent relapse in a RRMS population (82%; Low strength evidence) followed by followed by alemtuzumab 12 mg (17.3%) followed by fingolimod 0.5 mg (0.4%). Table 3 This is consistent with Cochrane's NMA[25] which found alemtuzumab the most effective drug against relapse recurrence. However, Cochrance's NMA did not include ocrelizumab in its analysis.

Figure 2. Network meta-analysis: relapsing-remitting multiple sclerosis



We also conducted subgroup analyses and stratified trials into those with a duration of 16 months or less (short duration) versus trials longer than 16 months (long duration) to compare difference in effect estimates (Table 3). Comparisons involving teriflunomide 7 mg, interferon beta-1a 30µgIM and interferon beta-1a 44µgSC were the most affected by mixed treatment comparisons stratified by duration.

Another sensitivity analysis removed ocrelizumab and found no change in point estimates or confidence limits likely because the included ocrelizumab trial was small. We also looked at the effect of removing both ocrelizumab and alemtuzumab from the NMA and found minor shifts in effect estimates (e.g., RR 1.19, 95% CI 0.88 to 1.62 with all included study drugs became 1.20, 95% CI 0.87 to 1.64 with the removal of ocrelizumab and alemtuzumab from the NMA).

An additional sensitivity analysis removing 4 studies with relapse rates inconsistent with other studies based on duration of study in the placebo or interferon arm also made little difference on effect estimates and their significance.

Table 3. Network Meta-analysis: Relapsing-remitting multiple sclerosis risk of relapse

	Primary Analysis	**Subgroup Analysis**	**Subgroup Analysis**
Comparison	**All studies[a]**	**≤16 months**	**>16 months**
Drug vs. Drug (by dose)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Teriflunomide 7 mg vs. Teriflunomide 14 mg	1.21 (1.00,1.48)	**1.32 (1.08,1.62)**	1.06 (0.90,1.25)
Teriflunomide 7 mg vs. Rebif 44 µg	**1.32 (1.01,1.72)**	**2.07 (1.47,2.93)**	1.09 (0.91,1.30)

	Primary Analysis	Subgroup Analysis	Subgroup Analysis
Comparison	**All studies[a]**	**≤16 months**	**>16 months**
Teriflunomide 7 mg vs. Rebif 22 µg	**1.10 (0.83, 1.45)**		0.99 (0.83,1.18)
Teriflunomide 7 mg vs. Plegridy	1.41 (0.97,2.05)	1.23 (0.91,1.66)	
Teriflunomide 7 mg vs. Ocrelizumab 600 mg	**4.01 (1.23,13.10)**	**4.20 (1.30,13.52)**	
Teriflunomide 7 mg vs. Glatiramer 40 mg	1.31 (0.94,1.83)	1.14 (0.89,1.47)	
Teriflunomide 7 mg vs. Glatiramer 20 mg	1.12 (0.89,1.43)	0.87 (0.63,1.21)	1.04 (0.87,1.23)
Teriflunomide 7 mg vs. Fingolimod 0.5 mg	**1.58 (1.18,2.11)**	**2.30 (1.45,3.66)**	**1.56 (1.25,1.96)**
Teriflunomide 7 mg vs. Dimethyl Fumarate 240 mg	1.29 (0.95,1.76)		1.22 (0.97,1.53)
Teriflunomide 7 mg vs. Daclizumab HYP 150 mg	**1.45 (1.06,1.98)**	1.42 (0.96,2.10)	1.26 (1.00,1.59)
Teriflunomide 7 mg vs. Betaseron 250 mg	1.17 (0.91,1.51)	2.08 (0.94,4.61)	1.07 (0.90,1.27)
Teriflunomide 7 mg vs. Avonex	0.94 (0.74,1.21)	1.41 (0.96,2.08)	0.86 (0.70,1.05)
Teriflunomide 7 mg vs. Alemtuzumab 12 mg	**2.21 (1.57,3.11)**		**1.78 (1.42,2.23)**
Teriflunomide 14 mg vs. Rebif 44 µg	1.09 (0.84,1.40)	**1.57 (1.09,2.25)**	1.02 (0.85,1.23)
Teriflunomide 14 mg vs. Rebif 22 µg	0.90 (0.69, 1.18)		0.93 (0.78,1.11)
Teriflunomide 14 mg vs. Plegridy	1.16 (0.80,1.69)	0.93 (0.68,1.27)	
Teriflunomide 14 mg vs. Ocrelizumab 600 mg	**3.30 (1.01,10.79)**	3.18 (0.98,10.26)	
Teriflunomide 14 mg vs. Glatiramer 40 mg	1.08 (0.77,1.51)	0.87 (0.66,1.13)	
Teriflunomide 14 mg vs. Glatiramer 20 mg	0.93 (0.73,1.17)	**0.66 (0.47,0.92)**	0.97 (0.82,1.16)
Teriflunomide 14 mg vs. Fingolimod 0.5 mg	1.30 (0.97,1.74)	**1.74 (1.08,2.80)**	**1.47 (1.17,1.85)**
Teriflunomide 14 mg vs. Dimethyl Fumarate 240 mg	1.06 (0.78,1.45)		1.15 (0.91,1.45)
Teriflunomide 14 mg vs. Daclizumab HYP 150 mg	1.19 (0.88,1.62)	1.07 (0.72,1.60)	1.19 (0.94,1.50)
Teriflunomide 14 mg vs. Betaseron 250 mg	0.96 (0.75,1.23)	1.57 (0.70,3.51)	1.00 (0.84,1.20)
Teriflunomide 14 mg vs. Avonex	**0.78 (0.61,0.99)**	1.07 (0.71,1.60)	**0.81 (0.66,0.99)**
Teriflunomide 14 mg vs. Alemtuzumab 12 mg	**1.82 (1.31,2.53)**		**1.67 (1.33,2.11)**
Rebif 44µgvs. Rebif 22 µg	0.83 (0.67,1.02)		0.91 90.81,1.02)
Rebif 44 µg vs. Plegridy	1.07 (0.74,1.54)	**0.60 (0.40,0.89)**	
Rebif 44 µg vs. Ocrelizumab 600 mg	3.04 (0.93,9.88)	2.03 (0.62,6.58)	
Rebif 44 µg vs. Glatiramer 40 mg	0.99 (0.71,1.38)	**0.55 (0.38,0.80)**	
Rebif 44 µg vs. Glatiramer 20 mg	0.85 (0.71,1.01)	**0.42 (0.27,0.64)**	0.95 (0.85,1.07)
Rebif 44 µg vs. Fingolimod 0.5 mg	1.19 (0.91,1.56)	1.11 (0.79,1.56)	**1.44 (1.18,1.75)**
Rebif 44 µg vs. Dimethyl Fumarate 240 mg	0.98 (0.74,1.30)		1.12 (0.92,1.37)
Rebif 44 µg vs. Daclizumab HYP 150 mg	1.10 (0.84,1.43)	0.69 (0.42,1.11)	1.16 (0.96,1.42)
Rebif 44 µg vs. Betaseron 250 mg	0.89 (0.73,1.07)	1.00 (0.47,2.15)	0.98 (0.86,1.11)
Rebif 44 µg vs. Avonex	**0.71 (0.59,0.86)**	**0.68 (0.54,0.85)**	**0.79 (0.67,0.93)**
Rebif 44 µg vs. Alemtuzumab 12 mg	**1.67 (1.37,2.04)**		**1.63 (1.42,1.88)**
Rebif 22 µg vs. Plegridy	1.29 (0.89,1.88)		
Rebif 22 µg vs. Ocrelizumab 600 mg	3.66 (1.12,11.97)		
Rebif 22 µg vs. Glatiramer 40 mg	1.20 (0.85,1.68)		
Rebif 22 µg vs. Glatiramer 20 mg	1.03 (0.83,1.27)		1.05 (0.93,1.18)
Rebif 22 µg vs. Fingolimod 0.5 mg	1.44 (1.08,1.92)		**1.58 (1.30,1.92)**
Rebif 22 µg vs. Dimethyl Fumarate 240 mg	1.18 (0.81,1.60)		**1.23 (1.01,1.50)**
Rebif 22 µg vs. Daclizumab HYP 150 mg	1.32 (0.99,1.77)		**1.28 (1.05,1.56)**
Rebif 22 µg vs. Betaseron 250 mg	1.07 (0.88,1.30)		1.08 (0.96,1.21)
Rebif 22 µg vs. Avonex	0.86 (0.69,1.07)		0.87 (0.74,1.02)
Rebif 22 µg vs. Alemtuzumab 12 mg	**2.02 (1.51,2.70)**		**1.80 (1.49,2.16)**
Plegridy vs. Ocrelizumab 600 mg	2.84 (0.85,9.54)	**3.40 (1.05,11.09)**	
Plegridy vs. Glatiramer 40 mg	0.93 (0.61,1.42)	0.93 (0.69,1.24)	
Plegridy vs. Glatiramer 20 mg	0.80 (0.56,1.13)	0.71 (0.50,1.01)	
Plegridy vs. Fingolimod 0.5 mg	1.12 (0.76,1.65)	**1.87 (1.12,3.11)**	

	Primary Analysis	Subgroup Analysis	Subgroup Analysis
Comparison	**All studies[a]**	**≤16 months**	**>16 months**
Plegridy vs. Dimethyl Fumarate 240 mg	0.91 (0.61,1.37)		
Plegridy vs. Daclizumab HYP 150 mg	1.03 (0.69,1.53)	1.15 (0.76,1.75)	
Plegridy vs. Betaseron 250 mg	0.83 (0.58,1.18)	1.68 (0.74,3.82)	
Plegridy vs. Avonex	**0.67 (0.47,0.95)**	1.14 (0.74,1.78)	
Plegridy vs. Alemtuzumab 12 mg	**1.56 (1.03,2.39)**		
Ocrelizumab 600 mg vs. Glatiramer 40 mg	0.33 (0.10,1.08)	**0.27 (0.08,0.88)**	
Ocrelizumab 600 mg vs. Glatiramer 20 mg	**0.28 (0.09,0.91)**	**0.21 (0.06,0.68)**	
Ocrelizumab 600 mg vs. Fingolimod 0.5 mg	0.39 (0.12,1.29)	0.55 (0.16,1.83)	
Ocrelizumab 600 mg vs. Dimethyl Fumarate 240 mg	0.32 (0.10,1.06)		
Ocrelizumab 600 mg vs. Daclizumab HYP 150 mg	0.36 (0.11,1.18)	0.34 (0.10,1.13)	
Ocrelizumab 600 mg vs. Betaseron 250 mg	**0.29 (0.09,0.95)**	0.49 (0.12,1.97)	
Ocrelizumab 600 mg vs. Avonex	**0.24 (0.07,0.76)**	0.34 (0.10,1.09)	
Ocrelizumab 600 mg vs. Alemtuzumab 12 mg	0.55 (0.17,1.82)		
Glatiramer 40 mg vs. Glatiramer 20 mg	0.86 (0.63,1.17)	0.76 (0.55,1.05)	
Glatiramer 40 mg vs. Fingolimod 0.5 mg	1.20 (0.84,1.72)	**2.01 (1.24,3.27)**	
Glatiramer 40 mg vs. Dimethyl Fumarate 240 mg	0.99 (0.68,1.43)		
Glatiramer 40 mg vs. Daclizumab HYP 150 mg	1.11 (0.76,1.60)	1.24 (0.85,1.82)	
Glatiramer 40 mg vs. Betaseron 250 mg	0.89 (0.65,1.23)	1.82 (0.81,4.06)	
Glatiramer 40 mg vs. Avonex	**0.72 (0.52,0.99)**	1.23 (0.82,1.86)	
Glatiramer 40 mg vs. Alemtuzumab 12 mg	**1.69 (1.14,2.49)**		
Glatiramer 20 mg vs. Fingolimod 0.5 mg	**1.40 (1.09,1.80)**	**2.64 (1.56,4.47)**	**1.51 (1.24,1.83)**
Glatiramer 20 mg vs. Dimethyl Fumarate 240 mg	1.15 (0.89,1.48)		1.18 (0.98,1.42)
Glatiramer 20 mg vs. Daclizumab HYP 150 mg	1.29 (1.00,1.67)	**1.63 (1.06,2.52)**	**1.22 (1.02,1.47)**
Glatiramer 20 mg vs. Betaseron 250 mg	1.04 (0.88,1.23)	**2.38 (1.04,5.47)**	1.03 (0.93,1.14)
Glatiramer 20 mg vs. Avonex	0.84 (0.71,1.00)	**1.62 (1.02,2.56)**	**0.83 (0.72,0.96)**
Glatiramer 20 mg vs. Alemtuzumab 12 mg	**1.97 (1.50,2.58)**		**1.72 (1.43,2.06)**
Fingolimod 0.5 mg vs. Dimethyl Fumarate 240 mg	0.82 (0.59,1.14)		0.78 (0.61,1.00)
Fingolimod 0.5 mg vs. Daclizumab HYP 150 mg	0.92 (0.68,1.25)	0.62 (0.35,1.09)	0.81 (0.63,1.04)
Fingolimod 0.5 mg vs. Betaseron 250 mg	**0.74 (0.57,0.96)**	0.90 (0.39,2.07)	**0.68 (0.56,0.83)**
Fingolimod 0.5 mg vs. Avonex	**0.60 (0.47,0.76)**	**0.61 (0.48,0.79)**	**0.55 (0.44,0.68)**
Fingolimod 0.5 mg vs. Alemtuzumab 12 mg	1.40 (1.00,1.97)		1.14 (0.89,1.45)
Dimethyl Fumarate 240 mg vs. Daclizumab HYP 150 mg	1.12 (0.80,1.57)		1.04 (0.81,1.33)
Dimethyl Fumarate 240 mg vs. Betaseron 250 mg	0.91 (0.69,1.19)		0.88 (0.72,1.06)
Dimethyl Fumarate 240 mg vs. Avonex	**0.73 (0.55,0.96)**		**0.70 (0.57,0.88)**
Dimethyl Fumarate 240 mg vs. Alemtuzumab 12 mg	**1.71 (1.20,2.43)**		**1.46 (1.14,1.86)**
Daclizumab HYP 150 mg vs. Betaseron 250 mg	0.81 (0.62,1.05)	1.46 (0.62,3.45)	0.84 (0.70,1.01)
Daclizumab HYP 150 mg vs. Avonex	**0.65 (0.53,0.81)**	0.99 (0.60,1.65)	**0.68 (0.61,0.76)**
Daclizumab HYP 150 mg vs. Alemtuzumab 12 mg	**1.53 (1.09,2.13)**		**1.41 (1.10,1.79)**
Betaseron 250 mg vs. Avonex	**0.81 (0.68,0.96)**	0.68 (0.31,1.50)	**0.80 (0.70,0.93)**
Betaseron 250 mg vs. Alemtuzumab 12 mg	**1.89 (1.43,2.50)**		**1.66 (1.38,2.02)**
Avonex vs. Alemtuzumab 12 mg	**2.34 (1.78,3.09)**		**2.07 (1.67,2.57)**

a. References included in NMA: 27-60

Abbreviations: mg, milligrams; RR, Relative Risk; 95% CI, 95% Credible Interval; RRMS, Relapsing-remitting multiple sclerosis; HYP, high yield process

To evaluate study drug tolerance/safety we conducted a network meta-analysis with withdrawals due to adverse events/study drug discontinuations as the outcome (Figure 3). This analysis included 32 studies (N=18,752), 105 comparisons with 13% involving a head-to-head comparison (Table 4). There were few significant differences between treatments. We did not conduct sensitivity analysis for study withdrawal due to adverse events. Alemtuzumab 12 mg had the highest probability of being the best treatment with lower rates of study withdrawals due to adverse events (70.5%) followed by placebo (13.1%) and is consistent with Cochrane's NMA.[25]

Figure 3. Network meta-analysis: withdrawal due to adverse events

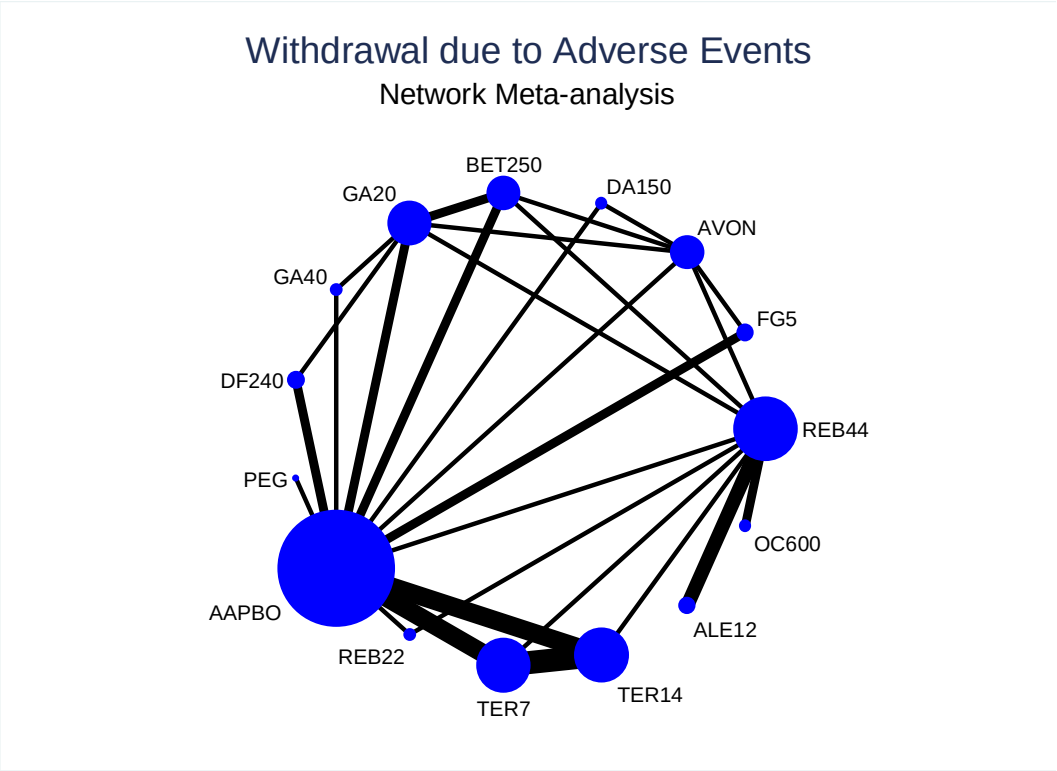


Table 4. Network Meta-analysis Results: Withdrawals due to adverse events

Comparison	RRMS: WAE
Drug vs. Drug (by dose)	**RR (95% CI)[a]**
Teriflunomide 7 mg vs. Teriflunomide 14 mg	0.79 (0.53,1.17)
Teriflunomide 7 mg vs. Rebif 44 µg	0.57 (0.32,1.02)
Teriflunomide 7 mg vs. Rebif 22 µg	0.76 (0.23,2.54)
Teriflunomide 7 mg vs. Plegridy	0.38 (0.13,1.09)
Teriflunomide 7 mg vs. Ocrelizumab 600 mg	0.92 (0.44,2.22)
Teriflunomide 7 mg vs. Glatiramer 40 mg	0.69 (0.26,1.85)
Teriflunomide 7 mg vs. Glatiramer 20 mg	0.85 (0.45,1.60)
Teriflunomide 7 mg vs. Fingolimod 0.5 mg	0.84 (0.46,1.53)
Teriflunomide 7 mg vs. Dimethyl Fumarate 240 mg	1.00 (0.55,1.83)
Teriflunomide 7 mg vs. Daclizumab high yield process 150 mg	0.60 (0.26,1.40)
Teriflunomide 7 mg vs. Betaseron 250 mg	0.55 (0.24,1.25)
Teriflunomide 7 mg vs. Avonex	0.98 (0.50,1.92)
Teriflunomide 7 mg vs. Alemtuzumab 12 mg	1.92 (0.82,4.48)
Teriflunomide 14 mg vs. Rebif 44 µg	0.72 (0.42,1.25)
Teriflunomide 14 mg vs. Rebif 22 µg	0.97 (0.29,3.17)
Teriflunomide 14 mg vs. Plegridy	0.48 (0.17,1.37)
Teriflunomide 14 mg vs. Ocrelizumab 600 mg	1.25 (0.56,2.76)
Teriflunomide 14 mg vs. Glatiramer 40 mg	0.87 (0.33,2.32)
Teriflunomide 14 mg vs. Glatiramer 20 mg	1.07 (0.59,1.96)
Teriflunomide 14 mg vs. Fingolimod 0.5 mg	1.07 (0.59,1.91)
Teriflunomide 14 mg vs. Dimethyl Fumarate 240 mg	1.27 (0.70,2.28)
Teriflunomide 14 mg vs. Daclizumab high yield process 150 mg	0.76 (0.34,1.74)

Comparison	RRMS: WAE
Teriflunomide 14 mg vs. Betaseron 250 mg	0.70 (0.31,1.54)
Teriflunomide 14 mg vs. Avonex	1.24 (0.64,2.38)
Teriflunomide 14 mg vs. Alemtuzumab 12 mg	**2.42 (1.05,5.60)**
Rebif 44 µg vs. Rebif 22 µg	1.33 (0.45,3.97)
Rebif 44 µg vs. Plegridy	0.66 (0.22,1.98)
Rebif 44 µg vs. Ocrelizumab 600 mg	1.72 (0.97,3.06)
Rebif 44 µg vs. Glatiramer 40 mg	1.20 (0.43,3.33)
Rebif 44 µg vs. Glatiramer 20 mg	1.48 (0.88,2.50)
Rebif 44 µg vs. Fingolimod 0.5 mg	1.47 (0.79,2.73)
Rebif 44 µg vs. Dimethyl Fumarate 240 mg	1.75 (0.94,3.26)
Rebif 44 µg vs. Daclizumab high yield process 150 mg	1.06 (0.49,2.29)
Rebif 44 µg vs. Betaseron 250 mg	0.96 (0.48,1.92)
Rebif 44 µg vs. Avonex	1.71 (0.95,3.08)
Rebif 44 µg vs. Alemtuzumab 12 mg	**3.35 (1.76,6.36)**
Rebif 22 µg vs. Plegridy	0.49 (0.11,2.25)
Rebif 22 µg vs. Ocrelizumab 600 mg	1.29 (0.38,4.43)
Rebif 22 µg vs. Glatiramer 40 mg	0.90 (0.21,3.87)
Rebif 22 µg vs. Glatiramer 20 mg	1.11 (0.34,3.63)
Rebif 22 µg vs. Fingolimod 0.5 mg	1.10 (0.33,3.73)
Rebif 22 µg vs. Dimethyl Fumarate 240 mg	1.31 (0.39,4.43)
Rebif 22 µg vs. Daclizumab high yield process 150 mg	0.79 (0.21,2.94)
Rebif 22 µg vs. Betaseron 250 mg	0.72 (0.20,2.57)
Rebif 22 µg vs. Avonex	1.28 (0.38,4.32)
Rebif 22 µg vs. Alemtuzumab 12 mg	2.51 (0.71,8.89)
Plegridy vs. Ocrelizumab 600 mg	2.62 (0.76,9.07)
Plegridy vs. Glatiramer 40 mg	1.83 (0.49,6.87)
Plegridy vs. Glatiramer 20 mg	2.26 (0.75,6.77)
Plegridy vs. Fingolimod 0.5 mg	2.24 (0.77,6.50)
Plegridy vs. Dimethyl Fumarate 240 mg	2.66 (0.91,7.75)
Plegridy vs. Daclizumab high yield process 150 mg	1.61 (0.47,5.48)
Plegridy vs. Betaseron 250 mg	1.46 (0.43,4.97)
Plegridy vs. Avonex	2.60 (0.88,8.02)
Plegridy vs. Alemtuzumab 12 mg	**5.09 (1.44,18.08)**
Ocrelizumab 600 mg vs. Glatiramer 40 mg	0.70 (0.22,2.25)
Ocrelizumab 600 mg vs. Glatiramer 20 mg	0.86 (0.40,1.88)
Ocrelizumab 600 mg vs. Fingolimod 0.5 mg	0.85 (0.37,1.99)
Ocrelizumab 600 mg vs. Dimethyl Fumarate 240 mg	1.02 (0.43,2.37)
Ocrelizumab 600 mg vs. Daclizumab high yield process 150 mg	0.61 (0.23,1.61)
Ocrelizumab 600 mg vs. Betaseron 250 mg	0.56 (0.23,1.37)
Ocrelizumab 600 mg vs. Avonex	0.99 (0.44,2.26)
Ocrelizumab 600 mg vs. Alemtuzumab 12 mg	1.94 (0.82,4.60)
Glatiramer 40 mg vs. Glatiramer 20 mg	1.24 (0.45,3.37)
Glatiramer 40 mg vs. Fingolimod 0.5 mg	1.23 (0.45,3.30)
Glatiramer 40 mg vs. Dimethyl Fumarate 240 mg	1.46 (0.54,3.92)
Glatiramer 40 mg vs. Daclizumab high yield process 300 mg	0.54 (0.12,2.35)
Glatiramer 40 mg vs. Daclizumab high yield process 150 mg	0.88 (0.28,2.79)
Glatiramer 40 mg vs. Betaseron 250 mg	0.80 (0.25,2.52)
Glatiramer 40 mg vs. Avonex	1.43 (0.50,4.07)
Glatiramer 40 mg vs. Alemtuzumab 12 mg	2.79 (0.84,9.25)
Glatiramer 20 mg vs. Fingolimod 0.5 mg	0.99 (0.53,1.85)
Glatiramer 20 mg vs. Dimethyl Fumarate 240 mg	1.18 (0.67,2.06)
Glatiramer 20 mg vs. Daclizumab high yield process 300 mg	0.44 (0.13,1.49)
Glatiramer 20 mg vs. Daclizumab high yield process 150 mg	0.71 (0.32,1.58)

Comparison	RRMS: WAE
Glatiramer 20 mg vs. Betaseron 250 mg	0.65 (0.33,1.27)
Glatiramer 20 mg vs. Avonex	1.15 (0.62,2.15)
Glatiramer 20 mg vs. Alemtuzumab 12 mg	2.25 (0.98,5.18)
Fingolimod 0.5 mg vs. Dimethyl Fumarate 240 mg	1.19 (0.65,2.17)
Fingolimod 0.5 mg vs. Daclizumab high yield process 150 mg	0.72 (0.33,1.55)
Fingolimod 0.5 mg vs. Betaseron 250 mg	0.65 (0.29,1.48)
Fingolimod 0.5 mg vs. Avonex	1.16 (0.65,2.08)
Fingolimod 0.5 mg vs. Alemtuzumab 12 mg	2.27 (0.94,5.51)
Dimethyl Fumarate 240 mg vs. Daclizumab high yield process 150 mg	0.60 (0.26,1.39)
Dimethyl Fumarate 240 mg vs. Betaseron 250 mg	0.55 (0.25,1.23)
Dimethyl Fumarate 240 mg vs. Avonex	0.98 (0.50,1.93)
Dimethyl Fumarate 240 mg vs. Alemtuzumab 12 mg	1.91 (0.79,4.66)
Daclizumab high yield process 150 mg vs. Betaseron 250 mg	0.91 (0.36,2.33)
Daclizumab high yield process 150 mg vs. Avonex	1.62 (0.94,2.80)
Daclizumab high yield process 150 mg vs. Alemtuzumab 12 mg	**3.17 (1.16,8.67)**
Betaseron 250 mg vs. Avonex	1.78 (0.80,3.94)
Betaseron 250 mg vs. Alemtuzumab 12 mg	**3.48 (1.35,8.98)**
Avonex vs. Alemtuzumab 12 mg	1.95 (0.82,4.65)

a. References included in NMA: 27-31,33-36,38-41,43-47,49,54,56,58,59,61-67

Abbreviations: mg, milligrams; RR, Relative Risk; 95% CI, 95% Credible Interval; RRMS, Relapsing-remitting multiple sclerosis; WAE, Withdrawal due to adverse events

Key Question 1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?

Summary of the Evidence

Relapsing-Remitting Multiple Sclerosis

Ocrelizumab

- There was low strength evidence that treatment with ocrelizumab 600 mg is associated with similar risk of relapse as treatment with interferon beta-1a 30µgIM (RR 0.32, 95% CI 0.09 to 1.14)), although annualize relapse rates favored ocrelizumab (0.13 vs. 0.36, p=0.03).
- There was low strength evidence that treatment with ocrelizumab 600 mg is associated with reduced confirmed disability progression at 6 months (HR for risk reduction 0.60, 95% CI 0.43 to 0.84) and improved annualized relapse rate (0.16 vs. 0.29) compared with interferon beta-1a 44µgSC

Daclizumab HYP

- There was low strength evidence that daclizumab HYP 150 mg is associated with less confirmed disability progression (HR 0.73, 95% CI 0.55 to 0.98) and lower risk of relapse (HR 0.59, 95% CI 0.50 to 0.69) compared with interferon beta-1a 30µgIM

Alemtuzumab

- There was moderate strength evidence that treatment with alemtuzumab 12 mg resulted in improved sustained accumulation of disability at 6 months (RR, 0.59; 95% CI, 0.40 to

0.86) and risk of relapse (RR, 0.61, 95% CI, 0.52 to 0.71) compared to treatment with interferon beta-1a 44 µg SC

Teriflunomide

- There was low strength evidence that treatment with teriflunomide 7 mg but not 14 mg was associated with increased risk of relapse compared with interferon beta-1a 44µgSC (RR 2.74, 95% CI 1.66 to 4.53; RR 1.52, 95% CI 0.87 to 2.67, respectively)

Fingolimod

- Based on moderate-strength evidence, treatment with fingolimod 0.5 mg once daily resulted in lower risk of relapse than treatment with interferon beta-1a 30 µg IM (RR 0.58, 95% CI 0.45 to 0.75)

Glatiramer acetate

- Head-to-head trials provided low-strength evidence of no difference in relapse-related outcomes with glatiramer acetate versus interferon beta-1a (30 µg IM and 44 µg SC) and 1b (250 µg)
- There was moderate-strength evidence that treatment with glatiramer results in similar disease progression as treatment with interferon beta-1b and low-strength evidence of similar disease progression between glatiramer and interferon beta-1a IM and SC
- There was moderate strength evidence that glatiramer 40 mg three times weekly improved relapse rates over placebo

Beta interferons

- There was moderate strength evidence that pegylated interferon beta-1a 125µgwas associated with improved disability progression (HR 0.62, 95% CI 0.40 to 0.97) and relapse (HR 0.61, 95% CI 0.47 to 0.80) compared with placebo
- There was moderate strength evidence that treatment with interferon beta-1b 250µgor interferon beta-1a 44µgresults in improved relapse outcomes compared with interferon beta-1a 30µgIM. There was conflicting evidence on disease progression outcomes.
- Current evidence is unable to identify differences between interferon beta-1b SC and interferon beta-1a SC in terms of effectiveness. Indirect analyses of placebo-controlled trial data agreed with these results.

Primary Progressive Multiple Sclerosis

- There was moderate-strength evidence that ocrelizumab delayed disability progression compared with placebo in patients with PPMS (HR 0.75, 95% CI 0.58 to 0.98).

Mixed Populations: Clinically Isolated Syndrome and Relapsing-Remitting Multiple Sclerosis

- One small fair-quality study compared interferon beta-1b SC (Betaseron®) to glatiramer acetate and found no differences in relapse related outcomes.

Mixed Populations: Progressive Multiple Sclerosis

- A good-quality systematic review assessed strength of evidence as high that relapse rates over 36 months were lower with interferon beta-1b than with placebo in patients with all progressive phenotypes combined (SPMS, PRMS, and PPMS). No other differences in efficacy were found between interferon or glatiramer and placebo (SOE very low to low).

Mixed Populations: All Types of Multiple Sclerosis

Persistence rates with interferon beta-1b are similar to or less than persistence rates with interferon beta-1a and glatiramer based on three observational studies. One study showed a statistically significant difference in persistence at 18 months (32.9% for interferon beta-1b, compared with 54.6 to 58.3% for the other drugs, $P<0.0001$)

Detailed Assessment

Previously Conducted Systematic Reviews of Disease-Modifying Drugs for Multiple Sclerosis

We found 2 recent systematic reviews that assessed multiple drugs for the treatment of multiple sclerosis.[25,68] Both reviews conducted a network meta-analysis (NMA); one limited comparisons to interferons with other injectable therapies,[68] the other compared all included drugs, with the exception of ocrelizumab, in the NMA.[25] In addition, we conducted our own NMA in patients with RRMS. Our NMA differed by including only approved doses and dosing schedules of approved medications and the inclusion of ocrelizumab to the NMA. We included all formulations of the 2 drugs currently pending FDA approval (ocrelizumab and daclizumab) and we included all treatment durations (3-36 months), whereas the Cochrane NMA[25] limited analysis to 12 and 24 months. We present the results of network meta-analyses under each drug comparison, where appropriate, under "indirect evidence." Overall, there was good agreement between the three reviews. Most disagreements between NMAs could be explained by differing drug dose and/or dosing schedule. When our NMA results differ from published results, we highlight these differences.

Relapsing-Remitting Multiple Sclerosis

Ocrelizumab compared with interferon beta-1a IM/SC

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targetsCD-20 expressing B cell and is not yet approved by the FDA, although break-through status for its use in patients with PPMS has been granted.[69] Ocrelizumab has also been given to patients with relapsing forms of MS and the evidence for this population is below.

Direct evidence

One trial of ocrelizumab in patients with RRMS has been fully published[32] and compared ocrelizumab with interferon beta-1a 30 µg, as well placebo. Information from two additional trials were available in poster format and dossier submission (OPERA I and OPERA II) that compared ocrelizumab with interferon beta-1a 44 ug.[63,70]

The published RCT included 220 patients from North America, east-central Europe and Asia, western Europe, and Latin America, although most patients were white (96%), female (65%), and had 2 or 3 relapses in the past 3 years (83%).[32] The mean time since MS diagnosis was 2.7 years (placebo group) to 4.4 years (ocrelizumab 2000 group). However, 70% and 69% of the placebo and interferon groups, respectively had received no previous immunomodulatory treatment which was a larger proportion than in the two groups treated with ocrelizumab (47% and 49%). There were 32 patients who experienced relapses within 24 weeks of treatment. Compared to interferon beta-1a 30µgIM (Avonex®), treatment with ocrelizumab 600 mg and 2000 mg resulted in a similar risk of relapse (5% vs. 17%, RR 0.33, 95% CI 0.09 to 1.14; 7% vs. 17%, RR 0.44, 95% CI 0.14 to 1.33, respectively), although annualized relapse rates versus interferon beta-1a 30µgIM were significantly lower for ocrelizumab 600 mg (0.13 vs. 0.36, p=0.03). When the two doses of ocrelizumab were combined (the relapse rate for ocrelizumab 2000 mg was higher than the rate for 600 mg), there was low strength evidence that ocrelizumab was associated with lower relapse rates than interferon beta-1a (Avonex®), 6% vs 17%, RR 0.38, 95% CI 0.15 to 0.97. Annualized relapse rates by week 24 were 0.13 to 0.17 with ocrelizumab, 0.36 with interferon beta-1a (Avonex®), and 0.64 for placebo.

In two unpublished randomized trials (OPERA I and OPERA II)[63,70] patients were treated with ocrelizumab 600 mg or interferon beta-1a 44µgSC (Rebif®). Patient characteristics were similar in the two trials; approximately two thirds were female with a mean age of 37 years with 4 years since diagnosis and, on average, 1.3 relapses in the past 12 months. Annualized relapse rates were 0.16 in the ocrelizumab arms of both studies and 0.29 in the interferon beta-1a (Rebif®) arms which were statistically significant (p<0.001). Confirmed disability progression was also reduced 40% with ocrelizumab (pooled HR at 12 weeks HR 0.6 (95% CI 0.45 to 0.81, p<0.001; 24 weeks HR 0.6, 95% CI 0.43 to 0.84, p<0.01).

Indirect evidence

In network meta-analysis, treatment with ocrelizumab 600 mg was associated with lower risk of relapse when compared with interferon beta-1a 30µg (RR 0.24, 95% CI 0.07, 0.76) and interferon beta-1a 22µgSC (RR 0.27, 95% CI 0.08 to 0.89) but not interferon beta-1a 44µgSC (RR 0.33, 95% CI 0.10 to 1.07). Treatment with ocrelizumab 2000 mg was also associated with lower risk of relapse compared with interferon beta-1a 30µgIM (RR 0.31, 95% CI 0.11 to 0.87). The results from indirect analysis are consistent with the results from direct comparison for ocrelizumab compared with interferon beta-1a 30µgIM, after pooling ocrelizumab arms. The OPERA I and OPERA II trials did not report numbers of patients who experienced a relapse but only reported annualized rates and therefore a comparison of direct versus indirect evidence for risk of relapse was not possible. The Cochrane review[25] did not include ocrelizumab in its network meta-analysis.

Daclizumab HYP compared with interferon beta-1a 30µgIM

Daclizumab is a humanized monoclonal antibody that modulates interleukin-2 signaling and is not yet approved by the FDA. Daclizumab High Yield Process (HYP) is a newer form (different glycosylation profile) of daclizumab developed for long-term SC administration with less antibody-dependent cytotoxicity than earlier formulations[51] One published study compared daclizumab HYP with interferon beta-1a 30µgIM and is described below.[51] Two placebo-controlled trials, one of the newer formulation and one of the original formulations are also mentioned below.

Direct evidence

An RCT conducted in 1,841 patients with RRMS found that treatment with daclizumab HYP 150 mg SC every 4 weeks resulted in a lower estimated risk of relapse at week 144 (the maximum length of treatment) than treatment with interferon beta-1a 30µg (33% vs. 49%, HR 0.59, 95% CI 0.50 to 0.69) and less estimated confirmed disability progression at 24 weeks (13% vs. 18%. HR 0.73, 95% CI 0.55 to 0.98), but there were no statistically significantly difference in 12-wee sustained disability progression.[51] Patients in this study were primarily female (68%), white (90%), had an average of 4.1 years since diagnosis and a mean of 1.6 relapses in the past 12 months. Annualized relapse rates were also lower with daclizumab (0.22 vs. 0.39, p<0.001). However, disability progression at week 144 was not significantly different between daclizumab and interferon beta-1a 30µgSC (16% vs. 20%, HR 0.84, 95% CI 0.66 to 1.07).

Indirect evidence

Evidence from a placebo-controlled trial (SELECT, N=600) found fewer relapses at 52 weeks with daclizumab HYP 150 mg (19%) and daclizumab HYP 300 mg (20%) compared with placebo (36%) but no difference in relapse or annualized relapse rate (0.21 vs. 0.23) between the two daclizumab doses.[29] Nor were there differences between doses in confirmed disability progression at 52 weeks: daclizumab HYP 150 mg (6%) versus daclizumab HYP 300 mg (8%) while 13% of the placebo group experienced disability progression.

Results from our NMA indicated that treatment daclizumab HYP 150 mg and 300 mg results in lower risk of relapse compared with interferon beta-1a 30µgIM (RR 0.63, 95% CI 0.42 to 0.94; RR 0.65, 95% CI 0.53 to 0.81, respectively). The Cochrane NMA included only the SELECT trial and reported no difference in annualized relapse rates between daclizumab and interferon beta-1a 30 µg.

Alemtuzumab compared with interferon beta-1a SC

Direct evidence

Three fair-quality trials compared alemtuzumab 12 mg with interferon beta-1a 44 µg SC.[43-45] Two of these trials also included an alemtuzumab 24 mg arm,[44,45] although in 1 trial the alemtuzumab 24 mg arm was discontinued to facilitate recruitment into other study arms.[44] One trial treated patients for 36 months[45] while the other 2 were 24-month studies.[43,44]

Annualized relapse rates ranged from 0.11[45] to 0.26[44] in patients receiving alemtuzumab 12 mg compared with 0.36[45] to 0.52[44] in patients treated with interferon beta-1a. The 3 primary studies provided moderate-strength evidence that alemtuzumab 12 mg was associated with less risk of relapse and reduced rates of sustained accumulation of disability defined as an increase from baseline of at least 1 Expanded Disability Status Scale point (or ≥ 1.5 points if the baseline Expanded Disability Status Scale score was 0) at 6 months. Additionally, there was greater disease free survival when compared with interferon beta-1a (Table 5). There was low-strength evidence of no difference in change in Expanded Disability Status Scale scores from baseline (MD, -0.35; 95% CI, -0.73 to 0.03; I^2=87%), however significant statistical heterogeneity was present. Two of three studies found a significant improvement in Expanded Disability Status Scale score with alemtuzumab[44,45] while a third found no difference.[43] After examination of patient characteristics and study design, there was no clear explanation for the differences between studies to explain the heterogeneity.

Table 5. Comparative effectiveness outcomes of alemtuzumab compared with interferon beta-1a

Drug A	Drug B	Outcome (Number studies; N)	Effect estimate (95% CI)	Strength of evidence
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Sustained disability 6 months (3 studies; 1,414)	RR 0.59 (0.40 to 0.86)	Moderate
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Relapse (# patients) (3 studies; 1.414)	RR 0.61 (0.52 to 0.71)	Moderate
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Annualized relapse rate (3 studies; 1,414)	Rate ratio 0.42 (0.31 to 0.56)	Moderate
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Disease free survival (2 studies; 1,191)	RR 1.38 (1.23 to 1.54)	Moderate
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Change in EDSS score (3 studies; 1,414)	MD -0.35 (-0.73 to 0.03)	Low
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Sustained disability 6 months (1 study, 221)	RR 0.42 (0.21 to 0.84)	Low
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Relapse (# patients) (1 study; 221)	RR 0.38 (0.23 to 0.62)	Low
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Annualized relapse rate (1 study; 221)	Rate ratio 0.22 (0.14 to 0.36)	Low
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Change in EDSS score (1 study; 221)	MD -0.83 (-1.17 to -0.49)	Low

Abbreviations: EDSS, Expanded Disability Status Scale; MD, mean difference; RR, relative risk; SC, subcutaneous.

The annualized relapse rate for patients receiving alemtuzumab 24 mg in a single trial was 0.08 (95% CI, 0.05 to 0.12). Treatment with alemtuzumab 24 mg was associated with reduced risk of relapse and greater improvement in Expanded Disability Status Scale scores from baseline compared with interferon beta-1a 44 µg SC but resulted in similar rates of sustained accumulation of disability at 6 months (Table 5).[45]

Indirect evidence

Treatment with interferon beta-1a 44µgSC resulted in higher risk of relapse when compared to alemtuzumab 12 mg in our NMA (RR 1.67, 95% CI 1.37 to 2.04) which was consistent with Cochrane's analysis of annualized relapse rates.[25] We also calculated effect estimates for interferon beta-1a 22µgSC compared with alemtuzumab 12 mg in the absence of direct evidence and found similar results (RR 2.03, 95% CI 1.51 to 2.74).

Dimethyl fumarate compared with glatiramer

Direct evidence

One fair-quality, 2-year, phase 3, placebo-controlled trial (N=1,417) comparing dimethyl fumarate and glatiramer 20 mg with placebo (study was not designed to compare dimethyl fumarate with glatiramer) randomized glatiramer and dimethyl fumarate-naïve patients to glatiramer, dimethyl fumarate 240 mg twice daily, three times daily, or to placebo.[71] There was low strength of evidence that dimethyl fumarate 480 mg daily is associated with similar risk of relapse compared with glatiramer 20 mg (RR 0.91, 95% CI 0.73 to 1.13) whereas 720 mg was associated with lower risk of relapse and lower annualized relapse rate versus glatiramer at 24 months (RR, 0.75; 95% CI, 0.59 to 0.96; rate ratio, 0.69; 95% CI, 0.51 to 0.94, respectively). However, treatments were not different in preventing disability progression (RR, 0.82; 95% CI,

0.57 to 1.17) with identical estimates for dimethyl fumarate 480 and 720 mg compared with glatiramer. [72]

Indirect evidence
Our NMA found no differences in risk of relapse between either glatiramer 40 mg or glatiramer 20 mg compared with dimethyl fumarate 240 mg twice daily (RR 0.99, 95% CI 0.68 to 1.43; RR 1.15, 95% CI 0.89 to 1.48, respectively). Likewise, there was no difference in annualized relapse rates between dimethyl fumarate and glatiramer based on Cochrane's NMA.[25]

Teriflunomide compared with interferon beta-1a 44µgSC

Direct evidence
One randomized trial (N=324) compared a minimum of 48 weeks treatment (maximum 115 weeks) with teriflunomide 7 mg, teriflunomide 14 mg, and interferon beta-1a 44 µg SC and found no differences between treatments in time to failure, defined as confirmed relapse or permanent treatment discontinuation (36% vs 33% vs 37%, respectively) at 48 weeks.[59] There was a higher risk of relapse with lower dose teriflunomide compared with higher dose (42% vs 23%, RR 1.80, 95% CI 1.21 to 2.69) and low strength evidence of increased relapse risk with teriflunomide 7 mg versus interferon beta-1a 44ug SC (42% vs 16%, RR 2.74, 95% CI 1.66 to 4.53). There was low strength evidence no difference in risk of relapse between higher dose teriflunomide and interferon beta-1a (RR 1.52, 95% CI 0.87 to 2.67). Adjusted annualized relapse rates were also higher with teriflunomide 7 mg compared with interferon beta-1a (0.41 vs 0.22, RR 1.90, 95% CI 1.05 to 3.43).

Indirect evidence
Our NMA found no differences in risk of relapse between treatment with teriflunomide 7 mg, teriflunomide 14 mg, interferon beta-1a 22µgSC (RRs 0.82 to 1.10). However, treatment with teriflunomide 7 mg was associated with borderline increased risk of relapse compared with interferon beta-1a 44µg (RR 1.32, 95% CI 1.01 to 1.72). There was no difference between teriflunomide and interferon beta-1a in annualized relapse rates based on Cochrane's NMA but teriflunomide doses were combined.[25]

Fingolimod compared with interferon beta-1a 30 µg IM

Direct evidence
Based on the results from one head to head trial (TRANSFORMS, N=860) there was moderate strength evidence that fingolimod resulted in lower risk of relapse compared with interferon beta-1a 30 µg SC (17% vs. 30%, RR 0.58, 95% CI 0.45 to 0.75) after 12 months.[46] The primary outcome measure, annualized relapse rate, was significantly lower with either dose of fingolimod compared with interferon beta-1a, but no difference between the doses was found (Table 6). Reduction in Expanded Disability Status Scale scores after treatment was greater in patients receiving fingolimod 1.25 mg compared with interferon beta-1a but the small reduction was of questionable clinical significance. There was low strength evidence of no difference in EDSS score between treatment with fingolimod 0.5 mg and interferon beta-1a 30 µg. One note regarding this study is that previous recent therapy with any type of interferon was not an

exclusion criterion. This may have resulted in patients with demonstrated benefit or lack of benefit with interferon beta-1a IM being randomized to the interferon arm of the study.

Table 6. Comparative effectiveness of outcomes of fingolimod compared with interferon beta-1a 30 µg

Drug A	Drug B	Outcome (Number studies; N)	Effect estimate (95% CI)
Fingolimod 0.5 mg	interferon beta-1a 30 µg	Relapse (# patients) (1 study; 860 patients)	RR 0.58 (0.45 to 0.75)
Fingolimod 0.5 mg	interferon beta-1a 30 µg	Annualize relapse rate (1 study; 860 patients)	Rate ratio 0.49 (0.34 to 0.70)
Fingolimod 0.5 mg	interferon beta-1a 30 µg	Change in EDSS score (1 study; 860 patients)	MD -0.09 (-0.20 to 0.02)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg	Relapse (# patients) (1 study; 851 patients)	RR 0.66 (0.52 to 0.84)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg	Annualize relapse rate (1 study; 851 patients)	Rate ratio 0.61 (0.43 to 0.85)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg	Change in EDSS score (1 study; 851 patients)	MD -0.12 (-0.23 to -0.01)

Abbreviations: EDSS, Expanded Disability Status Scale; MD, mean difference; RR relative risk.
[a] Fingolimod 1.25 mg is a higher and unapproved dose.

Indirect evidence

Our NMA included treatment with fingolimod at the approved dose (0.5 mg) only and found treatment with fingolimod associated with lower risk of relapse that treatment with interferon beta-1a 30 µg IM (RR 0.60, 95% CI 0.47 to 0.76). Fingolimod was associated with reduced annualized relapse rate compared with interferon beta-1a 30 µg at 24 months but not at 12 months.[25]

Glatiramer acetate compared with beta interferons

Direct evidence

Five trials directly comparing glatiramer acetate to another disease-modifying drug were identified, 2 comparing to interferon beta-1b and 3 comparing to interferon beta-1a.[49,56,58,61,73] The BEYOND trial comparing glatiramer acetate to interferon beta-1b was a good-quality study,[56] as was the CombiRx trial comparing glatiramer with and without interferon beta-1a.[49] Two trials were rated fair quality[58,61] and 1 was rated poor quality due to lack of information regarding baseline characteristics at randomization and unclear blinding and is not discussed further.[73] The BECOME trial[61] was small with a mixed population of patients with relapsing-remitting multiple sclerosis and clinically isolated syndrome and is discussed under mixed populations. The three trials discussed here all enrolled primarily white females with a mean age between 35 and 39 years. In two trials duration of disease was between 5 and 7 years,[56,58] whereas MS was recently diagnosed in patients in the CombiRx trial with duration of disease between 1 and 1.5 years.[49] There was low strength evidence of no differences between glatiramer and any of the interferons in included relapse or disability outcomes with the exception of moderate strength evidence for no difference in disease progression between glatiramer and interferon beta-1b.

In the REGARD trial[58] (N=764), patients with RRMS were treated with glatiramer or interferon beta-1a 44 µg SC for 96 weeks. There was no difference between treatments in risk of

relapse (35% vs. 33%, RR 1.07, 95% CI 0.88 to 1.31), annualized relapse rates (0.29 vs. 0.30) or in 6-month confirmed EDSS progression (8.7% vs. 11.7%, p=0.117).

In the CombiRx trial (N=509 for the glatiramer and interferon along groups) there were no differences in risk of protocol-defined relapse and disability progression between glatiramer and interferon beta-1a 30 µg IM (RR 1.15, 95% CI 0.82 to 1.59; RR 0.79, 95% CI 0.57 to 1.08, respectively).[49] In the BEYOND trial (N=2244)[56] patients were randomized to receive daily glatiramer or interferon beta-1b 250 µg or 500 µg SC every other day (250 µg is the approved dose). The estimated proportion of patients relapse free in the glatiramer group was 59% which was not different than the 250 µg group (58%) or the 500 µg group (60%). Annualized relapse rates were also similar (0.34 vs. 0.36 vs. 0.33, respectively). There were also no differences in estimated proportions with confirmed EDSS (20% vs. 21% vs. 22%) at 2 years. A systematic review that included the five trials of beta interferons compared with glatiramer also found no difference at 24 months in number of participants with relapse (RR 1.04, 95% CI 0.87 to 1.24 and in confirmed progression (RR 1.11, 95% CI 0.91 to 1.35).[74]

Indirect evidence

Moderate strength of evidence was provided by one trial that compared the new dosing of glatiramer 40 mg three times weekly and found glatiramer associated with lower annualized relapse rates compared with placebo (0.33 vs. 0.51, p<0.001).[33] This trial was included in our network meta-analysis. Our NMA found treatment with glatiramer 20 mg and 40 mg to be associated with borderline lower risk of relapse compared with interferon beta-1a 30 µg IM only (RR 0.84, 95% CI 0.71 to 1.00; RR 0.72, 95% CI 0.52 to 0.99, respectively). There were no differences in relapse rates between glatiramer 20 mg, glatiramer 40 mg, interferon beta-1a 44 µg SC, interferon beta-1a 22 µg SC, and interferon beta-1b 250 µg.

Cochrane NMA results[25] for annualized relapse rate were consistent with our NMA results for risk of relapse with the exception that glatiramer was not significantly different in risk of relapse compared with interferon beta-1a 30 µg IM although point estimate favored glatiramer at 12 and 24 months (RR 0.86, 95% CI 0.68 to 1.08; RR 0.91, 95% CI 0.79 to 1.05, respectively).

Beta interferons

New to this report is the pegylated interferon beta-1a 125 µg given SC every 2 weeks. There is no direct evidence comparing this interferon with any other drug included in this report. However, we do include evidence from one placebo-controlled trial in our NMA and we report on the findings of this trial in this section under indirect evidence.

Direct evidence

Eight trials directly compared 1 beta interferon to another, ranged from 3 to 24 months in duration in patients with relapsing-remitting multiple sclerosis.[47,48,53,54,75-78] Three trials were rated poor quality due to unclear randomization and allocation concealment, baseline characteristics provided not adequate or not for groups as randomized, on and/or high dropout rate and are not further discussed,[77-79] While the remainder were all fair-quality trials, there was variation in their features and risk of bias. The INCOMIN trial and the REFORMS trial of interferon beta-1a IM (Avonex®) and interferon beta-1b SC (Betaseron®) were open-label, while the other 4 were single-blinded studies. The EVIDENCE trial compared the 2 beta-1a interferons to each other and original data was published in 2002.[50] A crossover phase followed in which all

patients were either switched to or continued on interferon beta-1a SC (Rebif®). Given the lack of comparative data on this crossover phase, it will only be included in the discussion of harms that follows.[80] The 2 Etemadifar trials compared all 3 beta interferons to another, and in the most recent trial, also to azathioprine. This later study did not report relapse related outcomes.[75] Both Etemadifar studies were small, ≤30 patients per group and as low as 13 in the second trial. In the first trial, the baseline mean or median Expanded Disability Status Scale in the groups ranged from 1.9 to 2.98 and the mean number of relapses in the 2 years prior to the study ranged from 1.38 to 3.2. In the second trial the mean baseline Expanded Disability Status Scale score was 1.55 and although the authors provide data on the mean Expanded Disability Status Scale score for each drug, it was not designed to compare the 3 drugs to each other. While dosing for interferon beta-1b SC (Betaseron®) 250 µg every other day and interferon beta-1a IM (Avonex®) 30 µg once weekly were consistent across the studies, the dosing for interferon beta-1a SC (Rebif®) ranged from 22 µg once weekly to 44 µg 3 times weekly. Additionally, the Danish Multiple Sclerosis Study Group patients were more severely ill compared with the other studies and the studies differed in terms of whether the endpoint reported was primary or secondary. Results from these trials are presented in Tables 7 and 8 below. We limited the pooling of data to the 44 µg dose of interferon beta-1a SC (Rebif®) only. Overall, these studies supported the use of the beta interferons for improving relapse-related outcomes, with less effect on the disability-related outcomes.

Table 7. Relapse-related outcomes in trials comparing beta interferons

Study N, duration	Intervention, dose	Annualized relapse rate	Relapse-free (%)	Rate of steroid use
Durelli 2002 INCOMIN trial N=188, 2 years	Interferon β-1a IM (Avonex®) 30 mcg vs. interferon β-1b SC (Betaseron®) 250 mcg	0.7 vs. 0.5 *P*=0.03	36% vs. 51% *P*=0.03	0.5 vs. 0.38 *P*=0.09
Panitch 2005 EVIDENCE trial N=677, 16 months	Interferon β-1a IM (Avonex®) 30 mcg vs. interferon β-1a SC (Rebif®) 44 mcg	0.65 vs. 0.54 *P*=0.009	48% vs. 56% *P*=0.023	0.28 vs. 0.19 *P*=0.033
Koch-Henriksen 2006 Danish Multiple Sclerosis Study Group N=301, 2 years	Interferon β-1a SC (Rebif®) 22 mcg weekly vs. interferon β-1b SC (Betaseron®) 250 mcg	0.70 vs. 0.71 *P*=0.91	NR	0.21 vs. 0.20 *P*=0.77
Etemadifar 2006 N=90, 2 years	Interferon β-1a IM (Avonex®) 30 mcg vs. interferon β-1a SC (Rebif®) 44 mcg vs. interferon β-1b SC (Betaseron®) 250 mcg	(mean) 1.2 vs. 0.6 vs. 0.7	20% vs. 57% vs. 43% *P*<0.05 Betaseron® vs. Rebif® *P*=0.3017	NR
Singer 2012 REFORMS N=129, 3 months	interferon β-1a SC (Rebif®) 44 mcg vs. interferon β-1b SC (Betaseron®) 250 mcg	NR	86% vs. 89% p=NS	NR
Pooled Relative Risk	Interferon β-1b SC (Betaseron®) 250 mcg vs. interferon β-1a IM (Avonex®) 30 mcg	--	**RR 1.51** **(1.11 to 2.07)**[a]	--

Abbreviations: IM, intramuscular; SC, subcutaneous.
[a] RR = Relative risk (95% confidence interval), random effects model.

Table 8. Disease progression-related outcomes in trials comparing beta interferons

Study N, duration	Intervention, dose	Disease progression[a]	Mean change in EDSS	Mean EDSS at endpoint
Durelli 2002 INCOMIN trial N=188, 2 years	Interferon β-1a IM (Avonex®) 30 mcg vs. interferon β-1b SC (Betaseron®) 250 mcg	30% vs. 13% *P*=0.0036	0.54 vs. 0.13 *P*<0.0001	2.5 vs. 2.1 *P*=0.0002
Koch-Henriksen 2006 Danish Multiple Sclerosis Study Group N=301, 2 years	Interferon β-1a SC (Rebif®) 22 mcg weekly vs. interferon β-1b SC (Betaseron®) 250 mcg	36% vs. 33% *P*=0.3736	NR	NR
Etemadifar 2006 N=90, 2 years	Interferon β-1a IM (Avonex®) 30 mcg vs. interferon β-1a SC (Rebif®) 44 mcg vs. interferon β-1b SC (Betaseron®) 250 mcg	NR	−0.1 vs. −0.3 vs. −0.7 Interferon β-1b SC (Betaseron®) vs. interferon β-1a SC (Rebif®) *P*=0.001	1.8 vs. 1.8 vs. 1.2 Interferon β-1b SC (Betaseron®) vs. interferon β-1a SC (Rebif®) *P*=0.0023
Etemadifar 2007 N=47, 1 year	Interferon β-1a IM (Avonex®) 30 mcg vs. interferon β-1a SC (Rebif®) 44 mcg vs. interferon β-1b SC (Betaseron®) 250 mcg	NR	−0.2 vs. −0.4 vs. −0.1 *P*<0.05	1.4 (0.7 SD) vs. 1.2 (0.7 SD) vs. 1.4 (1.0 SD)
Panitch 2002 EVIDENCE trial N=677, 16 months	Interferon β-1a IM (Avonex®) 30 mcg vs. interferon β-1a SC (Rebif®) 44 mcg	54% vs. 57%	NR	NR
Pooled weighted mean difference:	Interferon β-1b SC (Betaseron®) 250 mcg vs. interferon β-1a IM (Avonex®) 30 mcg	--	−0.330 (95% CI, −0.686 to 0.025) I^2=59.9%	--
Pooled weighted mean difference EDSS:	Interferon β-1a IM (Avonex®) 30 mcg vs. interferon β-1a SC (Rebif®) 44 mcg	--	0.200 (95% CI, −0.076 to 0.476) I^2=0%	

Abbreviations: EDSS, Expanded Disability Status Scale; IM, intramuscular; NR, not reported; SC, subcutaneous.
[a] Weighted mean difference, random effects model.

Interferon beta-1b SC (Betaseron®) compared with interferon beta-1a SC (Rebif®)

The REFORMS trial[54] treated patients for three months and found no difference in risk of relapse between interferon beta-1a (Rebif®) 44 mcg SC and interferon beta-1b 250 mcg SC (14% vs 11%, RR 1.27, 95% CI 0.50 to 3.19). Data for disease progression were not provided.

One small study[75] showed a statistically significant improvement in Expanded Disability Status Scale scores with interferon beta-1a SC (Rebif®) compared with interferon beta-1b SC (Betaseron®), whereas an earlier trial by Etemadifar found interferon beta-1b SC (Betaseron®) numerically superior to interferon beta-1a SC (Rebif®) for outcomes related to disease progression (endpoint and mean change in Expanded Disability Status Scale; see Table 8 above).[48,75] Due to the significant heterogeneity between the 2 studies, the results could not be combined (I^2=83.1%). In both trials, the difference between the scores was small, most likely were not clinically important, and given the discrepant results, conclusions could not be made. Only the earlier Etemadifar study evaluated relapse related outcomes and found no difference between interferon beta-1a SC (Rebif®) compared with interferon beta-1b SC (Betaseron®).

Koch-Henrikson enrolled a somewhat more severely ill population (multiple sclerosis duration > 6 years with one quarter having ≥ 4 relapses in last two years and most with EDSS scores >3.0 at baseline) and used a lower dose of interferon beta-1a SC (Rebif®) dosed once weekly. They did not find significant differences in annualized relapse rates, rate of steroid use, or the proportion with disease progression at 2 years. Other outcomes reported in the Koch-Henriksen trial also were unable to identify a difference between the 2 beta interferons, including exacerbations requiring hospitalization and time to confirmed progression. The lower dose and dosing frequency in this trial limits our ability to draw conclusions from this trial.

Interferon beta-1a IM (Avonex®) compared with interferon beta-1a SC (Rebif®)

Three trials compared the 2 forms of interferon beta-1a SC (Rebif®) and IM (Avonex®).[48,75,76] Two trials found higher rates of patients who were relapse-free at the end of the study in the interferon beta-1a SC (Rebif®) groups compared with interferon beta-1a IM (Avonex®).[48,76] Statistical heterogeneity was large enough to discourage statistical pooling in this case (P=0.0278). Additionally, the EVIDENCE trial [50,76] also found interferon beta-1a SC (Rebif®) superior to interferon beta-1a IM (Avonex®) in annualized relapse rates (a secondary outcome measure in this trial), the use of steroids to treat relapse, and in the time to first relapse (median 13.4 months vs. 6.7 months; HR, 0.70; 95% CI, 0.56 to 0.88). The Etemadifar trials did not report these outcomes, but 1 trial did report a greater change in relapses per person-per year in the interferon beta-1a SC (Rebif®) group compared with the interferon beta-1a IM (Avonex®) group (1.8 vs. 0.8; P<0.001).[48]

Disability-related outcomes were reported differently in the trials, but statistically significant differences between the drugs were not found.[48,75,76] Disease progression was very similar in the EVIDENCE study regardless of the classification scheme, although this study was only 16 months in duration, shorter than the standard 2 years for monitoring progression of multiple sclerosis. The Expanded Disability Status Scale at endpoint was identical between the groups in the 2 studies. While Etemadifar noted that the change from baseline Expanded Disability Status Scale was statistically significant in the interferon beta-1a SC (Rebif®) group in both trials (mean change 0.3 and 0.4) and not in the interferon beta-1a IM (Avonex®) group (mean change 0.1 and 0.2), the combined mean difference did not find this to be statistically significant. Additionally, the difference between the scores was small and most likely not clinically important.[75,76]

Interferon beta-1b SC (Betaseron®) compared with interferon beta-1a IM (Avonex®)

Three trials evaluated the comparison of interferon beta-1b SC (Betaseron®) and interferon beta-1a IM (Avonex®) with only 2 reporting relapse-related outcomes. They found higher rates of patients who were relapse-free at 2 years with interferon beta-1b SC (Betaseron®) (pooled RR, 1.51; 95% CI, 1.11 to 2.07).[47,48] However, data for disability were conflicting. The mean change in the Expanded Disability Status Scale was greater with interferon beta-1a IM (Avonex®) in the Durelli trial (INCOMIN) and the second Etemadifar trial, but larger with interferon beta-1b SC (Betaseron®) in the first trial by Etemadifar. The combined weighted mean difference was −0.330 (95% CI, −0.686 to +0.025; I^2=59.5%), indicating no significant difference. The INCOMIN trial was the only trial of the 3 that measured disease progression and found it to be significantly lower in the interferon beta-1b SC (Betaseron®) group compared with the interferon beta-1a IM (Avonex®) group. Of the 5 head-to-head trials, these 3 represented the lowest-quality evidence such that these findings should be interpreted with caution.

Indirect evidence

The placebo-controlled ADVANCE trial (N=1512) treated patients with RRMS to pegylated interferon beta-1a 125 µg SC given every 2 weeks or every 4 weeks.[57] There was moderate strength of evidence that risk of relapse was reduced with peginterferon compared with placebo (18% vs. 29%, HR 0.61, 95% CI 0.47 to 0.80; 22% vs. 29%, RR 0.74, 95% CI 0.59 to 0.92, respectively). Annualized relapse rates were 0.26 and 0.29 for peginterferon compared with 0.40 for placebo (p-values<0.05). Disability progression also favored peginterferon versus placebo (7% vs. 11%, HR 0.62, 95% CI 0.40 to 0.97 for both treatment regimens).

The NMA we conducted found interferon beta-1a (Rebif®) 44 mcg SC and interferon beta-1b (Betaseron®) associated with lower risk of relapse compared with interferon beta-1a (Avonex®) by 19% and 29% (RR 0.81, 95% CI 0.68 to 0.96; RR 0.71, 95% CI 0.59 to 0.86, respectively). Pegylated interferon beta-1a was also associated with lower relapse risk versus interferon beta-1a 30 µg (RR 0.67, 95% CI 0.47 to 0.95). Other treatment comparisons between interferons were not significantly different. There were no differences in annualized relapse rates based on the Cochrane NMA[25] between interferons at 12 or 24 months, including pegylated interferon beta-1a. An additional systematic review compared pegylated interferon beta-1a with the other interferons.[68] Although pegyinterferon was numerically superior to the other interferons in annualized relapse rates, no comparison achieved statistical significance.

Data Synthesis

We examined the direct and indirect evidence comparing interferon beta-1a 44 µg SC, interferon beta-1a 30 µg IM, and interferon beta-1b 250 µg SC for risk of relapse. (There was no direct evidence for pegylated interferon.) In all comparisons we found indirect evidence consistent with evidence from head-to-head trials (p-values for inconsistency 0.22 to 0.93). Treatment with either interferon beta-1a 44 µg or interferon beta-1b 250 µg were associated with lower risk of relapse than treatment with interferon beta-1a 30 µg IM. These results are consistent with the previous exploratory Bayesian meta-analysis from Update 1 indicating that interferon beta-1a 30 µg IM was the least effective in proportion of patients who were relapse-free. The Cochrane NMA[25] found no differences between the interferons in annualize relapse rates although point estimates favored interferon beta-1a 44 µg SC (at 12 and 24 months) and beta-1b 250 µg SC (at 24 months) over interferon beta-1a 30 µg IM.

Primary Progressive Multiple Sclerosis

Ocrelizumab compared with placebo

We found no head-to-head evidence for included drugs in primary progressive multiple sclerosis (PPMS) populations. ORATORIO is a fair-quality placebo-controlled trial of ocrelizumab in PPMS patients (N=732).[81] Because we have no head-to-head evidence for this drug in populations other than RRMS, and because the FDA has granted Breakthrough Therapy status for ocrelizumab in PPMS, we include evidence from ORATORIO here. The ORATORIO trial provided moderate strength of evidence that ocrelizumab delayed disability progression compared with placebo (HR 0.75, 95% CI 0.58 to 0.98).

Mixed Populations: Clinically Isolated Syndrome and Relapsing-Remitting Multiple Sclerosis

One small single-blinded head-to-head trial (N=75) of patients with either relapsing-remitting multiple sclerosis or clinically isolated syndrome compared interferon beta-1b (Betaseron®) to glatiramer acetate and evaluated clinical exacerbations over 2 years as a secondary outcome.[61,82] Randomization was stratified by clinical site and presence of enhancement on screening magnetic resonance imaging, which introduced bias to the results. Relapse was defined as a change in the Expanded Disability Status Scale of at least 1 point and/or a change in the Scripps Neurological Rating Scale of at least 7 points, and a neurological examination was performed by a blinded examining neurologist. Most of the patients had relapsing-remitting multiple sclerosis (79%) with a baseline median annualized relapse rate and Expanded Disability Status Scale score of 1.85 (0-7.5) and 2.0 (0-5.5) respectively. No difference was found in the annualized relapse rate (interferon beta-1b [Betaseron®] 0.37, glatiramer acetate 0.33, P=0.68), six-month confirmed disability progression (interferon beta-1b [Betaseron®] 0.12, glatiramer acetate 0.18, P=0.51), or percent relapse-free at 18 months (interferon beta-1b [Betaseron®] 62%, glatiramer acetate 70%). Because these were secondary outcomes, the study may not have had an adequate sample size (statistical power) to identify a statistically significant difference if one exists. It did, however, agree with findings from 2 other trials where the population was restricted to relapsing-remitting multiple sclerosis, both of which found no difference in clinical measures including relapse rate between the interferon studied and glatiramer acetate (see section on relapsing-remitting multiple sclerosis, above).[56,58]

Mixed Populations: Progressive Multiple Sclerosis

A good-quality 2013 Cochrane review[83] searched for trials of interferons and glatiramer in all phenotypes of multiple sclerosis, including SPMS, PRMS, and PPMS. Results were reported pooled across these three progressive genotypes. For progressive MS, the review reported only comparisons to placebo for drugs included in this DERP review. Because head-to-head evidence was not available in these populations, we include comparisons to placebo here.

Table 9 shows results and strength of evidence as assessed by Cochrane authors. For most comparisons in progressive MS populations, the review found no difference between interferon or glatiramer and placebo in effects on disability or relapse, with strength of evidence assessed as low or very low. The one exception was that patients given interferon beta-1b (Betaseron®) were less likely to relapse over 36 months than those given placebo (OR 0.71, 95% CI 0.56 to 0.90; high strength of evidence).

Table 9. Efficacy of interferons and glatiramer compared with placebo in progressive multiple sclerosis:[a] results from 2013 Cochrane review[83]

Outcome	Drug	Number of studies; Number of subjects	Odds Ratio (95% CI)	GRADE strength of evidence
Chance of disability getting worse over 24 months	Interferon beta-1a IM (Avonex®)	2; 486	0.95 (0.66 to 1.36)	Very low
	Interferon beta-1a SC (Rebif®)	1; 618	0.78 (0.55 to 1.10)	Very low
	Interferon beta-1b (Betaseron®)	1; 73	0.62 (0.22 to 1.69)	Very low
	Glatiramer	2; 1,049	0.94 (0.73 to 1.23)	NR
Chance of	Interferon beta-1a	2; 989	1.10 (0.68 to 1.80)	Very low

disability getting worse over 36 months	SC (Rebif®)			
	Interferon beta-1b (Betaseron®)	2; 1,657	0.87 (0.57 to 1.33)	Very low
Chance of experiencing one or more relapses over 24 months	Interferon beta-1a IM (Avonex®)	1; 436	0.74 (0.51 to 1.08)	Low
Chance of experiencing one or more relapses over 36 months	Interferon beta-1a SC (Rebif®)	1; 371	1.22 (0.82 to 1.48)	Low
	Interferon beta-1b (Betaseron®)	2; 1,657	0.71 (0.56 to 0.90)	High

Abbreviations:.IM, intramuscular; SC, subcutaneous.
[a]Including secondary progressive MS, progressive-relapsing MS, and primary progressive MS.

Mixed Populations: All Categories of Multiple Sclerosis

One poor-quality randomized trial (N=90) of beta interferons enrolled patients with unspecified types of multiple sclerosis patients.[79] This study, downgraded because baseline patient characteristics of groups were not reported and groups differed in steroid use, unclear blinding, and failure to report attrition, found no differences between interferon beta-1a SC, interferon beta-1a IM, and interferon beta-1b in relapse rate or reduction in Expanded Disability Status Scale score and is not discussed further.

Three observational studies, which also enrolled patients with all types of multiple sclerosis, compared persistence rates with glatiramer and the beta interferons (Table 10).[84-86] In a study where the disease-modifying drug was a second-line treatment, persistence on the study drug was 230 days with interferon beta-1b compared with 253-288 days for other beta interferons and 274 days with glatiramer.[84] In a second study where the disease-modifying drug reported was the initial disease-modifying drug (other disease-modifying drugs may have been added later during the study), persistence rates were decreased with interferon beta-1b relative to glatiramer and other beta interferons ($P<0.0001$).[85] However, there was no difference in persistence in those newly treated with a disease-modifying drug (41.5% to 47.4%).[86]

Table 10. Observational studies of persistence comparing glatiramer and beta interferons

Study Author **Year** **N** **Length of treatment** **Role of study drug**	**Comparisons**	**Persistence**
Halpern 2011 1,381 36 months 2nd line treatment	Glatiramer 20 mg Interferon beta-1a SC Interferon beta-1a IM Interferon beta-1b	274 days 288 days 253 days 230 days
Reynolds 2010 6,134 24 months Initial study drug, may have ≥ 1 study drug	Glatiramer 20 mg Interferon beta-1a SC Interferon beta-1a IM Interferon beta-1b	Persistence at 18 months: 58.3% 54.6% 57.7% 32.9% *P*<0.0001 for interferon beta-1b vs. glatiramer and other interferons
Wong 2011 682	Glatiramer 20 mg Interferon beta-1a SC	Similar rates (*P*=0.80), ranged from 41.5% to 47.4%

Study Author Year N Length of treatment Role of study drug	Comparisons	Persistence
24 months Newly treated with study drug	Interferon beta-1a IM Interferon beta-1b	at 2 years

Key Question 2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?

Summary of the Evidence

- Interferon beta-1a IM (Avonex®) appeared to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 0% to 14% reported, starting around 9 months of treatment
- With interferon beta-1a SC (Rebif®), antibodies also appeared around 9 months, with rates of immunogenicity from 11% to 46%; with interferon beta-1b SC (Betaseron®), neutralizing antibodies appeared as early as 3 months into treatment in 15% to 45% of patients.
- Forty to fifty percent of antibody-positive patients will become antibody negative over time, while small numbers of patients will become antibody positive into the second year of treatment.
- Evidence for interferon beta-1b SC (Betaseron®) and interferon beta-1a SC (Rebif®) indicated that consistent positive neutralizing antibody status with high titer increases relapse rates by about 60 to 90 percent during longer periods of follow-up
- This difference in relapse rates was not seen for any of the products in shorter follow-up (2 years or less), and there was inadequate evidence to conclude that there is an impact on disease progression.

Detailed Assessment

Neutralizing antibodies are known to develop in some patients taking beta interferons, potentially interfering with effectiveness.

Two systematic reviews summarized the current state of understanding about the impact of these antibodies on relapse and disease progression, and how the products differ.[87,88] There were several factors that can impact the prevalence of such antibodies, including assay method (varying sensitivity/specificity), dose (conflicting evidence), host cell source (*Escherichia coli* more antigenic than mammalian source), definition of positive status, and route of administration (subcutaneous more antigenic than intramuscular). Because there is no standardized universal assay, comparisons across studies of the beta interferons is fraught with uncertainty. It appears that antibody development occurs earlier and in greater frequency with interferon beta-1b SC (Betaseron®), appearing as early as 3 months into treatment in approximately 30% to 40% of patients. Evidence reported in the Namaka review[88] indicated that antibodies occur somewhat later (9 months) with interferon beta-1a SC (Rebif®), with rates as low as 12% and as high as 25% (see Table 11). Interferon beta-1a IM (Avonex®) appeared to have the lowest immunogenicity with rates of 2% to 6% reported, starting around 9 months of treatment.

Importantly, 40% to 50% of antibody-positive patients will become antibody-negative over time, while small numbers of patients will become antibody-positive into the second year of treatment.

Table 11. Comparison of neutralizing antibodies in beta interferon products[88]

	Avonex	Betaseron	Rebif
Percent developing neutralizing antibodies	2% to 6%	30% to 40%	12% to 25%
Time to appear	First 9-15 months	First 3-6 months, can occur up to month 18	First 9-15 months

Data from 9 comparative observational studies reporting the presence of neutralizing antibodies in patients taking beta interferons are shown in Table 12 below.[89-97] The proportion of patients developing antibodies was lower for interferon beta-1a IM (Avonex®), 0% to 14%, compared with 11% to 44% with interferon beta-1a SC (Rebif®) and 15% to 44% with interferon beta-1b SC (Betaseron®), consistent with findings from the Namaka systematic review. The usefulness of these studies in making comparisons across drugs was limited because most did not study patients on therapy for more than 2 years.

Table 12. Proportion of patients testing neutralizing antibody-positive after beta interferon therapy reported in comparative observational studies

Author, Year	Duration of treatment	Avonex®	Betaseron®	Rebif®	Association of clinical outcomes with neutralizing antibody status
Boz, 2007	≥3 years	0/12 (0%)	18/119 (15%)	16/131 (12.2%)	More relapses in neutralizing antibody-positive patients in years 3 and 4.
Farrell, 2008	>3 years	4/242 (6%)	11/115 (28%)	24/292 (30%)	Relapse rates higher in neutralizing antibody-positive groups, risk greater in those with higher titres
Dubois, 2006	Median 26 months, range 2-85 months	0/18 (0%)	12/32 (38%)	10/23 (44%)	No significant association between antibody status and outcomes.
Kivisakk, 2000	1-46 months	1/20 (5%)	21/48 (44%)		No effect of neutralizing antibodies on clinical outcome
Koch-Henriksen 2009	21,963 months of observation		N=417 33.0%	N=892 31.4%	Effect of neutralizing antibody status on relapses did not differ between treatments (*P*=0.89)
Sbardella, 2009	At least 1 year	1/12 (6%)	5/36 (29%)	22 mcg: 6/48 (35%) 44 mcg: 5/45 (29%)	Significant interaction between clinical response and neutralizing antibody development, but only 17% of patients with a poor response were neutralizing antibody-positive
Aarskog 2009	At least 1 year	4.6%	45.1%	33.9%	Not reported
Fernandez, 2001	1 year	3/22 (14%)	7/31 (23%)		No association with antibody status and relapse rate in either group.
Malucchi 2008	1 year	2/34 (5.1%)	6/20 (20.7%)	22 mcg: 4/33 (10.8%) 44 mcg: 5/26 (15.6%)	Time to first relapse shorter in neutralizing antibody-positive groups; more neutralizing antibody-negative patients were relapse-free.

Several additional non-comparative observational studies reported the rate of neutralizing antibodies associated with beta interferon therapy. They are not discussed in detail here because they provided no additional evidence beyond the Namaka and Goodin systematic reviews.[96,98-106] The duration of many studies was not adequate to assess the impact of antibody status on progression clearly. Namaka, et al. found that in the first 2 years of treatment a difference in outcome based on antibody status could not be identified, but that relapse rates were higher in years 3 and 4 among patients who were antibody-positive (Table 13). The review by Goodin, et al.[87] also found that relapse rates were affected by positive neutralizing antibody status of high titer only in studies of 2 years or longer in duration. The evidence for the impact on disease progression was less compelling, with only 2 of 8 studies showing a significant increase in progression among those with neutralizing antibodies.

Table 13. Duration of treatment and clinical impact of antibody status[88]

Duration	Interferon β-1b SC (Betaseron®)	Interferon β-1a SC (Rebif®)	Interferon β-1a IM (Avonex®)
2nd year	"Correlation not observed"	Relapse rate 1.8 antibody negative vs. 1.77 antibody positive 22 mcg (NS) Relapse rate 1.75 antibody negative vs. 1.74 antibody positive 44 mcg (NS)	"No clinical impact of relapse rate or disease progression"
13 to 36 months	Relapse rate 1.08 antibody positive vs. 0.56 antibody negative	--	--
4th year follow-up	--	Relapse rate 0.81 antibody positive vs. 0.5 antibody negative	--

Abbreviations: NS, not statistically significant.

Two trials published subsequent to the Goodin and Namaka systematic reviews reported rates of interferon beta neutralizing antibodies occurring in enrolled patients. Most of these may not have been of sufficient duration to show clinical effects of antibody development, however. In the EVIDENCE trial, which compared high-dose, high-frequency interferon beta-1a (Rebif®) 44 mcg to low-dose interferon beta-1a IM (Avonex®) 30 mcg over 2 years, neutralizing antibodies were detected at least once in 26% of patients receiving high-dose Rebif® and in 3% of those receiving low dose Avonex® ($P<0.001$). Neutralizing antibodies developed earlier with high-dose treatment (58% by week 24, vs. 14% in the low-dose group). Relapse rates were similar in antibody-positive and antibody-negative patients.[80]

The proportion of patients developing neutralizing antibodies was reported in the REGARD study of interferon beta-1a (Rebif®). The rate was 60/138 (16%) at 24 weeks, 93/355 (26%) at 48 weeks, 91/319 (29%) at 72 weeks, and 102/374 (27%) at 96 weeks or last observation carried forward. Neutralizing antibodies had no effect on clinical efficacy: there was no difference in time to first relapse for those positive at any time and those negative (HR, 1.24; 95% CI, 0.86 to 1.77), although the study may not have been long enough to show clinical effects.

Eight observational studies reported clinical outcomes based on antibody status.[90-97] Although there was an association between neutralizing antibody status and clinical outcome

shown in several studies, none found the detrimental effect of positive antibody status to be greater with 1 of the beta interferons than another. The conclusions that could be drawn from these studies were limited for several reasons: most were not of sufficient duration to show an effect of neutralizing antibodies on clinical status, the numbers of patients taking each drug may not have been sufficient to show a difference between treatments, and lack of control for confounding factors limited the validity of their results.

Evidence correlating comparative clinical outcomes to the antibody status of the individual beta interferons was incomplete and inadequate to make conclusions. Longer-term trials will be needed to clarify the role of this difference in antigenicity and its correlation of clinical outcomes over longer periods of time.

Key Question 3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?

Summary of the Evidence

- There were no head-to-head trials of included drugs in patients with clinically isolated syndrome. Indirect analysis showed no statistically significant differences in progression to multiple sclerosis among the three interferons and two doses of teriflunomide.

Detailed Assessment

We identified no trials with head-to-head comparisons of included drugs in patients with clinically isolated syndrome (CIS). Six trials compared included drugs to placebo, and we used network meta-analysis to provide indirect treatment comparisons. Evidence was available in patients with CIS for interferon beta-1a IM (Avonex®), interferon beta-1a SC (Rebif®) 44 mcg, interferon beta-1b (Betaseron®), teriflunomide 7 mg, and teriflunomide 14 mg. Figure 4 shows the evidence network for the efficacy outcome of progression to multiple sclerosis, including evidence for interferons and teriflunomide compared with placebo, and teriflunomide doses with each other.

Figure 4. Network meta-analysis: clinically isolated syndrome

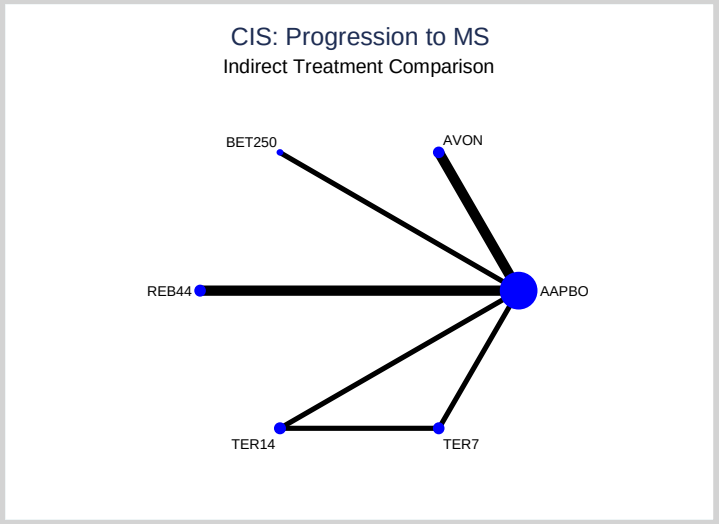


Table 14 shows the results of our indirect analysis of the comparative effectiveness of glatiramer, interferon, and two doses of teriflunomide. We found no statistically significant differences in rates of progression to MS, though the analysis estimated the highest probability (45.6%) that interferon beta-1b (Betaseron®) was the best of these drugs for this efficacy outcome.

Table 14. Indirect analysis of the comparative effectiveness of disease-modifying agents in clinically isolated syndrome

Comparison	Progression to MS RR (95% CI)[a]
Teriflunomide 7 mg vs. teriflunomide 14 mg	1.08 (0.65, 1.81)
Teriflunomide 7 mg vs. interferon beta-1a SC (Rebif®)	0.93 (0.53, 1.61)
Teriflunomide 7 mg vs. interferon beta-1b (Betaseron®)	1.17 (0.62, 2.21)
Teriflunomide 7 mg vs. interferon beta-1a IM (Avonex®)	0.86 (0.49, 1.51)
Teriflunomide 14 mg vs. interferon beta-1a SC (Rebif®)	0.86 (0.49, 1.49)
Teriflunomide 14 mg vs. interferon beta-1b (Betaseron®)	1.08 (0.57, 2.05)
Teriflunomide 14 mg vs. interferon beta-1a IM (Avonex®)	0.79 (0.45, 1.40)
Interferon beta-1a SC (Rebif®) vs. interferon beta-1b (Betaseron®)	1.27 (0.77, 2.07)
Interferon beta-1a SC (Rebif®) vs. interferon beta-1a IM (Avonex®)	0.92 (0.62, 1.38)
Interferon beta-1b (Betaseron®) vs. interferon beta-1a IM (Avonex®)	0.73 (0.44, 1.21)

a. References included in NMA: 107-111
Abbreviations: CI, confidence interval; MS, multiple sclerosis; NA, not available; RR, relative risk

Key Question 4. Do disease-modifying treatments for multiple sclerosis differ in harms?

Summary of the Evidence

Adverse Events and Long-term Safety

Ocrelizumab

- Two unpublished trials provided low strength evidence that treatment with ocrelizumab 600 mg is associated with fewer study withdrawals due to adverse events (RR 0.58, 95% CI 0.37 to 0.91) and similar risk of any serious adverse event (RR 0.79, 95% CI 0.57 to 1.11) as treatment with interferon beta-1a 44 µg SC

Daclizumab HYP

- There was low strength evidence that treatment with daclizumab HYP 150 mg increased study withdrawals due to adverse events (RR 1.57, 95% CI 1.21 to 2.03) compared with interferon beta-1a 30 µg IM, although there was similar risk of experiencing any or any serious adverse event.

Alemtuzumab

- There was moderate strength evidence that treatment with alemtuzumab 12 mg is associated with lower probability of withdrawing from the study due to an adverse event (RR, 0.31; 95% CI, 0.17 to 0.55) compared with interferon beta-1a 44 µg SC. However,

treatment with alemtuzumab was associated with increased risk of thyroid dysfunction and immune thrombocytopenic purpura

Dimethyl fumarate

- Low-strength evidence indicated that treatment with dimethyl fumarate 480 mg increased the risk of experiencing any adverse event compared with glatiramer 20 mg (RR, 1.09; 95% CI, 1.04 to 1.14) but there was no difference in withdrawal due to adverse events or in risk of experiencing a serious adverse event

Teriflunomide

- One randomized trial provided low strength evidence of fewer study withdrawals due to adverse events with teriflunomide compared with interferon beta-1a 44 µg (RR 0.44, 95% CI 0.25 to 0.76) although there were no differences in risks of experiencing any adverse event or serious adverse event

Fingolimod

- Differences in adverse events between fingolimod 0.5 mg once daily and interferon beta-1a 30 µg IM were found for some specific adverse events:
    - Higher rates of pyrexia (RR, 4.26; 95% CI, 2.62 to 6.97), influenza-like illness (RR, 10.55; 95% CI, 6.39 to 17.57), and myalgia (RR, 3.13; 95% CI, 1.76 to 5.59) were found with interferon beta-1a
    - A higher rate of increased alanine aminotransferase (RR, 3.52; 95% CI, 1.66 to 7.50) was found with fingolimod
    - Fingolimod 1.25 mg was associated with higher risk of herpes virus infections than fingolimod 0.5 mg (RR, 2.61; 95% CI, 1.75 to 5.49) or interferon beta-1a (RR, 1.97; 95% CI, 1.01 to 3.86)
- After the first dose of fingolimod, dose-dependent bradycardia and atrioventricular block occurred in the first 6 to 8 hours; none persisted or occurred later in treatment

Glatiramer acetate

- One placebo-controlled trial of glatiramer 40 mg given three times weekly found glatiramer associated with borderline increase withdrawals due to adverse events compared with placebo (3% vs. 1%, RR 2.36, 95% CI 0.99 to 5.65), SOE: Low
- There was low strength of evidence of no difference between glatiramer and the beta interferons in study withdrawals due to adverse events
- Patients treated with glatiramer acetate were more likely to have higher rates of injection site reactions and lipoatrophy while patients treated with the interferons experienced higher rates of flu-like syndrome and elevated liver enzymes

Beta interferons

- Comparative adverse event reporting was limited with multiple studies using different doses of the same product, most frequently with interferon beta-1a SC (Rebif®). We have used data pertaining to interferon beta-1a SC (Rebif®) 44µg SC 3 times weekly dosing when pooling all trial data.

- Although generally well tolerated, adverse events were reported frequently with all 3 beta interferon products and although the ranges were wide, differences between the products were apparent.
- There was low strength evidence from one trial that treatment with pegylated interferon beta-1a 125 µg SC resulted in increased study withdrawals due to adverse events than placebo (RR 3.49, 95% CI 1.52 to 7.99) and increased severe adverse events (RR 1.66, 95% CI 1.21 to 2.28, although there was no difference in risk of experiencing a serious adverse event

Detailed Assessment

Ocrelizumab compared with Interferon beta-1a IM/SC

Direct Evidence

Three fair-quality trials provided safety and tolerability evidence for ocrelizumab.[32,63,70,112] One placebo-controlled trial (N=218) compared ocrelizumab treatment with interferon beta-1a 30 µg IM[32] and found no difference between ocrelizumab 600 mg or 2000 mg compared with interferon beta-1a 30 µg IM in withdrawals due to adverse events (4% vs. 2%, RR 1.97, 95% CI 0.18 to 21; 2% vs 2% RR 0.98, 95% CI 0.06 to 15, respectively) or in serious adverse events (2% vs. 4%, RR 0.49, 95% CI 0.05 to 5.26; 6% vs 4%, RR 1.47, 95% CI 0.26 to 8.47, respectively). However, one patient who was treated with ocrelizumab 2000 mg died following the development of thrombocytopenia followed by disseminated intravascular coagulopathy and multi-organ-dysfunction; she suffered brain edema and died on day 15 of hospitalization from transcranial herniation. The relation to ocrelizumab is unknown. Additionally, treatment with ocrelizumab was associated with mild to moderate infusion-related reactions, especially with the initial dose which affected 39% the first day of treatment.

Two unpublished randomized trials (OPERA I and OPERA II) treated 1651 total patients with ocrelizumab 600 mg or interferon beta-1a 44 µg SC.[63,70,112] Withdrawals due to adverse events were similar for both trials and were lower in the ocrelizumab arms (4% vs. 6%, RR 0.58, 95% CI 0.37 to 0.91) although the same percentage of patients experienced at least one adverse event (83%) in both treatment groups. Serious adverse events were not different between groups (7% vs. 9%, RR 0.79, 95% CI 0.57 to 1.11). There was one death due to completed suicide in the ocrelizumab 600 mg group and two deaths in the interferon beta-1a 44 µg SC group due to complete suicide and mechanical ileus (RR 0.50, 95% CI 0.05 to 5.51). The most common adverse events were infusion-related reactions in the ocrelizumab groups resulting in 11 study withdrawals during the first ocrelizumab treatment (1%).

Indirect Evidence

Estimates of withdrawals due to adverse events from our NMA are consistent with direct evidence above which indicates no difference between ocrelizumab 600 mg and either interferon beta-1a 30 µg IM or interferon beta-1a 44 µg SC.

Daclizumab HYP compared with Interferon Beta-1a 30 µg IM

Direct Evidence

Treatment with daclizumab high-yield process (HYP) 150 mg SC every four weeks was compared with treatment with interferon beta-1a 30 µg IM weekly for up to 144 weeks in a RCT of 1841 RRMS patients.[51] While almost all patients experienced at least one adverse event (91% both groups), there was low strength evidence that patients who received daclizumab HYP were more likely to withdraw from the study due to adverse events, excluding relapse compared with patients treated with interferon beta-1a (14% vs. 9%, RR 1.57, 95% CI 1.21 to 2.03). However, there was low strength evidence that the risk of having a serious adverse event was similar between study treatments (24% vs 21%, RR 1.14, 95% CI 0.96 to 1.35). Both infections and serious infections were more likely with daclizumab HYP (65% vs. 57%, RR 1.14, 95%CI 1.06 to 1.23; 4% vs. 2%, RR 2.68, 95% CI 1.49 to 4.81). Additionally, there were 5 deaths during the study, although none were considered treatment-related by investigators blinded to treatment allocation--1 death in the daclizumab group vs. 4 in the group receiving interferon (RR 0.25, 95% CI 0.03 to 2.24).

Indirect Evidence

In a randomized trial of daclizumab HYP 150 mg and HYP 300 mg compared with placebo, most patients experienced at least one adverse event (daclizumab doses pooled 74% vs. 79%, RR 0.94, 95% CI 0.86 to 1.03) and there was no differences between treatment in risk of experiencing any serious adverse event, excluding relapse (8% vs. 6%, RR 1.39, 95% CI 0.73 to 2.62).[29]

Our NMA found no difference in withdrawals due to adverse events between daclizumab HYP 150 mg or HYP 300 mg and interferon beta-1a 30 µg IM (RR 1.62, 95% CI 0.94 to 2.79; RR 2.62, 95% CI 0.85 to 8.12, respectively) but confidence intervals are imprecise.

Alemtuzumab compared with Interferon Beta-1a 44 µg SC

Direct Evidence

Three fair-quality trials (two 2-year studies[43,44] and one 3-year study[45] provided moderate-strength evidence that treatment with alemtuzumab 12 mg resulted in fewer study withdrawals due to adverse events than treatment with interferon beta-1a 44 µg SC (Table 15). However, alemtuzumab 12 mg was associated with increased risks of thyroid disease. In a publication detailing thyroid dysfunction in the CAMMS223 trial, 42 out of 108 patients (39%) treated with alemtuzumab 12 mg and 31 out of 108 patients (29%) treated with alemtuzumab 24 mg developed thyroid dysfunction as compared with 7 out of 107 patients treated with interferon beta-1a 44 µg SC (7%).[113] Types of thyroid dysfunction ranged from over hyperthyroidism to over hypothyroidism.

Table 15. Comparative harm outcomes of alemtuzumab compared with interferon beta-1a 44 µg SC

Drug A	Drug B	Outcome (Number studies; N)	Effect estimate (95% CI)
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Withdrawal due to AE (3 studies; 1,415)	RR 0.31 (0.17, 0.55)
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Serious immune thrombocytopenic purpura (3 studies; 1,415)	RR 3.25 (0.57, 18.67)

Drug A	Drug B	Outcome (Number studies; N)	Effect estimate (95% CI)
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Any thyroid event (3 studies; 1,415)	RR 3.66 (2.11, 6.36)
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	All-cause mortality (3 studies; 1,415)	RR 2.19 (0.36, 13.36)
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Cancer (3 studies; 1,415)	RR 0.64 (0.15, 2.75)
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Any infection (3 studies; 1,415)	RR 1.32 (1.10, 1.58)
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Any liver toxicity (3 studies; 1,415)	RR 0.30 (0.12, 0.76)
Alemtuzumab 12 mg	interferon beta-1a 44 µg SC	Any serious AE (1 study; 215)	RR 0.99 (0.60, 1.63)
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Withdrawal due to AE (2 studies; 578)	RR 0.24 (0.04, 1.58)
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Serious immune thrombocytopenic purpura (2 studies; 578)	RR 7.53 (0.92, 61.38)
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Any thyroid event (2 studies; 578)	RR 4.50 (2.49, 8.11)
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	All-cause mortality (1 study; 215)	RR 2.92 (0.12, 72.16)
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Cancer (2 studies; 578)	RR 2.24 (0.56, 9.04)
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Any infection (2 studies; 578)	RR 1.28 (1.15, 1.43)
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Any liver toxicity (2 studies; 578)	RR 0.32 (0.13, 0.81)
Alemtuzumab 24 mg	interferon beta-1a 44 µg SC	Any serious AE (1 study; 215)	RR 1.12 (0.69, 1.80)

Compared with interferon beta-1a 44 µg SC, there was less liver toxicity with alemtuzumab 12 mg but increased risk of any infection. Additional evidence indicated that treatment with alemtuzumab 12 mg and interferon beta-1a 44 µg SC were not different in risk of any serious adverse event, serious immune thrombocytopenic purpura, all-cause mortality, and cancer. However, large upper bounds of 95% confidence intervals for estimates of serious immune thrombocytopenic purpura and all-cause mortality should raise concerns of serious harms with alemtuzumab compared to interferon beta-1a. In the earliest trial[45] treatment with alemtuzumab was discontinued after 3 patients developed immune thrombocytopenic purpura, one of whom died. In total, six patients (3%) from the CAMMS223 trial[45] who were treated with alemtuzumab went on to develop immune thrombocytopenic purpura and did so as early as 19 months from the first dose of alemtuzumab (range 19-39 months) and as late as 15 months after the last dose of alemtuzumab (range 1-15 months).[114] One patient treated with interferon beta-1a 44 µg SC also developed immune thrombocytopenic purpura 3 months after beginning treatment.

A higher than approved dose of alemtuzumab (24 mg) had similar adverse event profiles as alemtuzumab 12 mg.

Indirect Evidence

Our NMA was consistent with direct evidence in finding increased study withdrawals due to adverse events with interferon beta-1a 44 µg SC (RR 3.35, 95% CI 1.76 to 6.36), but not interferon beta-1a 22 µg SC (RR 2.51, 95% CI 0.71 to 8.89), compared with alemtuzumab 12 mg.

Dimethyl Fumarate compared with Glatiramer

Direct Evidence

Low-strength evidence from 1 fair-quality trial indicated that treatment with dimethyl fumarate 480 mg daily increased the risk of experiencing any adverse event compared with glatiramer 20 mg (Table 16) over a 2-year period.[71] Higher daily dose of dimethyl fumarate, but not lower dose, resulted in lower risk of depression compared with glatiramer. There were no differences between both dimethyl fumarate doses and glatiramer in serious adverse events and cancer. Evidence was insufficient to draw conclusion regarding mortality due to infrequency of events (1 person died in the dimethyl fumarate 720 mg and the glatiramer groups).

Table 16. Comparative harms of dimethyl fumarate and glatiramer

Drug A	Drug B	Outcome (Number studies; N)	Effect estimate (95% CI)
Dimethyl fumarate 480 mg	Glatiramer 20 mg	Withdrawal due to AE (1 study; 710)	RR 1.23 (0.81, 1.87)
Dimethyl fumarate 480 mg	Glatiramer 20 mg	Any adverse event (1 study; 710)	RR 1.09 (1.04, 1.14)
Dimethyl fumarate 480 mg	Glatiramer 20 mg	Any serious adverse event (1 study; 710)	RR 0.99 (0.72, 1.38)
Dimethyl fumarate 480 mg	Glatiramer 20 mg	All-cause mortality (1 study; 710)	RR 0.33 (0.01, 7.97)
Dimethyl fumarate 480 mg	Glatiramer 20 mg	Cancer (1 study; 710)	RR 0.11 (0.01, 2.01)
Dimethyl fumarate 480 mg	Glatiramer 20 mg	Depression (1 study; 710)	RR 0.78 (0.47, 1.31)
Dimethyl fumarate 720 mg[a]	Glatiramer 20 mg	Withdrawal due to AE (1 study; 695)	RR 1.16 (0.75, 1.77)
Dimethyl fumarate 720 mg[a]	Glatiramer 20 mg	Any adverse event (1 study; 695)	RR 1.06 (1.01, 1.12)
Dimethyl fumarate 720 mg[a]	Glatiramer 20 mg	Any serious adverse event (1 study; 695)	RR 0.92 (0.66, 1.29)
Dimethyl fumarate 720 mg[a]	Glatiramer 20 mg	All-cause mortality (1 study; 695)	RR 1.02 (0.06, 16.25)
Dimethyl fumarate 720 mg[a]	Glatiramer 20 mg	Cancer (1 study; 710)	RR 0.11 (0.01, 2.01)
Dimethyl fumarate 720 mg[a]	Glatiramer 20 mg	Depression (1 study; 695)	RR 0.51 (0.28, 0.93)

[a] Dimethyl fumarate 720 mg is a higher and unapproved dose.

Indirect Evidence

Our NMA found no differences between dimethyl fumarate 240 mg twice daily and either glatiramer 20 mg (RR 0.85, 95% CI 0.49 to 1.48) or glatiramer 40 mg (RR 0.69, 95% CI 0.26 to 1.85) in study withdrawal due to adverse events.

Teriflunomide compared with interferon beta-1a 44 µg SC

Direct Evidence

One head-to-head trial (N=324) provided low strength evidence of fewer study withdrawals with teriflunomide (data from 7 mg and 14 mg pooled) compared with interferon beta-1a 44 µg SC (10% vs. 22%, RR 0.44, 95% CI 0.25 to 0.76), although there was no difference between treatments in serious adverse events (8% vs 7%, RR 1.18, 95% CI 0.51 to 2.74) or in risk of experiencing any adverse event (93% vs. 96%, RR 0.97, 95% CI 0.92 to 1.02). Gastrointestinal

disorders were more common in the groups receiving teriflunomide (40% vs. 27%, RR 1.51, 95% CI 1.06 to 2.17) while influenza-like illness was less likely (3% vs. 53%, RR 0.06, 95% CI 0.03 to 0.13).

Indirect Evidence

Treatment with teriflunomide 7 mg and 14 mg were associated with no difference in withdrawals due to adverse events when compared with interferon beta-1a 44 µg SC (RR 0.57, 95% CI 0.32 to 1.02; RR 0.72, 95% CI 0.42 to 1.25, respectively) based on our NMA, although point estimates favored teriflunomide. The NMA conducted by Cochrane[25] found no difference at 24 months but found interferon beta-1a all doses associated with lower risk of withdrawal compared with teriflunomide all doses (RR 0.46, 95% CI 0.28 to 0.78). However, confidence limits for all comparisons lack precision.

Fingolimod compared with Interferon Beta-1a 30 µg

Direct Evidence

In the large (N=1292), fair-quality head-to-head trial of patients who were randomized to either a low-dose fingolimod group (0.5 mg once daily), a moderate dose group (1.25 mg once daily), or a weekly dose of 30 mcg of interferon beta-1a intramuscularly for 1 year,[115] there was moderate-strength evidence of a statistically significant increased risk of discontinuation due to adverse events for fingolimod 1.25 mg once daily compared with interferon, although rates of overall adverse events were not different (86-92% for all groups) (Table 17). The overall rate of serious adverse events or withdrawal due to an adverse event was not statistically significantly different between the 0.5 mg fingolimod and interferon beta-1a groups.

Table 17. Comparative harms of fingolimod and interferon beta-1a 30 µg

Drug A	Drug B	Outcome (Number studies; N)	Effect estimate (95% CI)
Fingolimod 0.5 mg	interferon beta-1a 30 µg IM	Withdrawal due to AEs (1 study; 860)	RR 1.61 (0.87, 2.98)
Fingolimod 0.5 mg	interferon beta-1a 30 µg IM	Any serious AE (1 study; 860)	RR 1.21 (0.72, 2.02)
Fingolimod 0.5 mg	interferon beta-1a 30 µg IM	Herpes virus infection (1 study; 860)	RR 0.75 (0.32, 1.77)
Fingolimod 0.5 mg	interferon beta-1a 30 µg IM	Bradycardia (1 study; 860)	RR 5.02 (0.24, 104)
Fingolimod 0.5 mg	interferon beta-1a 30 µg IM	AV block (1 study; 860)	RR 5.02 (0.24, 104)
Fingolimod 0.5 mg	interferon beta-1a 30 µg IM	Respiratory disorder (1 study; 860)	RR 1.26 (0.66, 2.39)
Fingolimod 0.5 mg	interferon beta-1a 30 µg IM	Cancer (1 study; 860)	RR 8.04 (1.01, 64)
Fingolimod 0.5 mg	interferon beta-1a 30 µg IM	Depression (1 study; 860)	RR 0.66 (0.39, 1.13)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg IM	Withdrawal due to AEs (1 study; 851)	RR 2.69 (1.54, 4.72)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg IM	Any serious AE (1 study; 851)	RR 1.85 (1.15, 2.96)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg IM	Herpes virus infection (1 study; 851)	RR 1.97 (1.01, 3.86)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg IM	Bradycardia (1 study; 851)	RR 21.55 (1.27, 366)
Fingolimod 1.25 mg[a]	interferon beta-1a	AV block	RR 11.29

	30 µg IM	(1 study; 851)	(0.63, 203)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg IM	Respiratory disorder (1 study; 851)	RR 1.92 (1.07, 3.48)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg IM	Cancer (1 study; 851)	RR 4.11 (0.46, 36.57)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg IM	Depression (1 study; 851)	RR 0.58 (0.33, 1.01)
Fingolimod 1.25 mg[a]	interferon beta-1a 30 µg IM	All-cause mortality (1 study; 851)	RR 5.11 (0.25, 106)

[a] Fingolimod 1.25 mg is a higher and unapproved dose.

Two deaths occurred during the trial, both in patients taking the 1.25 mg dose of fingolimod and both related to severe viral infections (primary varicella zoster and herpes simplex encephalopathy). Factors that may have contributed to these deaths included that both patients were treated with high-dose steroids, and in the case of the patient with herpes simplex encephalitis, treatment with acyclovir was withheld for 7 days. The overall rate of infections across the groups did not differ but the rate of herpes virus infections was higher in the 1.25 mg fingolimod group (5.5%) compared with the 0.5 mg dose (2.1%) or the interferon group (2.8%). Ten skin cancers were diagnosed during the study, all were localized, but 8 of the 10 occurred in fingolimod groups. Other deaths due to varicella zoster infections, including one patient who had received fingolimod 0.5 mg for 6 months in a postmarketing observational study have also occurred.[116]

Many of the serious adverse events and the difference in discontinuation rates were attributed to bradycardia and atrioventricular block, which occurred with the first dose of fingolimod 1.25 mg. Based on experience with placebo-controlled trials, patients were required to remain under observation for 6 hours after the first dose, with electrocardiogram monitoring. It was reported that the transient, dose-dependent reduction in heart rate developed within 1 hour of the dose, reached its peak at 4-5 hours, and had a mean decrease of 12 beats per minute with the 1.25 mg dose and 8 beats with the 0.5 mg dose. Bradycardia following the first dose was symptomatic in 4 of 420 patients receiving 1.25 mg fingolimod (0.9%) and in 3 of 429 patients receiving 0.5 mg fingolimod (0.7%). Additionally, 3 patients (0.7%) and 1 patient (0.2%) in the fingolimod 1.25 and 0.5 mg groups, respectively, had second-degree atrioventricular block. With continued treatment very small increases in mean arterial pressure were seen in both fingolimod groups (1-3 mmHg). None of these cardiac effects were seen in the interferon group.

Macular edema occurred in 4 patients in the 1.25 mg fingolimod group (1%), 2 in the 0.5 mg group (0.5%), and none in the interferon group. Five of 6 were diagnosed within 4 months of starting the drug, and 4 of 6 resolved after discontinuing the drug. Pulmonary function was reduced in fingolimod patients, as measured by a 2% to 3% reduction in the forced expiratory volume in 1 minute (FEV1) measured at 1 month. No further decreases were seen, and lung volume and diffusion were not affected. Because there is no mention of reductions in pulmonary function in the interferon beta-1a group in the study report or in the US Food and Drug Administration documents regarding this trial, we assume there were none.[117]

Direct comparison of the dose of fingolimod currently approved by the US Food and Drug Administration (0.5 mg once daily) and interferon beta-1a indicated that the overall adverse event rate is significantly lower with fingolimod (RR, 0.94; 95% CI, 0.89 to 0.98), but no difference in the rate of withdrawal due to an adverse event or in the rate determined to be serious. Other adverse events showing differential rates between these are shown in Table 18 below. An integrated analysis of fingolimod trials, including placebo-controlled trials and extensions supports these findings.[118]

Table 18. Specific adverse events with fingolimod 0.5 mg compared with interferon beta-1a 30 µg IM

Adverse event	Fingolimod 0.5 mg once daily (%)	Interferon beta-1a 30 mcg once weekly (%)	Relative risk (95% CI)
Interferon higher			**Interferon vs. fingolimod**
Pyrexia	4.2	17.9	4.26 (2.62 to 6.97)
Influenza-like illness	3.5	36.9	10.55 (6.39 to 17.57)
Myalgia	3.3	10.2	3.13 (1.76 to 5.59)
Fingolimod higher			**Fingolimod vs. interferon**
Increased alanine aminotransferase	6.5	1.9	3.52 (1.66 to 7.50)

Indirect Evidence

Our NMA found no difference between fingolimod 0.5 mg and interferon beta-1a 30 µg IM in study withdrawals due to adverse events (RR 1.16, 95% CI 0.65 to 2.08) which is consistent with direct evidence.

Glatiramer compared with Beta Interferons

Direct Evidence

One randomized trial each provided low strength evidence of rates of study withdrawal due to adverse events for glatiramer 20 mg compared with interferon beta-1a 44 µg SC[58] (RR 1.07, 95% CI 0.88 to 1.31), interferon beta-1a 30 µg IM[49] RR 0.64, 95% CI 0.32 to 1.31), and interferon beta-1b 250 µg SC[56] (RR 1.38, 95% CI 0.56 to 3.21). Few study participants withdrew from the trials due to adverse events.

Two head-to-head trials in patients with relapsing-remitting multiple sclerosis compared glatiramer acetate to a beta interferon and reported adverse events (Table 19).[56,58] The BEYOND trial (N=2244), comparing daily glatiramer acetate 20 mg SC to interferon beta-1b 250µg or 500µg SC every other day in patients with relapsing-remitting multiple sclerosis, lasted 3.5 years and was a good-quality study,[56] while the REGARD trial (N=764) compared daily glatiramer acetate 20 mg SC to interferon beta-1a 44 µg SC 3 times per week, lasted 96 weeks, and was of fair quality.[56,58] Adverse events from these 2 trials suggested that both drugs have similar tolerability, with severe adverse events being reported by 11% of patients taking interferon beta-1b 250µg and 13% of patients taking glatiramer acetate in the BEYOND trial, and no significant differences in withdrawal due to adverse events noted in the REGARD trial.[56,58] Overall, the interferons had higher frequency of influenza-like illness ($P<0.001$), elevated liver enzymes ($P<0.0001$), and fever ($P=0.003$) in the BEYOND trial, with similar findings as well as headache and myalgia in the REGARD trial.[58] Glatiramer acetate had higher frequency of injection site reactions and post-injection systemic response (which may include dyspnea, chest pain, flushing, or post-procedural complication).[56,58] Lipoatrophy was only reported in patients receiving glatiramer acetate.[56,58]

Table 19. Adverse events: Glatiramer acetate compared with interferons in relapsing-remitting multiple sclerosis

Adverse event	Interferon beta-1b SC 250µg or 500µg[56]	Interferon beta-1a SC 44 µg[58]	Glatiramer acetate
Flu-like syndrome	40%-45%	31%	6% (BEYOND), *P*<0.0001 1% (REGARD), *P*<0.0001
Any injection site reaction	48%-55%		58% (BEYOND), *P*=0.0005
Injection site pruritus	1%-2%	2%	8% (BEYOND), *P*<0.0001 20%, (REGARD), *P*<0.0001
Injection site swelling	1%	1%	4%, BEYOND), *P*=0.005 11%, (REGARD), *P*<0.0001
Injection site induration	1%-2%	2%	5% (BEYOND), *P*<0.0001 7%, (REGARD), *P*=0.005
Fever	9%-13%	6%	5% (BEYOND), *P*=0.003 4% (REGARD), *P*=0.18
Myalgias		6%	2% (REGARD), *P*=0.01
Fatigue	22%-24%	NR	21% (BEYOND), NS
Headache	32%-33%	19%	27% (BEYOND), NS 9%, *P*<0.0001
Increased AST	9%-13%	NR	3% (BEYOND), *P*<0.0001
Increased ALT	11%-16%	6%	4% (BEYOND), *P*<0.0001 1% (REGARD), *P*=0.002
Post injection systemic reaction	5%-6%	0%	17% (BEYOND) 5% (REGARD), *P*<0.0001
Withdrawal due to adverse event	NR	6%	5% (REGARD), NS

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reported; SC, subcutaneous.

An additional head-to-head trial (CombiRx) of glatiramer compared with interferon beta-1a 30 µg IM reported only serious adverse events (Table 20) (Overall adverse events were recorded in the trial but not adequately published in supplemental tables.).[49] The CombiRx trial was rated good quality and randomized patients to glatiramer, interferon beta-1a 30 µg IM, or their combination. There were no differences between groups in any serious adverse event category, again indicating similar tolerability between glatiramer and interferon beta.

Table 20. Comparative harms of glatiramer compared with interferon beta-1a 30 µg IM

Event	Glatiramer	Interferon beta-1a
Patients with any serious adverse event	30 (11.6%)	38 (15.2%)
Death	1 (0.4%)	1 (0.4%)
Hepato-biliary disorders	3 (0.8%)	1 (0.4%)
Infections and infestations	1 (0.4%)	4 (1.6%)
Neoplasm (benign and malignant)	3 (0.4%)	6 (2.0%)
Nervous system disorders	5 (1.9%)	11 (4.4%)
Psychiatric disorders	8 (1.9%)	4 (1.6%)

Rates of depression were similar in trials comparing glatiramer with beta interferons, although studies did not report how depression was measured. The REGARD trial reported no difference

in depression following treatment with glatiramer or interferon beta-1a 44 µ SC (6% vs. 8%).[58] The BEYOND trial also found similar rates of depression with interferon beta-1b 250 and 500 µg and glatiramer (17% vs. 14%, respectively).

Although reporting higher rates of depression than head-to-head studies, a small (N=163) cohort study by Patten, et al[119] using a Canadian reimbursement database, also found no difference between glatiramer (N=97) and any beta interferon (N=66) in incidence of depression.[119] There was some heterogeneity between the groups. Specifically, the beta interferon-treated patients had slightly higher Expanded Disability Status Scale and depression scores and slightly lower quality of life scores at baseline. In addition, depression was common among multiple sclerosis patients, both at baseline (28.8% for beta interferons and 22.7% for glatiramer acetate) and at follow-up, regardless of intervention. While glatiramer acetate-treated patients tended to have lower depression scores, there was no significant difference in depression score at 3-month follow-up between beta interferons and glatiramer acetate (40.0% compared with 21.3% respectively, P=0.12). This difference remained insignificant when any time points of follow-up were considered: 34.0% for beta interferons and 25.3% for glatiramer acetate; P=0.312.

Indirect Evidence

One placebo-controlled trial of glatiramer 40 mg given three times weekly found glatiramer associated with borderline increased withdrawals due to adverse events compared with placebo (3% vs. 1%, RR 2.36, 95% CI 0.99 to 5.65, Table 21). These results are included in our network meta-analysis. Our NMA indicated no differences between glatiramer 20 mg or 40 mg and any of the interferons (beta-1a 44 µg SC, 22 µg SC, 30 µg IM, and beta-1b 250 µg) including pegylated interferon in withdrawals due to adverse events.

Table 21. Network meta-analysis of withdrawal due to adverse events of glatiramer compared with the beta interferons

Comparison	WAE RR (95% CI)
Glatiramer 20 mg vs. interferon beta-1a 44 µg SC (Rebif®)	0.67 (0.40, 1.13)
Glatiramer 20 mg vs. interferon beta-1a 22 µg SC (Rebif®)	0.90 (0.28, 2.93)
Glatiramer 20 mg vs. interferon beta-1a 30 µg IM (Avonex®)	1.15 (0.62, 2.15)
Glatiramer 20 mg vs. interferon beta-1b 250 µg (Betaseron®)	0.65 (0.33, 1.27)
Glatiramer 20 mg vs. pegylated interferon beta-1a 125 µg (Plegridy TM)	0.44 (0.15, 1.33)
Glatiramer 40 mg vs. interferon beta-1a 44 µg SC (Rebif®)	0.83 (0.30, 2.31)
Glatiramer 40 mg vs. interferon beta-1a 22 µg SC (Rebif®)	1.11 (0.26, 4.77)
Glatiramer 40 mg vs. interferon beta-1a 30 µg IM (Avonex®)	1.43 (0.50, 4.07)
Glatiramer 40 mg vs. interferon beta-1b 250 µg (Betaseron®)	0.80 (0.25, 2.52)
Glatiramer 40 mg vs. pegylated interferon beta-1a 125 µg (Plegridy TM)	0.55 (0.15, 2.06)

Abbreviations: CI, confidence interval; MS, multiple sclerosis; NA, not available; RR, relative risk

Other harms

One observational study (N=412) of patients with multiple sclerosis or clinically isolated syndrome evaluated injection-site reactions with glatiramer and interferon betas (Table 22).[120]

Table 22. Observational study of comparative harms of glatiramer and beta interferons[120]

Event	Glatiramer (N=23)	interferon beta-1a IM (N=82)	interferon beta-1a SC (N=184)	interferon beta-1b SC (N=123)
Necrosis *P* value vs. GA	0 (0%)	0 (%) NS	11 (6.0%) *P*=0.23	7 (5.7%) *P*=0.24
Lipoatrophy *P* value vs. GA	3 (13%)	1 (1.2%) *P*=0.009	19 (10.3%) *P*=0.69	11 (8.9%) *P*=0.54

Another, fair-quality observational study (the Swiss Analysis of Multiple Sclerosis or SAME study) analyzed patients treated for 2 years or more with glatiramer or an interferon. Ninety percent of included patients had RRMS, and 10% CIS. Rates of any adverse event were similar across the three interferon formulations (range 53% to 56%), and lower in patients given glatiramer (38.6%), though differences across all groups did not reach statistical significance (p=0.052). Flu-like symptoms did differ across treatments, as did injection-site reactions (both p<0.001; Table 23).

Table 23. Comparative harms of glatiramer and beta interferons in the SAME observational study[121]

Event	Glatiramer (N=88)	interferon beta-1a IM (N=105)	interferon beta-1a SC (N=186)	interferon beta-1b SC (N=167)
Flu-like symptoms P < 0.001	2 (2.3%)	49 (46.7%)	74 (39.8%)	43 (25.8%)
Injection-site reactions P < 0.001	23 (26.1%)	11 (10.5%)	63 (33.9%)	64 (38.3%)

We rated another observational study of cutaneous adverse events[122] as poor-quality because of baseline differences in patient characteristics, with no adjustment for confounding in results reported by drug, and do not include evidence from this study here.

Beta Interferon

Four head-to-head trials (N=1295) comparing the interferons in patients with relapsing-remitting multiple sclerosis reported adverse events.[47,50,53,54] Additional data was obtained from observational studies.

Adverse events were considered typical in all of the trials, with flu-like syndrome and injection site reactions being common. However, across the studies and types of beta interferons, the ranges were wide even within studies of the same beta interferon. Study withdrawals due to adverse events were similar across all beta interferons, including pegylated interferon based on network meta-analysis (Table 24).

Table 24. Network meta-analysis of withdrawal due to adverse events for beta interferons

Comparison	WAE RR (95% CI)
Interferon beta-1a 44 µg SC vs. Interferon beta-1a 22 µg SC	1.33 (0.45, 3.97)
Interferon beta-1a 44 µg SC vs. Interferon beta-1a 30 µg IM	1.71 (0.95, 3.08)
Interferon beta-1a 44 µg SC vs. Interferon beta-1b 250 µg SC	0.96 (0.48, 1.92)
Interferon beta-1a 44 µg SC vs. Pegylated interferon beta-1a 125 µg SC	0.66 (0.22, 1.98)

Comparison	WAE RR (95% CI)
Interferon beta-1a 22 µg SC vs. Interferon beta-1a 30 µg IM	1.28 (0.38, 4.32)
Interferon beta-1a 22 µg SC vs. Interferon beta-1b 250 µg SC	0.72 (0.20, 2.57)
Interferon beta-1a 22 µg SC vs. Pegylated interferon beta-1a 125 µg SC	0.49 (0.11, 2.25)
Interferon beta-1a 30 µg IM vs. Interferon beta-1b 250 µg SC	0.56 (0.25, 1.24)
Interferon beta-1a 30 µg IM vs. Pegylated interferon beta-1a 125 µg SC	0.38 (0.12, 1.18)
Interferon beta-1b 250 SC µg vs. Pegylated interferon beta-1a 125 µg SC	0.68 (0.20, 2.32)

Abbreviations: CI, confidence interval; MS, multiple sclerosis; NA, not available; RR, relative risk

Of the 5 observational studies in patients with relapsing-remitting multiple sclerosis, the best of these was a retrospective cohort study based on data from patients in Austria, Switzerland, and Germany, with 4754 patients exposed to 1 of the 3 interferons.[123] An analysis of the reasons for discontinuation of treatment indicated that discontinuations due to injection site reactions were significantly lower in the interferon beta-1a 30 µg IM weekly group compared with either the interferon beta-1a SC 22 mcg SC 3 times weekly or interferon beta-1b SC 250 µg every other day groups, but no different than the interferon beta-1a SC 44µg SC twice weekly group. Differences in frequency of flu-like syndrome was statistically significant only for interferon beta-1a SC 22 mcg group compared with the interferon beta-1b group with the interferon beta-1a SC 22 mcg being lower. Discontinuations due to lack of efficacy was greatest in the interferon beta-1a SC 22 mcg group, compared with the interferon beta-1a IM group or the interferon beta-1b group (Table 25). The other 2 studies were of patients being treated at large multiple sclerosis specialty centers (1 in Spain, 1 in Italy), enrolled and followed every 3 months.[124,125] These studies had a high risk of bias due to clinically important differences among groups at baseline, and because at the outset of data collection only Betaseron® was marketed in those countries, while Avonex® and Rebif® were approved during the time period of the study.

Table 25. Discontinuation due to adverse events: Observational evidence in patients with relapsing-remitting multiple sclerosis[51]

Adverse event	Rates of discontinuation due to adverse events, adjusted analysis
Flu-like syndrome	Interferon β-1a SC (Rebif®) 22 mcg< Interferon β-1b (Betaseron®) 0.2% vs. 1.2%, *P*=0.0038
Injection-site reactions	Interferon β-1a IM (Avonex®)<Interferon β-1a SC (Rebif®) 22 mcg 0.1% vs. 2%, *P*=0.0001 Interferon β-1a IM (Avonex®)<Interferon β-1b (Betaseron®) 0.1% vs. 2.5%, *P*<0.0001
Lack of efficacy	Interferon β-1a SC (Rebif®) 22 mcg> Interferon β-1a IM (Avonex®) 9.3% vs. 7.4%, *P*=0.0027 Interferon β-1a SC (Rebif®) 22 mcg>Interferon β-1b (Betaseron®) 9.3% vs. 6.8%, *P*<0.001

Abbreviations: IM, intramuscular; SC, subcutaneous.

Other non-trial evidence was limited and low quality and did not provide better information on tolerability than the trial data (Table 26).[104,126-140]

Table 26. Comparative tolerability of beta interferons

Adverse event	Relative frequencies based on pooled trial rates
Injection site reaction	Interferon β-1a SC (Rebif®) 60.6% (22.8 to 88.9) ~ Interferon β-1b SC (Betaseron®) 58.9% (48.6 to 69.3) > Interferon β-1a IM (Avonex®) 8.5% (4.5 to 15.2)
Flu-like syndrome	Interferon β-1a IM (Avonex®) 62.2% (39.0 to 80.8) >Interferon β-1b SC (Betaseron®) 41.7% (25.0 to 58.5) > Interferon β-1a SC (Rebif®) 28.7 (16.5 to 45.1)

Fatigue	Interferon β-1b SC (Avonex®) 26.3% (4.1 to 74.6) > Interferon β-1a SC (Rebif®) 10.2% (2.8 to 30.9)
Fever	Interferon β-1b SC (Betaseron®) 38.1% (12.4 to 63.7) > Interferon β-1a IM (Avonex®) 20.4% (5.6 to 52.5) > Interferon β-1a SC (Rebif®) 4.9% (0.7 to 26.9)
Depression	Interferon β-1a IM (Avonex®) 19.7% (10.8 to 33.1) ~ Interferon β-1b SC (Betaseron®) 18.4% (8.1 to 28.6) >Interferon β-1a SC (Rebif®) 14.4% (5.6 to 32.0)
Overall withdrawal	Interferon β-1b SC (Betaseron®) 19.4% >Interferon β-1a SC (Rebif®) 14.2% (8.3 to 23.2) >Interferon β-1a IM (Avonex®) 13.1% (8.7 to 19.4)
Discontinuation due to adverse event	Interferon β-1b SC (Betaseron®) 7.5% (3.7 to 11.5) >Interferon β-1a SC (Rebif®) 6.1% (4.6 to 8.0) > Interferon β-1a IM (Avonex®) 3.6% (1.7 to 7.4)

Abbreviations: IM, intramuscular; SC, subcutaneous.

Synthesis of direct and indirect evidence

Pooled rates of tolerability of adverse effects for each of the beta interferons, based on all head-to-head and placebo-controlled trial rates and controlling for study effects, are presented in Table 27 below. Given the differences in events reported with the different doses of interferon beta-1a SC (Rebif®), only data using the 44 µg dose was pooled. This analysis indicated higher rates of injection site reactions, fever, and overall or adverse event-related discontinuation with interferon beta-1b SC (Betaseron®). Interferon beta-1a IM (Avonex®) led to higher rates of flu-like syndrome than the others, but the lowest rates of fatigue, fever, injection-site reaction and overall or adverse event-related discontinuations. Interferon beta-1a SC (Rebif®) 44 µg had slightly higher rates of fatigue, but lower rates of depression than the others. Although a small observational study of 225 patients with relapsing-remitting multiple sclerosis did not agree with the pooled evidence, suggesting that interferon beta-1a SC (Rebif®) 44 µg had the lowest overall rates of withdrawal due to adverse event or perceived lack of efficacy, the lower quality of the evidence precludes making any conclusion on its results.[141]

Table 27. Interferon beta-1b and 1a: pooled adverse event rates

Adverse event	Interferon beta-1b SC (Betaseron®)	Interferon beta-1a IM (Avonex®)	Interferon beta-1a SC (Rebif®) 44µg
	Rate (95% CI)	**Rate (95% CI)**	**Rate (95% CI)**
Injection site reaction	58.9% (48.6 to 69.3)	8.5% (4.5 to 15.2)	60.6% (22.8 to 88.9)
Flu-like syndrome	41.7% (25.0 to 58.5)	62.2% (39.0 to 80.8)	28.7% (16.5 to 445.1)
Fatigue	--	26.3% (4.1 to 74.6)	10.2% (2.8 to 30.9)
Myalgias	29.1% (23.0 to 35.1)	--	--
Fever	33.3% (19.0 to 47.6)	20.4% (5.6 to 52.5)	5.4% (2.2 to 12.9)
Depression	18.4% (8.1 to 28.6)	19.7% (10.8 to 33.1)	14.4% (5.6 to 32.0)
Overall withdrawal	19.4% (14.7 to 24.1)	13.1% (8.7 to 19.4)	14.2% (8.3 to 23.2)
Discontinuation due to adverse event	7.5% (3.7 to 11.2)	3.6% (1.7 to 7.4)	6.1% (4.6 to 8.0)

Interferon beta-1a SC (Rebif®) compared with beta-1b SC (Betaseron®)

Direct Evidence

Two head-to-head trials provided direct evidence that compared interferon beta-1b 250 µg SC with interferon beta-1a 44 µg SC[54] or beta-1a 22 µg SC.[53] but only one study (N=129) provided numbers of patients affected by specific adverse events by treatment group.[54] In this trial alanine

aminotransferase levels were increased with interferon beta-1a 44 µg SC (12% vs. 2%, RR 7.88, 95% CI 1.01 to 61) compared with interferon beta-1b. Injection site reactions were also doubled with interferon beta-1a (28% vs. 14%, RR 1.97, 95% CI 0.96 to 4.05) compared with interferon beta-1b 250 µg, whereas fatigue (14% vs. 7%, RR 3.05, 95% CI 0.86 to 11) and depression were twice as common with interferon beta-1b (13% vs. 6%, RR 2.03, 95% CI 0.64 to 6.41) although these differences were not statistically significant. There was no difference between treatment with interferon beta-1a 44 µg SC and interferon beta-1b in withdrawals due to adverse events (14% vs. 11%, RR 1.27, 95% CI 0.50 to 3.19).

Indirect Evidence

One trial (N=1512) compared pegylated interferon beta-1a 125 µg SC given every two weeks and interferon beta-1a 125 µg SC given every 4 weeks to placebo and found that interferon beta-1a 125 µg SC every two weeks (the approved dose) was associated with increased withdrawals due to adverse events and severe adverse events compared with placebo (5% vs. 1%, RR 3.49, 95% CI 1.52 to 7.99; 18% vs. 11%, RR 1.66, 95% CI 1.21 to 2.28). There was little difference between the two dosing schedules of pegylated interferon on frequency of adverse events.

Our NMA indicated no difference between either treatment with interferon beta-1a 44 µg SC or interferon beta-1a 22 µg SC and interferon beta-1b 250 µg SC in study withdrawals due to adverse events (RR 0.96, 95% CI 0.48 to 1.92; RR 0.72, 95% CI 0.20 to 2.57, respectively) which is consistent with direct evidence.

One retrospective observational study comparing the 3 different interferons (N=4754) found that flu-like syndrome was higher in the interferon beta-1b (Betaseron®) group (1.2% compared with 0.2%; *P*=0.0038), however, discontinuations due to lack of efficacy was greatest in the interferon beta-1a SC (Rebif®) 22 mcg group (9.3% compared with 6.8%; *P*<0.001).[123] A small observational study of patients with relapsing-remitting multiple sclerosis (N=454) compared injection site pain and injection site reactions in patients receiving interferon beta-1b SC (Betaseron®) with interferon beta-1b SC (Rebif®) 44 µg and found that interferon beta-1b SC (Betaseron®) had fewer injection site reactions (48.2% compared with 66.2%; *P*<0.0001) and greater patients that experience no pain, or the pain they did experience had no impact on continuing treatment (76.9% compared with 64.1%; *P*=0.006).[130] The results of these studies however are contrary to the direct trial evidence. In reviewing the 4 placebo-controlled trials in patients with relapsing-remitting multiple sclerosis and 2 systematic reviews of the 4 trials, only the 3 times weekly interferon beta-1a SC (Rebif®) was not associated with significantly increased rates of flu-like syndrome, fever, and myalgias while leukopenia was significantly higher with this drug.[36,40,65,142,143] This was contrary to pooled analysis from the 5 trials of the beta interferons compared with placebo in secondary progressive multiple sclerosis which suggested that significantly higher rates of injection site reactions, abnormal liver function tests, and withdrawal due to adverse events with interferon beta-1a SC (Rebif®) and flu-like syndrome and withdrawal due to adverse events with interferon beta-1b SC (Betaseron®) compared with placebo. Our pooled analysis of all head-to-head and placebo-controlled trial data indicated that interferon beta-1b SC (Betaseron®) had higher rates of injection site reactions, fever, overall withdrawal, and discontinuation rates due to adverse events (Table 27).

Interferon beta-1a IM (Avonex®) compared with interferon beta-1a SC (Rebif®)

Direct Evidence

One head-to-head trial in relapsing-remitting multiple sclerosis reported adverse event data. The 16-month EVIDENCE trial (N=677) compared interferon beta-1a IM (Avonex®) 30 µg SC once weekly to interferon beta-1a SC (Rebif®) 44 µg SC 3 times weekly and found that significantly more patients taking interferon beta-1a SC (Rebif®) experienced injection site reactions (85% compared with 33%; $P<0.001$), abnormal liver function tests (18% compared with 10%; $P=0.003$), and leukocyte abnormalities (14% compared with 5%; $P<0.001$).[44] Significantly more patients taking interferon beta-1a IM (Avonex®) experienced flu-like symptoms (53% compared with 45%; $P=0.031$). Differences in withdrawal or early discontinuation overall or due to adverse events (4% vs. 5%, RR 0.88, 95%CI 0.44 to 1.77) were not found. Data on compliance or patient satisfaction with treatment were not recorded. This study then had a crossover phase in which patients initially receiving weekly interferon beta-1a IM (Avonex®) once weekly were switched to interferon beta-1a SC (Rebif®) 3 times weekly while those taking interferon beta-1a SC (Rebif®) continued to do so.[80] For those transitioning to the interferon beta-1a SC (Rebif®) there was a significant increase in injection site reactions (10% compared with 23%), liver function abnormalities (3% to 6%), and white blood cell abnormality (1.5% compared with 4.5%). Similarly, there was a significant decrease in flu-like symptoms with the interferon beta-1a SC (Rebif®) (16% to 4%).

Indirect Evidence

Our NMA found no difference between treatment with interferon beta-1a 30 µg IM and interferon beta-1a 44 µg SC or interferon beta-1a 22 µg SC in study withdrawals due to adverse events (RR 0.59, 95% CI 0.33 to 1.05; RR 0.78, 95% CI 0.23 to 2.63, respectively) which is consistent with direct evidence.

One large retrospective observational study in patients with relapsing-remitting multiple sclerosis (N=4754) compared the 3 different interferons and found that discontinuations due to injection site reactions and lack of efficacy were higher in the interferon beta-1a (Rebif®) 22 µg group compared with the interferon beta-1a IM (Avonex®) group (2% compared with 0.1%; $P=0.0001$ and 9.3% compared with 7.4%; $P=0.0027$, respectively).[123] A short-term, 6-month, observational study compared interferon beta-1a IM (Avonex®) to interferon beta-1a (Rebif®) 44 µg and found that there were no notable differences between the 2 treatment groups regarding any of the adverse responses, with 1 patient in the interferon beta-1a (Rebif®) 44 µg group discontinuing due to an adverse event while 78.3% in the interferon beta-1a IM (Avonex®) group and 79.1% in the interferon beta-1a (Rebif®) 44 µg group reporting any adverse event.[140] In reviewing the 4 placebo-controlled trials and 2 systematic reviews of the 4 trials in patients with relapsing-remitting multiple sclerosis, interferon beta-1a IM (Avonex®) was associated with increased rates of flu-like syndrome, fever, and myalgias while interferon beta-1a (Rebif®) was associated with higher rates of leukocyte and liver enzyme abnormalities.[36,40,65,142,143] Our pooled analysis of all head-to-head and placebo-controlled trial data indicated that interferon beta-1a SC (Rebif®) had higher rates of injection site reactions and withdrawal due to adverse events (Table 25). Interferon beta-1a IM (Avonex®) was associated with higher rates of flu-like syndrome, fatigue, fever, and depression.

Interferon beta-1b SC (Betaseron®) compared with interferon beta-1a IM (Avonex®)

Direct Evidence

One head-to-head trial in patients with relapsing-remitting multiple sclerosis, the 2-year INCOMIN trial (N=188), compared interferon beta-1a IM (Avonex®) with interferon beta-1b SC (Betaseron®) and found both drugs equally tolerable, with the only difference being a higher incidence of injection site reactions and headaches in patients receiving interferon beta-1b SC (Betaseron®) (37% compared with 8%; $P<0.001$) compared with interferon beta-1a IM (Avonex®) (16% compared with 7%; $P=0.05$).[47] There was no difference in withdrawal due to adverse events between interferon beta-1b 250 µg SC and interferon beta-1a 30 µg IM (5% vs. 1%, RR 4.79, 95% CI 0.57 to 40).

Indirect Evidence

Our NMA found no difference in risk of study withdrawal due to adverse events between interferon beta-1b 150 µg SC and interferon beta-1a 30 µg IM (RR 1.77, 95% CI 0.80 to 3.91) which is consistent with direct evidence.

The 1 retrospective observational study in patients with relapsing-remitting multiple sclerosis that compared the 3 different interferons (N=4754) found that discontinuation rates due to injection site reactions were higher in the interferon beta-1b (Betaseron®) group compared with the interferon beta-1a IM (Avonex®) group (2.5% compared with 0.1%; $P<0.0001$).[123]

In reviewing the 4 placebo-controlled trials and 2 systematic reviews of the 4 trials in patients with relapsing-remitting multiple sclerosis, interferon beta-1b SC (Betaseron®) was associated with higher flu-like syndromes, injection site reactions, leukopenia, and abnormal liver tests compared with interferon beta-1a IM (Avonex®).[36,40,65,142,143] Our pooled analysis of all head-to-head and placebo-controlled trial data indicates that interferon beta-1b SC (Betaseron®) had higher rates of injection site reactions, fever, and rates of overall withdrawal and discontinuation due to an adverse event (Table 27). Interferon beta-1a IM (Avonex®) was associated with higher rates of flu-like syndrome.

Interferon beta-1a (Avonex® or Rebif ®) compared with interferon beta-1b (Betaseron®)

A retrospective chart review of 844 patients compared alanine aminotransferase elevations based on treatment with interferon beta-1a IM (Avonex®), interferon beta-1a SC (Rebif®), or interferon beta-1b SC (Betaseron®).[144] There were significant baseline differences in the patients involved; differences in gender, age at initiation of treatment and at diagnosis with multiple sclerosis, median Expanded Disability Status Scale, and ethnicity were all statistically significant. Perhaps most important clinically, mean duration of treatment was also different among the included drugs, ranging from 14.7 months to 29.5 months. *De novo* alanine aminotransferase elevations ≥ grade 1 ranged from 23% for interferon beta-1a IM (Avonex®) to 38.9% for interferon beta-1b SC (Betaseron®). *De novo* changes ≥ grade 2 and ≥ grade 3 occurred less frequently (pooled rate 5.0% and 1.4% respectively, for all interferons; $P<0.005$); only 1 interferon beta-1a IM (Avonex®) patient had a ≥ grade 2 elevation, and no interferon beta-1a IM (Avonex®) patient had a ≥ grade 3 elevation (Table 28). While these changes were significant from baseline, there was no statistically significant difference in between-group comparisons.

Table 28. Severity of alanine aminotransferase elevations in beta interferon-treated patients[144]

Intervention	Dosage	Mean duration	Mean *de novo* ALT elevation		
			≥Grade 1	≥Grade 2	≥Grade 3
Interferon β-1a IM (Avonex®)	30 µg 1x/week	14.7 months	23. 0%	1.9%	0.0%
Interferon β-1a SC (Rebif®)	22 µg 3x/week	15.7 months	33.6%	4.7%	1.6%
	44 µg 3x/week		38.0%	7.8%	1.6%
Interferon β-1b SC (Betaseron®)	250 µg every other day	29.5 months	38.9%	4.3%	1.1%

Abbreviations: ALT, alanine aminotransferase; IM, intramuscular; SC, subcutaneous.

Depression

Our adjusted indirect analysis (Table 29) indicates no significant difference among the interferons for risk of depression although the relative risks favored interferon beta-1b SC (Betaseron®) over the beta-1a products. Because these analyses are based on so few trials, these results should be interpreted with caution.

Table 29. Adjusted indirect analysis of risk of depression with interferon use

Comparison	Relative risk (95% CI)
Interferon β-1b SC (Betaseron®) vs. interferon β-1a SC (Rebif®) 44µg	0.74 (0.401 to 1.36)
Interferon β-1b SC (Betaseron®) vs. interferon β-1a IM (Avonex®)	0.79 (0.42 to1.48)
Interferon β-1a SC (Rebif®) 44 µg vs. interferon β-1a IM (Avonex®)	1.05 (0.68 to 1.63)

Abbreviations: SC, subcutaneous.

Cancer

A pooled analysis of the risk of malignancy in patients treated with interferon beta-1a SC (Rebif®) included evidence from five placebo-controlled trials.[145] The authors also reported data from single-arm trials and post-marketing surveillance, neither of which included a concurrent comparison group so we do not include those results here. The analysis of placebo-controlled trials showed a lower incidence of cancer in patients treated with interferon than in those receiving placebo; however, the difference was not statistically significant (incidence 2.5 neoplasms per 1000 patient-years, 95% CI 0.9 to 5.4 for interferon vs. 6.3, 95% CI 2.9 to 11.9 for placebo).

Primary Progressive Multiple Sclerosis

Ocrelizumab compared with Placebo

ORATORIO is a fair-quality placebo-controlled trial of ocrelizumab in PPMS patients (N=732).[81] The trial provided insufficient evidence to compare all-cause mortality between the two treatment groups (RR 2.0, 95% CI 0.30 to 13; 5 deaths occurred; 4/486 in ocrelizumab group; 1/239 in placebo group). There was low-strength evidence that rates of serious adverse events did not differ between groups (RR 0.92, 95% CI 0.69 to 1.2). Overall withdrawals were less likely with ocrelizumab (RR 0.59, 95% CI 0.46 to 0.76), but withdrawals due to adverse events were not reported. Rates of infection did not differ between treatment arms (RR 1.0, 95% CI 0.93 to 1.1). More malignancies (2.3% vs. 0.8%) occurred in patients given ocrelizumab than in those receiving placebo, but the difference was not statistically significant (RR 2.7, 95% CI 0.68 to 11).

Clinically isolated syndrome

As discussed in Key Question 3, we found no head-to-head evidence in patients with clinically CIS. Five trials[107-111] compared included drugs to placebo, and we used network meta-analysis to provide indirect treatment comparisons. Evidence was available in patients with CIS for glatiramer 20 mg, interferon beta-1a IM (Avonex®), interferon beta-1a SC (Rebif®) 44 mcg, interferon beta-1b (Betaseron®), teriflunomide 7 mg, and teriflunomide 14 mg. Figure 5 shows evidence available for the harms outcome analyzed, withdrawals due to adverse events.

Figure 5. Network meta-analysis: clinically isolated syndrome

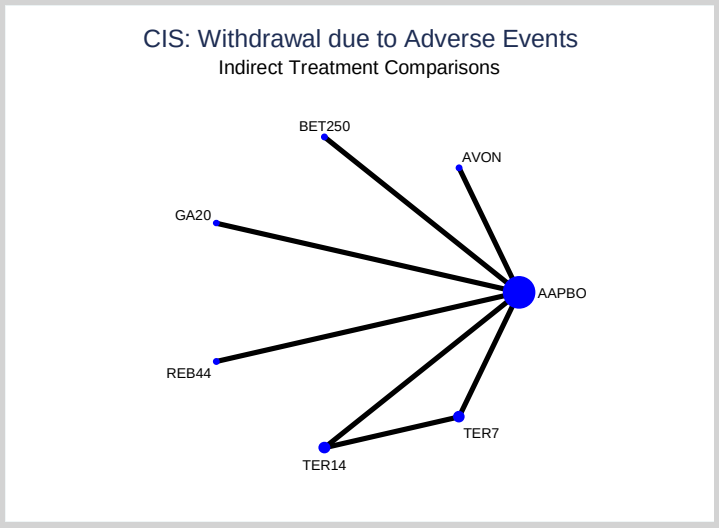


Table 30 shows the results of our indirect analysis of the comparative harms of glatiramer, interferon, and two doses of teriflunomide. For withdrawals due to adverse events, confidence intervals for many comparisons were wide; however, available evidence suggested that withdrawal rates were higher with teriflunomide 7 mg, glatiramer, or interferon beta-1b (Betaseron®), each compared with interferon beta-1a IM (Avonex®). The analysis estimated a probability of 90.6% that Avonex® was the best of this group of drugs for withdrawals due to adverse events. There was also a statistically significant difference in withdrawals due to adverse events between teriflunomide 14 mg and glatiramer (RR 0.24, 95% CI 0.07 to 0.86).

Table 30. Indirect analysis of comparative harms of disease-modifying agents in clinically isolated syndrome

Comparison	Withdrawals due to adverse events RR (95% CI)
Teriflunomide 7 mg vs. teriflunomide 14 mg	1.45 (0.82, 2.58)
Teriflunomide 7 mg vs. glatiramer 20mg	0.35 (0.10, 1.22)
Teriflunomide 7 mg vs. interferon beta-1a SC (Rebif®)	0.28 (0.01, 5.75)
Teriflunomide 7 mg vs. interferon beta-1b (Betaseron®)	0.25 (0.03, 2.15)
Teriflunomide 7 mg vs. interferon beta-1a IM (Avonex®)	8.63 (1.00, 75)
Teriflunomide 14 mg vs. glatiramer 20mg	0.24 (0.07, 0.86)
Teriflunomide 14 mg vs. interferon beta-1a SC (Rebif®)	0.20 (0.01, 4.01)
Teriflunomide 14 mg vs. interferon beta-1b (Betaseron®)	0.17 (0.02, 1.51)
Teriflunomide 14 mg vs. interferon beta-1a IM (Avonex®)	5.96 (0.68, 52.4)

Comparison	Withdrawals due to adverse events RR (95% CI)
Interferon beta-1a SC (Rebif®) vs. glatiramer	1.25 (0.05, 29.3)
Interferon beta-1a SC (Rebif®) vs. interferon beta-1b (Betaseron®)	0.89 (0.02, 32.8)
Interferon beta-1a SC (Rebif®) vs. interferon beta-1a IM (Avonex®)	31 (0.82, 1135)
Glatiramer vs. interferon beta-1b (Betaseron®)	0.71 (0.07, 7.4)
Glatiramer vs. interferon beta-1a IM (Avonex®)	24\ (2.31, 257)
Interferon beta-1b (Betaseron®) vs. interferon beta-1a IM (Avonex®)	34 (1.81, 648)

Abbreviations: CI, confidence interval; MS, multiple sclerosis; NA, not available; RR, relative risk

Key Question 5. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

Summary of the Evidence

- Alemtuzumab outperformed interferon beta-1a SC in sustained accumulation of disability, relapse rate, clinical disease activity, and sustained reduction in disability for all subgroups analyzed (e.g., gender, age, disease duration)
- There was a significant improvement in annualized relapse rate in patients aged 35 or less versus those greater than 35 when daclizumab HYP 150 mg was compared with interferon beta-1a 30 µg IM; rate ratios between the two treatments were not significantly different based on gender, disease duration, number of relapses in prior year or prior interferon use
- There were no differences based between fingolimod 0.5 mg and interferon beta-1a 30 µg IM when patients were stratified based on demographic or disease characteristics, although the treatment effect with fingolimod on annualized relapse rates were greatest in females and those under 40 years of age
- Based the findings of 1, good quality systematic review, there was moderate strength evidence that maternal exposure to beta interferons was associated with lower infant birth weight and shorter mean birth length and increased risk of preterm birth, but not spontaneous abortion, cesarean delivery, or low birth weight
- Fingolimod exposure in utero may be associated with increased risk of poor fetal outcomes
- There was some evidence that response to beta interferons and glatiramer differs in men and women, but there was no evidence that this difference favors 1 product over another.

Detailed Assessment

Geography

In a post hoc analysis of a randomized trial comparing alemtuzumab 12 mg and 24 mg with interferon beta-1a 44 µg SC, European patients had significantly reduced clinical disease activity than US patients with alemtuzumab.[45,146] There were no subgroups of patients who fared better with interferon beta-1a SC on sustained accumulation of disability, relapse rate, clinical disease activity, and sustained reduction in disability based on gender, age, geographic region, disease

duration, number of relapses, brain volume, lesion volume, and number of alemtuzumab cycles received.

Prior Exposure

There was no difference between treatment with fingolimod 0.5 mg and interferon beta-1a 30 µg IM based on subgroups from the TRANSFORMS study when patients were stratified based on gender, age, treatment history and number of relapses in the past year or two years in annualized relapse rate.[147] Although treatment effects with fingolimod were greater in females and those less than 40 years of age, confidence intervals overlapped.

There was no difference in effect on annualized relapse rates of daclizumab HYP 150 mg compared with interferon beta-1a 30 µg IM based on prior interferon beta exposure (Prior exposure: Yes, ARR 0.64, 95% CI 0.50 to 0.81; No, ARR 0.49, 95% CI 0.40 to 0.61).[66]

Age

There was a significant difference in effect on annualized relapse rates of daclizumab HYP 150 mg compared with interferon beta-1a 30 µg IM based on age (≤ 35 years, ARR 0.46, 95% CI 0.35 to 0.62; > 35 years, ARR 0.74, 95% CI 0.59 to 0.92). The improvement in ARR seen with daclizumab HYP compared with interferon beta-1a 30 µg IM was significantly greater in those aged 35 or less.[66]

Disease Duration

There was no difference in effect on annualized relapse rates of daclizumab HYP 150 mg compared with interferon beta-1a 30 µg IM based on disease duration (< 3 years, ARR 0.47, 95% CI 0.37 to 0.60; ≥ 3 years < 10 years, ARR 0.63, 95% CI 0.49 to 0.81; ≥ 10 years, ARR 0.66, 95% CI 0.45 to 0.64).[66]

Pregnancy

Based the findings of 1, good-quality systematic review, there was moderate-strength evidence that maternal exposure to beta interferons was associated with lower birth weight babies with shorter mean birth length and preterm birth, but not spontaneous abortion, cesarean delivery, or low birth weight.[148] There was low-strength evidence that maternal exposure to glatiramer was not associated with shorter mean birth length, lower mean birth weight, or lower gestational age; there was insufficient evidence to assess the effects of exposure to fingolimod. This review also evaluated the effect of paternal exposure to disease-modifying drugs. Based on 46 pregnancies fathered by 32 men treated with beta interferons, glatiramer, fingolimod, natalizumab, or mitoxantrone, pregnancy outcomes and congenital anomaly were similar to the general population. In a meta-analysis of individual patient data from 8 studies of interferon beta-1a SC (Rebif®) or IM (Avonex®), including open-label extension phase studies and involving patients with relapsing-remitting or secondary progressive multiple sclerosis or clinically isolated syndrome, 41 pregnancies occurred with in utero exposure to interferon. Twenty-two pregnancies occurred in women with previous exposure (discontinued interferon more than 2 weeks prior to conception) and only 6 occurred in women receiving placebo.[149] In the group with in utero exposure to interferon beta-1a, pregnancy loss occurred in 29%, compared with 0 in either the placebo or prior exposure groups. The authors indicated that the rate of pregnancy loss

with in utero exposure was greater than the average reported in the overall population, although they reported that taking the small sample size into consideration, the rate may be within the expected range. Prematurity and full-term infants with congenital anomalies occurred in 4.9% of the in utero exposure group, 9.1% in the prior treatment group, and 16.7% in the placebo group, and no teratogenic effects were seen.

In a prospective cohort study conducted in Germany between 1996 and 2007, pregnancy outcomes for women who were exposed to beta interferons (n=69) or glatiramer (n=31) during pregnancy were compared with 2 control groups: pregnant women with multiple sclerosis who had not taken beta interferons or glatiramer (n=64), and pregnant women without multiple sclerosis (n=1557).[150] Overall, the miscarriage rate in all 4 cohorts was within normal range and did not differ among the cohorts. Among interferon-exposed pregnancies, however, there was a significantly higher rate of miscarriage in the interferon beta-1b group (27.8%; 5 of 18) compared with the interferon beta-1a group (4.8%; 2 of 42; *P*=0.02), the non-multiple sclerosis control group (9.1%; *P*=0.02), and the glatiramer group (3.9%; *P*=0.03). Two major birth defects (club feet and atrioventricular canal) occurred in the glatiramer group, but the rate was not significantly different from the comparison cohorts. Birth weight was within normal range in all groups, but was significantly lower in the (combined) interferon group. Birth weight was also lower in the subgroup of women who relapsed during pregnancy, regardless of drug exposure.

Pregnancy outcomes in patients enrolled` fingolimod during phase II, III, and IV clinical trials were reported in patients who has a negative serum pregnancy test prior to study entry and who were required to use 2 forms of contraception.[151] The results of 74 pregnancies (66 pregnancies with in utero exposure to fingolimod) resulted in 35 deliveries with 1 congenital unilateral posteromedial bowing of the tibia and 1 infant with acrania (both were exposed in utero). There were 25 elective abortions with 1 Tetrology of Fallot, 1 ectopic pregnancy, 1 intrauterine death, and 1 pregnancy not developing normally. Four pregnancies were ongoing and 1 was lost to followup. In the 4 pregnancies in the interferon beta-1a group, two were delivered and two were electively aborted. In the 11 pregnancies in the placebo group, one was delivered, one was spontaneously aborted and 9 were electively aborted. In the placebo and interferon groups, there were no reported congenital abnormalities.

Gender

Two studies analyzed the association of gender with response to glatiramer or beta interferons.[152,153] In the PROMISE trial of glatiramer (Copaxone®) in primary progressive multiple sclerosis, there was no effect of glatiramer on progression of disability in the total group,[154] but a post hoc subgroup analysis showed a delayed time to progression of disability in the subgroup of men randomized to glatiramer (HR, 0.71; 95% CI, 0.53 to 0.95).[152] An observational study of 2570 patients with relapsing remitting multiple sclerosis treated with beta interferon and followed for up to 7 years found a lower risk of relapse in men compared with women, especially in the subgroup of patients with lower pre-treatment disease activity (less than 1 relapse in the year before treatment initiation). Although these studies suggested that men with multiple sclerosis may respond differently than women to treatment, they did not provide evidence to make conclusions about comparative effectiveness or safety of the different products in men.

There was no difference in effect on annualized relapse rates of daclizumab HYP 150 mg compared with interferon beta-1a 30 µg IM based on gender (Male, ARR 0.46, 95% CI 0.35 to 0.62; Female, ARR 0.59, 95% CI 0.49 to 0.72).[66]

Risk Factors for Discontinuation of Treatment

In a fair-quality prospective study of patients with early relapsing-remitting multiple sclerosis or clinically isolated syndrome (N=2,314), patient characteristics were examined to determine their association with stopping treatment for multiple sclerosis.[155] Female gender was associated with increased termination with interferon beta-1a SC and IM (P=0.018; P=0.048, respectively) with a trend for interferon beta-1b (P=0.094) but not for glatiramer (P=0.842). Increasing disability, based on Expanded Disability Status Scale score, was a risk factor for discontinuation for interferon beta-1a SC (P<0.001), interferon beta-1a IM (P<0.001), and glatiramer (P=0.021), but not for interferon beta-1b (P=0.857). Discontinuation rates were greater for patients living in Canada (51%) and Australia (47%) compared with patients living in Italy (38%) and Spain (29%).

SUMMARY

We identified 39 head-to-head trials, 6 observational studies, and 4 systematic reviews for inclusion in this review. Most of the evidence was in patients with relapsing-remitting multiple sclerosis (RRMS). In patients with RRMS we conducted a network meta-analysis, which included placebo-controlled trials, for risk of relapse (32 trials, N=18,576) and study withdrawal due to adverse events (33 trials, N=19,191). These analyses included two drugs not yet approved by the Food and Drug Administration for the treatment of multiple sclerosis (ocrelizumab and daclizumab HYP). Our network meta-analysis (NMA) provided low strength evidence that treatment with ocrelizumab 600 mg was associated with the lowest risk of relapse. However, these results must be interpreted with caution as there was limited or no evidence for many drug comparisons. Of the currently approved drugs for multiple sclerosis, our analysis suggests that treatment with alemtuzumab 12 mg is associated with the lowest risk of relapse and also the lowest rate of study withdrawals due to adverse events. See Table 31 for a summary of the evidence.

Table 31. Summary of the evidence

Key Question	Strength of the evidence	Type of multiple sclerosis	Conclusion
1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of	Low	Relapsing-remitting multiple sclerosis	Ocrelizumab • There was low strength evidence that treatment with ocrelizumab 600 mg is associated with similar risk of relapse as treatment with interferon beta-1a 30 µg IM (RR 0.32, 95% CI 0.09 to 1.14) although annualized rates favored ocrelizumab • There was low strength evidence that treatment with ocrelizumab 600 mg is associated with reduced confirmed disability progression at 6 months (HR for risk reduction 0.60, 95% CI 0.43 to 0.84) and lower risk of relapse (annualized relapse rate 0.16 vs. 0.29, p<0.001) than interferon beta-1a 44 µg SC

administration?	Low	Relapsing-remitting multiple sclerosis	Daclizumab HYP • There was low strength evidence that daclizumab HYO 150 mg is associated with less confirmed disability progression (HR .73, 95% CI 0.55 to 0.98) and lower risk of relapse (HR 0.59, 95% CI 0.50 to 0.69) compared with interferon beta-1a 30 µg IM
	Moderate	Relapsing-remitting multiple sclerosis	Alemtuzumab • There was moderate-strength evidence that treatment with alemtuzumab 12 mg resulted in improved sustained accumulation of disability at 6 months (RR, 0.59; 95% CI, 0.40 to 0.86) and risk of relapse (RR, 0.61; 95% CI, 0.52 to 0.71) compared to treatment with interferon beta-1a 44 µg SC
	Low	Relapsing-remitting multiple sclerosis	Dimethyl fumarate • Low-strength evidence indicated that dimethyl fumarate 480 mg daily and glatiramer 20 mg have similar risk of relapse (RR 0.91, 95% CI 0.73 to 1.13)
	Low	Relapsing-remitting multiple sclerosis	Teriflunomide • There was low-strength evidence that teriflunomide 7 mg, but not 14 mg, is associated with increased risk of relapse compared with interferon beta-1a 44 µg SC (RR 2.74, 95% CI 1.66 to 4.53; RR 1.52, 95% CI 0.87 to 2.67, respectively)
	Moderate	Relapsing-remitting multiple sclerosis	Fingolimod • Based on moderate-strength evidence, fingolimod 0.5 mg once daily resulted in lower risk of relapse than treatment with interferon beta-1a 30 µg SC (RR 0.58, 95% CI 0.45 to 0.75)
	Low to moderate	Relapsing-remitting multiple sclerosis	Glatiramer acetate • There was moderate strength evidence that glatiramer 40 mg thrice weekly resulted in improved annualized relapse rate over placebo (0.33 vs. 0.51, p<0.001) • Head-to-head trials provided low-strength evidence of no difference in relapse related outcomes with glatiramer versus beta interferons • There was moderate-strength evidence of no effect of glatiramer acetate on disease progression compared with interferon beta-1b and low strength evidence of similar disease progression between glatiramer and interferon beta-1a IM and SC

	Low-Moderate	Relapsing-remitting multiple sclerosis	Beta interferons • There was moderate strength evidence that pegylated interferon beta-1a 125 mg was associated with improved disability and disease progression outcomes compared with placebo • There was moderate strength evidence that treatment with interferon beta-1b 250 µg or interferon beta-1a 44 µg results in improved relapse outcomes compared with interferon beta-1a 30 µg IM. There was conflicting evidence on disease progression outcomes. • Current evidence is unable to identify differences between effectiveness of interferon beta-1b SC and interferon beta-1a Sc. Indirect analyses of placebo-controlled trial data agreed with these results. • The rates of disease progression in beta interferon groups in head-to-head trials at 2 years ranged from 13% to 57%. Annualized relapse rates for beta interferon groups ranged from 0.4 to 0.7 • The evidence supported a benefit of interferon beta-1b SC over interferon beta-1a IM in relapse outcomes (% relapse-free RR, 1.51; 95% CI, 1.11 to 2.07; number needed to treat, 6). There was conflicting evidence on disease progression outcomes with only 1 trial reporting on percent progressed and finding a significant benefit of interferon beta-1b SC over interferon beta-1a IM (RR, 0.44; 95% CI, 0.25 to 0.79; number needed to treat, 6), however, despite a trend toward benefit, there was no statistically significant difference in mean change in EDSS score (−0.330; 95% CI, −0.686 to +0.025). • Three head-to-head trials suggested a benefit of interferon beta-1a SC over interferon beta-1a IM in terms of relapse outcomes. No differences in disease progression outcomes were found, although the larger trial followed patients for only 16 months such that differences may not yet have been seen. Indirect analyses of placebo-controlled trial data did not result in a significant difference. • Current evidence is unable to identify differences between interferon beta-1b SC and interferon beta-1a SC in terms of effectiveness. Indirect analyses of placebo-controlled trial data agreed with these results.
	Moderate	Primary progressive multiple sclerosis	• There was moderate-strength evidence that ocrelizumab delayed disability progression compared with placebo in patients with PPMS (HR 0.75, 95% CI 0.58 to 0.98 over 24 weeks).
	High	Mixed populations: progressive multiple sclerosis	A good-quality systematic review concluded that interferon beta-1b had lower relapse rates over 36 months than placebo in patients with SPMS, PRMS, or PPMS.
	Very low/Low		The review found no other differences in efficacy between interferons or glatiramer and placebo.

2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?	Moderate		• Evidence for interferon β-1b SC (Betaseron®) and interferon β-1a SC (Rebif®) indicates that high titers of neutralizing antibodies increase relapse rates by about 60 to 90% during longer periods of follow-up. • No difference in relapse is seen for any of the products in shorter follow-up (2 years or less), and there is inadequate evidence to conclude that there is an impact on disease progression. • Interferon β-1a IM (Avonex®) appears to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 0-14% starting around 9 months of treatment. • Interferon beta-1a SC antibodies also appear around 9 months, with rates of immunogenicity from 11 to 46%. • Interferon beta-1b SC neutralizing antibodies appear as early as 3 months into treatment in 15 to 45% of patients. • Importantly, 40-50% of antibody positive patients will become antibody negative over time, while small number of patients will become antibody positive into the second year of treatment.
3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?	Low	Clinically isolated syndrome	• No direct evidence comparing 1 DMD to another in patients with a clinically isolated syndrome was available. • Indirect analysis showed no statistically significant differences among the three interferons and two doses of teriflunomide in progression to multiple sclerosis in patients with CIS.
4. Do disease-modifying treatments for multiple sclerosis or clinically isolated syndrome differ in harms?	Low		Ocrelizumab • There was low strength evidence that treatment with ocrelizumab 600 mg is associated with fewer study withdrawals due to adverse events (RR 0.58, 95% CI 0.37 to 0.91) and similar risk of serious adverse events (RR 0.79, 95% CI 0.57 to 1.11) as treatment with interferon beta-1a 44 µg SC
	Low		Daclizumab • There was low strength evidence that treatment with daclizumab HYP 150 mg increased study withdrawals due to adverse events (RR 1.57, 95% CI 1.21 to 2.03), compared with interferon beta-1a 30 µg IM, although there was similar risk of experiencing any or any serious adverse event.
	Moderate		Alemtuzumab • There was moderate-strength evidence that treatment with alemtuzumab 12 mg is associated with lower probability of withdrawing from the study due to an adverse event (RR 0.31, 95% CI 0.17 to 0.55) compared with interferon beta-1a 44 µg SC. However, treatment with alemtuzumab was associated with increased risk of thyroid dysfunction and immune thrombocytopenic purpura.

	Low	Dimethyl fumarate • Low-strength evidence indicated that treatment with dimethyl fumarate 480 mg daily increased the risk of experiencing any adverse event compared with glatiramer 20 mg (RR, 1.09; 95% CI, 1.04 to 1.14) but there was no difference in withdrawal due to adverse events or in risk of experiencing a serious adverse event
	Low	Teriflunomide • One randomized trial provided low strength evidence of fewer study withdrawals due to adverse events with teriflunomide compared with interferon beta-1a 44 µg (RR 0.44, 95% CI 0.25 to 0.76), although there were no differences in risks of experiencing any adverse event or serious adverse event
	Low	Fingolimod • Differences in adverse events between fingolimod 0.5 mg once daily and interferon beta-1a were found for some specific adverse events: • Higher rates of pyrexia (RR, 4.26; 95% CI, 2.62 to 6.97), influenza-like illness (RR, 10.55; 95% CI, 6.39 to 17.57), and myalgia (RR, 3.13; 95% CI, 1.76 to 5.59) were found with interferon beta-1a • A higher rate of increased alanine aminotransferase (RR, 3.52; 95% CI, 1.66 to 7.50) was found with fingolimod • Fingolimod 1.25 mg was associated with higher risk of herpes virus infections than fingolimod 0.5 mg (RR, 2.61; 95% CI, 1.75 to 5.49) or interferon beta-1a (RR, 1.97; 95% CI, 1.01 to 3.86). • After the first dose of fingolimod, dose-dependent bradycardia and atrioventricular block occurred in the first 6 to 8 hours; none persisted or occurred later in treatment
	Low	Glatiramer acetate • There was low strength of evidence of no differences between glatiramer and the beta interferons in study withdrawals due to adverse events • Patients treated with glatiramer acetate were more likely to have higher rates of injection site reactions and lipoatrophy while patients treated with the interferons experienced higher rates of flu-like syndrome and elevated liver enzymes • There was low strength evidence that treatment with glatiramer 40 mg three times weekly was associated with increased withdrawals due to adverse events than placebo (RR 2.36, 95% CI 0.99 to 5.65)

	Moderate	Beta interferons • Comparative adverse event reporting was limited with multiple studies using different doses of the same product, most frequently with interferon beta-1a SC (Rebif®). We have used data pertaining to interferon beta-1a SC (Rebif®) 44µg SC 3 times weekly dosing when pooling all trial data. • Although generally well tolerated, adverse events were reported frequently with all 3 beta interferon products and although the ranges were wide, some differences between the products were apparent • There was moderate strength evidence that compared with other interferons: treatment with interferon beta-1a 30 µg IM results in lower risk of flu-like syndrome. Also compared with other interferons treatment with interferon beta-1b 250 µg is associated with higher risk of fever and greatest likelihood of withdrawal from the study due to adverse events • Treatment with pegylated interferon beta-1a 125 µg resulted in increased withdrawals due to adverse events (RR 3.49, 95% CI 1.52 to 7.99) and increased severe adverse events (RR 1.66, 95% CI 1.21 TO 2.28) than placebo
	Insufficient	Ocrelizumab • A trial comparing ocrelizumab to placebo in patients with PPMS provided insufficient evidence to compare mortality across treatment arms (5 patients died).
	Low	• The trial showed no difference in serious adverse events between ocrelizumab and placebo (RR 0.92, 95% CI 0.69 to 1.2)
	Low	Clinically isolated syndrome • Indirect analysis suggested that: o Withdrawals due to adverse events were more likely in patients with CIS treated with teriflunomide 7 mg, glatiramer, or interferon beta-1b (Betaseron®), each compared with interferon beta-1a IM (Avonex®). o Withdrawals due to adverse events were less likely with teriflunomide 14 mg than with glatiramer (RR 0.24, 95% CI 0.07 to 0.86).

5. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?	Low-Moderate	• Alemtuzumab outperformed interferon beta-1a in sustained accumulation of disability, relapse rate, clinical disease activity, and sustained reduction in disability for all subgroups analyzed (e.g., gender, age, disease duration); Europeans had significantly reduced clinical disease activity than US patients • There was no difference between fingolimod 0.5 mg and interferon beta-1a 30 µg IM based on subgroups from the TRANSFORMS study. Although treatment effects with fingolimod were greater in females and those less than 40 years of age, confidence intervals overlapped. • Based the findings of 1, good-quality systematic review, there was moderate-strength evidence that maternal exposure to beta interferons was associated with lower birth weight babies with shorter mean birth length and preterm birth, but not spontaneous abortion, cesarean delivery, or low birth weight • In utero exposure to fingolimod may result in increased risk for poor fetal outcomes • A post hoc subgroup analysis of a head-to-head trial of interferon beta-1a products (Avonex® and Rebif®) found that African-American patients experienced more exacerbations and were less likely to be exacerbation-free compared with white patients over the course of the study • There was some evidence that response to beta interferons and glatiramer differs in men and women, but there was no evidence that this difference favors 1 product over another

Abbreviations: ALT, alanine aminotransferase; EDSS, Expanded Disability Status Scale; IM, intramuscular; DMD; disease-modifying drug; MS, multiple sclerosis; NAb, neutralizing antibody; PRMS, progressive relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SC, subcutaneous.

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