

Drug Class Review

Disease-modifying Drugs for Multiple Sclerosis

Final Update 3 Report

Executive Summary

May 2016

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INTRODUCTION

Multiple sclerosis is a chronic, autoimmune disease of the central nervous system affecting 2.3 million people worldwide. Prevalence estimates in the United States range from 250,000 to 400,000 people. 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, and neuronal degeneration may occur. Impaired neuronal conduction ultimately causes the neurological symptoms associated with multiple sclerosis.

The 2010 McDonald Criteria 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. Progression of multiple sclerosis is measured by the disability caused by the disease. 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. The treatment of multiple sclerosis involves acute relapse treatment with corticosteroids, symptom management with appropriate agents, and disease modification with disease-modifying drugs.

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 consultation with the Drug Effectiveness Review Project (DERP) participating organizations, The Pacific Northwest Evidence-based Practice Center (EPC) developed the following key questions and inclusion criteria 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
 - 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).

Interventions (all formulations)

Table A. Included interventions

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.

^aAdministered 20 mg in 1 ml once daily

^bBiologics License Application (BLA) submitted 4/29/2015

^cNot yet submitted for FDA approval (expected first half of 2016).

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.

Study Designs

- 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.
- 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.

We followed standard DERP methods for literature searching, study selection, data abstraction, validity assessment, data synthesis, and grading the strength of the body of evidence. Detailed methods can be found in the full report. We searched electronic databases through December 2015. We attempted to identify additional studies through searches of ClinicalTrials.gov and the US Food and Drug Administration's website for medical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from pharmaceutical companies.

We conducted meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough to combine their results. When necessary, indirect meta-analyses were done to compare interventions for which there were no head-to-head comparisons and where there was a common comparator intervention across studies. The I^2 statistic (the proportion of variation in study estimates due to heterogeneity) was calculated to assess heterogeneity in effects between studies. When meta-analysis could not be performed, the data were summarized qualitatively.

RESULTS

Table B. 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 administration?	Low	Relapsing-remitting multiple sclerosis	<p>Ocrelizumab</p> <ul style="list-style-type: none"> 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
	Low	Relapsing-remitting multiple sclerosis	<p>Daclizumab HYP</p> <ul style="list-style-type: none"> 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	<p>Alemtuzumab</p> <ul style="list-style-type: none"> 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	<p>Dimethyl fumarate</p> <ul style="list-style-type: none"> 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	<p>Teriflunomide</p> <ul style="list-style-type: none"> 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	<p>Fingolimod</p> <ul style="list-style-type: none"> 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	<p>Glatiramer acetate</p> <ul style="list-style-type: none"> 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	<p>Beta interferons</p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<p>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.</p>
Very low/Low		<p>The review found no other differences in efficacy between interferons or glatiramer and placebo.</p>

2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?	Moderate	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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)

<p>Moderate</p>	<p>Beta interferons</p> <ul style="list-style-type: none"> 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
<p>Insufficient</p>	<p>Ocrelizumab</p> <ul style="list-style-type: none"> A trial comparing ocrelizumab to placebo in patients with PPMS provided insufficient evidence to compare mortality across treatment arms (5 patients died).
<p>Low</p>	<ul style="list-style-type: none"> The trial showed no difference in serious adverse events between ocrelizumab and placebo (RR 0.92, 95% CI 0.69 to 1.2)
<p>Low</p>	<p>Clinically isolated syndrome</p> <ul style="list-style-type: none"> Indirect analysis suggested that: <ul style="list-style-type: none"> 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®). 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).

<p>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?</p>	<p>Low-Moderate</p>	<ul style="list-style-type: none"> • 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
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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.

Limitations of this Report

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English. The main limitations of the included studies were:

- There were many comparisons without any direct head-to-head evidence.
- Few studies evaluated newly approved or unapproved drugs.
- Populations other than relapsing-remitting multiple sclerosis were not well represented in the included studies.

CONCLUSIONS

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.