

# Disease-modifying Drugs for Multiple Sclerosis

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## Preliminary Scan Report #3

June 2018

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## Objective

The purpose of this literature scan is to preview the volume and nature of new research that has emerged since the last full review on this topic. The literature search for this scan focuses on new randomized controlled trials and comparative effectiveness reviews, as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP Participating Organizations agreed to proceed with a full report update or other review product.

## Topic History

Update #3: May 2016, searches through January 2016

Scan #2: December 2017, searches through November 2017

## Scope and Key Questions

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?

## Inclusion Criteria

### Populations

- Adult outpatients (age  $\geq 18$  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

Table 1. Included interventions

Generic name	Brand name	Route of administration and frequency	FDA approval date
Ocrelizumab	Ocrevus™	Intravenous infusion	3/28/17
Daclizumab	Zinbryta™	Monthly subcutaneous injection	5/27/16
Glatiramer Acetate <sup>a</sup>	Glatopa™	Subcutaneously three times weekly	4/16/15
Peginterferon beta-1a	Plegridy™	Subcutaneous injection every 14 days	8/15/14
Dimethyl fumarate (BG-12)	Tecfidera®	Orally twice daily (maintenance)	3/27/13
Teriflunomide	Aubagio®	Orally once daily	9/12/12
Fingolimod	Gilenya™	Orally once daily	9/21/10
Interferon beta-1a	Rebif®	Subcutaneously three times weekly	3/7/02
Alemtuzumab	Lemtrada™	Intravenous infusion for 2 treatment courses	5/7/01
Glatiramer Acetate <sup>a</sup>	Copaxone®	Subcutaneously once daily	12/20/96
Interferon beta-1a	Avonex®	Intramuscularly once weekly	5/17/96
Interferon beta-1b	Betaseron®, Extavia®	Subcutaneously every other day	7/23/93

Abbreviations: MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable; PPMS, primary-progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

<sup>a</sup>Administered 20 mg in 1 ml once daily

### Comparators

- Direct comparisons of included drugs in head-to-head trials

### **Efficacy and Effectiveness Outcomes**

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

### **Harms Outcomes**

- Withdrawals due to adverse effects, 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  $\geq 1$  year are also included for evaluation of harms.
2. Placebo-controlled trials (PCT) were included in the last report for network meta-analysis, and for new drugs or formulations with no head-to-head evidence in a given population. PCTs not included in this preliminary update scan.

## **Methods for Scan**

### **Literature Search**

To identify relevant citations, we searched Ovid MEDLINE<sup>®</sup>, Ovid MEDLINE<sup>®</sup> In-Process & Other Non-Indexed Citations, and the Cochrane Central Registry of Controlled Trials from October 2017 through May Week 2 2018 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan. We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm>) to identify new drugs, new populations, and new serious harms (i.e., boxed warnings). To identify new drugs, we also searched CenterWatch (<http://www.centerwatch.com>), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>) (<http://www.effectivehealthcare.ahrq.gov/>), the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>), and the VA Evidence-based Synthesis Program (<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>). All citations were imported into an electronic database (EndNote X8) and duplicate citations were removed.

### **Study Selection**

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## Results

### New Drugs

Ocrelizumab (Ocrevus™) — approved on 3/28/2017 for relapsing or primary progressive forms of multiple sclerosis

Daclizumab (Zinbryta™) — approved on 5/27/2016 for adult patients with relapsing forms of multiple sclerosis

### New Serious Harms (i.e., Boxed Warnings)

Daclizumab (Zinbryta™): Boxed warnings regarding hepatic injury were edited to include acute liver failure and fatalities. Boxed warnings on other immune-mediated disorders were edited slightly. August 2017.

Teriflunomide (Aubagio®): a boxed warning on the risk of teratogenicity was edited in November 2016; however, this risk was known at the time of approval in 2012.

### Comparative Effectiveness Reviews

We identified 2 potentially relevant reviews that could be used to answer specific parts of an update report. These reviews are not comprehensive as they only include formulations of the following agents: Beta-interferon and Glatiramer Acetate. We did not identify any comprehensive comparative effectiveness reviews. Abstracts or full reports are available upon request.

Dosing Strategies for Copaxone for Multiple Sclerosis: Comparative Clinical Effectiveness and Guidelines. Canadian Agency for Drugs and Technologies in Health. (2017).

Melendez-Torres G, et al. Clinical and cost-effectiveness of beta interferon and glatiramer acetate for treating multiple sclerosis: systematic review and economic evaluation. *Health Technology Assessment* 2017; 21(52)

### Randomized Controlled Trials

Searches identified more than 200 citations, resulting in one new head-to-head RCT (Table 2) and 11 secondary publications being identified. Cumulatively since Update 3, there are 2 new head-to-head trials and 21 secondary analyses potentially relevant to an update of the full report. The new head-to-head trials include a total of 247 patients treated with fingolimod or interferons. We have identified no head-to-head trials of ocrelizumab or daclizumab, the drugs approved since the last update report.

Table 2. New head-to-head trials (N=2) Shading indicates new studies found in this scan.

Author, Year	N	Population	Comparison
Rocca, 2017	N=157 18 months	RRMS	Fingolimod vs. interferon beta-1b
Mokhber, 2015	N=90 12 weeks	Newly diagnosed, definite MS patients	Interferon beta-1a (Rebif) vs. Interferon beta-1a (Avonex) vs. Interferon beta-1b (Betaferon)

## Summary

Since the last scan, one new head-to-head trial was found, and 11 secondary publications of previously identified trials. No new drugs were approved, and no new systematic reviews found. Since the 2016 update report, 2 drugs have been approved to treat multiple sclerosis, ocrelizumab and daclizumab, and 2 systematic reviews published. Cumulatively, there are 2 new head-to-head trials; neither includes ocrelizumab or daclizumab. We have identified 21 relevant secondary analyses.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

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## Preliminary Scan Report #3 Appendices

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## APPENDIX A. TRIALS OF DISEASE-MODIFYING DRUG FOR MULTIPLE SCLEROSIS

### New Head-to-Head Trials

Shading indicated trials new to this scan

Mokhber, N., et al. (2015). Therapeutic effect of Avonex, Rebif and Betaferon on quality of life in multiple sclerosis. *Psychiatry and Clinical Neurosciences*. **69**: 649-657.

AIMS: The aim of this study was to evaluate the effect of various disease-modifying therapies (DMT) on quality of life in multiple sclerosis (MS).

METHODS: This was a three-arm parallel study with balanced randomization in which 90 newly diagnosed, definite MS subjects referred to Ghaem Medical Center, Mashhad, Iran were enrolled between 2006 and 2009. Patients were randomly allocated into three DMT groups: Avonex, Rebif and Betaferon. Health-related quality of life was assessed in MS patients at baseline and 12 months after treatment with DMT using the MS Quality of Life-54 questionnaire.

RESULTS: Both mental and physical health scores improved within all three treatment groups after 12 months of treatment; however, this increase was only significant in the mental health composite in the Betaferon group ( $P=0.024$ ). Betaferon had the highest mental health score change (14.04) while this change was 7.26 for Avonex ( $P=0.031$ ) and 5.08 for Rebif ( $P=0.017$ ). A physical health composite score comparison among the three treatment groups revealed no significant results.

CONCLUSIONS: With a positive impact of DMT on mental and physical dimensions of QOL in MS patients, initiation of treatment soon after diagnosis is recommended. In MS patients with more mental issues and fewer physical disabilities, Betaferon might be considered as a better choice of treatment.

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Rocca, M. A., et al. (2017). "Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing-remitting multiple sclerosis: an 18-month, open-label, rater-blinded, randomised, multicentre study (the GOLDEN study)." *Journal of Neurology*.

Cognitive impairment (CI) affects 40-65% of multiple sclerosis (MS) patients. This study attempted evaluating the effects of fingolimod and interferon beta-1b (IFN beta-1b) on CI progression, magnetic resonance imaging (MRI) and clinical outcomes in relapsing-remitting MS (RRMS) patients over 18 months. The GOLDEN study was a pilot study including RRMS patients with CI randomised (2:1) to fingolimod (0.5 mg daily)/IFN beta-1b (250 micro g every other day). CI was assessed via Rao's Brief Repeatable Battery and Delis-Kaplan Executive Function System test. MRI parameters, Expanded Disability Status Scale scores and relapses were measured. Overall, 157 patients were randomised, of whom 30 discontinued the study (fingolimod, 8.49%; IFN beta-1b, 41.18%;  $p \leq 0.0001$ ). Patients randomised to fingolimod had more severe clinical and MRI disease characteristics at baseline compared with IFN beta-1b. At Month (M) 18, both treatment groups showed improvements in all cognitive parameters. At M18, relapse rate, total number and volume of T2/T1 gadolinium-enhancing lesions were higher with IFN beta-1b, as well as the percentage brain volume change during the study. Safety and tolerability of both treatments were similar to previous studies. Both treatments showed improvements in cognitive parameters. Fingolimod demonstrated significantly better effects on MRI parameters and relapse rate. Imbalance in baseline characteristics and the drop-out pattern may have favoured IFN beta-1b. A longer duration trial may be needed to observe the complete expression of differential effects on CI scales reflecting the between-groups differences on MRI. Although limited in size, the GOLDEN study confirms the favourable benefit-risk profile of fingolimod reported in previous studies. Copyright (C) 2017 The Author(s)