Drug Class Review

Disease-modifying Drugs for Multiple Sclerosis

Single Drug Addendum: Fingolimod

Final Original Report

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The Agency for Healthcare Research and
Quality has not yet seen or approved this report

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Marian McDonagh, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

STRUCTURED ABSTRACT

Purpose

We compared the effectiveness and harms of fingolimod (Gilenya™) to other disease-modifying drugs in the treatment of multiple sclerosis.

Data Sources

We searched Ovid MEDLINE® and the Cochrane Library and the Database of Abstracts of Reviews of Effects through November 2010. For additional data we also hand searched reference lists, US Food and Drug Administration medical and statistical reviews, 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 and Conclusions

In patients with relapsing-remitting multiple sclerosis, fingolimod 0.5 mg and 1.25 mg once daily was superior to interferon beta-1a in improving relapse-related outcomes, including annualized relapse rates and proportion without relapse, over a 1 year period. Progression of disability was not different between the treatments at 12 months. The higher dose (1.25 mg once daily) of fingolimod resulted in higher numbers and more severe adverse events, including herpes zoster infections and symptomatic bradycardia after the first dose, as well as more patients discontinuing treatment. Differences in adverse events between 0.5 mg fingolimod (the dose approved by the US Food and Drug Administration) and interferon beta-1a were limited to more patients with pyrexia, myalgia, and flu-like symptoms with interferon, and more patients with elevated liver enzymes with fingolimod. While the absolute event rates were low, ongoing concerns with the safety of fingolimod included the risk of macular edema, the effect of lung function, cancers, and serious viral infections. Further studies are underway to better determine the risk with fingolimod.

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INTRODUCTION

In the Drug Effectiveness Review Project Report on Disease-modifying Drugs for Multiple Sclerosis, 5 injectable drugs were reviewed in comparison with each other (most recent update, August 2010). Since that time, an oral medication, fingolimod (Gilenya™) was approved in the United States and Canada for patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Fingolimod is a sphingosine 1-phosphate receptor modulator and is reported to work at least in part though reducing lymphocyte migration into the central nervous system. It is thought to result in redistribution of autoaggressive lymphocytes (T cells and B cells) to the lymph nodes and away from the central nervous system.

The purpose of this addendum to the larger report on drugs to treat multiple sclerosis is to review the evidence on the comparative effectiveness and harms of fingolimod compared to the other 5 drugs previously reviewed.[2] Placebo-controlled evidence will be used only where comparative data are not available. A glossary of terms used in Drug Effectiveness Review Project Reports is included in the main report on disease-modifying drugs for multiple sclerosis. There are no black box warnings for fingolimod.

Table 1. Included drugs

Agent	Dosage and administration	Indication	Mechanism of action
Fingolimod Gilenya™[(a)]	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	A sphingosine 1-phosphate receptor modulator and is reported to work at least in part though reducing lymphocyte migration into the central nervous system
Glatiramer Acetate Copaxone®	20 mg Subcutaneously once daily	Reduce frequency of relapses in patients with RRMS including patients who experienced a first clinical episode and have MRI features consistent with MS	May interfere with antigen presentation by mimicking and competing with MBP, a self-antigen, for binding to the MHC on the APC. The glatiramer-MHC competes with the MBP-MHC for binding to the TCR on T helper cells, which down-regulates Th1 activity and promotes a Th2 cell response, leading to increased anti-inflammatory cytokine production
Interferon beta-1a Avonex®, Avonex PS	30 mcg 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	Modulates the immune system by reducing T cell migration from the periphery into the CNS by decreasing the production of adhesion molecules and increasing the production of metalloproteases on the vascular endothelium that constitutes the blood brain barrier. These agents may also inhibit the generation of pro-inflammatory cytokines from Th1 cells (TNFα, IFNγ, IL-12).
Interferon beta-1a Rebif®	22 or 44 mcg 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®	0.25 mg Subcutaneously Every other day	Treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Effective in patients who experienced first	

Agent	Dosage and administration	Indication	Mechanism of action
		clinical episode and have MRI features consistent with MS	
Interferon beta-1b Extavia®	0.25 mg Subcutaneously every other day	Treatment of relapsing forms of MS to reduce frequency of clinical exacerbations. Effective in patients who experienced a first clinical episode and have MRI features consistent with MS	
Mitoxantrone Novantrone®[b]	12 mg/m^2 Intravenously Every 3 months (Maximum cumulative dose is 140 mg/m^2)	Reduce neurologic disability and/or the frequency of clinical relapses in SPMS, PRMS or worsening RRMS	Inhibits cell division and impairs the proliferation of T cells, B cells and macrophages by intercalating and crosslinking DNA, thus inhibiting DNA replication and RNA synthesis of these cells. Impairs antigen presentation by causing apoptosis of APCs and other cells that associate with APCs.
Natalizumab Tysabri®[c]	300 mg Intravenously every 4 weeks	Treatment of relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce frequency of clinical exacerbations	Binds to α_4 integrins expressed on leukocytes, which prevents binding to adhesion cells VCAM-1 and MAdCAM-1 on the vascular endothelium and prevents migration of leukocytes from the periphery into the CNS.

Abbreviations: APC, antigen-presenting cell; CIS, clinically isolated syndrome; CNS, central nervous system; DNA, deoxyribonucleic acid; IL, interleukin; MAdCAM-1, mucosal vascular addressin cell adhesion molecule-1; MBP, myelin basic protein; MHC, major histocompatibility complex; MRI, magnetic resonance imaging; MS, multiple sclerosis; RNA, ribonucleic acid; PRMS, progressive relapsing multiple sclerosis; PS, prefilled syringes; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TCR, T cell receptor; Th, T-helper; TNF, Tumor Necrosis Factor; VCAM-1, vascular cell adhesion molecule-1.
[a] Not available in Canada.
[b] Generic products available in Canada.
[c] Recommended for patients who have had an inadequate response to or are unable to tolerate an alternate multiple sclerosis therapy.

Scope and Key Questions

The goal of this report is to compare the effectiveness and adverse event profile of fingolimod to the other disease-modifying drugs in the treatment of multiple sclerosis. The key questions for this addendum are based on those in the complete report. There may be questions below that are not relevant to this addendum; these are noted by brackets [ ]. A draft of these questions and inclusion and exclusion criteria were posted on the Drug Effectiveness Review Project website. The draft was reviewed and revised by representatives of the organizations participating in the Drug Effectiveness Review Project. Revision took into consideration input from the public and the organizations' desire for the key questions to reflect populations, drugs, and outcome measures of interest to clinicians and patients. These organizations approved the following key questions to guide the review for this report:

Key Questions

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

2. [Do disease-modifying treatments for multiple sclerosis in effects on the development or recurrence of interferon beta neutralizing antibodies?]

3. [What is the evidence that interferon beta neutralizing antibody status has an impact on clinical outcomes (relapse and disease progression) in patients with multiple sclerosis?]

4. What is the effectiveness of fingolimod and other disease-modifying treatments for patients with a clinically isolated syndrome?

5. Do fingolimod and other disease-modifying treatments for multiple sclerosis differ in harms?

6. 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 fingolimod is more effective or associated with fewer adverse events than other disease-modifying treatment?

METHODS

Inclusion Criteria

Population(s)

- Adult outpatients with multiple sclerosis[3, 4]
  - Primary progressive multiple sclerosis
  - Secondary progressive multiple sclerosis
  - Relapsing-remitting 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).[3]

Intervention

Generic Name	Trade Name	Form
Fingolimod	Gilenya™	Capsule

Comparators

Generic name	Trade name(s)	Form(s)
Glatiramer acetate	Copaxone®	Injectable
Interferon beta-1a	Avonex® Rebif®	Vial Syringe
Interferon beta-1b	Betaseron® Extavia®[a]	Vial Injectable
Mitoxantrone	Novantrone®	Injectable
Natalizumab	Tysabri®	Vial
Placebo		

[a] Not available in Canada.

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. time lost from work)
- Progression to multiple sclerosis diagnosis
- Persistence (discontinuation rates)

Safety Outcomes

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

Study Designs

1. For effectiveness, controlled clinical trials and good-quality systematic reviews. Observational studies with 2 concurrent arms of at least 100 patients each and duration ≥1 year are included (e.g. cohort, case-control).
2. For harms, in addition to controlled clinical trials, observational studies are included.

Literature Search

We searched Ovid MEDLINE® (1996-week 4 December 2010), Ovid MEDLINE® In-Process & Other Non-Indexed Citations (November 08, 2010), the Cochrane Database of Systematic Reviews® (4th Quarter, 2010), the Cochrane Central Register of Controlled Trials® (4th Quarter, 2010), and Database of Abstracts of Reviews of Effects (DARE) using included drugs,

indications, and study designs as search terms (see Appendix A 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 US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the pharmaceutical manufacturer of fingolimod. The dossier received was screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® version X2, 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 abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by 2 reviewers. Disagreements were resolved by consensus. Posters of studies presented at conferences were considered for inclusion on the basis of our ability to conduct a thorough quality assessment based on the information provided in the poster. Results published *only* in abstract form were not included because inadequate details were available for quality assessment.

Data Abstraction

The following data were abstracted from included trials: eligibility criteria; interventions (dose and duration); population characteristics, including sex, age, ethnicity, and diagnosis; numbers randomized, withdrawn, lost to follow-up and analyzed; and results for each included outcome. We recorded intention-to-treat results when reported. If true intention-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 intention-to-treat results if the data for these calculations were available. Data abstraction was performed independently by 2 reviewers and differences were resolved by consensus.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria (see www.ohsu.edu/drugeffectiveness). These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.[5, 6] 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 intention-to-treat analysis. Trials that had a fatal flaw 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 *possibly* valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared

drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, one for effectiveness and another for adverse events.

The criteria used to rate 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. We rated the internal validity based a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met.

Two reviewers independently assessed each study 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.[7] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (including 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 fingolimod. 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.

For the direct comparisons, the strength of the evidence was rated for the 2 primary effectiveness outcomes, relapse rate and time to progression, as well as overall adverse events and withdrawal due to adverse events.

Table 2. Definitions of the grades of overall strength of evidence[8]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

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 fingolimod against another disease-modifying drug provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. Direct comparisons were preferred over indirect comparisons; similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

In theory, trials that compare fingolimod with other drug classes or with placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily heterogeneity of trial populations, interventions, and outcomes assessment. Data from indirect comparisons are used to support direct comparisons, where they exist, and are used as the primary comparison where no direct comparisons exist.

Quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in 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.[9] Forest plots graphically summarize results of individual studies and of the pooled analysis.[10]

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.[11, 12] Potential sources of heterogeneity were examined by analysis of subgroups of study design, study quality, patient population, and variation in interventions. Meta-regression models were used to formally test for differences between subgroups with respect to outcomes.[9, 13] All meta-analyses were conducted using StatsDirect (Camcode, UK).

Public Comment

This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 3 pharmaceutical companies: Biogen Idec, Novartis Pharmaceuticals Corporation, and Teva Pharmaceuticals.

RESULTS

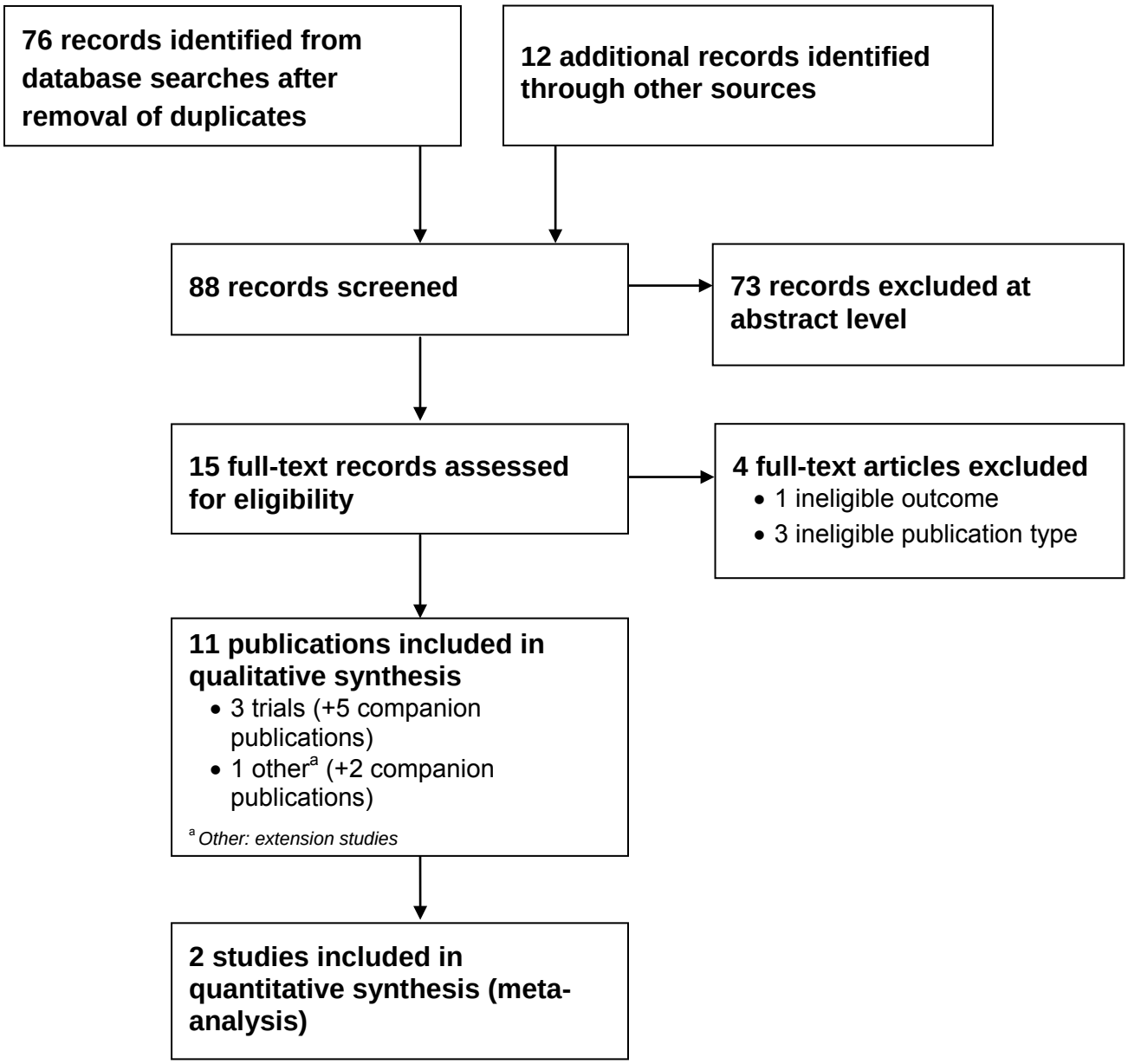
Overview

Electronic literature searches identified 76 citations. We received a dossier from the pharmaceutical manufacturer, which supplied additional data on studies in the form of posters and slide sets from presentations at conferences. We reviewed the US Food and Drug Administration Medical and Statistical reviewer reports regarding the New Drug Application for fingolimod. By applying the eligibility criteria, we ultimately included 4 unique studies enrolling

a combined 2845 patients: 1 head-to-head comparison trial, 2 placebo-controlled trials, and 1 randomized extension study of 1 placebo-controlled trial. The US Food and Drug Administration documents included some data on these studies.[14] Two posters relating to an additional extension study of the head-to-head comparison trial submitted for consideration by the manufacturer were not included due to inadequate information provided to conduct a full quality assessment.[15, 16] All included studies enrolled patients with relapsing-remitting multiple sclerosis, except for 31 patients with secondary progressive multiple sclerosis enrolled in the first placebo-controlled trial.[14] Appendix B shows list of excluded studies and reasons for exclusion at this stage. Figure 1 shows the flow of study selection.[14, 17-26]

The trials and extension studies identified included doses that are higher than the US Food and Drug Administration approved 0.5 mg once daily dose for treating relapsing-remitting multiple sclerosis. These are included and discussed here as appropriate, but the discussion focuses on the comparative benefits and harms of the 0.5 mg dose. Although it is clear that higher doses lead to more frequent and more severe adverse events, studies using the 1.26 mg once daily dose are continuing in patients with primary progressive multiple sclerosis or in patients who tolerated the dose and entered extension studies. The US Food and Drug Administration has suggested that the manufacturer pursue studies of lower doses (e.g. 0.25 mg once daily).[14]

Figure 1. Results of literature search



DERP uses a modified PRISMA flow diagram.[1]

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

Summary of Findings

- Fingolimod 0.5 mg once daily and 1.25 mg once daily resulted in lower annualized relapse rates than interferon beta-1a (0.16, 0.20, and 0.33 respectively; $P< 0.001$)
- Fingolimod 0.5 mg once daily and 1.25 mg once daily resulted in more patients having no confirmed relapse at 1 year compared with interferon beta-1a (82.5%, 80.5%, and 70.1% respectively); numbers needed to treat are 8.3 for fingolimod 0.5 mg once daily and 10 for 1.25 mg once daily
- Differences between the lower dose of fingolimod and the higher dose were not statistically significant
- The rate of confirmed disability progression over 12 months was low in both groups and not statistically significant between groups, although the change in ratings on 2 scales measuring disability and function showed slightly better results with fingolimod than interferon beta-1a.

Detailed Assessment

Direct evidence

There was moderate strength of evidence that fingolimod resulted in lower annualized relapse rates than interferon beta-1a, but that progression of disease was not different between the treatments after one year of treatment. In a single fair-quality head-to-head trial, fingolimod was compared with interferon beta-1a in patients with relapsing-remitting multiple sclerosis.[18] The trial was large, relative to other trials of drugs to treat multiple sclerosis, enrolling 1292 patients who were randomized to 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. 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 3). Other measures of relapse (relapse-free, proportion with multiple relapses, and the time to first relapse) also showed both fingolimod doses to be superior. However, the numbers needed to treat for the proportion relapse-free with fingolimod compared with interferon beta-1a at 1 year were not very small (8.3 and 10; Table 3).

The benefit of fingolimod over interferon beta-1a was greater in the subgroup of patients who had prior exposure to a disease-modifying drug than in patients who had no prior exposure. Among patients with prior exposure, the benefit from fingolimod over interferon beta-1a ranged from 0.20 to 0.27 relapses for interferon beta-1a 1.25 mg and 0.5 mg, respectively, compared with a difference of 0.13 to 0.16 relapses in patients with no prior experience with the drugs. While the difference in annualized relapse rate between those with prior exposure and those without was not statistically significant, the sample sizes may have been too small to identify the difference as significant.

Trial eligibility criteria required that participants had experienced at least 1 documented relapse during the previous year or at least 2 documented relapses during the previous 2 years. Recent use of an interferon was allowed; 47.6% of patients in the interferon beta-1a group,

50.8% of those in the fingolimod 0.5 mg group, and 49.1% of those in the fingolimod 1.25 mg group had received an interferon prior to enrollment and had relapsed despite treatment.

Although the trial used a double-dummy design, patients with prior experience with interferon may have been more likely to have guessed which treatment they were on, due to previously experiencing adverse effects associated with interferons but not fingolimod, such as injection site reactions. Because identifying the primary outcome of relapse requires subjective assessments by patients and neurologists, blinding of both parties is important to prevent potential bias (regardless of direction). The investigators attempted to maintain blinding of neurologists by having patients cover the injection site on days they were attending clinic for assessment. The success of blinding patients or neurologists was not evaluated, however.

It is notable that the annualized relapse rates reported in all groups in this study (0.16 to 0.33) were much lower than reported in previous trials of the disease-modifying drugs, potentially indicating that the population included here was clinically distinct to those included in previous trials. In the Drug Effectiveness Review Project report on Disease-modifying Drugs for Multiple Sclerosis, we found that annualized relapse rates ranged from 0.61 to 1.83 for beta interferon groups in placebo-controlled trials and from 0.5 to 1.2 in head to head comparisons of interferons. Explanations for this apparent difference may include the difference in duration of the trials, with the current study of fingolimod being only 12 months long, while the other studies were mostly 2 years in duration. However, it is also possible that the patients enrolled in this study were clinically distinct from those enrolled in the other studies, given that both diagnosis and treatment have changed over the past 10 years (the first head-to-head study of interferons was published in 2002). For example, review of the duration of multiple sclerosis at study enrollment revealed some variation, with a range of 4 to 6.8 years in the head-to-head studies of interferons, compared with 7.3 to 7.5 years in this recent study. This potential clinical heterogeneity in the patient populations reinforced the decision to not conduct an adjusted indirect comparison meta-analysis of these data. It is also noteworthy that interferon beta-1a was found to be the least effective interferon in our report, although it may have better tolerability than interferon beta-1b SC (Betaseron®). Confirmed disability progression (sustained worsening of disability score over 3 months) or time to progression, however, did not show a difference between the drugs or doses. The rate of progression was low in all groups. Mean change from baseline on 2 scales measuring disability and function did show somewhat better results with both fingolimod doses compared with interferon, although these differences did not translate into differences in progression rates.

Overall, there were no differences in the rate of discontinuation of the assigned treatment over 1 year (including both discontinuations for lack of efficacy and due to adverse events). The rate of progression reported in this trial ranged from 5.9% with fingolimod 0.5 mg to 7.9% with interferon beta-1a. These rates were much lower than those found previously in the trials we reviewed of other disease-modifying drugs where rates of progression in beta interferon groups at 2 years ranged from 11.4% to 26.6%, and in placebo groups from 20.3% to 36.4%.

Table 3. Relapse rates with fingolimod compared with interferon beta-1a 30 mcg intramuscular weekly

Outcome measure	Fingolimod 0.5 mg once daily N = 429	Fingolimod 1.25 mg once daily N = 420	Interferon beta-1a N = 431
Annualized relapse rate[a]	0.16	0.20	0.33
P value vs. interferon beta-1a	*P*<0.001	*P*<0.001	--
Relapse-free[b] (%)	82.5	80.5	70.1
P value vs. interferon beta-1a	1.18 (1.09 to 1.27) *P*<0.001	1.15 (1.06 to 1.24) *P*<0.001	--
Number needed to treat	8.3	10	--
Progression-free (%)	94.1	93.3	92.1
P value vs. interferon beta-1a	0.25	0.5	--

[a] Adjusted for study group, country, number of relapses in past 2 years, and baseline disability score.
[b] Patients with confirmed 0 relapses.

Additional outcomes were presented in 2 posters submitted by the manufacturer. A *post hoc* analysis of the severity of relapse based on steroid use on an outpatient basis or hospitalization included all patients (N=1292). The rate of mild relapses (not requiring steroid use or hospitalization) was similar across the groups (3.3% to 4.6%). The rate of outpatient steroid use was higher in the interferon group and when assessing the annualized relapse rate associated with patients requiring outpatient steroid use, fingolimod resulted in lower rates than interferon (Table 4). Similarly, the rate of hospitalization was lowest in the 0.5 mg once daily fingolimod group and highest in the interferon group, and annualized relapse rates in this group of patients were significantly lower with both fingolimod doses compared with the interferon group (Table 4).

Table 4. Relapse outcomes based on steroid use or hospitalization

Outcome measure	Fingolimod 0.5 mg once daily N = 429	Fingolimod 1.25 mg once daily N = 420	Interferon beta-1a N = 431
Steroid use (%)	11.2	13.1	18.3
Annualized relapse rate requiring steroids	0.084	0.115	0.176
P value vs. interferon beta-1a	*P*<0.001	*P*<0.012	--
Hospitalization (%)	1.9	3.1	7.0
Annualized relapse rate requiring hospitalization	0.022	0.039	0.077
P value vs. interferon beta-1a	*P*=0.001	*P*=0.049	--

Analysis of a patient-assessed measure of disability called the Patient Reported Indices for Multiple Sclerosis scale (PRIMUS, rated as a score of 0 to 30 based on 15 items rated 0, 1, or 2, with higher numbers indicating worse disability) did not indicate important benefits with one drug over another. This analysis was based on a subset of the patients (64%) who had both baseline and 12 month assessments and a version of the PRIMUS scale in their language. The analysis of these results showed significantly greater worsening of total score in the interferon

group when compared with either fingolimod group (mean change +0.43 with interferon beta-1a, +0.08 with fingolimod 0.5 mg once daily, and +0.12 with fingolimod 1.25 mg once daily; comparisons between fingolimod groups and interferon statistically significant). However, the degree of change was not clinically meaningful in any group based on the definition of ≥ 2 point improvement given in the study methods. An analysis comparing the percent of patients with improvement or worsening did not show differences between the drugs.

Duration of effect

Very little information was available on the duration of the beneficial effects with fingolimod beyond the 1-year trial. An extension study based on the study directly comparing these 2 drugs has been done (check posters), but has not been fully published to date. An extension study based on the placebo-controlled trial (below) has been reported and is discussed below.

Indirect evidence

Two fair-quality placebo-controlled trials, and 1 extension study of the smaller, have been conducted.[19, 22, 25] The first study was small (N=277), had MRI findings as the primary outcome, only lasted 6 months, and used doses higher than was ultimately approved by the US Food and Drug Administration (5 mg once daily and 1.25 mg once daily). While 89% of patients enrolled had relapsing-remitting multiple sclerosis, 11% had secondary progressive disease.[14] The study also reported annualized relapse rates.[19] The second study was larger (N=1272), lasted 2 years, used annualized relapse rates as the primary outcome measure, and used the lower doses of 0.5 mg once daily and 1.25 mg once daily. This study enrolled only patients with relapsing-remitting disease.[22]

As can be seen in Table 5 below, the annualized relapse rates in the placebo groups were different between the 2 studies. The study that included patients with secondary progressive disease had higher rates, as might be expected. Because the 2 studies are so different, we did not feel that pooling results from these studies would be clinically relevant. A US Food and Drug Administration analyses aggregated rates from all studies available at the time of the submission and found a rate of 0.21 with fingolimod 0.5 mg and 0.47 with placebo.[14] The reduction in the rate between the fingolimod 0.5 mg dose and placebo was 50% to 55% across all analyses.

Results from placebo-controlled trials of fingolimod and interferon beta-1a and 1b (from the main Drug Effectiveness Review Project report on Disease-modifying Drugs for Multiple Sclerosis) are reported in Tables 5 and 6 below. Focusing on data relevant to the lower, approved dose of fingolimod, the annualized relapse rates in the placebo groups of the Kappos 2010 trial of fingolimod 0.5 mg (0.4)[22] was lower than those in the placebo groups of the interferon studies (range 0.9 to 2.6).[2] Similarly, the proportion of patients in the placebo groups with at least 1 relapse ranged from 44.8% to 84% in the interferon studies and was 54.4% in the Kappos 2010 study of fingolimod 0.5 mg. Data on progression were more comparable, and patients having progressed at 2 years ranged from 20.3% to 36.4% in the placebo groups of the interferon studies[2] and was 24.2% in the Kappos 2010 study of fingolimod 0.5 mg.[22] The relative risk of having sustained progression of disability with fingolimod 0.5 mg was 0.73; 95% CI, 0.56 to 0.95, similar to the reduction seen with interferon beta-1b SC (Betaseron®) (0.73; 95% CI, 0.46 to 1.15), and with interferon beta-1a SC (Rebif®) 44 µg (0.73; 95% CI, 0.54 to 0.99).

Table 5. Clinical outcomes in placebo-controlled trials of fingolimod

Outcome measure	Kappos 2006 1.25 mg	Kappos 2006 Placebo	Kappos 2010 0.5 mg	Kappos 2010 Placebo
Annualized relapse rate	0.35	0.77	0.18	0.4
Patients with ≥ 1 relapse (%)	15.9	34.4	29.6	54.4
Relative risk (95% CI)	0.46 (0.27 to 0.79)		0.55 (0.46 to 0.65)	
Patients with progression of disability (%)	NR		17.7	24.2
Relative risk (95% CI)			0.73 (0.56 to 0.95)	

Abbreviations: NR, not reported.

Table 6. Clinical outcomes in placebo-controlled trials of interferons

Outcome measure (Interferon vs. placebo)	Interferon beta-1b SC (Betaseron®)	Interferon beta-1a IM (Avonex®)	Interferon beta-1a SC (Rebif®) 44 µg
Patients with ≥ 1 relapse at 2 years (%)	63.7% vs. 76.4%	33.5% vs. 44.8%	67.9% vs. 84.0%
Relative risk (95% CI)	0.83 (0.71 to 0.98),	0.75 (0.56 to 1.00)	0.81 (0.72 to 0.91)
Annualized/mean relapse rate	0.96 1.6 MIU vs. 1.12 0.78 8 MIU vs. 1.12	0.61 vs. 0.90	1.82 22 mcg 3 times weekly vs. 2.56 1.73 44 mcg 3 times weekly vs. 2.56
Progressed at 2 years (%)	20.2% vs. 27.6%	11.4% vs. 20.3%	26.6% vs. 36.4%
Relative risk (95% CI)	0.73 (0.46 to 1.15)	0.56 (0.33 to 0.97)	0.73 (0.54 to 0.99)

Abbreviation: MIU, million international units.

Durability of effect

The smaller placebo-controlled trial included an extension study where patients in the placebo arms were re-randomized to 1.25 mg or 5 mg of fingolimod (open-label).[25] Because these doses were higher than those approved by the US Food and Drug Administration, and even the 1.25 mg dose has shown significantly higher rates of serious adverse events, the value of these findings is quite limited. There are now up to 4 years of data on this group of patients, however.[21] At the end of the core study, 250 of the 277 enrolled patients joined the extension study. At 2 years, the proportion of patients in the 1.25 mg group who remained relapse-free while continuing on their originally assigned fingolimod dose decreased from 86% at original trial end to 63% after a total of 2 years on drug. Based on a slide presentation submitted by the manufacturer, data after 4 years showed the rate in this group to remain at 63%.[21] So, it appeared that there was an initial decrease over 2 years, but then stabilization for up to 4 years. It is noteworthy that the rate of relapse in the placebo group at the end of the core study was 66%, although it was only 6 months in duration. In contrast, the rate in the placebo group in the 2 year study was 46% at study end, indicating a potential benefit of drug over placebo after 2 and 4 years.

While only preliminary data are available to date, the similar extension study based on the direct comparison study of fingolimod and interferon included the 0.5 mg dose.[16] At the end of the 1 year trial, the proportion without relapse in the 0.5 mg fingolimod group was 82.5%. After and additional year of taking the drug the rate was 73%, again indicating a drop off in

effect over time but still remaining above the level of placebo. These results should not be used in clinical decisionmaking until full a publication of the study is available. A study directly comparing fingolimod to other treatments over longer periods of time is needed to determine the comparative effectiveness.

Key Question 2. [Do disease-modifying treatments for multiple sclerosis in effects on the development or recurrence of interferon beta neutralizing antibodies?]

Not relevant to this drug.

Key Question 3. [What is the evidence that interferon beta neutralizing antibody status has an impact on clinical outcomes (relapse and disease progression) in patients with multiple sclerosis?]

Not relevant to this drug.

Key Question 4. What is the effectiveness of fingolimod and other disease-modifying treatments for patients with a clinically isolated syndrome?

No evidence found.

Key Question 5. Do fingolimod and other disease-modifying treatments for multiple sclerosis differ in harms?

Summary of Findings

- 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 (relative risk, 4.26; 95% CI, 2.62 to 6.97), influenza-like illness (relative risk, 10.55; 95% CI, 6.39 to 17.57), and myalgia (relative risk, 3.13; 95% CI, 1.76 to 5.59) were found with interferon beta-1a
    - A higher rate of increased alanine aminotransferase (relative risk, 3.52; 95% CI, 1.66 to 7.50) was found with fingolimod
    - While no deaths occurred in the interferon or fingolimod 0.5 mg groups, 2 deaths (0.48%) occurred with fingolimod 1.25 mg, both due to viral infections
        - Fingolimod 1.25 mg was associated with higher risk of herpes virus infections than fingolimod 0.5 mg (relative risk, 2.61; 95% CI, 1.75 to 5.49; number needed to harm, 30) or interferon beta-1a (relative risk, 1.97; 95% CI, 1.01 to 3.86; number needed to harm, 37).
        - Differences in rates of herpes zoster infections between fingolimod 0.5 mg once daily and interferon beta-1a were not significant
- Discontinuations due to adverse events and serious adverse events occurred more frequently with fingolimod 1.25 mg than with fingolimod 0.5 mg or interferon beta-1a
    - The increased risk of discontinuing drug due to an adverse event with fingolimod 1.25 mg once daily compared with 0.5 mg was relative risk, 1.79 (95% CI, 1.11 to

2.89) and compared with interferon beta-1a was relative risk, 2.69 (95% CI, 1.55 to 4.69), with numbers needed to harm of 23 and 16, respectively
    - Differences in rates of discontinuations due to adverse events between fingolimod 0.5 mg once daily and interferon beta-1a were not significant
- 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
    - Across all 3 trials, 1.2% of patients taking 1.25 mg fingolimod, 0.6% taking 0.5 mg fingolimod, 0.2% taking placebo, and 0% taking interferon experienced bradycardia
    - Across all 3 trials, 0.4% of patients taking 1.25 mg fingolimod, 0.1% taking 0.5 mg fingolimod, and 0% taking placebo or interferon experienced second-degree atrioventricular blockade
- During a 1-year head-to-head trial of fingolimod and interferon beta-1a:
    - Eight of 10 cases of localized skin cancer and 2 cases of breast cancer were diagnosed during the trial in patients taking fingolimod
    - 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
    - Pulmonary function was reduced in fingolimod patients (2% to 3% reduction FEV1).

Detailed Assessment

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,[18] there was moderate-strength evidence (see Appendix C) that the overall adverse event rate is similar across the 3 treatment arms. But the rate of discontinuation due to an adverse event was higher in the fingolimod 1.25 mg once daily group (10%) compared with the 0.5 mg dose (5.6%) and interferon beta-1a (3.7%). These percentages resulted in a statistically significant increased risk of discontinuation due to adverse events for fingolimod 1.25 mg once daily compared with 0.5 mg (relative risk, 1.79; 95% CI, 1.11 to 2.89) or interferon (relative risk, 2.69; 95% CI, 1.55 to 4.69), with numbers needed to harm of 23 and 16, respectively. 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.

Moderate-strength evidence (see Appendix C) indicated increased risk for several specific adverse events with fingolimod over interferon beta-1a, in particular with the higher 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%). The resulting relative risks were 2.61 (95% CI, 1.75 to 5.49); number needed to harm, 30 and 1.97 (95% CI, 1.01 to 3.86); number needed to harm, 37 for fingolimod 1.25 mg compared with

0.5 mg and interferon beta-1a, respectively. Ten skin cancers were diagnosed during the study, all were localized, but 8 of the 10 occurred in fingolimod groups. Two cases of breast cancer were diagnosed during the trial, both in fingolimod patients. These cancers were not screened for at study entry.

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 EKG 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.

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 (relative risk, 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 7 below.

Table 7. Specific adverse events with fingolimod 0.5 mg compared with interferon beta-1a

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

In light of the emerging picture of somewhat infrequent but serious adverse events associated with fingolimod, the US Food and Drug Administration reviewed pooled data from all 3 trials to estimate the frequency of rates of serious adverse events.[14] These analyses were not meta-analyses and did not maintain individual study randomization, but did provide a larger population base from which estimates the frequency of events can be drawn in a preliminary way. The analyses indicated dose-dependent increases in adverse events with fingolimod compared with placebo or interferon beta-1a in the following categories: cardiac disorders, nervous system disorders, and infections and infestations (Table 8). Within cardiac disorders, bradycardia after the first dose is the primary adverse event. Using data from all 3 trials, analyses done by the US Food and Drug Administration showed that 1.2% of patients taking 1.25 mg fingolimod, 0.6% taking 0.5 mg fingolimod, 0.2% taking placebo and 0% taking interferon experienced bradycardia. In these studies 0.4% of patients taking 1.25 mg fingolimod, 0.1% taking 0.5 mg fingolimod, and 0% taking placebo or interferon experienced second-degree atrioventricular blockade.

With nervous system disorders, events other than exacerbations of multiple sclerosis (similar across groups) epilepsy, grand mal convulsion, and headache occurred with the 1.25 mg dose of fingolimod (2 cases each), but no cases were seen in the other groups. Within the infections category, the percentages of patients experiencing serious infections were not very much different across the groups, but the types of infections indicated a higher rate of herpes infections with the 1.25 mg dose of fingolimod. Rates of other serious adverse events were similar across the groups, with the exception that the placebo group had a higher proportion with neoplasm (2.3%, compared with 0.5% to 1.6%). Depression was reported as a serious adverse event in 2 patients taking fingolimod 1.25 mg, and none in the other groups, including the interferon beta-1a group.

Table 8. Proportions of patients with serious adverse events across all trials

	Fingolimod 1.25 mg once daily N=943	Fingolimod 0.5 mg once daily N=854	Interferon beta-1a N=431	Placebo N=511
Cardiac disorders (%)	2.4	1.2	0	0.2
Nervous system disorders (%)	1.9	1.4	0.7	1.0
Infections and infestations (%)	1.9	0.9	1.4	1.6

Based on US Food and Drug Administration review of the trial data, it appears that there is a dose-dependent increase in macular edema with fingolimod.[14] The analysis indicated a rate of 1.3% with 1.25 mg once daily and 0.2% with 0.5 mg once daily, but additional data are expected from an ongoing trial with further safety analyses. These events included both those rated as serious and those that were considered significant but not serious. It was estimated that most occurred between 2 and 6 months of drug initiation, but can occur much later.

While the current studies are insufficient to determine whether there is indeed increased risk, concern has been raised about other potentially serious and important adverse events that may be associated with fingolimod. These include cardiac ischemia, pulmonary fibrosis, changes in lung function, seizures, and severe headache or migraine.

Two-year data from a small extension study were included in the US Food and Drug Administration analyses above. In the extension, the rate of patients experiencing an adverse event was high: 88.5% at 2 years and 96.8% at 4 years. Eight percent had a serious adverse event at 2 years and 12.8% at 4 years. Because the dose reported is higher than is recommended for clinical use, and because the reporting of adverse events is not adequate to determine when they occurred, further evaluation of these data is not warranted at this time.

Key Question 6. 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 fingolimod is more effective or associated with fewer adverse events than other disease-modifying treatment?

Very limited evidence is currently available on fingolimod in patient subgroups. An analysis of change in depression scale scores based on 1 of the placebo-controlled trials above has been presented at a conference, but a full publication is not available at this time.[27] The US Food and Drug Administration Clinical Reviewer document reported on their pooled analyses of data from the 2 most recent trials. Both used 1.25 mg and 0.5 mg of fingolimod, with comparisons to either placebo or interferon beta-1a.[14] They found no clear difference in effect of fingolimod by gender or age, but noted that "a higher overall ARR was seen in the subgroup of patients that were younger, which is consistent with published data on the natural history of MS". A similar analysis by US Food and Drug Administration reviewers found no difference in the effect of fingolimod based on baseline disability score, but noted that patients with worse disability at baseline have higher annualized relapse rates than those with lower scores, as would be expected.

SUMMARY

Strength of Evidence

Overall, the strength of the evidence for the comparison of fingolimod 1.25 mg or 0.5 mg with interferon beta-1a was moderate for all relevant outcomes. These findings were based on a single study, however, and further studies, particularly longer studies or studies using a different interferon, may change the results. Strength of evidence was not evaluated for the durability of effect because it is not comparative. Nor was there evidence for direct comparison to any other interventions.

Limitations of this Report

As with other types of research, the limitations of this systematic review are important to recognize. Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English, limiting the analyses to direct comparisons of fingolimod with other disease modifying drugs or placebo and not conducting indirect comparison meta-analyses. Given the limited amount of data, we feel that there is not adequate power to pursue such analyses at this time. Another possible limitation is the lack of a specific search for unpublished studies, other than the request for information from the manufacturer of the drug.

Applicability

The applicability of the results were limited by the scope of the Key Questions and inclusion criteria and by the generalizability of the studies included. The trials included narrowly defined populations of patients who met strict criteria for case definition, had few or no comorbidities, and used few or no concomitant medications. Minorities, older patients, and the most seriously ill patients were underrepresented. The evidence was largely applicable to patients with relapsing-remitting multiple sclerosis of moderate severity. The comparative evidence was limited to treatment for 1 year and did not reflect changes beyond that time. Outcomes related to disability progression may require 2 or more years to evaluate. The conclusions about benefit or harm relative to other disease-modifying drugs were limited only to interferon beta-1a.

Trials in Progress

According to the US Food and Drug Administration documents, there are 5 studies currently on-going. One of these is a 2 year placebo-controlled trial of 0.5 mg and 1.25 mg fingolimod compared with placebo in patients with relapsing-remitting multiple sclerosis. This study is very similar to the recently published placebo-controlled study,[22] except that it includes additional safety measurements such as ophthalmologic testing, high resolution computerized tomography, pulmonary function tests, and echocardiography. A total of 1089 patients have been enrolled. A smaller placebo-controlled trial in patients with relapsing-remitting multiple sclerosis is also being conducted in Japan, and a multi-country trial is being conducted in patients with primary progressive multiple sclerosis comparing 1.25 mg fingolimod to placebo. In addition there are 2 ongoing extension studies (one reported above).

Table 9. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
Key Question 1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?	Fingolimod 1.25 mg or 0.5 mg once daily vs. interferon beta-1a: Moderate All others: Insufficient	Fingolimod 0.5 mg once daily and 1.25 mg once daily resulted in lower annualized relapse rates than interferon beta-1a (0.16, 0.20, 0.33 respectively; *P*< 0.001). Fingolimod 0.5 mg once daily and 1.25 mg once daily resulted in more patients having no confirmed relapse at 1 year compared with interferon beta-1a (82.5%, 80.5%, and 70.1% respectively); NNT, 8.3 for fingolimod 0.5 mg and 10 for 1.25 mg daily. Differences were not found between the lower dose of fingolimod and the higher dose. Rates of confirmed disability progression were low, and similar between groups.
Key Question 5. Do disease-modifying treatments for multiple sclerosis differ in harms?	Fingolimod 1.25 mg or 0.5 mg once daily vs. interferon beta-1a: Moderate All others: Insufficient	Higher rates of pyrexia (RR, 4.26 (2.62 – 6.97), Influenza-like illness (RR, 10.55 (6.39 – 17.57)), and myalgia (RR, 3.13 (1.76 – 5.59)) were found with interferon beta-1a, while a higher rate of increased alanine aminotransferase (RR, 3.52 (1.66 – 7.50)) was found with fingolimod. The rate of herpes zoster infections was similar between fingolimod 0.5 mg once daily and interferon beta-1a. 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; NNH, 30) or interferon beta-1a (RR, 1.97; 95% CI, 1.01 to 3.86; NNH, 37). 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. After the first dose of fingolimod, 1.2% of patients taking 1.25 mg fingolimod, 0.6% taking 0.5 mg fingolimod, 0.2% taking placebo, and 0% taking interferon experienced bradycardia. The risk of discontinuing drug due to an adverse event increased with fingolimod 1.25 mg once daily compared with fingolimod 0.5 mg once daily (RR, 1.79 (1.11 to 2.89); NNH, 23) and with interferon beta-1a (RR, 2.69 (1.55 to 4.69); NNH,16).
Key Question 6. 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?	Age, gender, baseline disability score: Moderate All others: Insufficient	Differences in efficacy based on age, gender, or baseline disability score were not found with fingolimod.

Abbreviations: NNH, number needed to harm; NNT, number needed to treat; RR, relative risk.

CONCLUSIONS

In patients with relapsing-remitting multiple sclerosis, fingolimod 0.5 mg and 1.25 mg once daily was superior to interferon beta-1a in improving relapse-related outcomes, including annualized relapse rates and proportion without relapse, over a 1 year period. Progression of disability was not different between the treatments. The higher dose (1.25 mg once daily) of fingolimod resulted in higher numbers and more severe adverse events, including herpes zoster infections and symptomatic bradycardia after the first dose, as well as more patients discontinuing treatment. Differences in adverse events between 0.5 mg fingolimod and interferon beta-1a were limited to more patients with pyrexia, myalgia, and flu-like symptoms with interferon and more with elevated liver enzymes with fingolimod. Ongoing concerns with the safety of fingolimod included the risk of macular edema, the effect of lung function, cancers, and serious viral infections. Further studies are underway to better determine the risk with fingolimod.

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21. Kappos L, Radue EW, O'Connor P, et al. Majority of patients with relapsing multiple sclerosis receiving oral fingolimod (FTY720, a sphingosine-1-phosphate receptor modulator) remain free from any inflammatory activity: Results of a 4-year, Phase II extension [presentation]. *Presented at: The 19th European Neurological Society.* Vol Milan, Italy: June 20-24, 2009; 2009.

22. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* Feb 4 2010;362(5):387-401.

23. Khatri B, Barkhof F, Comi G, et al. Oral fingolimod (FTY720) reduces the rate of relapses that require steroid intervention or hospitalization compared with intramuscular interferon β-1a: results from a phase III study (TRANSFORMS) in multiple sclerosis [poster]. *Presented at: The American Academy of Neurology 62nd Annual Meeting.* Vol Toronto, Canada: April 10-17, 2010; 2010.

24. O'Connor P, Polman C, Hohlfeld R, et al. Oral fingolimod (FTY720) vs placebo in relapsing remitting multiple sclerosis: 24 month safety and tolerability results from a randomized, double-blind, multicenter phase III study (FREEDOMS) [poster - P06.171]. *Presented at: The American Academy of Neurology 62nd Annual Meeting.* Vol Toronto, Canada: April 10-17, 2010; 2010.

25. O'Connor P, Comi G, Montalban X, et al. Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study. *Neurology.* Jan 6 2009;72(1):73-79.

26. von Rosenstiel P, Hohlfeld R, Calabresi P, et al. Clinical Outcomes in subgroups of patients treated with fingolimod (FTY720) or placebo: 24 month results from FREEDOMS [poster-P434]. *Presented at: The 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis.* Vol Gothenberg, Sweden: October 13-16, 2010; 2010.

27. Kappos L, Comi G, Montalban X, et al. Oral FTY720 (fingolimod) in relapsing multiple sclerosis: impact on patient-reported depression, as measured by the Beck Depression Inventory II in a 6-month, placebo-controlled study. *Neurology.* 2007;68:A276.

Appendix A. Search Strategies

Database: Ovid MEDLINE(R) <1996 to October Week 4 2010>
Search Strategy:
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1 fingolimod.mp. (657)
2 multiple sclerosis.mp. or exp *Multiple Sclerosis/ (25001)
3 1 and 2 (102)
4 limit 3 to (english language and humans) (73)

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Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 08, 2010>
Search Strategy:
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1 fingolimod.mp. (22)
2 multiple sclerosis.mp. or exp *Multiple Sclerosis/ (1090)
3 1 and 2 (19)

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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2010>
Search Strategy:
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1 fingolimod.mp. (20)
2 multiple sclerosis.mp. or exp *Multiple Sclerosis/ (2328)
3 1 and 2 (13)

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Searches of Cochrane Database of Systematic Reviews and DARE did not return any citations. Searches of the US Food and Drug Administration website did not return any Review documents as of November 8, 2010.

Appendix B. Excluded studies

The following full-text publications were considered for inclusion but failed to meet the criteria for this report.

Exclusion codes: 2=ineligible outcome, 5=ineligible publication type

Excluded studies	Exclusion code
Placebo-controlled trials	
Radue EW, O'Connor P, Polman C, et al. Oral fingolimod (FTY720) reduces inflammatory activity vs placebo in relapsing remitting multiple sclerosis: 24 month MRI results from a randomized, double-blind, multicenter phase III study (FREEDOMS) [presentation]. *Presented at: The America Academy of Neurology 62nd Annual Meeting.* Vol Toronto, Canada: April 10-17, 2010; 2010.	2
Kappos L, Comi G, Montalban X, et al. Oral FTY720 (fingolimod) in relapsing multiple sclerosis: impact on patient-reported depression, as measured by the Beck Depression Inventory II in a 6-month, placebo-controlled study. *Neurology.* 2007;68:A276.	5

Appendix C. Strength of evidence

Table 1: Fingolimod (0.5 mg or 1.25 mg once daily) vs. interferon beta-1a

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; 1 Number of subjects 1292	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Outcome 1						
Annualized Relapse Rate 1.25 mg vs Interferon	Moderate	NA	Direct	Precise	1.25 mg RR 1.15 (1.06 to 1.24)	Moderate
Annualized Relapse Rate 0.5 mg vs Interferon	**Moderate**	NA	Direct	Precise	0.5 mg: RR 1.18 (1.09 to 1.27)	Moderate
Outcome 2						
Progression of Disability (either dose)	Moderate	NA	Direct	Precise	No differences between groups	Moderate
Outcome 3						
DC due to AE 1.25 mg vs 0.5 mg fingolimod	Moderate	NA	Direct	Precise	RR 1.79 (1.11 to 2.89)	Moderate
DC due to AE 1.25 mg fingolimod vs Interferon	Moderate	NA	Direct	Precise	RR 2.69 (1.55 to 4.69)	Moderate
Outcome 4						
Overall AE	Moderate	NA	Direct	Imprecise	High in all groups, not statistically different.	Moderate
Outcome 5						
Bradycardia/AV Block after first dose of fingolimod	Moderate	NA	Direct	Imprecise	0.47% Symptomatic bradycardia 0.47% AV block	Moderate
Outcome 6						
Herpes virus Infections 1.25 mg vs 0.5 mg fingolimod	Moderate	NA	Direct	Precise	RR 2.61 (1.75 – 5.49)	Moderate
Herpes virus Infections 1.25 mg fingolimod vs Interferon	Moderate	NA	Direct	Precise	RR 1.97 (1.01 – 3.86)	Moderate