Original article

Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States

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Abstract

Objective:
To assess the cost-effectiveness of delayed-release dimethyl fumarate (DMF, also known as gastro-resistant DMF), an effective therapy for relapsing forms of multiple sclerosis (MS), compared with glatiramer acetate and fingolimod, commonly used treatments in the US.

Methods:
A Markov model was developed comparing delayed-release DMF to glatiramer acetate and fingolimod using a US payer perspective and 20-year time horizon. A cohort of patients, mean age 38 years, with relapsing-remitting MS and Kurtzke Expanded Disability Status Scale (EDSS) scores between 0–6 entered the model. Efficacy and safety were estimated by mixed-treatment comparison of data from the DEFINE and CONFIRM trials and clinical trials of other disease-modifying therapies. Data from published studies were used to derive resource use, cost, and utility inputs. Key outcomes included costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios. Alternative scenarios tested in a sensitivity analysis included drug efficacy, EDSS-related or relapse-related costs, alternative perspectives, drug acquisition costs, and utility.

Results:
Base-case results with a 20-year time horizon indicated that delayed-release DMF increased QALYs +0.450 or +0.359 compared with glatiramer acetate or fingolimod, respectively. Reductions in 20-year costs with delayed-release DMF were $70,644 compared with once-daily glatiramer acetate and $32,958 compared with fingolimod. In an analysis comparing delayed-release DMF to three-times-weekly glatiramer acetate and assuming similar efficacy and safety to the once-daily formulation, 20-year costs with delayed-release DMF were increased by $15,806 and cost per QALY gained was $35,142. The differences in costs were most sensitive to acquisition cost and inclusion of informal care costs and productivity losses. The differences in QALYs were most sensitive to the impact of delayed-release DMF on disease progression and the EDSS utility weights.

Conclusion:
Delayed-release DMF is likely to increase QALYs for patients with relapsing forms of MS and be cost-effective compared with fingolimod and glatiramer acetate.

Introduction

Multiple sclerosis (MS) is a chronic, recurrent inflammatory disorder of the central nervous system characterized by periodic exacerbations accompanied or followed by progressive neurologic disability. MS generally is first diagnosed in young adults between 20–50 years of age, with the peak incidence at 30 years.
Life expectancy for those with MS may be reduced by 5–10 years compared to those without MS. The annual prevalence in the non-institutionalized US adult population has been estimated to be 0.21% based on the nationally representative Medical Expenditure Panel Survey (MEPS) data from 1998–2009. MS has a significant detrimental and highly debilitating effect on the lives of most patients over many years, with the disease lasting an average of 30 years. The average direct annual medical care costs per patient for those with a diagnosis of MS in the US were estimated to be $23,434 in 2009, varying with disease symptoms and other co-morbid conditions and accounting for the fact that many people with MS are not taking disease-modifying therapies (DMTs). DMTs that reduce the rate of relapse and slow disease progression in relapsing forms of MS account for the majority of the annual medical care costs.

Several DMTs are currently indicated for relapsing forms of MS, including the beta interferons, glatiramer acetate, natalizumab, delayed-release dimethyl fumarate, teriflunomide, and fingolimod. In randomized clinical trials, all these drugs have been shown to reduce the annualized risk for a relapse, and some have also been shown to slow disease progression, measured using the Kurtzke Expanded Disability Status Scale (EDSS). These drugs vary both in their efficacy and safety profiles and in their dosing formulations and convenience to patients.

Delayed-release dimethyl fumarate, the most recently approved oral drug, has been shown in a pooled analysis of two clinical trials to reduce the annualized relapse rate, slow disease progression, and reduce the rate of appearance of new brain lesions on a magnetic resonance image. In one of the clinical trials, glatiramer acetate was also included as a reference comparator and, in a post-hoc analysis, twice-a-day delayed-release dimethyl fumarate was shown to have greater efficacy for T2 lesions than glatiramer acetate and similar clinical efficacy. The most common adverse events associated with delayed-release dimethyl fumarate treatment were flushing and gastrointestinal events including diarrhea, nausea, and abdominal pain. Other safety signals of note included a decrease in mean white blood cell and lymphocyte counts and a transient increase in hepatic transaminases.

Because of the high costs associated with DMTs for MS, an economic evaluation for a new DMT, in addition to the efficacy and safety data, is an important piece of information for healthcare decision-makers. Many health plans in the US use estimates of the cost-effectiveness of a new drug as an input into their decision on whether to add the new drug to their formulary and what co-pays or co-insurance rates or other restrictions to apply. In this article we present the results of a cost-effectiveness analysis for delayed-release dimethyl fumarate compared with glatiramer acetate, a commonly used injectable DMT, and fingolimod, an oral DMT, for the treatment of relapsing-remitting multiple sclerosis (RRMS).

**Methods**

**Overview**

A Markov model was developed in which a cohort of patients with RRMS progressed through a series of disability states based upon the EDSS. The model structure was adapted from a previously developed UK model for delayed-release dimethyl fumarate DEFINE and CONFIRM clinical trials entered the model. In this cohort, ~60% of patients were treatment-naive, and 40% had previously received at least one DMT. Because delayed-release dimethyl fumarate is indicated for patients with relapsing forms of MS in the US without mention of previous treatments, this cohort is likely to be representative of those who might be prescribed the drug.

During the model time horizon patients could either progress to higher or lower EDSS states or remain in the same state at rates that depended on their EDSS state and the DMT treatment. Although no patients with secondary progressive MS (SPMS) were included in the DEFINE and CONFIRM clinical trials, in the model, patients could also progress to SPMS, where patients typically experienced fewer relapses but progressed to higher EDSS states at a faster rate than patients with RRMS. Patients who progressed to SPMS were assumed to enter the next stage of disease severity, as defined by the EDSS at the moment of transition.

Costs and utility values were assigned to each EDSS health state, as well as to adverse events (AEs) using published data or treatment algorithms. The model used efficacy data from all published trials and assumed discontinuation rates were the same for all DMTs and all patients who were still receiving a DMT discontinued it when their EDSS score reached 7. Patient mortality rate was assumed dependent on age, sex, and EDSS state (i.e., disease severity).

The effect of treatment was modeled by changes to the EDSS progression/regression risks and relapse rates and the associated changes in health state—related costs and utilities. The model used 1-year cycles and was programmed to provide estimates for any time horizon between 1–50 years, with a base case of 20 years. The model outcomes, costs, life-years, and quality-adjusted life-years (QALYs) per patient during the model time horizon were dependent on the time spent in each EDSS state, the incidence of MS relapses, AEs from treatment, and the DMT received.
as well as the time spent on treatment. A diagram of the model is shown in Figure 1.

**Setting and perspective**

The model was developed for the US and presents the results from a payer perspective including only direct medical and formal care costs.

**Population**

The RRMS population initiating treatment was assumed to match that included in the delayed-release dimethyl fumarate clinical trials DEFINE and CONFIRM. Patients with SPMS were excluded from these trials.

**Treatment comparisons**

The primary intervention in the model was a twice-daily regimen of delayed-release dimethyl fumarate. The two comparators used in the model were glatiramer acetate 20 mg once daily and fingolimod. Glatiramer acetate 40 mg three times weekly was used in an alternative scenario analysis.

**Input parameter values**

The model input parameters can be broadly classified into the following categories: population demographics; natural history parameters; treatment efficacy and safety and duration on treatment; costs; and utilities.

**Population demographics**

The population characteristics for the entering patient cohort included mean age, female-to-male ratio, and the distribution of EDSS scores at model entry. These characteristics were taken from the delayed-release dimethyl fumarate clinical trial data (DEFINE and CONFIRM) or from a US national survey (see Table 1). In these trials, ~60% of the patients were treatment naive and 40% had previously taken one or more DMTs.

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**Table 1. Cohort characteristics used in the delayed-release dimethyl fumarate cost-effectiveness model (all patients).**

| Demographic variable | Value | Source |
|----------------------|-------|--------|
| Cohort starting age  | 37.9  | Delayed-release dimethyl fumarate clinical trial data (DEFINE and CONFIRM) |
| Female/male ratio    | 3.27  | Campbell et al. (using the US MEPS database) |
| EDSS distribution    |       | Delayed-release dimethyl fumarate clinical trial data, intent-to-treat population |
|                      | EDSS 0: 5.05% | (delayed-release dimethyl fumarate twice daily, DEFINE and CONFIRM) |
|                      | EDSS 1: 8.52% |
|                      | EDSS 2: 34.08% |
|                      | EDSS 3: 22.94% |
|                      | EDSS 4: 20.64% |
|                      | EDSS 5: 8.65% |
|                      | EDSS 6: 0.12% |
|                      | EDSS 7: 0.00% |
|                      | EDSS 8: 0.00% |
|                      | EDSS 9: 0.00% |

EDSS, Expanded Disability Status Scale; MEPS, Medical Expenditure Panel Survey.
Natural history
To fully evaluate progression of disease without DMT, three independent annual transition probability matrices were used in the model: (1) transition matrix representing the probabilities of movement between EDSS states for the patient with RRMS (EDSS 0–9), (2) transition matrix representing the probabilities of the patient moving from RRMS to SPMS (EDSS 1–9), and (3) transition matrix representing the probabilities of movement between EDSS states for the patient with SPMS (EDSS 1–9). The natural history transition probability rates for patients with RRMS were shown in Supplementary Appendix A, Table A1. These transition probabilities were taken from the observed placebo data from the delayed-release dimethyl fumarate clinical trials (DEFINE and CONFIRM), supplemented with data from 806 patients with RRMS followed for an average of 34.7 years from 1972–2000 in the London Ontario Multiple Sclerosis registry. Alternative natural history disease progression rates were tested in the sensitivity analysis. The delayed-release dimethyl fumarate placebo transition rates for those with RRMS were used for EDSS states up through 7, and transition probabilities derived from the London Ontario registry data were used for EDSS states 8 and 9 because of the limited number of observations beyond EDSS 7 in the delayed-release dimethyl fumarate trials. The delayed-release dimethyl fumarate clinical trial placebo data indicated regression as well as progression in EDSS states in the population not receiving DMTs. The impact of excluding regression of the EDSS was tested in the sensitivity analysis. The probability of converting from RRMS to SPMS in each 1-year cycle was estimated using the time-to-SPMS data from the London Ontario database (see Supplementary Appendix A, Table A2). The transition probability matrix for patients with SPMS was also estimated using the data from the London Ontario database (Supplementary Appendix A, Table A3).

Annualized natural history relapse rates per person per year were taken from pooled baseline data from the delayed-release dimethyl fumarate clinical trials, which documented the annual relapse rate in the 12 months before enrollment in the studies. Data with adequate sample size were available only up to EDSS 5. Therefore, the relapse rate was computed using the relative risk of relapse in EDSS states 6–9 compared with the previous EDSS state from Patzold and Pocklington. The Patzold and Pocklington study followed 102 patients with MS for 2 years and documented relapse rates. The relapse rates for those with SPMS were also derived from Patzold and Pocklington, by adjusting them to reflect the higher relapse rates for those with RRMS in the DEFINE and CONFIRM clinical studies. The resulting annual relapse rates used in the model are shown in Supplementary Appendix A, Table A4. These represent the relapse rates that patients would experience if they were untreated with any DMT. Alternative natural history relapse rates were tested in the sensitivity analysis.

Finally, mortality rates in patients with MS have been shown to be significantly higher than those of the general population, including suicide as a significant cause of death. Age- and sex-specific all-cause mortality rates for the general population were taken from US life tables. These mortality rates were then adjusted upwards using the relative risk of death in an MS population compared with the general population taken from a study by Pokorski performed for an insurance company in the US (see Supplementary Appendix A, Table A5). The relative risk of death for those with MS compared with the general population in this study varied by EDSS state, ranging from 1.3 for those with EDSS 1 to 5.31 for those with EDSS 9. It was assumed that the increased probability of mortality by age and EDSS state was the same across the RRMS and SPMS populations.

Treatment efficacy and duration on treatment
The effect of treatment with the DMTs was included in the model in three ways: (1) treatment effect on disability progression (hazard ratio for disability progression rates relative to placebo), (2) treatment effect on annualized relapse rates (relative rate in comparison to placebo), and (3) treatment effect multiplier on conversion to SPMS (multiplier set to 0% in the base case, i.e., no treatment effect on conversion to SPMS). The first two types of efficacy inputs were derived for all the DMTs included in the model using a mixed-treatment comparison (MTC) analysis based on a systematic literature search to identify all randomized clinical trials of DMTs for MS. The disability progression hazard ratios and the rate of relapses relative to placebo for the DMTs included in the model are shown in Table 2. The trials included in these estimates are shown in Supplementary Appendix A, Table A6.

In the model, patients who discontinued from their initial therapy were assumed to take no further DMT. This assumption was made to be consistent with other published models of the cost-effectiveness of DMTs for RRMS, including the cost-effectiveness analysis sponsored by the US Agency for Healthcare Research and Quality (AHRQ) by Tappenden et al. In addition, we assumed that the DMT annual discontinuation rates are the same for all DMTs and equal to 10% for the first 2 years after starting treatment and then fall to 3% per year for the remaining 10 years. These discontinuation rates were used in the Tappenden et al. US cost-effectiveness analysis sponsored by the AHRQ. In the model, all patients still taking DMTs were assumed to stop treatment when their EDSS score reached 7 or above, although stopping treatment after conversion to SPMS if before EDSS reached 7 was tested in the sensitivity analysis.
Disease-modifying therapy and multiple sclerosis health state costs

DMT costs are reported in 2015 US dollars using published wholesale acquisition costs for April 8, 2015. Other MS-related medical care costs are reported in 2015 US dollars and were inflated to 2015 values where necessary using inflation indices for May 2015 from the Bureau of Labor Statistics. For each DMT, acquisition, administration, and monitoring costs were estimated in May 2015 US dollars. The annual acquisition cost was calculated using wholesale acquisition cost per pack for the anticipated dose multiplied by the number of expected packs used per year (see Supplementary Appendix A, Table A7). Annual acquisition costs were $66,612 for delayed-release dimethyl fumarate, $74,547 for daily glatiramer acetate, $65,103 for three times weekly glatiramer acetate, and $70,752 for fingolimod. Administration costs were assumed to be zero for the oral drugs and require some nurse education time for the injectable drug glatiramer acetate ($109.92 in year 1 and $36.64 in year 2) (see Supplementary Appendix A, Table A8). The annual cost of monitoring while on treatment was considered separately for the first year on treatment ($435.42 for delayed-release dimethyl fumarate, $342.38 for glatiramer acetate, $365.64 for fingolimod). The cost of monitoring was estimated from the expected resource use per patient per year on treatment, multiplied by the appropriate unit costs (see Supplementary Appendix A, Table A9).

The cost-effectiveness model takes into account two different types of MS disease-related costs: costs associated with disability progression through EDSS states, excluding the costs for DMTs, and an average incremental cost associated with an MS relapse. The base-case values for the direct costs (medical care + formal care costs) for each EDSS state were calculated using linear interpolation from the values estimated from a survey of 1909 US patients by Kobelt et al. using their values for EDSS 5, EDSS 4–6, and EDSS 4–6. In the model, the EDSS-related costs for those with RRMS or SPMS are assumed to be the same for the same EDSS state. The cost for a relapse was estimated to be $2217, based on an estimate of the difference in annual costs for those with and without a relapse in the Kobelt et al. US study, inflated to May 2015 US dollars.

Utilities

Utility weights for EDSS states without a relapse and during a relapse were derived from the delayed-release
dimethyl fumarate clinical trial data by pooling observations for each EDSS state (0–9) and calculating the mean EuroQol EQ-5D index score for each state. The resulting base-case values are shown in Table 4. SPMS utilities were derived from the delayed-release dimethyl fumarate clinical trial data adjusted for the relationship between RRMS and SPMS utilities estimated in the UK MS survey.\(^{31}\)

Adverse events

The annual costs and disutility associated with AEs for each DMT were estimated based on the percentage of people experiencing each type of AE, the percentage of those AEs that were serious, the costs for serious and non-serious AEs, and the disutility and duration of each AE. AEs were included in the model if they met the following criteria: the most common AEs listed on the delayed-release dimethyl fumarate label\(^ {15}\) (≥5% incidence in any treatment group of delayed-release dimethyl fumarate studies) or the common delayed-release dimethyl fumarate AEs on the label that have been reported in the published literature. AEs that had an incidence at least 3% higher in the total delayed-release dimethyl fumarate group than in the placebo group were also included, even if overall incidence in the delayed-release dimethyl fumarate arm was less than 5%. The AEs included for comparators were only those reported in delayed-release dimethyl fumarate studies, a conservative assumption. The proportion of each AE that was serious (grade 3 or 4) was also estimated using trial data. The incidence (and hence cost and disutility) of AEs was assumed to remain constant for all years that the patient continues to take the DMT.

The cost of treating each non-serious or serious AE that was included in the model was estimated from the expected resource use of treating a patient with a specific AE, taken from publicly available literature, validated by clinical expert opinion, and multiplied by appropriate unit costs and presented in May 2015 US dollars. In some situations—for example, where publicly available data were not available—a clinical expert who treats patients with MS provided the resource use estimates. The average annual cost for the treatment of all AEs for a patient on each DMT was estimated based on the estimates of annualized incidence of each AE, the proportion of AEs that were serious for that DMT, the cost for each serious AE, and the cost for each non-serious AE.

The disutility from AEs was obtained from a variety of sources or assumed where no data were available. The duration for each AE was based on clinical expert opinion. The average annual cost and QALYs lost attributable to AEs for each DMT are shown in Table 5. A detailed description of the methods and the input data used to estimate these values is provided in Supplementary Appendix B.

Model assumptions

To construct a valid and robust model, a series of assumptions were made where there were no readily accessible data or where data limitations restricted the scope and
flexibility of the disease pathway. Many of these have been mentioned in the sections above. They include: the assumption that those discontinuing treatment do not switch to another DMT, but follow natural history disease progression; no direct impact of treatment on conversion to SPMS or mortality but an indirect effect through the estimated delay in disease progression; and relapse treatment cost and utility loss not variable by EDSS state. A comprehensive list of the model assumptions is shown in Supplementary Appendix A, Table A10.

**Base-case and sensitivity analyses**

The following outcomes were estimated by the model: total costs, QALYs, and life-years; incremental costs, QALYs, and life-years gained; and incremental cost per QALY gained for the base-case input parameter values. In line with common US practice, a base-case discounting rate of 3.0% was applied to both costs and outcomes in the cost-effectiveness model.

To evaluate the effect of parameter uncertainty on the cost-effectiveness estimates, one-way and probabilistic sensitivity analyses were performed. The one-way sensitivity analysis tested the sensitivity of the results to changes in specific variables as follows:

1. alternative estimates of delayed-release dimethyl fumarate treatment efficacy for disease progression and relapse using the 95% confidence interval estimates from the MTC analysis (see Table 2);
2. inclusion of informal care costs or informal care costs plus productivity losses in addition to direct medical and formal care costs for each EDSS state (see Table 3);
3. alternative values of the direct costs associated with each EDSS state, increasing and decreasing these values by 10%;
4. alternative estimates of the cost of a relapse, $5704 (in May 2015 US dollars), using the estimate presented in Goldberg et al., based on treatment algorithms for a mild, moderate, and severe relapse developed by O’Brien et al.;
5. alternative annual costs of delayed-release dimethyl fumarate, increasing and decreasing these costs by 10%;
6. alternative assumptions about natural history rates of disease progression assuming either no regression of EDSS for the trial-based estimates or using only data from the London Ontario survey;
7. alternative assumptions about natural history relapse rates using the Patzold and Pocklington rates (see Supplementary Appendix A, Table A11);
8. alternative utility values for EDSS states using the estimates from the Kobelt et al. study (the Kobelt US survey estimated a decrease of 0.094 in utility during a relapse, and utility values by EDSS were not presented separately for those with RRMS and SPMS [see Supplementary Appendix A, Table A11]);
9. assuming no costs or QALY losses associated with AEs;
10. assuming a 50 year time horizon instead of 20 years; and
11. assuming no transition from RRMS to SPMS until EDSS 3.

The probabilistic sensitivity analyses tested the sensitivity of the results in 1000 iterations allowing simultaneous changes in all the input parameter values using the following distributions: log-normal distributions for the efficacy parameters; gamma distributions for the cost inputs; log-normal distributions for treatment and AE disutility estimates and natural history relapse rates; and beta distributions for AE rates, discontinuation rates, and rates of transferring from RRMS to SPMS. For the efficacy parameters, the 95% confidence limits from the MTC were used to estimate the variability. For the other input parameters, a standard error of 10% was assumed.

**Results**

Results of the base-case analysis are shown in Table 6, with delayed-release dimethyl fumarate compared with glatiramer acetate, once daily and fingolimod. Base-case results with a 20-year time horizon indicated that delayed-release dimethyl fumarate was less costly and produced more QALYs than both fingolimod (−$33,059, +0.359 QALY) and glatiramer acetate, once a day (−$70,810, +0.450 QALY).

Results of the sensitivity analysis of delayed-release dimethyl fumarate compared with glatiramer acetate once a day and fingolimod are shown in Figure 2 and Table 7, respectively. The impact of delayed-release dimethyl fumarate on the disability progression rate, the use of the Kobelt utility values and the model time horizon had the greatest impact on the incremental QALYs for both comparisons. The acquisition cost for delayed-release dimethyl fumarate and including informal care and productivity losses in the EDSS state costs had the greatest impact on the incremental costs for both comparisons. The results of the probabilistic sensitivity analysis showed that, compared with fingolimod or glatiramer acetate once a day, there was at least a 98% probability that delayed-release dimethyl fumarate was the cost-effective treatment at all threshold levels.

**Discussion**

The results of the base-case analysis comparing treatment of RRMS with delayed-release dimethyl fumarate with
treatment with glatiramer acetate or fingolimod indicated that use of delayed-release dimethyl fumarate would result in an increase in quality-adjusted life years with a decrease in total treatment costs, including the cost of the DMT, over a 20-year time horizon. In an extensive one-way sensitivity analysis, the results were most sensitive to the acquisition cost of delayed-release dimethyl fumarate, the cost categories (direct costs, informal care costs, productivity costs) included in the disease-related costs, the efficacy of delayed-release dimethyl fumarate, and EDSS

Table 6. Discounted (3.0%) cost-effectiveness model outcomes per patient: 20-year costs and QALYs.

| Drug                 | Total cost (USD) | Total life-years* | Total QALYs | Incremental costs | QALYs gained | ICER (Cost/QALY) |
|----------------------|------------------|-------------------|-------------|-------------------|--------------|------------------|
| Delayed release DMF  | $850,332         | 14.200            | 6.856       | NA                | NA           | NA               |
| Glatiramer acetate   | $921,142         | 14.172            | 6.406       | -$70,810          | 0.450        | DMF dominant‡   |
| Fingolimod           | $883,391         | 14.176            | 6.497       | -$33,059          | 0.359        | DMF dominant‡   |

DMF, delayed-release dimethyl fumarate; DMT, disease-modifying therapy; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality-adjusted life-years; USD, United States dollars.

*20 life-years discounted at 3% is equal to 15.32 discounted life-years.
‡DMF is less costly and more effective (lower-right quadrant in the cost-effectiveness plane).

Figure 2. Sensitivity analysis: delayed-release dimethyl fumarate compared with glatiramer acetate.
utility weights. Our results for the comparison with fingolimod are similar to those estimated by Zhang et al.34. This economic evaluation use a Markov model with a shorter (5-year) time horizon to estimate the cost-effectiveness of delayed-release dimethyl fumarate compared with fingolimod and teriflunomide, and showed that delayed-release dimethyl fumarate had lower costs ($39,802 compared with fingolimod and $25,940 vs teriflunomide) and higher quality-adjusted life years (0.03 compared with fingolimod and 0.04 vs teriflunomide).

Several studies have shown that the economic burden of patients with MS increases with increasing levels of disability.30,33,35 The economic burden of MS includes both direct medical care and formal care (e.g., nursing home and home help) costs, as well as informal care costs by family members or friends and productivity losses for the patient and, possibly, also for family members.4,30,36,37 In the Kobelt et al.30 US survey, direct costs, other than those for DMTs, made up 29% of the total annual costs of MS, and informal care cost and productivity losses made up 37% of the total annual costs. Treatment with DMTs that can slow the rate of disease progression will prolong the time during which the patient is able to be functionally independent and is likely to reduce both the direct costs of care for MS symptoms and the costs associated with informal care and productivity losses.

There are several strengths in the modeling approach used in this article. First, we have presented the results of a detailed economic evaluation of delayed-release dimethyl fumarate compared with two other commonly prescribed DMTs for RRMS that was designed to meet the recently published ISPOR Task Force guidelines for cost-effectiveness analysis.38 The cost-effectiveness analysis used a Markov model structure and assumptions that have been used extensively in RRMS. Second, since the clinical trials for DMTs for MS included both placebo-controlled studies and active-comparator studies, a formal MTC analysis was performed based on a systematic literature search to identify all published clinical data. The results of this analysis were used to estimate reduction in annualized risk of relapse and the hazard ratio for disease progression for the DMTs compared in this analysis.

Limitations

Limitations in the modeling approach include the lack of long-term data for the more recently approved DMTs. Thus, assumptions were needed about long-term efficacy and safety and discontinuation rates for delayed-release dimethyl fumarate, fingolimod and 3-times weekly glatiramer acetate. Our sensitivity analyses indicated that the results would be sensitive to these assumptions.

Our focus on adverse events that were associated with delayed release dimethyl fumarate might have resulted in the omission of some adverse events associated only with fingolimod or glatiramer acetate. Our sensitivity analysis indicated that our results changed very little when adverse events were excluded from the analysis.

Finally, after discontinuation, the model did not include the possibility of switching to a second DMT, but assumed return to symptomatic treatment only.
This allowed us to isolate the impact of the initial treatments being compared but did not provide any information on the optimal sequencing of treatments for those with RRMS. Currently data are not available indicating how response to treatment differs depending on the sequence in which the treatment is used.

Conclusions

Delayed-release dimethyl fumarate is likely to increase QALYs for patients with relapsing forms of MS and be cost-effective compared with other commonly used DMTs.

Transparency

Declaration of funding

The study was sponsored by Biogen, Inc. and funding provided to RTI Health Solutions to develop the model. Employees from Biogen worked collaboratively with RTI Health Solutions to design the model, collect the input data, interpret the results and prepare the manuscript.

Declaration of financial/other relationships

JM is an employee of RTI Health Solutions, a consulting company that received funding from Biogen, the manufacturer of delayed-release dimethyl fumarate, to develop the cost-effectiveness model. RI, MF, SS, and TL are employees of Biogen Idc. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Supplementary material is available online.