Relapses Requiring Intravenous Steroid Use and Multiple-Sclerosis–related Hospitalizations: Integrated Analysis of the Delayed-release Dimethyl Fumarate Phase III Studies

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ABSTRACT

Purpose: The purpose was to report the effects of delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) on the number of relapses requiring intravenous (IV) steroids and multiple sclerosis (MS)-related hospitalizations using integrated data from the Phase III DEFINE and CONFIRM studies.

Methods: DEFINE and CONFIRM were randomized, double-blind, placebo-controlled, multicenter studies that evaluated the efficacy and safety of DMF over a 2-year period in patients with relapsing-remitting MS (RRMS). Patients were randomized (1:1:1) to receive oral DMF 240 mg BID or TID, placebo, or glatiramer acetate (CONFIRM only). Eligible subjects (aged 18–55 years) had an EDSS score of 0-5.0 and experienced either ≥1 relapse in the 12 months or had ≥1 gadolinium-enhanced lesion on brain MRI in the 6 weeks, before randomization. Data DEFINE and CONFIRM were pooled and analyzed using a negative binomial regression model (adjusted for study and region). Data obtained after subjects switched to an alternative MS therapy were not included in the analysis. Only relapses confirmed by the Independent Neurology Evaluation Committee were included in the analysis of relapses requiring IV steroids.

Findings: The study population (intention-to-treat) comprised 2301 patients who received either placebo (n = 771), DMF BID (n = 769), or DMF TID (n = 761). Baseline demographic and disease characteristics were generally well balanced among treatment groups. Throughout the 2-year studies, the total number of relapses treated with methylprednisolone was 402, 221, and 209 in the placebo, DMF BID, and DMF TID groups, respectively. A smaller proportion of patients in the DMF BID (168 of 769 [21.8%]) and DMF TID (151 of 761 [19.8%]) groups experienced ≥1 relapse requiring IV steroids compared with the placebo group (284 of 771 [36.8%]). The total number of MS-related hospitalizations over 2 years was 136, 94, and 74 in the placebo, DMF BID, and DMF TID groups. A smaller proportion of patients in the DMF BID (73 of 769 [9.5%]) and DMF TID (57 of 761 [7.5%]) groups had ≥1 MS-related hospitalization compared with the placebo group (104 of 771 [13.5%]).

Implications: DMF is an effective and well tolerated therapy for RRMS. In addition to clinical benefits, the use of DMF may be associated with reduced patient burden and health economic savings, resulting from a decrease in resource utilization associated with relapses. ClinicalTrials.gov identifiers: NCT00420212 and NCT00451451. (Clin Ther. 2015;37:2543–2551) © 2015 Elsevier HS Journals, Inc. All rights reserved.
Key words: costs, dimethyl fumarate, hospitalization, methylprednisolone, multiple sclerosis, relapse.

INTRODUCTION

Multiple sclerosis (MS) is 1 of the most commonly occurring neurologic disorders in young adults and affects in excess of an estimated 2.3 million people worldwide. The disease process involves several components, which include inflammation, demyelination, and neuronal and axonal degeneration. The pathology of MS manifests clinically in many different ways, including abnormalities of vision and eye movement, fatigue, pain, limb spasticity, bowel and bladder dysfunction, and cognitive changes.

The most common form of MS is relapsing-remitting MS (RRMS), which occurs in ~85% of newly diagnosed patients. RRMS is characterized by relapses (also known as exacerbations or attacks) that can last for weeks or months, during which several locations in the brain, optic nerves, and spinal cord may be affected. Acute relapses are often considered to be short-term increases in disability that subsequently resolve; however, some evidence suggests that relapses are associated with incomplete recovery and worsening disability. If a relapse requires management with steroid therapy or the patient needs to be hospitalized, it is likely that the relapse will be more severe and may have a long-term or even permanent negative impact on the patient’s functional ability. The resulting costs can be significant to both the patient and to the insurer; it has been estimated that the cost associated with managing a relapse in an outpatient setting in the United States is increased ~6-fold for patients requiring inpatient care. Therefore, a therapeutic agent that reduces the frequency and severity of relapses and slows the rate of disease progression is likely to have an additional positive impact on both the personal and overall economic burden of MS.

Delayed-release dimethyl fumarate (DMF; also know as gastro-resistant DMF), is indicated for the treatment of patients with relapsing MS in the United States and for RRMS in the European Union. It is thought that DMF elicits both anti-inflammatory and cytoprotective effects that are beneficial in patients with MS. Regulatory approval for DMF was granted on the basis of results from 2 Phase III clinical studies: DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis; ClinicalTrials.gov identifier, NCT00420212) and CONFIRM (Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis; ClinicalTrials.gov identifier, NCT00451451). In addition to the individual studies, an integrated analysis of data from DEFINE and CONFIRM was conducted to provide a more precise estimate of the treatment effect of DMF versus placebo.

In the individual DEFINE and CONFIRM studies, treatment with DMF compared with placebo significantly reduced the number of relapses that required intravenous (IV) steroid therapy. Furthermore, fewer MS-related complications required hospitalization in the DMF groups (Clinical Study Reports for the DEFINE and CONFIRM Phase III studies). The present article reports the results from the prespecified integrated analysis, which allows for a more precise estimate of the therapeutic effect of DMF than can be obtained from either study in isolation.

We evaluated both the number of relapses requiring IV steroid treatment and the number of hospitalizations related to MS in each treatment group.

PATIENTS AND METHODS

Patients

Patients eligible for enrollment into both DEFINE and CONFIRM have been described in detail elsewhere. Briefly, patients were aged 18 to 55 years with a diagnosis of RRMS that was made in accordance with the 2005 McDonald diagnostic criteria. Subjects were also required to have an Expanding Disability Status Scale score of 0 to 5.0 and to have experienced ≥1 relapse in the 12 months before randomization or had ≥1 gadolinium-enhanced lesion on brain magnetic resonance imaging in the 6 weeks before randomization. Subjects were excluded from DEFINE and CONFIRM if they had a progressive form of MS, another significant illness, or any prespecified abnormal laboratory parameters.
Subjects were ineligible if they had experienced a relapse or received corticosteroid therapy within 50 days before randomization. Previous treatment with glatiramer acetate, either within the past 3 months (in the DEFINE study) or at any time (in the CONFIRM study), was also a key exclusion criterion.

**Study Design**

DEFINE and CONFIRM were Phase III, randomized, double-blind, placebo-controlled, multicenter studies designed to evaluate the efficacy and safety of DMF over a 2-year period in patients with RRMS. Patients were randomized equally (1:1:1 ratio) to receive oral DMF at a dosage of 240 mg BID or TID, or matching placebo. CONFIRM included an additional active reference comparator arm (glatiramer acetate 20 mg SC once daily); however, these data were not included in the integrated analysis of health care utilization because glatiramer acetate was not used as a reference comparator in DEFINE.

The number of relapses requiring IV steroids and the number of MS-related hospitalizations were tertiary end points in DEFINE and CONFIRM. In both studies, IV methylprednisolone (1000 mg/d for 3 or 5 days) was used at the discretion of the treating neurologist to manage protocol-defined relapses in patients receiving DMF or placebo.

The DEFINE and CONFIRM study protocols were approved by the ethics committees of all participating institutions. The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice. All subjects were informed of approved MS therapies and provided their written informed consent before participating in the studies. Re-consent was obtained in the event of a confirmed relapse or disability progression.

**Prespecified Integrated Analysis**

The integrated analysis plan was finalized before unblinding of CONFIRM. Data were to be pooled only if baseline characteristics and treatment effects were consistent across DEFINE and CONFIRM. The annualized relapse rate for relapses requiring IV steroids was calculated as the total number of relapses requiring IV steroids for all subjects divided by the total number of subject-years used in the studies. The annualized rate for relapses resulting in MS-related hospitalizations was calculated in a similar manner.

Changes in the rates of relapses requiring IV steroids and MS-related hospitalizations with DMF versus placebo were analyzed by using a negative binomial regression model, adjusted for study and region. Only relapses confirmed by the Independent Neurology Evaluation Committee were included in the analysis of relapses requiring IV steroids. If patients switched to alternative MS medications, data obtained after the switch were not included in the analyses.

**Post Hoc Analysis**

An economic simulation model was developed to estimate the direct relapse-related medical costs (an analysis of direct medical costs was not included) of delayed-release DMF BID and TID treatment versus placebo; the model was based on frequency of MS relapses, relapse-related hospitalizations, and use of IV steroids after relapse. For frequency of MS relapses, the event rate for placebo (0.371) and the rate ratios for the DMF BID (0.515) and DMF TID (0.515) groups were obtained from the integrated efficacy analysis of DEFINE and CONFIRM at 2 years. The severity of relapse among those requiring steroids or among the MS-related hospitalizations was not considered in the analysis. For relapse-related hospitalizations and IV steroids use, event rates and rate ratios were also obtained from the prespecified integrated analysis of DEFINE and CONFIRM, as described here. Event costs were obtained from the literature from studies conducted by using US patient populations in retrospective claims databases (Table I). The costs of IV steroids were estimated based on 5 days of IV methylprednisolone treatment and a physician office visit. Probabilistic estimates were obtained via sampling model parameters by using SEs and appropriate distributions over 1000 simulations.

**RESULTS**

**Patient Characteristics**

In total, data from 2301 patients (the intention-to-treat population) were included in the integrated analysis. Of these, 769, 761, and 771 patients received DMF BID, DMF TID, or placebo, respectively. Table II presents the baseline demographic and disease characteristics for patients in the DEFINE and CONFIRM studies, both individually and for the pooled patients included in the integrated analysis. These characteristics were generally consistent between

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the 2 studies and were well balanced among the treatment groups.

Relapses Requiring IV Steroid Therapy at 2 Years

Over a 2-year period, the total number of relapses treated with IV methylprednisolone was 402, 221, and 209 in the placebo, DMF BID, and DMF TID groups, respectively. Fewer patients in the DMF BID (168 of 769 [21.8%]) and DMF TID (151 of 761 [19.8%]) groups experienced ≥1 relapse requiring IV steroid treatment compared with the placebo group (284 of 771 [36.8%]). The adjusted annualized rate of relapses requiring treatment with IV steroids at 2 years was also significantly lower in the DMF BID and DMF TID groups versus the placebo group (Figure 1), with reductions of 48% (rate ratio, 0.52 [95% CI, 0.43–0.64]) and 50% (rate ratio, 0.50 [95% CI, 0.41–0.61]) for the DMF BID and DMF TID groups, respectively (P < 0.0001 vs placebo for both comparisons).

MS-Related Hospitalizations at 2 Years

Over the 2-year study period, there were 136 hospitalizations in the placebo group, 94 in the DMF BID group, and 74 in the DMF TID group. A smaller proportion of patients in the DMF BID (73 of 769 [9.5%]) and DMF TID (57 of 761 [7.5%]) groups had ≥1 MS-related hospitalization compared with the placebo group (104 of 771 [13.5%]). The adjusted annualized rate of MS-related hospitalizations at 2 years was also lower in the DMF treatment groups versus the placebo group (Figure 2), with reductions of 34% (rate ratio, 0.66 [95% CI, 0.47–0.92]) in the DMF BID group (P = 0.0146 vs placebo) and 47% (rate ratio, 0.53 [95% CI, 0.37–0.75]) in the DMF TID group (P = 0.0004 vs placebo).

Annualized Relapse-Related Costs

Relative to placebo, DMF BID would be expected to annually reduce the costs of relapses, hospitalizations, and IV steroids by $2542, $278, and $76, respectively, per patient; DMF TID would be expected to reduce these respective annual costs by $2449, $397, and $78. In the probabilistic analysis, compared with placebo, both dose frequencies had >99.9% probability of reducing annualized relapse-related costs.

DISCUSSION

In addition to their impact on quality of life and long-term disability progression, MS relapses add significantly to the already high economic burden of this disease. A retrospective, US-based study found that mean all-cause health care costs for 1411 patients with MS during the first year after diagnosis alone were more than 4.5-fold higher than costs in a matched comparator group of 7055 healthy individuals ($18,829 vs $4038, respectively).23 The increase in economic burden can be substantial during periods of high relapse activity.10,12,24,25 A review of the literature by Naci et al found that almost all types of cost increased markedly during periods of relapses; the most notable of these were costs associated with inpatient admissions, ambulatory visits, informal care, and short-term sick leave.13

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Table I. Costs of MS-related resource utilization.

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost</th>
<th>SE</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS hospitalization</td>
<td>$17,512 (2013 US$)</td>
<td>$1724</td>
<td>19, 20</td>
</tr>
<tr>
<td>Office visit</td>
<td>$73</td>
<td>NA</td>
<td>21</td>
</tr>
<tr>
<td>IV methylprednisolone (5 days at 500 mg/d)</td>
<td>$53</td>
<td>NA</td>
<td>22</td>
</tr>
<tr>
<td>IV administration (5 days at $75.53/administration)</td>
<td>$378</td>
<td>NA</td>
<td>21</td>
</tr>
<tr>
<td>MS relapse</td>
<td>$13,735 (2013 US$)</td>
<td>$894</td>
<td>19, 20</td>
</tr>
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</table>

IV = intravenous; MS = multiple sclerosis; NA = not applicable.
The severity of individual relapses is also associated with increased resource utilization and higher costs. A recent study of data from a US insurance claims and employee disability database (N = 9421) found that the annual incremental direct costs for a low or moderate severity relapse were $8269 (95% CI, 6565–10,115) compared with $24,180 (95% CI, 20,263–28,482) for a high severity relapse. Furthermore, the costs-per-patient for treating relapses have increased over recent years. A US-based study of acute hospitalization costs for patients with MS found that total costs for inpatient care had risen from $184 million in 1993 to $445 million in 2006.

In light of the rising health care burden, there is a growing need to develop therapies that can reduce the cost of relapses to patients and payers. DMF is an orally administered treatment that has shown efficacy as first-line therapy for patients with RRMS. In the Phase III DEFINE and CONFIRM trials, DMF significantly reduced the annualized relapse rate and risk of relapse at 2 years compared with placebo. DMF also had significant effects on neuroradiologic measures, as well as an acceptable safety and tolerability profile. In addition, an integrated analysis of data from DEFINE and CONFIRM found that DMF significantly reduced the risk of 12- and 24-week confirmed disability progression at 2 years. The results from our integrated analysis add to these findings by showing that, compared with placebo, DMF significantly reduced both the number of relapses requiring IV steroids and the number of MS-related hospitalizations. This finding corroborates the results of the analyses of relapse rates and indicates a beneficial effect on clinical measures of disease activity.

The severity of relapse was not considered in this analysis. However, both the number of relapses requiring IV steroids (which may reflect relapses of greater severity than minor relapses) and the number of MS-related hospitalizations (which may be used as a surrogate for relapses of even greater severity) can serve as indicators of relapse severity. The results from this integrated analysis show that the effect of DMF on these outcomes was of the same magnitude; therefore, the effect was similar regardless of the grade of severity of relapses (ie, there was no preferential effect on relapses that were mild/minor). Accordingly, smaller proportions of DMF-treated patients than patients receiving placebo experienced either ≥1 relapse requiring steroids or ≥1 MS-related hospitalization.

When modeled, the difference in clinical efficacy between DMF and placebo observed in the integrated

<table>
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<th>Characteristic</th>
<th>DEFINE</th>
<th>CONFIRM</th>
<th>Pooled Analysis</th>
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<tr>
<td>Placebo</td>
<td>75</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>DMF BID</td>
<td>38.5 (9.1)</td>
<td>38.1 (9.1)</td>
<td>38.8 (8.8)</td>
</tr>
<tr>
<td>DMF TID</td>
<td>38.5 (6.8)</td>
<td>38.8 (5.8)</td>
<td>38.5 (5.8)</td>
</tr>
<tr>
<td>Time since first MS symptoms, y</td>
<td>8.5 (6.8)</td>
<td>8.5 (6.8)</td>
<td>8.5 (6.8)</td>
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<tr>
<td>Time since MS diagnosis, y</td>
<td>7.8 (6.5)</td>
<td>7.8 (6.1)</td>
<td>7.8 (6.1)</td>
</tr>
<tr>
<td>Prior approved MS treatment, %</td>
<td>42</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Relapses in year before study</td>
<td>1.3 (0.7)</td>
<td>1.3 (0.7)</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>EDSS score</td>
<td>2.5 (1.2)</td>
<td>2.4 (1.3)</td>
<td>2.4 (1.3)</td>
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</table>

**Note:**
- **DEFINE** = Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis; **CONFIRM** = Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis; **DMF** = delayed-release dimethyl fumarate; **MS** = multiple sclerosis; **EDSS** = Expanded Disability Status Scale.
- Interferon β-1a, interferon β-1b, natalizumab, or glatiramer acetate.
Figure 1. Rate of Relapses Requiring IV Steroid Therapy at 2 Years. Adjusted annualized rate of relapses requiring IV steroids (95% confidence interval [CI]) at 2 years in the placebo and DMF BID and TID groups. Negative binomial regression, adjusted for study and region. BID = twice daily; IV = intravenous; TID = 3-times daily. *P < 0.0001 vs placebo; †DMF = delayed-release DMF (also known as gastro-resistant DMF).

Figure 2. Rate of MS-Related Hospitalization at 2 Years. Adjusted annualized rate of MS-related hospitalization (95% CI) at 2 years in the placebo and DMF BID and TID groups. Negative binomial regression, adjusted for study and region. BID = twice daily; TID = 3-times daily. *P < 0.05, †P < 0.001 vs placebo; ‡DMF = delayed-release DMF (also known as gastro-resistant DMF).
analysis suggests that treatment with DMF can reduce costs associated with MS complications. These reductions in resource utilization may translate into real-world cost savings.

The present study did have some limitations. For both the integrated analysis and the economic modeling analysis, the data were obtained from Phase III studies that lasted for only 2 years. To obtain a more accurate picture of the long-term cost savings that may be achieved by using DMF, similar analyses conducted over a much longer time frame will be necessary. The ongoing ENDORSE (A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis; ClinicalTrials.gov identifier, NCT00835770) study is an 8-year extension of the DEFINE and CONFIRM studies. Once the results of this study become available, the effect of DMF on the long-term costs associated with the treatment of relapses can be estimated. Another limitation is that despite the many similarities between the DEFINE and CONFIRM studies (eg, study design, patient baseline demographic and disease characteristics, treatment history, treatment effects), there were some notable differences, such as the different options for discontinuing study treatment and initiating therapy with an approved, open-label, alternative MS medication due to 1 or multiple confirmed relapses. Finally, the DEFINE and CONFIRM studies enrolled relatively healthy patients with MS; for example, both studies excluded patients with other clinically significant illnesses. As a result, the data used in any subsequent analyses are not representative of the overall MS patient population, and the impact of DMF across a broader population is currently unknown.

CONCLUSIONS
The findings from this integrated analysis further support the efficacy of DMF in preventing relapses across different grades of severity. They suggest that DMF may have additional benefits in terms of reducing costs by decreasing health care resource utilization associated with relapses in patients with RRMS.

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AUTHOR CONTRIBUTIONS
Dr. Giovannoni, Dr. Gold, Dr. Fox, Dr. Kappos and Dr. Kita served on the steering committee, contributed to the conception and design of the study, participated as an investigator and collected data, interpreted the data, and reviewed the manuscript. Ms. Yang served on the steering committee, contributed to the conception and design of the study, analyzed the data, interpreted the data, and reviewed the manuscript. Dr. Sarda and Dr. Viglietta interpreted the data, and reviewed the manuscript. Dr. Zhang analyzed and interpreted the data and reviewed the manuscript. Dr. Havrdova: participated as an investigator and collected data, interpreted the data, and reviewed the manuscript.

CONFLICTS OF INTEREST
Biogen reviewed and provided feedback on the manuscript to the authors. The authors had full editorial control of the manuscript, and provided their final approval of all content.

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REFERENCES


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