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;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Accepted for publication September 23, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.09.011
0149-2918/$ - see front matter

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.[1,2] The disease process involves several components, which include inflammation, demyelination, and neuronal and axonal degeneration.[3] 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.[4]

The most common form of MS is relapsing-remitting MS (RRMS), which occurs in ~85% of newly diagnosed patients.[5,6] 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.[6] 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.[7,8] 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.[9] 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.[10–13]

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.[14] 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).[15,16] 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.[17] Compared with placebo, DMF 240 mg BID and DMF 240 mg TID significantly reduced the annualized relapse rate by 49% and 49%, respectively (both, $P < 0.0001$). Furthermore, both doses of DMF significantly reduced the risk of relapse and 12- and 24-week confirmed disability progression over 2 years versus placebo.

In the individual DEFINE and CONFIRM studies,[15,16] 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.[15,16] Briefly, patients were aged 18 to 55 years with a diagnosis of RRMS that was made in accordance with the 2005 McDonald diagnostic criteria.[18] 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.[15,16] Subjects were excluded from DEFINE and CONFIRM if they had a progressive form of MS, another significant illness, or any prespecified abnormal laboratory parameters.