Tolerability and Pharmacokinetics of Delayed-Release Dimethyl Fumarate Administered With and Without Aspirin in Healthy Volunteers☆

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ABSTRACT

Background: Delayed-release dimethyl fumarate (DR-DMF) has cytoprotective and antiinflammatory properties and has recently been approved in the United States as an oral treatment for relapsing forms of multiple sclerosis. The most common adverse events associated with DR-DMF are flushing and gastrointestinal (GI) events, the incidences of which diminish over time.

Objective: The purpose of this study was to evaluate the tolerability and pharmacokinetic (PK) profile of DR-DMF with or without concomitant acetylsalicylic acid (aspirin), a cyclooxygenase inhibitor.

Methods: Healthy volunteers (N = 56) were randomized to receive different dosing regimens of DR-DMF or matching placebo with or without pretreatment with 325 mg aspirin for 4 days. Plasma levels of the active metabolite monomethyl fumarate were assessed on days 1 and 4. Flushing and GI events were assessed using patient-reported scales. Potential flushing mediators were explored.

Results: DR-DMF showed a safety, tolerability, and PK profile consistent with previous clinical experience, with no evidence of accumulation. Pretreatment with aspirin had no effect on the primary PK parameters, $AUC_{0–10h}$, or C_{max}. Flushing severity, assessed by 2 subject-reported rating scales, was generally mild and was rated highest at the start of treatment. Pretreatment with aspirin reduced flushing incidence and intensity without affecting GI events or the PK profile of DR-DMF. In some DR-DMF–treated individuals, plasma concentrations of a prostaglandin D_2 (PGD_2) metabolite were increased.

Conclusions: In healthy volunteers, DR-DMF was well tolerated over 4 days of dosing, with a PK profile consistent with that previously reported and no evidence of accumulation. Aspirin pretreatment reduced the incidence and intensity of flushing without affecting GI events or the DR-DMF PK profile. Elevated levels of PGD_2 in some DR-DMF–treated individuals suggest that flushing may be, at least in part, prostaglandin mediated. ClinicalTrials.gov identifier: ID: NCT01281111. (*Clin Ther*. 2013;35:1582–1594)

Key words: dimethyl fumarate, flushing, multiple sclerosis, prostaglandin D_2.

INTRODUCTION

Delayed-release dimethyl fumarate (DR-DMF) is an oral treatment recently approved in the United States for

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relapsing forms of multiple sclerosis (MS),[1] a chronic disease of the central nervous system that may cause permanent disability.[2,3] The pharmacodynamic effects of DR-DMF appear to be mediated predominantly via activation of the nuclear factor (E2-related factor 2) (Nrf2) antioxidant response pathway, which up-regulates key molecules that allow cells to respond to inflammatory or oxidative stress[4] by promoting protective antiinflammatory and cytoprotective responses. In a variety of preclinical models, activation of the Nrf2 pathway has demonstrated neuroprotection in vitro and in vivo.[5]

Previous pharmacokinetic (PK) studies of DR-DMF demonstrated that DR-DMF is rapidly metabolized presystemically to the primary metabolite monomethyl fumarate (MMF) and that MMF exposure is dose-proportional with high intersubject variability. After single ascending doses of DR-DMF (120, 240, and 360 mg), mean (SD) C_{max} (C_{max} of MMF) were 0.58 (0.17), 1.43 (0.29), and 1.90 (0.57) μg/mL, respectively, with corresponding MMF AUC of 1.21 (0.37), 2.41 (0.58), and 3.78 (1.11) μg · h/mL, respectively (Biogen Idec data on file; Study IKP/ID 33). There was no evidence of accumulation after multiple doses (either 120 or 240 mg DR-DMF given TID for 2 days) in a cross-over study, with MMF concentrations below detectable limits at the end of both days 1 and 2 (Biogen Idec data on file; Study FG-PK-03/04).

In 2 recently completed, 2-year, Phase III studies in patients with MS, DEFINE (Efficacy and Safety of Oral BG-12 in Relapsing-Remitting Multiple Sclerosis; NCT00420212) and CONFIRM (Efficacy and Safety Study of Oral BG-12 With Active Reference in Relapsing-Remitting Multiple Sclerosis; NCT00451451), DR-DMF 240 mg given BID or TID resulted in significant improvements in clinical and neuroradiologic measures of MS disease activity accompanied by acceptable safety and tolerability compared with placebo.[6,7] The most commonly reported adverse events (AEs) in the Phase III MS studies were flushing and gastrointestinal (GI) events (mild or moderate for most patients).[6,7]

In general, the term "flushing" describes temporary symptoms occurring mainly on the face and neck, including redness, itching, tingling, and warmth sensation of the skin. Flushing may occur as a normal physiologic response to increased temperature, exercise, or consumption of spicy foods and in association with various conditions (allergic reactions, carcinoid tumors, and menopause), and medications (including niacin and selective serotonin reuptake inhibitors). Flushing is caused by vasodilation of small skin capillaries and can be mediated by different molecules, including histamine, bradykinin, serotonin, and prostaglandins.[8–12]

Although the mechanism underlying DR-DMF–induced flushing is not well understood, certain features, such as a comparable clinical course and timing, suggested that it may be similar to the niacin-induced mechanism of flushing. Flushing is a common side effect of niacin therapy, and it usually subsides with continued use.[13] Several studies have shown that niacin-induced flushing is mediated via prostaglandin (PG) release (including PGD_2 and PGE_2) from epidermal Langerhans cells[11,12,14,15] and keratinocytes.[16,17] If DR-DMF–induced flushing were mediated by PG, a known inhibitor of PG synthesis, aspirin (acetylsalicylic acid), would be expected to reduce the incidence and/or intensity of flushing. The present study was designed to evaluate the tolerability and PK profile of DR-DMF after 4 days of dosing and to evaluate and characterize flushing and GI events with and without 325 mg aspirin given 30 minutes before DR-DMF dosing.

METHODS

Study Design

This was a randomized, double-blind, placebo-controlled study in healthy adult volunteers. A total of 56 subjects were randomized; 8 groups of 6 subjects were assigned to receive 4 days of treatment with DR-DMF 240 mg BID, DR-DMF 240 mg TID, DR-DMF 360 mg BID, or placebo, with either aspirin 325 mg or matching placebo administered 30 minutes before each DR-DMF dose to allow sufficient time for the aspirin dose to begin to exert an effect. An additional 8 subjects were assigned to a modified dosing group receiving DR-DMF 120 mg (6 subjects) or placebo (2 subjects) given 6 times daily (3 doses at hourly intervals in the morning and a further 3 doses at hourly intervals in the evening) (see **Supplemental Figure 1** in the online version at http://dx.doi.org/10.1016/j.clinthera.2013.08.009). Here, we report the detailed findings for the 240 mg BID and TID dosing schedules since these correspond to the doses evaluated in the Phase III studies of DR-DMF in patients with MS[6,7]; results of the other dosing