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Delayed-Release Dimethyl Fumarate as Add-on Therapy to Beta Interferon or Glatiramer Acetate in Relapsing–Remitting MS: Safety and Tolerability

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2014 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC) and the 6th Cooperative Meeting with Americas Committee for Treatment and Reserach in Multiple Sclerosis (ACTRIMS)
May 28 – 31, 2014
Dallas, Texas

INTRODUCTION

Delayed-release dimethyl fumarate (DMF) is approved in the United States and Australia for the treatment of relapsing forms of multiple sclerosis (MS) and relapsing MS, respectively, and in the European Union and Canada for the treatment of relapsing–remitting MS (RRMS).

Delayed-release DMF demonstrated significant efficacy and an acceptable safety profile in patients with RRMS in placebo-controlled clinical trials.[1,2]

OBJECTIVE

- To describe the safety and tolerability of delayed-release DMF as add-on therapy to beta-interferon (IFNβ) or glatiramer acetate (GA) in the Phase 2, open-label EXPLORE study

METHODS

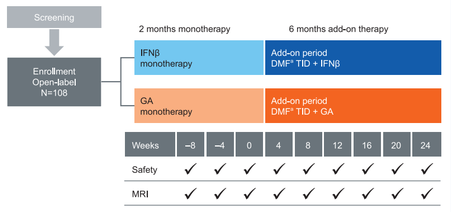
Patients

- Eligibility criteria included the following:
  - Age 18–55 years
  - RRMS diagnosis (McDonald criteria)[3]
  - Expanded Disability Status Scale (EDSS) score of 0–5.0
  - Established therapy with the same dose of IFNβ or GA for ⩾12 months
  - Disease activity defined by ⩾1 relapse within 12 months prior to enrollment or gadolinium-enhanced (GD+) lesion(s) on brain magnetic resonance imaging (MRI) within 6 weeks prior to enrollment
- Key exclusion criteria included the following:
  - Progressive forms of MS
  - MS relapse within 50 days prior to enrollment
  - Clinically significant medical history or laboratory test abnormalities

Study Design

- EXPLORE was a Phase 2, open-label study in the United States. The study design is presented in Figure 1
- After screening, patients continued on their prescribed MS therapy (IFNβ or GA) for 2 months (monotherapy period)
- Patients then received delayed-release DMF 240 mg three times daily (TID) in addition to their prescribed MS therapy for 6 months (add-on therapy period)
- Safety and MRI outcomes were monitored at study visits every 4 weeks during the monotherapy and add-on periods; a follow-up visit was scheduled at 2 weeks after the last delayed-release DMF dose, so that laboratory values over time extended to 26 weeks
- Primary safety endpoints included the following:
  - Adverse events (AEs) and serious AEs
  - AEs leading to treatment discontinuation
  - Laboratory abnormalities
- An exploratory analysis of efficacy was also performed. The average over three MRI scans during the monotherapy period (Weeks -8, -4, and Week 0) was compared with the average over three MRI scans at the end of add-on therapy (Weeks 16, 20, and 24) in a Gd+ cohort (patients with at least one Gd-enhanced lesion during the monotherapy period)

Figure 1: EXPLORE study design



[a]DMF, delayed-release DMF.
Follow-up visit was scheduled at 2 weeks after last delayed-release DMF dose (laboratory values over time extended to 26 weeks).

RESULTS

Patients

- A total of 108 patients were enrolled at 20 US study sites, 59 on IFNβ and 49 on GA, and 82 patients completed the study (76.3% of IFNβ group and 75.5% of GA group)
  - Four patients withdrew from the study before delayed-release DMF dosing was initiated:
    - Two patients in the IFNβ group (one withdrew consent and one for an "other" reason)
    - Two patients in the GA group (one withdrew consent and one at the discretion of an investigator)
  - Twelve patients in the IFNβ group discontinued delayed-release DMF treatment and withdrew from the study, including one due to disease activity and seven due to other AEs
  - Nine patients in the GA group discontinued delayed-release DMF treatment and withdrew from the study, including two due to disease activity and six due to other AEs
  - One patient in the delayed-release DMF plus GA group did not come in for the Week 20 visit but did come in for the Week 24/early termination visit. However, the patient did not appear for her MRI, and the study site was unable to reach the patient to reschedule
- Baseline characteristics of the 104 patients who completed the monotherapy period and were dosed with delayed-release DMF plus IFNβ or delayed-release DMF plus GA are presented in Table 1

Table 1: Baseline characteristics of patients who received delayed-release DMF

Characteristic[a] (ITT)/Prior Treatment	DMF[b] + IFNβ (n=57)	DMF[b] + GA (n=47)
Age, yr	39.5 (7.6)	40.7 (8.4)
Female, %	70	62
Time since first MS symptoms, yr	9.2 (6.1)	11.3 (8.5)
Median (mean) disease duration since diagnosis, yr	5.0 (7.5)	7.0 (8.5)
Relapses within previous yr	1.2 (0.7)	1.2 (0.6)
Prior approved MS treatment (IFN, GA, or natalizumab),[c] n (%)	16 (28)	20 (43)

[a]Values are mean (standard deviation) unless otherwise indicated; [b]Delayed-release DMF; [c]Includes only MS treatment that patient stopped using prior to study entry; otherwise, all patients were undergoing IFN or GA treatment at study entry.
ITT, intent-to-treat.

Safety Experience in Add-on Therapy Period of EXPLORE

- During the add-on therapy period, the overall incidence of AEs was 95% and 100% in the delayed-release DMF plus IFNβ and delayed-release DMF plus GA groups, respectively (Table 2)
- Most AEs were assessed as mild or moderate in severity
- Infections were reported by 32 patients (56%) in the delayed-release DMF plus IFNβ group and 29 patients (62%) in the delayed-release DMF plus GA group
- The most common AEs leading to drug discontinuance were flushing and gastrointestinal (GI) events in both treatment groups
- Five serious AEs were reported in three patients (3%), all of which resolved:
  - Three events were considered drug related: upper abdominal pain, GI pain, and clostridial infection
  - Clostridial infection led to one discontinuation/withdrawal

Table 2: Safety overview

Number of Patients Experiencing Event (%)	Add-on Therapy Period: DMF[a] + IFNβ (n=57)	Add-on Therapy Period: DMF[a] + GA (n=47)
Any event	54 (95)	47 (100)
Infections	32 (56)	29 (62)
DMF[a] discontinuations/withdrawal due to an event (%)	8 (14)	8 (17)
MS	1[b,c] (2)	1[b,c] (2)
Flushing	0	3 (6)
GI events	4 (7)	1 (2)
Drug hypersensitivity	1 (2)	0
Increased ALT levels	1 (2)	0
Palpitations	1 (2)	0
Depression	0	1 (2)
Serious infection	0	1[e] (2)
Muscular weakness	0	1[b] (2)
Serious events	2[f] (4)	1[g] (2)

[a]Delayed-release DMF; [b]Unrelated to study drug; [c]Relapse; [d]New left frontal lobe MS plaque; [e]Clostridial infection; [f]One diabetic patient with worsening diabetes and muscular weakness; [g]One patient with abdominal and GI pain.
ALT, alanine aminotransferase.

- There were no reported opportunistic infections or deaths
- The most common AE in both treatment groups during the add-on therapy period was flushing, followed by diarrhea and abdominal pain (Table 3)

Table 3: Most common AEs (⩾20%) and serious AEs in the add-on therapy period

Number of Patients Experiencing Event[a] (%)	Add-on Therapy Period: DMF[b] + IFNβ (n=57)	Add-on Therapy Period: DMF[b] + GA (n=47)
Number of patients with AE	54 (95)	47 (100)
Flushing	24 (42)	25 (53)
Diarrhea	18 (32)	7 (15)
Abdominal pain	12 (21)	3 (6)
Number of patients with serious AE	2 (4)	1 (2)
Clostridial infection	0	1 (2)
Diabetes	1 (2)	0
Abdominal pain (upper)	1 (2)	0
GI pain	1 (2)	0
Muscular weakness	1 (2)	0

[a]AEs listed according to preferred terms; [b]Delayed-release DMF.
Nausea was common in Phase 3 studies of delayed-release DMF and in EXPLORE occurred at a frequency of 19% with delayed-release DMF plus IFNβ and 9% with delayed-release DMF plus GA.

- During the add-on therapy period, AEs related to GI tolerability were reported in 35 patients (61%) in the delayed-release DMF plus IFNß group and 23 patients (49%) in the delayed-release DMF plus GA group (Table 4)
  - The most commonly reported GI tolerability events (>5 patients) were as follows:
    - Diarrhea (n=18 patients [32%]), abdominal pain (n=12 [21%]), nausea (n=11 [19%]), upper abdominal pain (n=8 [14%]), and abdominal discomfort (n=7 [12%]) in the delayed-release DMF plus IFNß group. All other GI events were reported by five or fewer patients
    - Diarrhea (n=7 [15%]), flatulence (n=6 [13%]), and abdominal distension (n=5 [11%]) in the delayed-release DMF plus GA group
- There were no malignancies
- Hepatic disorders were reported in 12% of patients with delayed-release DMF plus IFNß and 17% of patients with delayed-release DMF plus GA, and included the following:
  - Increased alanine aminotransferase (ALT) levels in six patients (11%), increased aspartate aminotransferase (AST) levels in four (7%), and increased γ-glutamyl transpeptidase (GGT) levels in two (4%) with delayed-release DMF plus IFNß
  - Increased ALT in seven patients (15%), increased AST in four (9%), increased GGT in three (6%), and increased bilirubin in one patient (2%) with delayed-release DMF plus GA
- There was a transient increase in liver transaminases during the add-on period (Table 5)
  - The majority of patients had elevations that were <3 x the upper limit of normal (ULN)
  - Three patients in the delayed-release DMF plus IFNβ group and one patient in the delayed-release DMF plus GA group experienced clinically relevant ALT elevations (⩾3x ULN); one patient from the delayed-release DMF plus IFNβ group experienced ALT elevation >5 x ULN
    - One patient (2%) receiving delayed-release DMF plus IFNβ withdrew due to increased ALT
  - One patient receiving delayed-release DMF plus IFNβ experienced a clinically relevant AST elevation (⩾3 x ULN)
  - No case fulfilled Hy's law for drug-induced liver injury (transaminase elevations ⩾3x ULN concurrent with bilirubin >2x ULN)

Table 4: Events of special interest in the add-on therapy period

Number of Patients Experiencing Event (%)	Add-on Therapy Period: DMF[a] + IFNβ (n=57)	Add-on Therapy Period: DMF[a] + GA (n=47)
Flushing and other related symptoms[b]	32 (56)	27 (57)
GI events[b]	35 (61)	23 (49)
Hepatic disorders[b]	7 (12)	8 (17)
Infections[b]	32 (56)	29 (62)
Ischemic CV disorders[b,c]	1 (2)	0

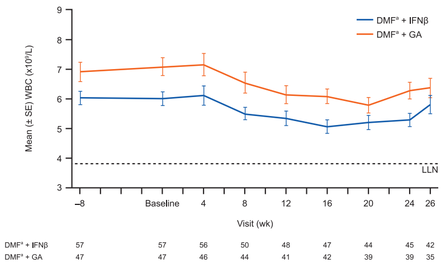
[a]Delayed-release DMF.
[b]Flushing and related symptoms are pre-specified terms. GI, hepatic, ischemic events, and potential malignancies are based on Standardized MedDRA Queries (SMQ). Infectious events are from the Infections and Infestations System Organ Class (SOC).
[c]Included a non-serious, non-related T-wave abnormality on ECG.
No malignancies were reported in either group.
CV, cardiovascular.

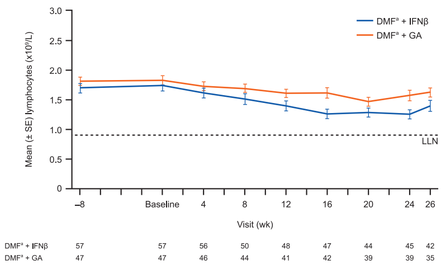
Table 5: Liver function tests in add-on therapy period

	Add-on Therapy Period: DMF[a] + IFNβ (n=57)	Add-on Therapy Period: DMF[a] + GA (n=47)
ALT, n (%)		
>1 x ULN[b]	30 (53)	25 (53)
⩾3 x ULN[c]	3 (5)	1 (2)
>5 x ULN	1 (2)	0
AST, n (%)		
>1 x ULN[b]	18 (32)	17 (36)
⩾3 x ULN[c]	1 (2)	0
>5 x ULN	0	0
ALT/AST ⩾3x ULN and bilirubin >2x ULN, n (%)	0	0

[a]Delayed-release DMF.
[b]Total of all patients with >1 x ULN, including patients with >3x and >5x ULN.
[c]Total of all patients with ⩾3x ULN, including patients with >5x ULN.
Data after patients switched to alternative MS medications are excluded. Total n is the number of patients in the safety population with >1 post-baseline value; this is the denominator for values in parentheses.

Figure 2: (A) White blood cell and (B) lymphocyte counts over time





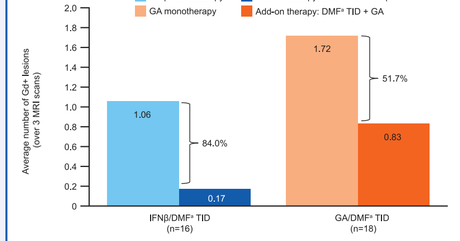
[a]DMF, delayed-release DMF.
Lower limit of normal (LLN) is lower limit in standard unit. If there are multiple values of LLN for a given parameter, the highest LLN is shown.

- Decreased mean white blood cell (WBC) and lymphocyte counts began at Week 8; mean counts were within normal limits throughout the study (Figure 2)
  - At Week 24, the mean percentage decrease of lymphocyte counts from baseline was 22% with delayed-release DMF plus IFNβ and 7% with delayed-release DMF plus GA, compared with an 18% decrease at Week 24 with delayed-release DMF TID in the Phase 3 studies
  - At Week 26, the safety follow-up visit scheduled at 2 weeks after treatment completion, there was a slight increase in lymphocyte counts
  - There was no overall increased risk of infection in either group

Secondary Efficacy Endpoints in EXPLORE

- During the add-on period there was a decrease in the number of Gd+ lesions in both the delayed-release DMF plus IFNβ and delayed-release DMF plus GA groups when compared with their respective monotherapy periods (Figure 3)
- The efficacy analysis was only exploratory, and no adjustment for multiple comparisons or missing value imputation was applied. Additional limitations of the analysis described here include small sample size, lack of parallel control group, and randomization
- Phase 3 monotherapy studies with delayed-release DMF showed a significant reduction of Gd+ lesions at 6 months (earliest assessment)[4]

Figure 3: Gd+ lesions during the monotherapy and add-on therapy periods



[a]DMF, delayed-release DMF.
Compares average number of Gd+ lesions over Weeks -8, -4, and Week 0 of monotherapy with average over three MRI scans at end of add-on therapy (Weeks 16, 20, and 24).

CONCLUSIONS

- Delayed-release DMF 240 mg TID demonstrated an acceptable safety profile as an add-on therapy for 6 months in patients on established monotherapy with IFNβ or GA
- The overall safety profile was similar to the known safety profile of delayed-release DMF monotherapy
- There were no unexpected safety signals
- Although these endpoints were exploratory, there was a decrease in the average number of Gd+ lesions in both the delayed-release DMF plus IFNß and delayed-release DMF plus GA treatment groups, when compared with the monotherapy period

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Acknowledgments

This study was sponsored by Biogen Idec (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by Erin Bekes, PhD, at Complete Medical Communications (Parsippany, NJ, USA); funding was provided by Biogen Idec.

Disclosures

JC: consultant fees from Acorda, Bayer Healthcare, Biogen Idec, EMD Serono, Genzyme, Novartis, Questcor, and Teva; grant/research support from Biogen Idec, Novartis, Roche, and XenoPort; *VV, RZ, MN, SIS:* employees of Biogen Idec; *TV:* activities such as advisory boards, lectures, and consultancy with Acorda, Biogen Idec, Cleveland Clinic, Deloitte Consulting, Global Prairie, Krog and Partners, Mandell Center for Multiple Sclerosis, Mylan, National Multiple Sclerosis Society, Novartis, Questcor, Teva, Teva Canada Innovation, University of St. Louis, and XenoPort; research support from Avanir, Biogen Idec, Elan Pharmaceuticals, Genzyme, Janssen Research and Development, National Institutes of Health, Novartis, Ono Pharmaceuticals, and Teva; *RJF:* consultant fees from Alloxyne, Avanir, Biogen Idec, Novartis, Questcor, Teva, and XenoPort; advisory committees for Biogen Idec and Novartis; research grant funding from Novartis.

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