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Gastrointestinal Tolerability of Delayed-Release Dimethyl Fumarate in Relapsing Multiple Sclerosis: A Multicenter, Open-Label Study (MANAGE)

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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).

Commonly reported adverse events (AEs) among the 2,667 patients enrolled in pivotal Phase 3 studies of delayed-release DMF included flushing and gastrointestinal (GI)–related events.[1,2] Most of these were typically mild or moderate in severity and decreased substantially in incidence after the first month of treatment.

MANAGE is a multicenter, open-label, single-arm study designed to further explore the tolerability of delayed-release DMF by evaluating GI-related events in patients with RRMS in clinical practice in the United States.

OBJECTIVE

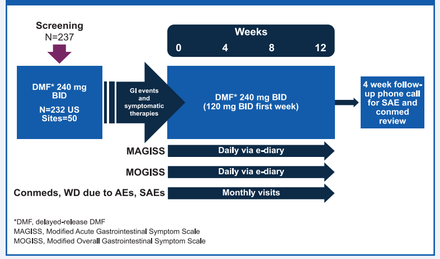
- To evaluate the incidence and prevalence of GI-related events reported by patients with RRMS initiating delayed-release DMF and to evaluate the effect of symptomatic therapies in a clinical practice setting

METHODS

Study Design

- Key eligibility criteria for the study were age ≥18 years, RRMS diagnosis, and a pre-enrollment decision to treat with delayed-release DMF. Patients had not previously received delayed-release DMF or fumaric acid esters
- Among the exclusion criteria were a history of significant GI disease and chronic use (≥7 consecutive days) of symptomatic GI therapy within 1 month prior to enrollment
- Figure 1 presents the design of the study

Figure 1: schematic representation of the MANAGE study design



*DMF, delayed-release DMF
MAGISS, Modified Acute Gastrointestinal Symptom Scale
MOGISS, Modified Overall Gastrointestinal Symptom Scale

- Patients were instructed to take delayed-release DMF with food
- Patients recorded pertinent information regarding any GI-related events occurring within 10 hours of each dose of delayed-release DMF using an eDiary device and the Modified Overall Gastrointestinal Symptom Scale (MOGISS) and Modified Acute Gastrointestinal Symptom Scale (MAGISS)
  - These are numeric rating scales in which the severity of an AE is rated from 0–10 as follows: 0 = none; 1–3 = mild; 4–6 = moderate; 7–9 = severe; and 10 = extreme
- Analysis was based on those patients who actually took symptomatic treatment
- Limitations of the study included lack of a control group and nonrandomization of patients who did and did not take their study medication with a meal

Endpoints

- Primary endpoint: frequency, severity, and duration of GI-related events (MOGISS and MAGISS scales) in delayed-release DMF-treated patients with relapsing forms of MS who used symptomatic therapy during the 12-week treatment period
- Secondary endpoints included the cumulative proportion of patients requiring therapy for GI symptoms during the 12-week treatment period; the type, frequency, and duration of such therapy; and discontinuation rates due to AEs requiring such therapy

RESULTS

Patients

- Two-hundred thirty-seven patients were enrolled in the study, of whom 233 were included in the safety population (mean age, 47 years [range, 18.0–74.0 years]) with MS for a mean duration of 9.5 years [range, 0–42.0 years]) (Table 1)
- Of the 233 patients, 31 patients discontinued study drug (24 [10.3%] because of AEs; Table 2), and 202 patients completed the study

Table 1: Baseline demographic and disease characteristics

Characteristic	N=233
Age, years	46.9 ± 11.7
Female, %	77.7
Race, % white	92.3
Duration of MS, years	9.4 ± 7.4
Relapses within past 1 year	0.7 ± 1.0
Relapses within past 2 years	1.0 ± 1.4
Relapses within past 3 years	1.4 ± 2.3
EDSS score at baseline	2.6 ± 1.6

Values are mean ± standard deviation unless otherwise stated.
EDSS, Expanded Disability Status Scale.

Table 2: AEs leading to study discontinuation

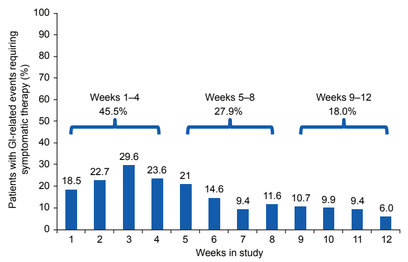
Any AE	24/233 (10.3)
GI disorders	17/233 (7.3)
Nausea	10/233 (4.3)
Diarrhea	7/233 (3.0)
Vomiting	6/233 (2.6)
Abdominal discomfort	2/233 (0.9)
Abdominal pain	2/233 (0.9)
Abdominal pain lower	2/233 (0.9)
Abdominal distension	1/233 (0.4)
Constipation	1/233 (0.4)
GERD	1/233 (0.4)

Values are n/N (%).
Besides GI-related events, only AEs that led to discontinuation were captured.
GERD, gastroesophageal reflux disease.

Incidence and Prevalence of GI-Related Events

- Slightly more lower than upper GI events were reported for patients who used symptomatic therapy
  - The most common acute lower GI-related events were flatulence (45.5% of patients), lower abdominal pain (39.5%), diarrhea (39.1%), bloating (38.2%), and constipation (27.5%)
  - The most common acute upper GI-related events were nausea (42.9% of patients), upper abdominal pain (39.9%), indigestion (35.2%), and vomiting (14.2%)
- Analysis of the prevalence of GI-related events over time showed that such events occurred most frequently during the first month of therapy, the prevalence decreased over time, and by Week 10, <10% of patients reported GI events requiring symptomatic therapies (Figure 2)

Figure 2: Prevalence of GI-related events (MOGISS) requiring symptomatic therapy (%) over time: safety population (N=233)



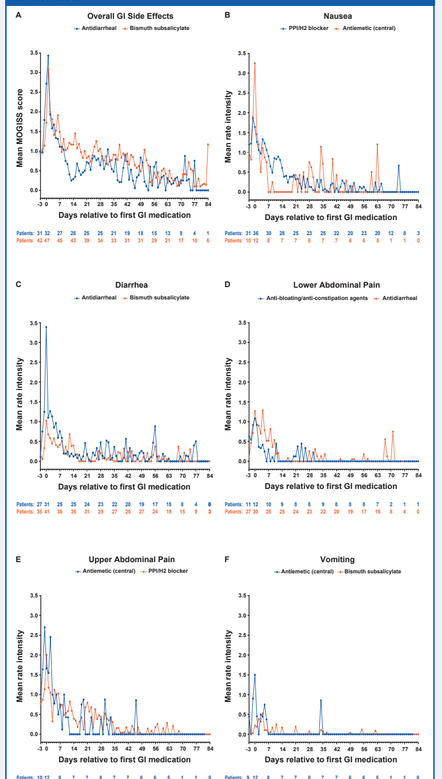
Therapy for GI Symptoms

- Of the 206 patients who reported GI-related events, 126 patients used therapy for GI symptoms (54.1% of study population and 61.2% of those reporting GI-related events)
- The most-used classes of therapy for GI symptoms in the study were antacids (33% of patients), acid-secretion blockers (proton-pump inhibitors [PPIs] and histamine type 2 receptor [H2] blockers, 27% of patients), anti-bloating/anti-constipation agents (25% of patients), bismuth subsalicylate (Pepto-Bismol®, Bismatrol®, and Kaopectate®, 21% of patients), and antidiarrheal therapy (15% of patients)
- By Week 12, <10% of patients were still using therapy for symptomatic GI-related events

Severity of GI-Related Events

- Among all patients who experienced a GI-related event, 80% reported a worst overall severity score (MOGISS) of mild or moderate
- Severity ratings were somewhat higher in users of symptomatic therapy compared with non-users
  - Of the patients who did not use symptomatic therapy, 51.9%, 16.3%, 6.7%, and 1.9% reported worst severity scores for GI-related AEs of "mild," "moderate," "severe," or "extreme," respectively
  - Of the patients who did use symptomatic therapy, 29.7%, 43.8%, 20.3%, and 4.7% reported worst severity scores for GI-related AEs of "mild," "moderate," "severe," or "extreme," respectively
- To assess use of symptomatic therapies in clinical practice and identify those that may have an effect on GI symptoms, the severity of GI-related events in patients who received symptomatic therapy were plotted over time (prior to and after initiation of therapy); however, it is important to note that patients may have received more than one medication for treatment of GI symptoms, as the study was not designed to investigate a treatment effect of specific medications
- In general, a decrease in the average severity of GI-related events was seen in patients who received treatment with one or more medications in the following categories: bismuth subsalicylate (Pepto-Bismol), acid-secretion blockers (PPIs and H2 blockers), antidiarrheals (antiperistaltic agents), centrally acting antiemetics, and anti-bloating/anti-constipation agents. The severities of GI-related events (overall and for individual symptoms of nausea, diarrhea, lower abdominal pain, upper abdominal pain, and vomiting) in patients who received select symptomatic therapies are shown in Figure 3 A-F

Figure 3: Severity of GI-related events over time in patients who took select GI medications



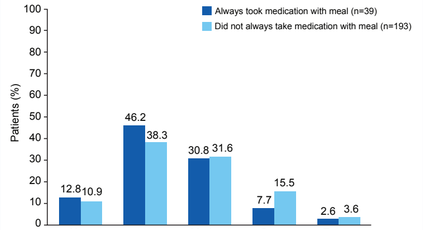
PPI, proton pump inhibitor; H2, histamine 2 receptor.
Patients may have received >1 therapy for GI symptoms.
Antidiarrheals include dicyclomine, diphenoxylate, and loperamide; PPIs include lansoprazole, omeprazole, and pantoprazole; H2 blockers include cimetidine, famotidine, and ranitidine; antiemetics (central) include dimenhydrinate, ondansetron, promethazine, and tetrahydrocannabinol; anti-bloating/anti-constipation agents include Beano® (alpha-D-galactosidase), docusate, and simethicone.

- Notable improvements in GI symptoms were also seen with the anti-allergy medications montelukast and diphenhydramine, although there were very small numbers of patients with events to be evaluated (n=2 and n=1, respectively). For these medications the effect was immediate, with GI symptom severity declining to and largely remaining at zero

Severity of GI-Related Events when Delayed-Release DMF was Taken with Food

- The incidence of severe or extreme GI-related events was reduced when the study drug was taken with meals (Figure 4)

Figure 4: Severity of GI-related events when delayed-release DMF was taken with or without food (MOGISS)



Patients were defined as "Always took medication with meal" if they always took their DMF dose with a meal or within 1 hour after a meal.

CONCLUSION

- Prevalence of GI-related events is consistent with previous data
  - Consistent with two Phase 3 studies of delayed-release DMF, the prevalence of GI-related events peaked during the first month of therapy and decreased over time; less than 10% of patients had GI events requiring symptomatic therapies by week 10
- Food and symptomatic therapy may help reduce the severity of GI symptoms
  - Food may have attenuated symptoms in those who experienced severe GI-related events, whereas symptoms were manageable with symptomatic therapy in the majority of patients who reported GI events
  - The most commonly used classes of symptomatic therapy were antacids, acid-secretion blockers (PPIs and H2 blockers), anti-bloating/anti-constipation agents, bismuth subsalicylate, and antidiarrheals
  - Overall, 54.1% of the safety population used therapy for GI symptoms
  - Of the patients who reported GI-related AEs, 61.2% used therapy for GI symptoms
  - The most notable symptomatic improvements were generally seen in patients who received one or more of the following therapies: bismuth subsalicylate, acid-secretion blockers, antidiarrheals, centrally acting antiemetics, and anti-bloating/anti-constipation agents
  - Few patients continued to use symptomatic therapy by Week 12
- In summary, GI-related events associated with delayed-release DMF in patients with RRMS were generally transient, mild to moderate in severity, and manageable

References

1. Gold R, Kappos L, Arnold DL, et al. *N Engl J Med* 2012;367:1098–1107.
2. Fox RJ, Miller DH, Phillips JT, et al. *N Engl J Med* 2012;367:1087–1097.

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