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Use of a Delphi Process to Gain Consensus on Effective Management of Gastrointestinal Side Effects Associated With Delayed-Release Dimethyl Fumarate

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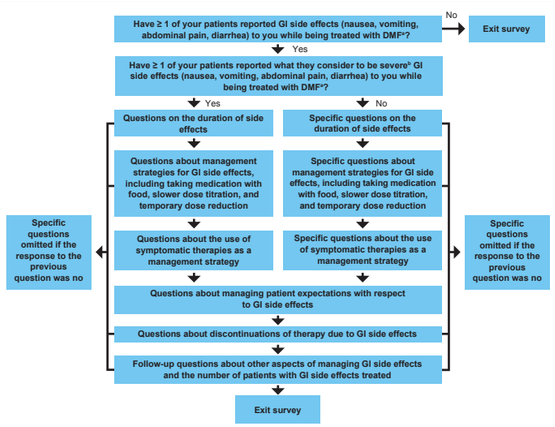
INTRODUCTION

- Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) 240 mg twice daily (BID) is an oral therapy indicated for the treatment of patients with relapsing multiple sclerosis (MS).
- In the Phase 3 studies, DMF significantly reduced clinical and magnetic resonance imaging disease activity vs. placebo, and had an acceptable safety profile. Gastrointestinal (GI) events (e.g., nausea, vomiting, abdominal pain, diarrhea) were more common in patients treated with DMF than placebo (40% vs. 31%).[1-3]
  - Study protocols permitted measures to optimize DMF tolerability, including taking medication with food, dose reduction, and use of symptomatic therapies.
  - GI events were mild or moderate in severity and the incidence decreased substantially after the first month of treatment.
- A Delphi consensus-building method was used to gain further insights into GI events associated with DMF in the real world:
  - Clarification of the incidence, frequency, and duration of DMF-associated GI events in the real world
  - Agreement of ≥ 70% on the most effective methods to manage DMF-associated GI events in a clinical setting
  - Consensus on managing patients' expectations around DMF-associated GI events.

METHODS

- A steering committee of 6 clinicians with experience managing patients treated with DMF was convened and the Delphi process selected as the method for obtaining consensus.[4]
- Two hundred clinicians in the United States and Canada with the most experience of treating MS patients with DMF (based on prescriptions; Biogen data on file) were invited to participate.
- Two rounds of questionnaires containing both open- and close-ended questions were developed. Results from Questionnaire 1 were used to develop Questionnaire 2 and were provided along with Questionnaire 1 in an effort to obtain consensus on the management of each specific GI event.
- The structure of Questionnaire 2 is shown in Figure 1.
- The questionnaires were administered online (Survey Monkey, www.surveymonkey.com) and respondents only answered questions relevant to ≥ 1 of their patients.
- Results from close-ended questions were presented descriptively (e.g., percentages) while open-ended responses were treated as qualitative data and, where possible, coded into bins.
- These analyses focus on questions relating to the management of specific side effects, and experience in typical patients with mild/moderate or severe GI side effects.

Figure 1. Structure of Questionnaire 2



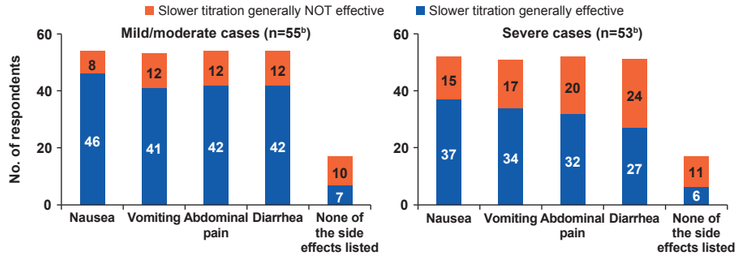
[a]DMF, delayed-release DMF (also known as gastro-resistant DMF). [b]Defined as causing severe discomfort, incapacitation, or significant impact on the patient's daily life, or cessation of treatment; treatment for symptom(s) may be given and/or the patient may be hospitalized.

RESULTS

- Questionnaire 1 was completed by 64 clinician respondents[5]; 57 completed Questionnaire 2 and some consensus results have been presented previously.[6]
- All but 1 respondent (98% [56/57]) had ≥ 1 patient(s) who had experienced a GI side effect with DMF and 96% (54/56) had ≥ 1 patients with severe GI side effects.
- Taking DMF with food was felt to be a useful management strategy for nausea (98% [54/55]), vomiting (89% [49/55]), and abdominal pain (93% [51/55]), but not for diarrhea (69% [38/55]).
- Overall, slower dose titration than that initially recommended (> 7 days to reach the approved maintenance dose of 240 mg BID) was thought to be effective for reducing the incidence and/or severity of nausea (98% [48/49]), vomiting (96% [47/49]), abdominal pain (94% [46/49]), and diarrhea (92% [45/49]).
  - Details of the physicians' experience of slower titration for mild/moderate and severe side effects are given in Figure 2.
- Temporary dose reduction was considered a useful management strategy for reducing the impact of nausea (100% [49/49]), vomiting (90% [44/49]), abdominal pain (90% [44/49]), and diarrhea (86% [42/49]).
  - Figure 3 shows the factors influencing the duration of temporary dose reduction.
- Consensus was reached on using antacids (73%), bismuth subsalicylate (71%), ondansetron (93%), or promethazine (71%) for nausea; bismuth subsalicylate (71%), ondansetron (93%), or promethazine (71%) for vomiting; antacids (75%), bismuth subsalicylate (77%), H_2 blockers (73%), or proton pump inhibitors (80%) for abdominal pain; and diphenoxylate/atropine (91%) or loperamide (95%) for diarrhea.
  - Further details on symptomatic therapies are given in Figure 4.
- The majority of responders (98% [55/56]) agreed that patients should be provided with information on the potential for GI side effects (e.g., occurrence, impact) as well as on management strategies (100% [56/56]) when initiating DMF therapy.

Figure 2. Experience using slower titration

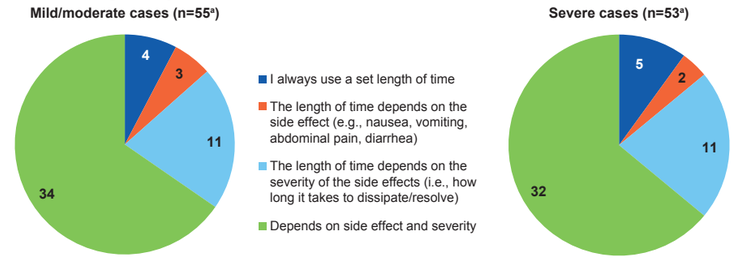
Based on your experience, please indicate if slower titration during initiation of treatment with DMF[a] is generally effective or is generally NOT effective to reduce the incidence of any of the following side effects (check all that apply).



[a]DMF, delayed-release DMF (also known as gastro-resistant DMF). [b]Question posed only to respondents who used slower titration in the appropriate patient group(s).

Figure 3. Factors influencing the duration of temporary dose reduction

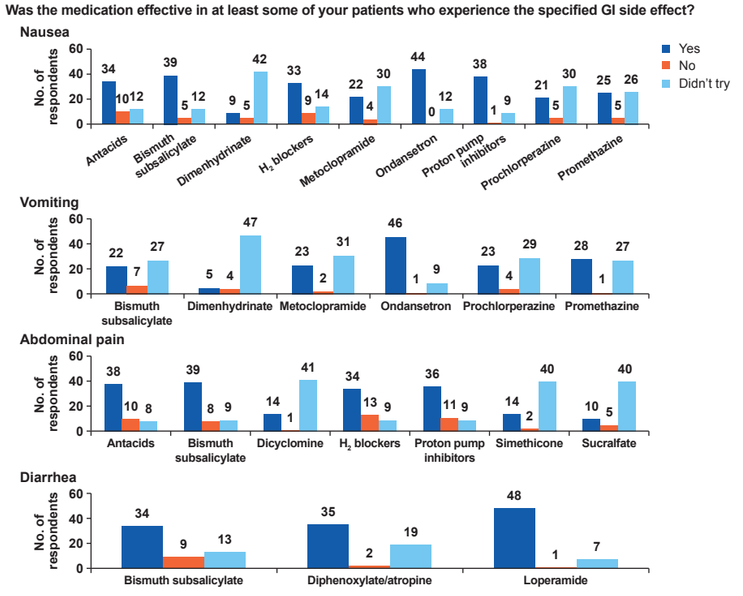
What factors weigh in on your decision for the duration of time to reduce dose?



[a]Question posed only to respondents who used temporary dose reduction in the appropriate patient group(s).

Figure 4. Symptomatic therapies

Was the medication effective in at least some of your patients who experience the specified GI side effect?



CONCLUSIONS

- Clinicians with experience using DMF reached consensus on several potentially useful strategies to manage nausea, vomiting, abdominal pain, and diarrhea including:
  - Administering DMF with food
  - Slower dose titration, which was generally effective in mild/moderate and severe cases
  - Temporary dose reduction, the duration of which is usually based on the side effect and severity
  - Use of symptomatic therapies.
- Results from this Delphi panel suggest that effective management strategies can reduce discontinuation rates of DMF due to GI side effects.
- Participants agreed that patient expectations can be managed more effectively by providing information on the potential occurrence and likely impact of GI side effects, and how these side effects can be managed when treatment with DMF is initiated.
- Strategies identified by clinicians to manage GI events associated with DMF may help improve treatment tolerability and adherence.

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Disclosures

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