DX30

A Delphi Panel to Address Management of Gastrointestinal Side Effects Observed With Use of Delayed-Release Dimethyl Fumarate

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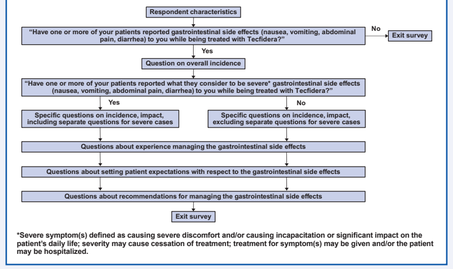
INTRODUCTION

- Delayed-release dimethyl fumarate (DMF) is an oral therapy 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).
- In the phase 3 DEFINE and CONFIRM studies, treatment with delayed-release DMF resulted in significant reductions in clinical and radiological disease activity versus placebo, and demonstrated an acceptable safety profile in relapsing patients with MS.[1–3]
  - Gastrointestinal (GI) events (eg, nausea, vomiting, abdominal pain, and diarrhea) were commonly reported in patients treated with delayed-release DMF (40% vs 31% with placebo).
  - Most events were mild to moderate in severity and decreased substantially in incidence after the first month of treatment.
- In these trials, measures were taken to optimize the tolerability of delayed-release DMF:
  - Patients were instructed to take delayed-release DMF with food;
  - Dose reduction of 50% (eg, to 120 mg twice daily [BID] from 240 mg BID) for up to 4 weeks was permitted as part of the protocol; and
  - Symptomatic therapies to manage observed adverse events (AEs) were allowed at the discretion of the study investigator (specific therapies were not predefined).
- In 2013, a steering committee of clinicians with experience managing patients treated with delayed-release DMF was convened to gain further insight into GI events associated with delayed-release DMF, with the objective of obtaining a consensus from a larger group of experienced clinicians on the most effective strategies to manage side effects and on setting appropriate expectations for patients with GI events.
- The Delphi process was selected as the method of obtaining consensus.
  - This is a widely accepted method of data collection that utilizes iterative rounds of data-gathering and hypothesis-testing questionnaires to build expert consensus on an issue.[4]
- The first round of the Delphi process has been completed; results from the first questionnaire are presented here.

METHODS

- A steering committee composed of 6 clinicians with considerable experience prescribing delayed-release DMF was convened to provide guidance on questionnaire development and interpretation of tabulated results.
- 200 clinicians with the most experience with delayed-release DMF in the United States and Canada (based on prescriptions; Biogen Idec, data on file) were selected for invitation to participate because their opinions were most likely to be well-informed by their experience.
- The first questionnaire focused on the following objectives (Figure 1):
  - To better understand the incidence, characteristics, and impact of the GI side effects associated with delayed-release DMF in the clinical practice setting;
  - To achieve consensus on strategies to manage GI side effects associated with delayed-release DMF in the clinical practice setting; and
  - To achieve consensus on how to best set patient expectations for management of GI side effects associated with delayed-release DMF.

Figure 1: Structure of the questionnaire



*Severe symptom(s) defined as causing severe discomfort and/or causing incapacitation or significant impact on the patient's daily life; severity may cause cessation of treatment; treatment for symptom(s) may be given and/or the patient may be hospitalized.

- The questionnaire contained both closed- and open-ended questions.
  - Respondents completing the questionnaire were asked to base their answers on the experience of a "typical" patient (their clinical population as an aggregate).
  - For respondents who had patients that had reported severe side effects (ie, symptoms that cause severe discomfort, incapacitation, or have a significant impact on patient's daily life; severity may cause cessation of treatment; treatment for symptoms may be given and/or the patient may be hospitalized), respondents were also asked the same or similar questions based on the most severe case.
  - Many of the questions were repeated for instances of each GI symptom: nausea, vomiting, abdominal pain, and diarrhea.
- Respondents completed the questionnaire and provided relevant demographic information through a Web-based survey tool (Survey Monkey®, www.surveymonkey.com).
  - Respondents responded only to questions that were reported by ≥1 of their patients during their clinical experience.
- Results from close-ended questions were presented descriptively (eg, percentages, means, medians).
  - The number of respondents to whom each question applied was used as the denominator.
- Open-ended responses were treated as qualitative data and, where possible, coded into bins

RESULTS

- Of 200 clinicians who were invited to participate, 64 (representing 58 clinical practice sites) completed the first-round questionnaire.
- Respondents included a range of clinicians (Table 1).

Table 1: Characteristics of respondents

Characteristic, n (%)	Respondents N=64
Country of practice	
United States	56 (87.5)
Canada	8 (12.5)
Role	
Physician	51 (79.7)
Nurse practitioner	9 (14.1)
Physician assistant	3 (4.7)
Nurse	1 (1.6)
Practice setting	
Free-standing private clinic	24 (37.5)
Academic hospital-based	22 (34.4)
Community hospital-based	14 (21.9)
Managed care clinic	1 (1.6)
Other	3 (4.7)
No. of patients with MS in practice	
Total from all practices*	79,570
Median per practice (range)*	1000 (45–5000)
Length of time treating patients with MS	
>10 years	46 (71.9)
>5 to ≤10 years	14 (21.9)
>1 to ≤5 years	4 (6.3)

MS, multiple sclerosis.
*In instances where respondents from the same practice entered different numbers, only the lower number was counted; where respondents entered an annual number, that number was used for the total.

- 63/64 (98%) respondents indicated that ≥1 of their patients had reported GI side effects; 60/63 (95%) had ≥1 patient who reported severe GI side effects.
- The majority of respondents indicated that each of the following side effects was reported by <20% of typical patients (median values: nausea, 15%; vomiting, 5%; abdominal pain, 15%; diarrhea, 10%) and severe side effects were reported in smaller proportions (median values: nausea, 5%; vomiting, 1%; abdominal pain, 5%; diarrhea, 5%).
- Respondents indicated that, for patients who experience any mild-to-moderate GI side effect, the order of frequencies from greatest to least was: (1) nausea; (2) abdominal pain; (3) diarrhea; and (4) vomiting.
  - Among patients who experienced severe side effects, the relative order of frequencies was the same, although each severe side effect was reported as experienced more frequently compared with mild-to-moderate side effects.
- Regarding the typical patient, >50% of respondents indicated that each of the GI side effects had mild-to-moderate impact on the daily activities, whereas >70% of respondents indicated that severe forms of each side effect had severe or extreme impact on daily activities.
  - For both cases, vomiting and abdominal pain each were considered to have more impact than diarrhea or nausea.
- 61/63 (97%) respondents had discontinued treatment with delayed-release DMF in ≥1 patient owing to GI side effects.
  - Rank order of side effects most frequently chosen as likely or highly likely to lead to discontinuation: (1) vomiting, 38%; (2) abdominal pain, 28%; (3) diarrhea, 21%; and (4) nausea, 10%.
  - Most frequently cited reasons for discontinuation were severity of the side effect (n=26), patient level of complaint (n=25), and duration of side effect (n=20).
- The most frequent management strategies and ratings of their effectiveness are shown in Table 2.

Table 2: Approaches attempted to manage GI side effects

Side effect	Rx medication, non-Rx medication, and/or complementary therapies*	Effectiveness of approaches
Nausea (n=61)	Ondansetron, bismuth subsalicylate, promethazine, food-based strategies, metoclopramide, prochlorperazine, H_2-blockers, proton-pump inhibitors, ulcer drugs (sucralfate, glycopyrrolate, misoprotol), dimenhydrinate, antacids	Effective all the time (2%); Effective some of the time (93%); Not effective (5%)
Vomiting (n=47)	Ondansetron, promethazine, bismuth subsalicylate, food-based strategies, prochlorperazine, metoclopramide, H_2-blockers, ulcer drugs, dimenhydrinate	Effective all the time (3%); Effective some of the time (95%); Not effective (1%)
Abdominal pain (n=54)	Bismuth subsalicylate, H_2-blockers, proton-pump inhibitors, food-based strategies, antacids, ulcer drugs, metoclopramide, Bentyl	Effective all the time (2%); Effective some of the time (89%); Not effective (6%); Not specified (3%)
Diarrhea (n=53)	Loperamide, bismuth subsalicylate, Lomotil, food-based strategies	Effective all the time (6%); Effective some of the time (94%); Not effective (0%)

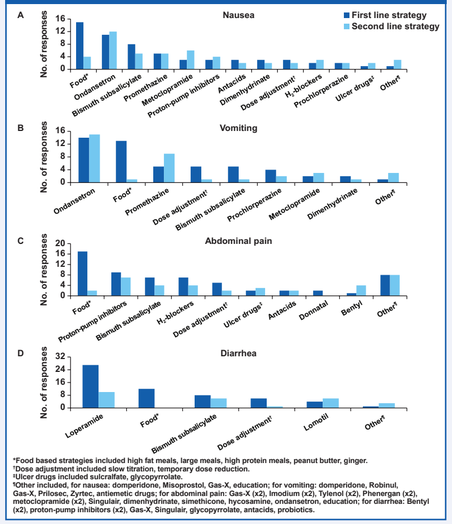
GI, gastrointestinal; Rx, prescription.
*Agents are shown in decreasing order of frequency of mention; only therapies attempted by ≥4 respondents are listed. Doses and durations were varied and some were used in combination.

- No approaches were consistently identified by the majority of respondents as either effective all of the time or not effective.
  - Approaches deemed effective all of the time by ≥1 respondent (ie, n≥1) included: for nausea, ondansetron (n=5) and prochlorperazine (n=1); for vomiting, promethazine (n=1) and H_2-blockers (n=1); for abdominal pain, food-based strategy (n=1) and 1-month titration (n=1); for diarrhea, loperamide (n=3), bismuth subsalicylate (n=1), and 1-month titration (n=1).
  - Approaches deemed not effective by ≥1 respondent included: for nausea, ondansetron (n=1), H_2 blockers (n=1), and ulcer drugs (n=1); for vomiting, bismuth subsalicylate (n=1); for abdominal pain, proton-pump inhibitors (n=3), bismuth subsalicylate (n=2), H_2-blockers (n=1), and antacids (n=1).
- 45/63 (71%) respondents reported effects of particular foods or types of foods, or timing of delayed-release DMF dose with respect to food, on the frequency, duration, or severity of GI side effects.
  - Among respondents who reported effects of food, most reported that food helped to prevent or reduce the severity or duration of each of the GI side effects.
  - Fatty foods were most consistently reported as helpful to manage each of the side effects.
- Almost all respondents indicated that they had attempted reducing the dose of delayed-release DMF temporarily as a method of managing the side effects for their typical patient (58/63 [92%] respondents) or for their most severe case (55/60 [91%] respondents).
  - ~75% of respondents who had attempted temporary dose reduction for a given side effect reported that it was effective for a typical patient, whereas the proportions of respondents who reported it as effective for their most severe case was between 56% and 65% for each side effect.
- 46/63 (73%) respondents indicated that they had tried slow titration of initial treatment as a means to prevent GI side effects and, of those 46, 41 (89%) indicated that they would recommend this approach for certain patients to improve GI tolerability while the effective 240 mg BID dose is being reached.
- Between 70% and 81% of respondents were more confident or much more confident in managing each side effect for their typical patient than when they first started using delayed-release DMF.
  - Between 62% and 67% were more or much more confident about managing severe cases of each side effect.
- When asked about how they set expectations of their typical patients about the potential GI side effects with delayed-release DMF, 60/63 (95%) respondents provided responses that could be grouped into one or more of 5 categories (not mutually exclusive; Figure 2).

Figure 2: Approaches used to set patient expectations

- Based on their experience, respondents provided their current strategies for managing each of the GI side effects (Figure 3).
  - Between 63% and 68% of respondents indicated that they would not do anything differently for a severe case of each side effect compared with a typical patient.

Figure 3: Approaches currently used to manage side effects



*Food based strategies included high fat meals, large meals, high protein meals, peanut butter, ginger.
†Dose adjustment included slow titration, temporary dose reduction.
‡Ulcer drugs included sucralfate, glycopyrrolate.
¶Other included, for nausea: domperidone, Misoprostol, Gas-X, education; for vomiting: domperidone, Robinul, Gas-X, Prilosec, Zyrtec, antiemetic drugs; for abdominal pain: Gas-X (x2), Imodium (x2), Tylenol (x2), Phenergan (x2), metoclopramide (x2), Singulair, dimenhydrinate, simethicone, hycosamine, ondansetron, education; for diarrhea: Bentyl (x2), proton-pump inhibitors (x2), Gas-X, Singulair, glycopyrrolate, antacids, probiotics.

CONCLUSIONS

- Each of the GI side effects was typically observed by respondents in <20% of patients and severe side effects were typically observed in <10% of patients.
- Although nausea was somewhat more frequent than other side effects, it was deemed to be less impactful on the daily activities of a typical patient.
- Most respondents had attempted a range of prescription medications, nonprescription medications, and/or complementary therapies to manage GI side effects in their patients.
  - The majority of responses for each approach to managing each of the GI side effects indicated that it was effective some of the time and none of the approaches were rated by a majority of respondents as not effective for any of the GI side effects.
  - Ondansetron and food-based strategies were the most frequently attempted approaches to manage nausea and vomiting, and were most frequently identified current strategies used to manage those side effects.
  - Food-based strategies were the most frequent current strategy to manage abdominal pain.
  - Loperamide was the most frequently attempted approach and most frequently identified current strategy used to manage diarrhea.
- Most respondents who had tried temporary dose reduction to manage side effects reported that it was effective, particularly for the typical patient.
- Most respondents who had tried slow titration to prevent side effects in a typical patient reported that it was effective.
- Respondents provided a range of suggestions regarding setting patient expectations, and a range of approaches they use currently to manage GI side effects with delayed-release DMF treatment; to obtain consensus, these approaches will be investigated further through the use of a second questionnaire.

References

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