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Tecfidera™ (Dimethyl Fumarate) Tolerability: Expert Panel Recommendations

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INTRODUCTION

- Tecfidera™ (dimethyl fumarate, referred to as BG-12 in clinical trials) was evaluated in two 2-year studies, DEFINE and CONFIRM.[1,2]
  - Significant improvements in clinical and radiological disease activity versus placebo were demonstrated with dimethyl fumarate 240 mg twice (BID) or 3 times (TID) daily.
- Flushing and GI adverse events (AEs; eg, nausea, vomiting, abdominal pain, diarrhea) were commonly reported in patients treated with dimethyl fumarate BID or TID (36% and 42%, respectively).
  - Most AEs were mild to moderate in severity and decreased in incidence after the first month of treatment.
  - Discontinuation rates were relatively low for these AEs; 2% for flushing and 4% for GI AEs, suggesting that the AEs were effectively managed in a clinical trial setting.
- In these trials, side effect management recommendations included:
  - Instruction to take dimethyl fumarate with food;
  - Temporary dose reduction of 50% (eg, from 240 mg BID to 120 mg BID) for ≤4 weeks was permitted as part of the protocol for the management of these AEs; the efficacy of this intervention has not been established; and
  - Symptomatic therapies to manage observed flushing and GI AEs were allowed in the clinical trials at the discretion of the study investigator; specific therapies were not predefined.

OBJECTIVE

- To further understand the management of flushing and GI AEs associated with dimethyl fumarate seen in phase 3 clinical trials and identify potential mitigation strategies for clinical practice.

METHODS

- The Delphi process was selected as the method of obtaining consensus.
  - This process 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.[3]
- From the pool of investigators from DEFINE and CONFIRM, invitations were issued to those investigators who had enrolled ≥10 patients across the studies, as investigators with at least this volume of patients would be most likely to have sufficient experience managing dimethyl fumarate AEs.
- A steering committee of 5 investigators who were members of the medical advisory boards from the DEFINE and CONFIRM clinical trials was formed to provide guidance on questionnaire development as well as interpretation of tabulated results.
- The steering committee focused on 4 objectives in the construction of the questionnaire (Figure 1).

Figure 1: Objectives of the Survey Questionnaire

1. To obtain greater details regarding the most common AEs associated with dimethyl fumarate in the phase 3 clinical trials
2. To gather opinions on the management of flushing and GI AEs associated with dimethyl fumarate
3. To gain insight on setting patient expectations regarding the management of flushing and GI AEs
4. To identify important messages to communicate with clinicians about dimethyl fumarate AEs

AEs, adverse events; GI, gastrointestinal.

- The questionnaire contained both closed- and open-ended questions.
  - Investigators completing the survey were asked to base their answers on the experience of a "typical" patient (their study population receiving dimethyl fumarate as an aggregate) and to provide a response for the single most severe case of a particular AE that they encountered.
  - Responses were not specific to BID or TID dosing of dimethyl fumarate.
  - Questions were repeated for the following specific AEs: 1) flushing, 2) nausea/vomiting, 3) abdominal pain, and 4) diarrhea.
- Investigators completed the questionnaire and provided relevant demographic information through a Web-based survey tool (Survey Monkey® [www.surveymonkey.com]).
  - Investigators only responded to questions regarding AEs that were reported by ≥1 of their patient(s) during the clinical trials.
- Results from close-ended questions were presented descriptively, including percentages, means, and standard deviations where appropriate.
- Open-ended responses were treated as qualitative data and coded into separate categories.
- The denominator in these analyses reflects the number of investigators who had ≥1 patient(s) with a specific AE.

RESULTS

- A total of 84 investigators were invited to participate in the Delphi panel; 30 investigators completed the questionnaire.
- Participating investigators represented a wide range of practice settings and geographic diversity.
- Patients of these participating investigators represented approximately 17% of the total dimethyl fumarate study population in DEFINE and CONFIRM and 377 patient-years of dimethyl fumarate exposure and had similar characteristics to the overall study population (Table 1).
- For typical patients with these AEs, most investigators noted that the AEs generally occurred after some but not all doses, were not overly bothersome, and often decreased with time (Figure 2).
- Interventions to manage these AEs were varied (Table 2).

TABLE 1: Characteristics of Patients in the Clinical Trial Population Receiving Dimethyl Fumarate and Those Seen by Participating Investigators

Characteristic	Integrated Analysis of Patients in DEFINE/CONFIRM Receiving Dimethyl Fumarate BID/TID N=1529	Patients of 30 Investigators Participating in Survey Receiving Dimethyl Fumarate BID/TID N=254
Completed study treatment, n (%)	1074 (70.2)	184 (72.4)
Median days on study drug	672	671
Flushing, n (%)	555 (36.3)	84 (33.1)
Treated for flushing, n (%)	47 (3.1)	5 (2.0)
Discontinued for flushing, n (%)	38 (2.5)	6 (2.4)
GI AEs,* n (%)	635 (41.5)	96 (37.8)
Treated for GI AEs, n (%)	312 (20.4)	48 (18.9)
Discontinued for GI AEs, n (%)	65 (4.3)	7 (2.8)

AEs, adverse events; BID, twice daily; GI, gastrointestinal; TID, 3 times daily.
*GI AEs were defined by preferred terms in the level 2 subordinate Standardised MedDRA Queries "gastrointestinal nonspecific inflammations" or "gastrointestinal nonspecific symptoms and therapeutic procedures."

TABLE 2: Investigator-Reported Strategies for Managing Observed Adverse Events During DEFINE/CONFIRM*

Flushing (n) n=28	Nausea/Vomiting (n) n=21	Abdominal Pain (n) n=18	Diarrhea (n) n=11
Patient counseling (12)	Patient counseling (4)	Patient counseling (3)	Patient counseling (3)
Take with food (5)	Take with food/ modifying food intake (5)	Take with food (9)	
Dose reduction (3)	Dose reduction (2)	Dose reduction (2)	Dose reduction (1)
Symptomatic therapies			
Aspirin (4)	Metoclopramide/domperidone (5)	Antacids (4)	Loperamide (5)
Antihistamines (4)	Proton pump inhibitors (4)	Proton pump inhibitors (3)	Hyoscyamine (1)
Ibuprofen (2)	H2 receptor antagonists (1)	H2 receptor antagonists (3)	Smecta® (1)
Acetaminophen (1)	Changing timing of administration (2)	Acetaminophen (2)	Dietary adaptation (1)
Metoprolol (1)	Dimenhydrinate/diphenhydramine (1)		
Slow titration (1)			

*Numbers are not mutually exclusive; combinations of some interventions were also reported.

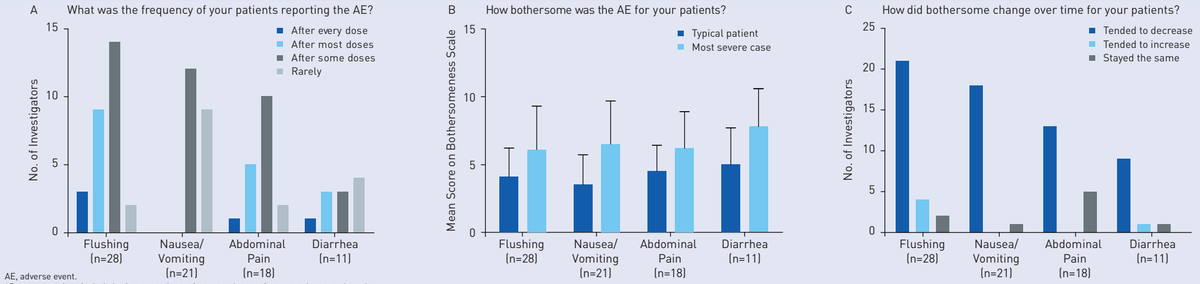
- Less than half of the investigators (13/30) indicated that they had used dose reduction or interruption of therapy as a method of managing these AEs.
  - About half (7/13) indicated that when these strategies were used they were always effective for managing these AEs.
- In open-ended questions asking investigators to provide strategies for communicating about dimethyl fumarate AEs with patients and clinicians, most investigators indicated the importance of education before treatment initiation, and provider education on effective management strategies (Table 3).

TABLE 3: Investigator Responses to Open-Ended Questions Regarding Communication With Patients and Clinicians

	n* (%)
"What are the effective ways of setting a *patient's* expectations around these side effects so that the patient will remain on drug in a standard clinical setting?"	
Education on the nature of AEs before starting treatment (eg, types, severity, frequency, transient nature)	23 (77)
Communicate management strategies (eg, symptomatic medications, taking with food, dose reductions)	11 (37)
Positive encouragement; emphasizing product efficacy and the importance of staying on therapy	6 (20)
Start medication during a convenient time (eg, not while traveling)	1 (3)
Recommend engaging with MS nurse	1 (3)
"What are the most important pieces of information on the management of these side effects that should be communicated to *clinicians* who would like to use dimethyl fumarate?"	
General education on characteristics of common AEs	18 (60)
Severity/bothersomeness	12 (40)
Duration	11 (37)
Frequency	4 (13)
General education on effective management strategies	15 (50)
Symptomatic medications†	8 (27)
Temporary dose reduction	6 (20)
Take with food	5 (17)
Importance of counseling patients and setting expectations	9 (30)
Education on favorable benefit-risk profile of the product	3 (10)

AEs, adverse events; MS, multiple sclerosis.
*Based on 30 investigators responding to the survey.
†Includes 1 respondent that recommended avoidance of gastrointestinal medication.

Figure 2: Investigator-Reported Impressions of the Impact of AEs on Patients Receiving Dimethyl Fumarate. (A) Investigator Response to the Closed-Ended Question "How Frequently Did Your Patients Report (Flushing, Nausea/Vomiting, Abdominal Pain, Diarrhea)?"*; (B) Investigator Responses to the Closed-Ended Question "How Bothersome Was (Flushing, Nausea/Vomiting. Abdominal Pain, Diarrhea) for Your Patients on a Scale of 0–10 Where 0 Is No Bother and 10 Is Extremely Bothersome?"; and (C) Investigator Responses to the Closed-Ended Question "How Did Bothersomeness of (Flushing, Nausea/Vomiting, Abdominal Pain, Diarrhea) Change Over Time for Your Patients?"†



AE, adverse event.
*Response options included: after every dose, after most doses, after some doses, and rarely.
†Response options included: tended to decrease, tended to increase, and stayed the same.

- When asked about recommendations for clinicians who would like to use dimethyl fumarate, investigators indicated that patient education and drug administration with food are important prophylactic measures (Table 4).

TABLE 4: Investigator Responses to "What Are the Most Important Pieces of Information on the Management of These Side Effects That Should Be Communicated to Clinicians Who Would Like to Use Dimethyl Fumarate?"

Prior to initiation of dimethyl fumarate	
Discuss the benefit/risk profile	
Discuss timing of symptom onset relative to dosing, frequency, severity, general transient nature, and management strategies for flushing, nausea/vomiting, abdominal pain, and diarrhea with patient	
Advise patient to take dimethyl fumarate with food	
No preventive therapies should be used when initiating dimethyl fumarate	
Symptomatic management following initiation of dimethyl fumarate*	
If patient reports:	Reinforce counseling points and consider recommending†:
Flushing	• Aspirin 325 mg prior to each dimethyl fumarate dose • Antihistamines
Nausea/vomiting	• Proton pump inhibitors • H2 receptor antagonists • Metoclopramide • Dimenhydrinate, diphenhydramine • Domperidone
Abdominal pain	• Proton pump inhibitors • H2 receptor antagonists
Diarrhea	• Antidiarrheals (loperamide, diphenoxylate, Smecta®)

*None of these therapies have been prospectively evaluated nor are they included in the product labeling.
†Not in any particular order.

LIMITATIONS

- Only some of the investigator recommendations for AE management have been evaluated in controlled clinical studies.
  - Nonenteric coated 325 mg aspirin, taken 30 minutes before the dose of dimethyl fumarate, has been shown to reduce the occurrence and severity of flushing in healthy volunteers.[4,5]
  - Slow titration of dimethyl fumarate did not reduce the incidence or severity of flushing or GI AEs in healthy volunteers.[5]

CONCLUSIONS

- The investigators confirmed that patient and provider education on AE characteristics and mitigation strategies is critical to the effective management of flushing and GI AEs in the clinical setting.
- Patient education and taking the drug with food are prophylactic measures that can be recommended for flushing and GI AEs.
- If patients report symptoms at a level severe or bothersome enough to warrant pharmacological intervention, over-the-counter symptomatic therapies are frequently recommended.
- Setting patient expectations on flushing and GI AEs and offering options to manage the tolerability profile of dimethyl fumarate will be important for supporting therapy adherence in clinical practice.

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