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A Retrospective Assessment of Real-World Discontinuation Rates in Patients with Multiple Sclerosis Treated with Delayed-Release Dimethyl Fumarate

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INTRODUCTION

- Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) is an oral multiple sclerosis (MS) disease-modifying therapy (DMT) administered at a dose of 240 mg BID.
- In two DMF Phase III clinical trials:
  - Relapse rates were reduced and neuroradiological outcomes improved compared with placebo.[1,2]
  - The most commonly-reported adverse events (AEs) in clinical trials were flushing and gastrointestinal (GI) intolerance. In addition, GI intolerance and flushing were the most common reasons for discontinuation, accounting for 4% and 3% of discontinuations, respectively.[3]
  - The incidence of GI events and flushing was higher early in the course of treatment (primarily in the first 3 months) and decreased over time[3,4]
  - Diarrhea, nausea, and abdominal pain were the most commonly reported GI events
- In MANAGE, a multicentre, open-label, single-arm study designed to further explore the tolerability of DMF by evaluating GI-related events in the real world setting, 7.3% of patients discontinued due to GI-related adverse events.[5]

OBJECTIVE

- The objective of this retrospective chart review was to evaluate baseline demographics and disposition for patients prescribed DMF as part of routine clinical practice.

METHODS

Design

- The study was designed as a clinical care initiative in the form of a chart review of patients with RRMS who received care at a single large medical institution in Australia.
- Data were collected retrospectively and in a de-identified manner from patients' medical charts and also related information sources such pharmacy records.
- All data were collected by institution staff.
- All data collected for the proposed clinical care initiative were entered onto a paper Case Report Form (CRF).
- Data collected included:
  - Demographic information, including age and gender
  - History of MS, including date of diagnosis of RRMS, and age at the time of diagnosis
  - Other comorbid conditions of interest
  - DMTs used prior to initiation of DMF
  - Date DMF was first prescribed, changes in dosage, use of concomitant medications during the period of DMF administration
  - Date DMF was discontinued, reason for discontinuation (if recorded), DMT replacing DMF, concomitant medications during treatment with DMF and the period following DMF discontinuation

Inclusion Criteria

- Charts were reviewed for cases that met the following criteria:
  - Diagnosed with RRMS
  - Completed ≥6 months of continuous therapy for their MS, either with DMF or an alternative MS medication initiated following discontinuation of DMF therapy
  - Experienced no change in their MS diagnosis during the 6-month follow-up period
  - ≥18 years of age at the start of DMF therapy.

Endpoints

Primary Endpoint

- Overall discontinuation rate for MS patients treated with DMF. (Discontinuation was defined as information in the patient's chart [or related patient information sources such as physician's notes, pharmacy records, etc.] indicating either that the patient stopped receiving DMF for ≥1 week or that DMF was terminated).

Secondary Endpoints

- Discontinuation rate due to AEs.
- Incidence of AEs (such as GI events) necessitating a change in dose.

Statistical Analysis

- Descriptive statistics were employed to report the overall discontinuation rate at 3 and 6 months following initiation of DMF.
- AEs, serious AEs (SAEs) and concomitant medications of interest were recorded and tabulated.
- To the degree possible based on the limitations of retrospective data, the events were categorised based on their relationship to DMF, ie, definitely related, probably related, not related and unable to determine.

RESULTS

- The analysis included 100 patients initially prescribed DMF between October 1, 2013 and June 30, 2014.
- The majority of patients (n=84; 84%) received ≥1 prior DMT; 16% of patients were treatment-naïve (Table 1).

Table 1. Patient demographics

Characteristic	Parameter
Age, years	
Mean (SD)	42.7 (10.95)
Median (range)	44.0 (18, 65)
Female, %	**80**
Disease duration, years	
Mean (SD)	8.5 (7.10)
Median (range)	7.2 (0, 29)
Number of prior DMTs, %	
0	16
1	45
2	26
3	8
4	3
5	2

- The most common reason for discontinuation of prior therapies was lack of efficacy (50%), followed by adverse events (17.5%), and poor tolerability (14.7%) (Table 2).
- Most patients used ≥1 concomitant medication at the time of treatment initiation with DMF. Amongst specific drug classifications the most common medications were for abdominal pain (used by 5% of patients).
- Overall discontinuation rate was 13%, with 9% of patients discontinuing due to GI tolerability issues. One patient discontinued DMF due to lack of efficacy.

Table 2. Reason for discontinuing prior DMTs

	Reason for discontinuing, n (%)						
Agent (n)	AE	Lack of efficacy	Injection fatigue	Request to go to oral Rx	Poor tolerability	Pregnancy	Other
Teriflunomide (9)	2 (22.2)	2 (22.2)	1 (11.1)	-	3 (33.3)	1 (11.1)	0
Interferon beta-1a IM QW (30)	3 (10.0)	11 (36.7)	3 (10.0)	4 (13.3)	6 (20.0)	0	3 (10.0)
Interferon beta-1b (29)	4 (14.3)	10 (35.71)	7 (25.0)	2 (7.1)	3 (10.7)	1 (3.6)	1 (3.6)
Glatiramer acetate (30)	7 (24.1)	13 (44.83)	3 (10.3)	2 (6.9)	3 (10.3)	0	1 (3.5)
Fingolimod (17)	6 (35.3)	7 (41.18)	0	-	2 (11.8)	1 (5.9)	1 (5.9)
Interferon beta-1a SC TIW (19)	3 (17.7)	6 (35.29)	2 (11.8)	3 (17.7)	3 (17.7)	0	0
Natalizumab (9)	0	1 (11.11)	0	0	1 (11.1)	0	7 (77.8)
Total	25	50	16	11	21	3	13

- No treatment-naïve patients discontinued therapy with DMF within 6 months of initiation.
- Dose changes due to AEs occurred in 15% of patients.
- The most common reason for discontinuing DMF was adverse events (n=11) followed by poor tolerability (n=5). All five patients who discontinued due to poor tolerability also discontinued due to AEs. Only one patient discontinued due to lack of efficacy. Of patients discontinuing due to AEs, 9 reported GI adverse events, 4 reported non-GI events (three of these also reported GI events) and one patient reported 'other' (weight loss).
- None of the AEs reported were serious.
- A total of 5 of the 13 patients who discontinued DMF within 6 months of therapy initiation had received one prior DMT (Table 4).
- Of patients with a history of discontinuing prior DMT due to poor tolerability, the majority (82%, 14/17) remained on DMF therapy at 6 months.
- Among patients who discontinued DMF, 2 started glatiramer acetate for injection, 3 patients started teriflunomide, 3 started fingolimod, 2 started natalizumab, and 1 started alemtuzumab.

Nursing Perspective and Experience

- Monash MS Clinic has a dedicated MS nurse who provides support, including telephone support, to all newly diagnosed patients and any patients starting, switching, or continuing therapy.
- When initiating DMF, it is recommended that patients enroll in Biogen's patient support program, MS Alliance, so that they can receive extra support. MS Alliance nurses and the Monash MS Clinic Nursing service communicate regularly.
- The goal of educating and supporting patients during the first month of therapy with DMF is that problems with tolerability can be quickly identified and addressed.
- Education and setting realistic expectations are often the keys to treatment persistence.
- Patients are educated to contact MS Alliance or the MS Clinic at the first sign of any GI side effects.
- GI problems and/or flushing can be managed with a variety of interventions (eg, taking aspirin 30 minutes before DMF to address flushing; making sure patients have appropriate food in their stomach before taking DMF; administration of buscopan; slower retitration after a small break in treatment).
- When DMF became available, patients initially started treatment as per the Prescribing Information (PI).[3] Anecdotally, about a third of patients experienced some GI problem that was serious enough to report to nursing staff (either MS alliance or the Clinic nurse).
- Consultation with other centres led to the adoption of a titration protocol that titrates DMF more slowly than the PI recommendations (Table 4). This titration regimen has offered time and cost savings as the need for the physicians to utilise the 120mg starter dose has decreased.
- A US study revealed that using a somewhat similar, nurse-designed protocol significantly reduced the number discontinuations from 14 (12%) in patients using the standard manufacturer-recommended protocol to 5 (2.5%) in patients using the slower titration protocol (P=0.0029). Discontinuations related to GI side effects were 10 (8%) and 4 (1.9%), respectively (P=0.0215).[6]

Table 3. Patients who discontinued DMF within 6 months of therapy initiation by number of prior DMTs

Number of prior DMTs	Patients discontinuing DMF within 6 months of therapy initiation (N=13)
1	5
2	6
3	2

Table 4. Consensus DMF titration protocol.

Week	Dose
Week 1	120 mg QD
Week 2	240 mg QD
Week 3	120 mg morning; 240 mg night
Week 4	240 mg BID

CONCLUSIONS

- This study demonstrates that DMF has an acceptable tolerability profile in the real world setting.
- In the real world, 13% of patients discontinue DMF within 6 months of therapy initiation.
- Overall, 9% of patients discontinued due to GI tolerability issues.
- Dose changes due to AEs occurred in 15% of patients.
- Of patients with a history of poor tolerability to prior therapy, the majority of patients did not discontinue DMF at 6 months, suggesting that history of prior tolerability issues are not an indicator for tolerability to DMF.

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Disclosures

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