Real-Word Effectiveness and Safety of Dimethyl Fumarate in a Multiple Sclerosis Portuguese Population

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Objectives: The aim of this study was to evaluate postmarketing dimethyl fumarate (DMF) safety and effectiveness in a real-world population with relapsing-remitting multiple sclerosis (RRMS).

Methods: This was a retrospective, single-center study with RRMS patients treated with DMF. Demographic, clinical, and imagiological characteristics were analyzed, including annualized relapse rate (ARR), Expanded Disability Status Scale, "No Evidence of Disease Activity 3," previous treatment, adverse events, treatment duration, and reason for discontinuation. We investigated which baseline variables were associated with clinical and radiological outcomes.

Results: We included 176 patients (70.4% females) with a median on-treatment follow-up time of 25.5 months. In total, 139 patients received prior disease-modifying therapies, and 37 were treatment-naive. Annualized relapse rate decreased by 77.1% in the total population ($P < 0.001$) and also decreased in the naive, tolerability switch, and efficacy switch groups by 95.8%, 56.7%, and 76.6% ($P < 0.001$). No Evidence of Disease Activity 3 status after 12 months of DMF treatment was maintained in 69.2% patients. Thirty patients (17%) discontinued treatment because of adverse drug reactions, and 21 (11.9%) because of lack of effectiveness. The occurrence of first relapse during follow-up was associated with higher ARR in the year before DMF start (hazard ratio, 4.833; $P < 0.001$) and prior exposure to multiple sclerosis treatments (tolerability and efficacy switchers).

Conclusions: In this real-world audit, DMF appeared to be effective and safe for RRMS. Additionally, the study suggested that naive patients strongly benefit from DMF, and DMF also improves ARR in patients who switched from injectable therapies due to tolerability and efficacy issues.

Key Words: dimethyl fumarate, multiple sclerosis, Portugal, safety, treatment response

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Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of the central nervous system. It is the most common nontraumatic cause of neurologic disability in young people.[1]

In recent years, there have been considerable advances in the trialing and approval of an increasing range of disease-modifying therapies (DMTs), with currently more than 12 DMTs approved for relapsing forms of the disease. With increasing choices available, therapeutic management of relapsing-remitting multiple sclerosis (RRMS) has become more complex and individualized. Physicians must carefully balance efficacy, safety, and treatment escalation as clinically appropriate.[2]

Dimethyl fumarate (DMF), a fumaric acid ester, has been shown to have antioxidant, cytoprotective, and immunomodulatory actions. Previous studies demonstrated that DMF activates the nuclear factor–related 2 antioxidant pathway[3] and modulates immune response, by reducing T-cell levels (particularly clustering differentiation of $CD8^+$), switching lymphocyte phenotypes, reducing the number of memory cells, and increasing naive lymphocytes.[4–6]

Dimethyl fumarate has been approved as a first-line oral agent for the treatment of RRMS at a dose of 240 mg twice a day, based on the efficacy and safety profile demonstrated in 2 randomized phase III clinical trials, DEFINE[7] and CONFIRM.[8] In the DEFINE study, compared with placebo, treatment with DMF significantly reduced the annualized relapse rate (ARR) by 53%. In the CONFIRM trial, whereas the study was not designed to test the superiority or noninferiority of DMF versus glatiramer acetate (GA), DMF showed a significant reduction in ARR by 44% compared with 29% of AG. Disability progression, predefined by a 12-week confirmed increase in the Expanded Disability Status Scale (EDSS), was significantly reduced by 38% in DEFINE.[7]

The rate of adverse events (AEs) in these 2 trials was similar in all treatment groups, reporting mild or moderate flushing and gastrointestinal (GI) symptoms (36% and 42%, respectively).[7,8] In phase III clinical trials, flushing led to discontinuation of DMF in 3% of cases, and GI events were the cause of discontinuation in 4% of patients.[7,8] Those trials furthermore established that GI events and flushing were transient; that is, the incidences were highest during the first month of treatment and declined in the months thereafter.[7,8] Grade 3 lymphocytopenia (absolute lymphocyte count [ALC] $<0.5 \times 10^9$/L) developed in approximately 5% of patients.[7,8] Lymphocytopenia has been suggested to be a potential factor that may predispose to the viral central nervous system infection progressive multifocal leukoencephalopathy, which has been reported to occur rarely in patients treated with fumarates as well as with DMF.[9,10] Overall, the prevalence of progressive multifocal leukoencephalopathy under DMF treatment appears to be quite low.

Postmarketing real-world studies provide additional important insight into drug profile and are more representative of the MS population than randomized clinical trials. Moreover, they can help to identify the best candidate patients for DMF therapy and reduce the potential selection bias inherent to controlled clinical trials. However, only a few studies have been published regarding DMF use in everyday practice so far. Therefore, the aim of this study was to assess the effectiveness, tolerability, and safety of DMF in a real-world clinical setting in a tertiary center in Portugal.

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MATERIALS AND METHODS

Patient Group

We retrospectively analyzed data from patients with RRMS[11] who regularly attended our tertiary MS outpatient clinic and who started treatment with DMF up to August 2018. Our hospital is responsible for the treatment of nearly 900 MS patients.

All information was recorded as part of routine clinical practice. Data were collected in May 2019.

Patients were included in the study if they fulfilled the following criteria: age older than 18 years, confirmed diagnosis of MS according to the 2010 McDonald criteria,[11] RRMS, DMF treatment initiation after October 2014, and at least 6 months of follow-up data available.

Exclusion criteria were as follows: diagnosis of a progressive form of MS during data collection, treatment with any formulations of DMF or compounded fumarates prior to DMF treatment initiation, and concurrent enrollment in any interventional clinical trial of an investigational product during the study period.

This study was approved by all relevant ethics committees.

Study Measures

Demographic, clinical, and imaging characteristics of the disease were collected for all patients meeting eligibility criteria from medical case records. The following data were extracted: age, gender, age at disease onset, age at DMF initiation, disease duration, prior DMTs, DMF treatment duration, ARR and EDSS, magnetic resonance imaging (MRI) data, AEs, laboratory results, and reason for treatment discontinuation or withdrawal.

Annualized relapse rate analysis started when the previous therapy was initiated or in naive patients after the first manifestation of MS and ended with the last follow-up during DMF or at the time of DMF withdrawal.

A relapse was defined as the occurrence, recurrence, or worsening of symptoms of neurologic dysfunction lasting more than 24 hours and usually ending with a partial or complete remission.[12] Disease progression was defined by an increase of 1 point in the EDSS score (or 0.5-point increase for patients with baseline EDSS >5.0) sustained for at least 3 months.[13] Confirmed EDSS improvement was defined as a decrease of at least 1.0 point in the EDSS score sustained for 6 months. Expanded Disability Status Scale measurements within 30 days of a relapse were excluded to avoid bias of falsely elevated scores during a relapse. Magnetic resonance imaging activity was defined as the presence of new or enlarging T2 lesions and/or gadolinium-enhancing T1 lesions in a follow-up brain scan. Annualized relapse rate and disability progression were compared 12 months after treatment initiation. All MRI findings underwent quality control check, and incomplete reports were excluded.

Adverse events were coded by using the Medical Dictionary for Regulatory Activities and grouped according to System Organ Class and Preferred Term. Grades of lymphocytopenia were assigned according to the common terminology criteria for AEs[14]: grade 1, ALCs of 0.8×10^9/L lower limit of normal; grade 2, ALC greater than 0.5 to 0.8×10^9/L; grade 3, ALC greater than 0.2 to 0.5×10^9/L; and grade 4, 0.2×10^9/L or less.

At 12 months after DMF start, "No Evidence of Disease Activity 3" (NEDA-3) status was calculated.[15] In detail, NEDA-3 status at 12 months was evaluated by assessing its 3 components: (1) no confirmed disability progression, (2) no relapse activity, and (3) no imagiological activity. The 12-month confirmed disability progression was defined as (1) ≥1.5-point increase if EDSS = 0 at baseline, or (2) ≥1.0-point increase if EDSS = 0.5 to 4.5 at baseline, or (3) ≥0.5-point increase if EDSS ≥5.0 at baseline. Confirmed disease progression was assessed at least 6 months after the initial EDSS score. Expanded Disability Status Scale scores collected during MS relapses (±30 days) were excluded from the analysis.

Data Analysis

All analyses were performed using IBM SPSS Statistics for Macintosh (version 23.0; Armonk, NY). Simple descriptive statistical tests (mean and SD) were used to describe continuous variables. Qualitative variables were presented as frequencies and percentages. Median and interquartile ranges were used to describe nonnormally distributed variables. In our sample, almost all variables had a nonnormal distribution; we therefore opted to use nonparametric tests. The Wilcoxon signed ranks test was used to compare related continuous and related ordinal samples, and the Mann-Whitney *U* test was used to compare different groups of patients. The McNemar test was used to compare related nominal samples.

Subgroups of patients were characterized in 4 groups by different reasons for DMF start: (1) naive (first therapy), (2) tolerability switch (switch to DMF due to tolerability concerns); (3) efficacy switch (switch to DMF because of ineffectiveness with previous DMT); and (4) safety switch (switch to DMF due to safety concerns, namely, increased risk of serious infections).

Multivariate shared frailty Cox regression models for time to first relapse and time to DMF withdrawal were fitted, adjusted for demographical and clinical variables. The Cox models were fitted after having verified the hypothesis of proportional hazards, which was tested using the Schoenfeld residuals method. The hazard ratio (HR) test was used to calculate the difference between survival curves of the 4 groups. Logistic regression was performed to calculate the risk of presenting AEs in association with gender, age, and age at DMF start.

$P < 0.05$ was considered statistically significant, and 95% confidence intervals were used in the graphs.

RESULTS

Demographic Characteristics of Patients

Longitudinal data from 195 patients treated with DMF were identified, of which 19 were excluded because of incomplete or censored records.

A total of 176 patients were included, 37 (21.0%) were naive to treatment before starting DMF, 100 (56.8%) switched to DMF because of tolerance reasons (tolerability switch group), 36 patients (20.5%) switched to DMF because of lack of efficacy (efficacy switch group), and 3 (1.7%) switched to DMF because of safety concerns (safety switch group). All patients have been diagnosed with RRMS. Among the 139 switching patients, 65.5% switched from interferon β1a (IFN-β1a), 12.9% from IFN-β1b, 15.8% from GA, 3.6% from teriflunomide, 1.4% from natalizumab, and 0.7% from rituximab.

Demographical and clinical baseline characteristics of the total population and subgroups are summarized in Table 1. Demographical characteristics were not statistically different between groups, apart from the gender (Table 1). Annualized relapse rate was significantly higher in the tolerability switch group. Expanded Disability Status Scale and disease duration were significantly lower in the naive group, in comparison with the other 3 groups.

Effectiveness

Annualized Relapse Rate

Overall, there was a 77.1% decrease in the mean ARR when compared between 1 year before DMF and at last follow-up visit

TABLE 1. Demographic and Clinical Baseline Characteristics of Population

	Total (n = 176)	Naive (n = 37)	Tolerability Switch (n = 100)	Efficacy Switch (n = 36)	Safety Group (n = 3)	*P*
Female, n (%)	124 (70.4)	19 (52.8)	76 (76.0)	27 (75.0)	2 (66.7)	**0.037**
Age at MS onset (min–max), y	30.8 (18–71)	36.0 (18–64)	30.6 (18–71)	29.1 (18–53)	27.1 (21–29)	0.188
Age at DMF start (min–max), y	39.1 (18–78)	37.2 (18–65)	40.8 (20–78)	37.8 (22–60)	38.8 (31–62)	0.244
Disease duration (min–max), y	6.3 (0.1–33.3)	0.2 (0.1–15.4)	7.9 (0.6–23.4)	8.3 (0.7–19.4)	11.7 (10.2–33.3)	**<0.001**
Treatment duration (min–max), mo	25.5 (0.5–55.0)	23.5 (6.0–51.0)	26.0 (6.0–55.0)	28.0 (12–40.0)	37.0 (16.0–44.0)	0.296
EDSS prior to DMF (min–max)	1.0 (0–7.0)	1.0 (0–2.5)	1.0 (0–7.0)	1.0 (0–6.0)	2.0 (1.5–6.5)	**0.002**
ARR*	0.51 ± 0.70	0.95 ± 0.78	0.30 ± 0.54	0.64 ± 0.80	0.33 ± 0.58	**<0.001**
Prior MS treatment, n (%)						
Naive	37 (21.0)	—	—	—	—	**<0.001**
IFN-β1a	91 (51.7)	—	62 (62.0)	29 (80.6)	—	
IFN-β1b	18 (10.2)	—	16 (16.0)	2 (5.6)	—	
GA	22 (12.5)	—	17 (17.0)	5 (13.9)	—	
TFN	5 (2.8)	—	5 (5.0)	—	—	
NTZ	2 (1.1)	—	—	—	2 (66.7)	
Rituximab	1 (0.6)	—	—	—	1 (33.3)	

Bold font indicates statistical significance.

*Mean ± SD.

NTZ, natalizumab; TFN, teriflunomide; y, years; mo, months.

(0.51 ± 0.70 vs 0.11 ± 0.39, $P < 0.001$). Annualized relapse rate analysis of grouped patients disclosed that DMF significantly reduced ARR by 95.8% in the naive group ($P < 0.001$), by 56.7.6% in the tolerability switch group ($P = 0.001$), by 76.6% in the efficacy switch group ($P < 0.001$), and by 100% in the safety switch group (Fig. 1). Annualized relapse rate decreased in patients previously treated with interferons by 64.9% (0.37 ± 0.63 vs 0.13 ± 0.43, $P < 0.001$, n = 109) and in those pretreated with GA by 66.1% (0.59 ± 0.67 vs 0.20 ± 0.47, $P = 0.001$). This analysis was limited in patients with previously active immunotherapy (such natalizumab and rituximab) or with teriflunomide due to small sample size.

Considering the population with at least 12 months of follow-up (n = 152), there was a 90.2% decrease in ARR (0.51 ± 0.70 vs 0.05 ± 0.21, $P < 0.001$). We also performed ARR analysis in the 99 patients who had at least 24 months of follow-up and in 37 patients who had at least 36 months of follow-up. Overall ARR significantly decreased after 24 and 36 months of DMF treatment (0.46 ± 0.65 vs 0.04 ± 0.15, $P < 0.001$; and 0.51 ± 0.80 vs 0.03 ± 0.12, $P < 0.001$, respectively).

Relapse-Free

The proportion of the total population who were relapse-free during the follow-up period (25.5 months) was 85.8% versus 57.4% at pretreatment (12 months before DMF initiation; $P = 0.005$). At month 12, the proportion was 95.4% (vs 42.4%, $P = 0.023$; n = 152 patients); by month 24, the proportion was 93.9% (n = 99 patients); by month 36, the proportion was 94.6% (n = 37 patients); and by month 48, the proportion was 100% (n = 10 patients).

We explored which baseline variables were associated with relapse risk occurring during follow-up. A multivariate Cox model adjusted for gender, age at disease onset, age at DMF start, EDSS at DMF start, ARR 1 year before DMF start, and patient group (naive, tolerability group, efficacy group and safety group) showed that a higher ARR in the year before DMF start increased the risk of relapse by 4.833 (95% confidence interval [CI], 2.67–9.04; $P < 0.001$) (Fig. 2 and Supplementary Table, available at http://links.lww.com/CNP/A11). Risk of relapse was also associated with prior exposure to MS treatments, according to the reason for treatment switch. There was an increased risk of relapse in efficacy switch and tolerability switch groups versus naive group (HR, 1.09 [95% CI, 0.67–3.65; $P = 0.029$] and 2.12 [95% CI, 1.23–3.65; $P = 0.006$], respectively).

The median interval to first relapse was 12 months (interquartile range 11, 1–36 months). A second relapse was reported in only 2 patients, with a median time between the first and second relapse of 5 months (4–6 months).

NEDA-3 Status

One hundred sixty-eight patients (95.4%) had no disability progression, with no change in the median EDSS under DMF treatment (1.0 vs 1.0, $P = 0.836$), and there was a confirmed EDSS improvement in 9 patients (5.1%).

Considering the patients who performed a control MRI at 12 months (n = 146, 83.0%), 109 (74.7%) achieved no evidence of imagiological activity, 37 (25.3%) had new MRI T2 lesions, and 12 (8.2%) had new MRI T1 gadolinium-enhancing lesions.

The proportion of patients who maintained NEDA-3 status at 12 months was 69.2% (n = 101).

Safety and Tolerability

Treatment with DMF was maintained by 92.7% (n = 152) of patients at 12 months and by 79.8% (n = 99) of patients at 24 months.

Treatment was withdrawn by 55 patients (31.2%) during the follow-up period. Mean time to dropout was 20.0 ± 13.2 months. The main reason for dropout was the occurrence of any AE (17.0%; mean time to dropout, 17.4 ± 13.1 months), followed by ineffectiveness (11.9%; mean time to dropout, 20.4 ± 8.4 months), lack of compliance (1.1%), and pregnancy (1.1%). Of the patients who discontinued DMF, 16.4% (n = 9) did so within 6 months.

We performed a multivariate Cox model adjusted for age at DMF start, gender, ARR in the previous year, reason of DMF

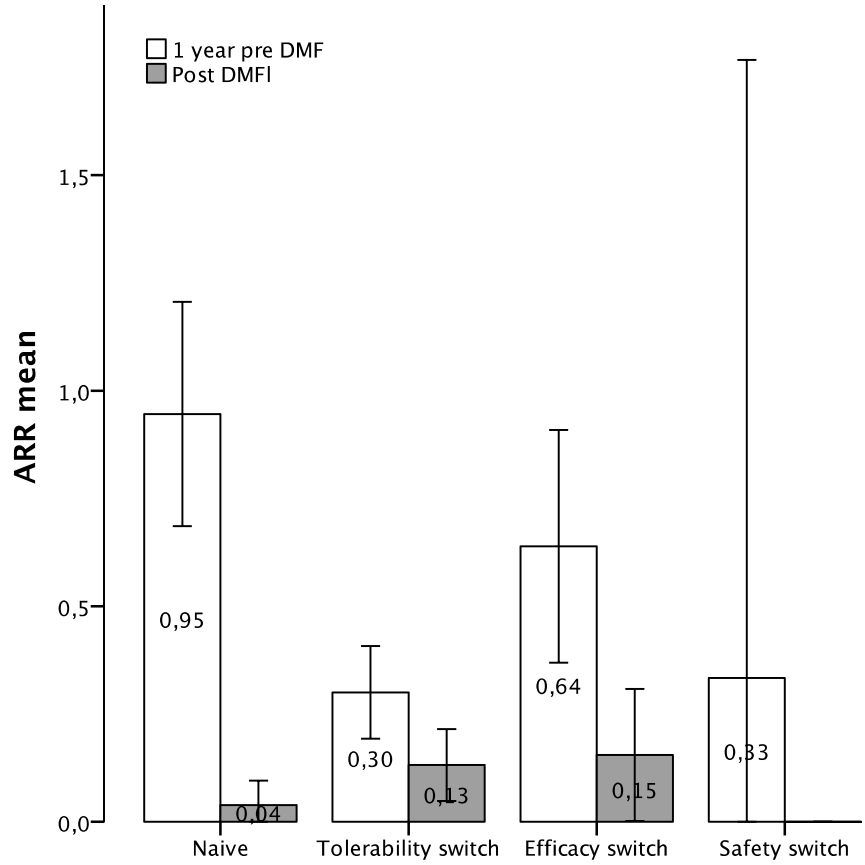

FIGURE 1. Annualized relapse rate in DMF therapy. Error bars indicate 95% confidence intervals.

start, presence of GI AEs, flushing, lymphocytopenia, presence of other AEs, being relapse-free on DMF, and ARR at last follow-up. The risk of dropout was increased by 0.5 times in patients with lymphocytopenia (HR, 0.5; 95% CI, 0.3–1.0; $P = 0.043$). Grade 3 lymphocytopenia increased the risk of dropout by 1.7 times (95% CI, 0.1–2.4; $P < 0.001$). Annualized relapse rate at last follow-up was also associated with an increased risk of DMF discontinuation (HR, 1.1; 95% CI, 1.0–4.7; $P < 0.001$).

Overall, 73.9% of patients reported at least 1 AE during follow-up (Table 2). The most frequent adverse effects were flushing and GI AEs, reported at least once by 81 patients (46%). No opportunistic infections occurred. One patient reported a severe AE (stroke), which are not related to DMF.

The most frequent laboratory testing abnormalities was lymphocytopenia (25.6%). Lymphocytopenia was mostly mild to moderate. Only 5.1% withdrew from DMF because of lymphocytopenia.

We identified no factor significantly associated with flushing, GI AEs, and lymphocytopenia in this cohort.

We found that treatment discontinuation was lower in treatment-naive patients compared with switchers; the OR for discontinuation was 1.5 among switchers (95% CI, 0.07–0.65; $P = 0.006$).

DISCUSSION

Randomized controlled trials provide high-level evidence of the efficacy of a therapy under ideal conditions, which are usually not illustrative of the clinical context in which a medication is used in real-world clinical practice. Therefore, postmarketing observational studies are crucial to confirm long-term safety and effectiveness.

In recent years, numerous DMTs have been approved, which has increased the complexity of the MS treatment algorithm. There are reports that horizontal switching may have positive effects.[16,17] However, in clinical practice, it is still an ongoing discussion which strategy is best for optimizing MS treatment. Data from clinical studies do not provide enough information for individual treatment decisions. Real-world data are increasingly used for comparison studies to examine therapy choice and sequencing decisions.

Our research was performed in a real-world setting to verify the effectiveness, tolerability, and safety of DMF when administered in clinical practice. To our knowledge, this is the first study that analyzed Portuguese population treated with DMF.

In this cohort, we found that DMF was associated with improvements in clinical outcome measures in patients with RRMS after a median observational period of 25.5 months. The results of our study regarding effectiveness were similar to those reported in clinical trials. In our cohort, DMF significantly reduced ARR by 77.1% after a follow-up period of 25.5 months and the proportion of relapse-free patients at 24 months was 93.9%, which is slightly better than what was observed in the DEFINE and CONFIRM trials.[7,8] The analysis of subgroups of patients divided according to the reason of DMF start emphasized that DMF significantly reduces ARR not only in naive patients, but also in those who switched to DMF due to efficacy, tolerability, and safety reasons.

In the present study, DMF reduced ARR by 64.9% in patients previously treated with interferons and by 66.1% in those

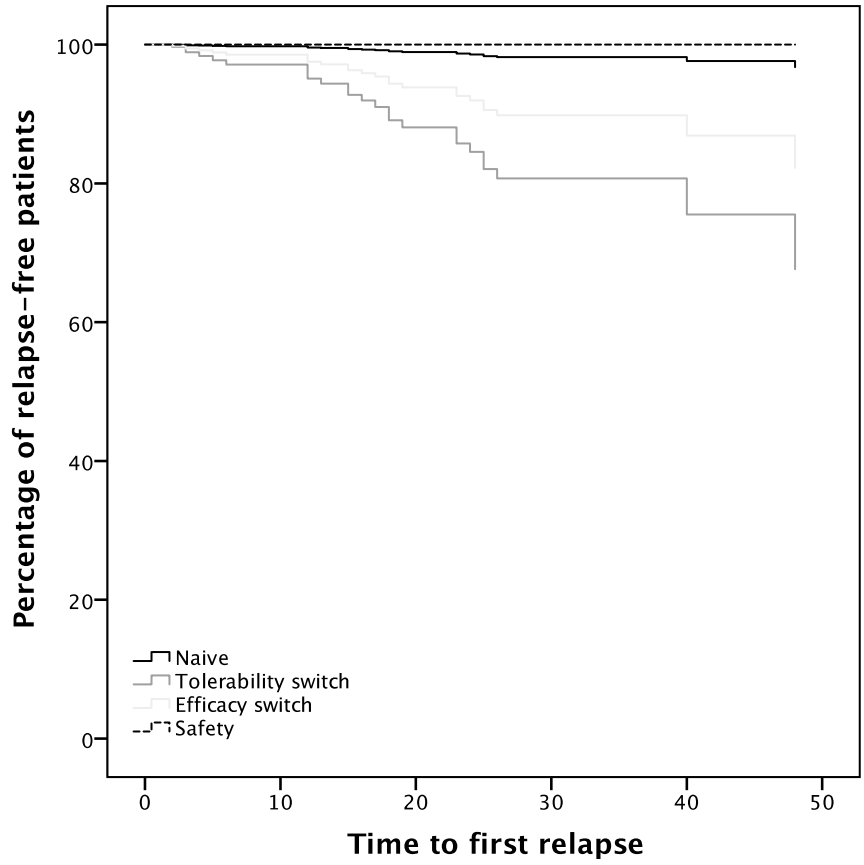

FIGURE 2. Survival curves for "first relapse" in different groups of patients according to previous therapy.

patients who switched from GA. Those results are similar to that reported in other studies.[18,19]

However, using a Cox regression model, we analyzed which baseline features increased the risk of relapse in our population. We found that a higher ARR in the previous year and patients who switched from other DMTs (namely, efficacy and tolerability switch) increased the risk of relapse. Thus, our study showed that DMF is more effective in patients naive to treatment and with low to moderate disease activity. This result could help to individualize treatments based on clinical variables.

TABLE 2. Adverse Events Reported During DMF Treatment

Adverse Events	Patients, n (%)
GI symptoms	
Abdominal pain	47 (26.7)
Diarrhea	26 (14.8)
Nausea	19 (9.6)
Vomiting	10 (5.7)
Flushing	81 (46.0)
Infections	
Upper respiratory infections	12 (6.8)
Urinary tract infections	4 (2.3)
Others	1 (0.6)
Lymphocytopenia	
Grade 1 (lymphocyte count >0.8–0.9 × 10^9/L)	14 (8.0)
Grade 2 (lymphocyte count >0.5–0.8 × 10^9/L)	18 (10.2)
Grade 3 (lymphocyte count >0.2–0.5 × 10^9/L)	13 (7.4)
Elevated liver enzymes	3 (1.7)
Stroke	1 (0.6)

In our population, the proportion of patients who maintained NEDA-3 status after 12 months of treatment was higher than those reported in the integrated post hoc analysis of DEFINE/CONFIRM studies (approximately 40%),[20] but it was similar to a multicenter Italian cohort.[21] In our study, NEDA-3 value at month 12 was likely overestimated by the high percentage (56.8%) of clinically stable patients—tolerability switchers.

In our cohort, with a median follow-up of 25.5 months, 31.2% of patients discontinued DMF, mainly due to lack of tolerability. This is very similar to the discontinuation rate observed in the clinical trials[7,8] and is also in agreement with results from German (28.7%),[18] Italian (30%),[21] and Dermark[22] groups. In our study, discontinuation rate is more frequent in switchers than in naives, which possibly reflects the more aggressive form of disease in patients who switch to DMF or an individual predisposition to poor tolerability.

Despite the percentage of GI AEs and flushing being higher in our cohort compared with other published studies and clinical trials, only 17% of patients withdrew from DMF because of AEs (similar to other study[18]). This divergence can be explained by the presence of an internal guideline for the management of these 2 major AEs. In our center, in cases of GI AEs, a slow titration and an intermediate dose of DMF increased tolerability. Managing patient expectations and handling tolerability issues with symptomatic treatment are essential as suggested in previous publications.[23]

Approximately, a quarter of our population developed at least grade 1 lymphocytopenia, which is lower than the results of DEFINE and CONFIRM.[7,8] This difference may be explained by the more frequently performed measurements over a longer period in the phase III clinical trials.

The limitations of our study are mostly related to the retrospective nature of data collection. Magnetic resonance imaging data were not available for all patients because some had not performed MRI at our institution. Another significant limitation is that information comes from a single center. Its strength, however, is that patients were followed up at regular intervals with clinical assessments, which led to increased undoubtedly regarding safety issues.

The results from this noninterventional study demonstrate the sustained effectiveness of DMF in the treatment of patients with RRMS over a median 2-year period. The safety profile of DMF remains favorable and is consistent with that reported in other studies and clinical trials. Our study also showed that DMF improves ARR of naive patients and is safe and effective in switcher patients.

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