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Dimethyl fumarate in the treatment of multiple sclerosis: real-world effectiveness in a Turkish cohort

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Background: Dimethyl fumarate (DMF) is approved as a first-line treatment in relapsing-remitting multiple sclerosis (RRMS).

Aim: To evaluate the demographic, clinical, and radiological outcomes of DMF treatment in a real-world setting.

Study design: Multicenter retrospective study based on data from 61 clinics across Türkiye.

Methods: Side effects, leukocyte and lymphocyte counts, liver enzymes, EDSS (Expanded Disability Status Scale), and upper- and lower-extremity test results were evaluated in patients with RRMS before DMF initiation and at 1, 6, 12, and 24 months. Additionally, NEDA-3 (No Evidence of Disease Activity-3) status was assessed at the 1 and 2-year follow-ups.

Results: 1,749 patients participated in this retrospective study. The most common side effects were flushing and gastrointestinal symptoms, which were more frequent in women and in patients with lower weight and lower Body Mass Index (BMI). Leukocyte and lymphocyte counts initially decreased and then

stabilized, whereas transient elevations in liver enzymes resolved during follow-up. EDSS scores showed a significant improvement beginning at the 6-month follow-up. Performance on the Nine-Hole Peg Test (9HPT) improved, whereas no significant change was observed in the Timed 25-Foot Walk (T25FW). In addition, approximately 70% of the patients achieved NEDA-3 status at both the 1 and 2-year follow-ups.

Conclusion: DMF demonstrated a favorable safety profile and was associated with significant improvements in EDSS while maintaining NEDA-3 status in approximately 70% of patients with RRMS. Adverse events occurred more frequently among women and among patients with lower body weight and lower BMI.

KEYWORDS

dimethyl fumarate, EDSS, multiple sclerosis, NEDA-3, real-life study, side effect

Introduction

Multiple Sclerosis (MS) is characterized by demyelinating and axonal damage of the central nervous system. Immunomodulatory therapies (IMTs) treat MS based on efficacy and safety data. Following the introduction of the first IMT approximately 30 years ago, many options have emerged (1). In recent years, oral tablets and capsules have been added to the injectable IMTs (2). Many treatment options are currently available in the form of injections, oral formulations, and infusions.

Efficacy data for IMTs are based on phase trials and subsequent extension studies. However, clinical experience and the resulting real-world data are also very instructive. Data obtained over a longer period, with the participation of a large number of patients and centers, is also valuable. Dimethyl fumarate (DMF) is one of the first-line MS treatments used orally twice daily worldwide (3). Although similar studies have been conducted for DMF (4–7), further studies involving more centers and a larger number of patients are needed. The present study aimed to obtain real-world efficacy and safety data on the use of DMF in treating MS in a multicenter study in Türkiye.

Methods

Study design

After the Ondokuz Mayis University Clinical Research Ethics Committee approved the study protocols (03.03.2021-2021/129), data on MS patients using DMF were collected from 61 clinics in Türkiye. The following data were obtained from the follow-up systems of the patients whose records and clinical follow-ups were available in the relevant centers: (1) Demographic characteristics (gender, age, height, weight, etc.), (2) Clinical profile [Expanded Disability Status Scale (EDSS), DMF usage time and order, comorbidity, side effects, etc.], (3) Laboratory findings (complete blood count, ALT, AST, etc.), (4) Clinical tests (25-Foot Walk Test, 9-Hole Peg Test), and (5) No Evidence of Disease Activity-3 (NEDA-3) status. NEDA-3 was defined as the absence of clinical relapses, new or newly enlarging T2 lesions, gadolinium-enhancing lesions on MRI, and disability progression. Disability progression was defined as an increase in EDSS of $\geq$1.0 points from baseline for patients with a baseline EDSS $\leq$5.0 or $\geq$0.5 points for patients with a baseline EDSS $>$5.0. Data were recorded at baseline (before DMF initiation) and at 1, 6, 12, and 24 months after treatment initiation. The number of patients included in each analysis is presented in the corresponding figures.

As this was a retrospective real-world study, data availability varied across patients and follow-up time points. Therefore, analyses were performed using the available data for each outcome variable and time point, and missing values were not imputed. The number of patients included in each analysis was reported according to the availability of relevant data. Inter-center variability was not specifically adjusted for, as neurological assessments, laboratory testing, MRI evaluation, and EDSS scoring were performed in accordance with routine clinical practice at each participating center. Sensitivity analyses were not performed due to the retrospective study design and the variable availability of follow-up data.

Patients were eligible for inclusion if they had a confirmed diagnosis of RRMS, were receiving DMF in routine clinical practice, and had baseline demographic and clinical data available at the participating centers. Previous disease-modifying therapy (DMT) exposure, comorbidities, and incomplete follow-up were not considered exclusion criteria, as the study was designed to reflect real-world clinical practice. Accordingly, patients were included in each analysis based on the availability of data at the respective follow-up time point.

Statistical analysis

Statistical analyses were performed using SPSS (v25.0; IBM Corp., Armonk, NY, USA). Longitudinal changes in laboratory test results and EDSS scores were evaluated using a repeated-measures mixed-effects model. When the assumption of sphericity was violated, the Greenhouse-Geisser correction was applied. The Tukey *post hoc* test was used for multiple comparisons with the baseline measurement. The associations of the factors (age, sex, BMI, smoking, disease duration, DMF use duration, comorbidity, EDSS, and time to reach the effective treatment dose) with side effects (positive vs. negative) were assessed using univariable and multivariable logistic regression analyses. The chi-square test was

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TABLE 1 Demographic and clinical profile of the study participants.

Variables	Values
Age (mean ± SD)	36.24 ± 10.60
Sex (male/female, *n*)	551/1,198
Weight, kg (mean ± SD)	69.56 ± 12.62
BMI (mean ± SD)	25.02 ± 4.00
Disease duration, year (mean ± SD)	5.08 ± 5.23
EDSS	1.49 ± 1.05
DMF usage time, year (mean ± SD)	1.82 ± 1.10
DMF usage order, *n* (%)	
1st choice	1,159 (66)
2nd choice	476 (27)
3rd choice and more	114 (7)
Time to reach the ETD, day (mean ± SD)	22.79 ± 8.13
Smoking status (Yes/Quit/Never)	413/458/878
Comorbidity, *n*	
Hypertension	48
Cardiac disease	19
Diabetes mellitus	43
Secondary autoimmune disease	54
Others	109

BMI, Body Mass Index; EDSS, Expanded Disability Status Scale; DMF, dimethyl fumarate; ETD, effective treatment dose.

used to compare the distribution of side effects across doses between males and females. Statistical significance was defined as a *p*-value < 0.05.

Results

Before statistical analyses, data quality was assessed. Three observations identified as extreme outliers using the interquartile range (IQR) method (lower limit: Q1 – 1.5 × IQR; upper limit: Q3 + 1.5 × IQR) were considered implausible values and excluded from the analyses to improve the reliability of the results.

After applying the study eligibility criteria and data quality assessment, a total of 1,749 patients with RRMS receiving DMF were included in the study. The mean age was 36.24 ± 10.60 years, and the female/male ratio was 2.17. The mean disease duration was 5.08 ± 5.23 years, and the mean DMF use duration was 1.82 ± 1.10 years. Demographic and clinical characteristics of the patients are presented in Table 1.

Compared with baseline, leukocyte levels decreased after 1 month of DMF use ($p < 0.001$). Furthermore, a significant decrease was observed at 6 months compared with 1 month ($p < 0.001$). Blood leukocyte levels were 7,735 ± 2,775, 7,086 ± 2,166, 6,377 ± 1,870, 6,466 ± 2,124, and 6,274 ± 2,017/ at baseline, 1, 6, 12, and 24 months, respectively (Figure 1A).

Lymphocyte levels decreased after 1 month of DMF use compared with baseline ($p < 0.001$). A further significant decrease was observed at 6 months compared with 1 month ($p < 0.001$). Lymphocyte counts were 2,078 ± 865, 1,871 ± 720, 1,539 ± 578, 1,498 ± 648, and 1,469 ± 626/μl at baseline, 1, 6, 12, and 24 months, respectively (Figure 1B).

ALT and AST levels increased at 1 month compared with baseline (both $p < 0.001$), followed by a significant decrease at 6 months compared with 1 month ($p < 0.001$). ALT levels at baseline, 1, 6, 12, and 24 months were 21.08 ± 15.24, 26.11 ± 20.16, 21.86 ± 15.74, 19.85 ± 13.01, and 20.45 ± 12.95 U/L, respectively (Figure 1C). AST levels at baseline, 1, 6, 12, and 24 months were 19.41 ± 10.37, 22.18 ± 14.10, 19.87 ± 11.38, 18.46 ± 7.59, and 19.35 ± 11.48 U/L, respectively (Figure 1D).

The EDSS score showed a significant decrease at 6 months compared with baseline ($p < 0.001$) and remained significantly lower than baseline at 12 and 24 months (both $p < 0.001$). The EDSS scores at baseline, 6, 12, and 24 months were 1.49 ± 1.05, 1.25 ± 1.01, 1.24 ± 1.12, and 1.22 ± 1.22, respectively (Figure 2A).

No significant differences were observed in the 25-foot walk test over the follow-up period (Figure 2B). The 9-hole peg test time for the dominant hand showed significant decreases at 6, 12, and 24 months compared with baseline (all $p < 0.001$). A further significant decrease was observed at 24 months compared with both 6 and 12 months (both $p < 0.001$). The 9-hole peg test times for the dominant hand at baseline, 6, 12, and 24 months were 21.65 ± 4.59, 20.95 ± 4.34, 20.61 ± 4.24, and 18.97 ± 4.61 s, respectively (Figure 2C). For the non-dominant hand, significant decreases were observed at 6, 12, and 24 months compared with baseline (all $p < 0.001$). The decrease at 24 months was also significant compared with 6- and 12-month measurements (both $p < 0.001$). The corresponding values for the non-dominant hand were 23.14 ± 5.29, 22.56 ± 5.04, 22.33 ± 4.94, and 21.17 ± 6.71 s, respectively (Figure 2D).

In the univariable logistic regression analysis, sex, BMI, and weight were significantly associated with the occurrence of side effects. Female sex (OR = 1.367, 95% CI: 1.095–1.706; $p = 0.006$), higher BMI (OR = 1.057, 95% CI: 1.027–1.087; $p < 0.001$), and higher weight (OR = 1.023, 95% CI: 1.013–1.032; $p < 0.001$) were associated with increased odds of side effects. In the multivariable logistic regression analysis, which included age, sex, BMI, weight, disease duration, DMF use duration, and pre-treatment EDSS as covariates, only weight remained significantly associated with side effects (OR = 1.022, 95% CI: 1.001–1.043; $p = 0.038$) (Table 2).

At a dose of 2 × 120 mg, side effects were more frequent among males (OR = 1.906, 95% CI: 1.204–3.040; $p = 0.006$), whereas at a dose of 1 × 120 mg + 1 × 240 mg, side effects were less frequent among males (OR = 0.510, 95% CI: 0.287–0.909; $p = 0.023$; Table 3).

NEDA-3 status at 1 and 2 years was assessed in 899 and 556 patients, respectively, as shown in Figure 3.

Discussion

DMF, one of the first-line therapies in MS treatment, is usually prescribed as an initial treatment (3, 6) as in the present study. While the overall safety and tolerability profile of DMF is favorable, patients often experience flushing and gastrointestinal complaints such as diarrhea, nausea, abdominal pain, vomiting, and dyspepsia (8). In this study, 38% of patients experienced side effects; the

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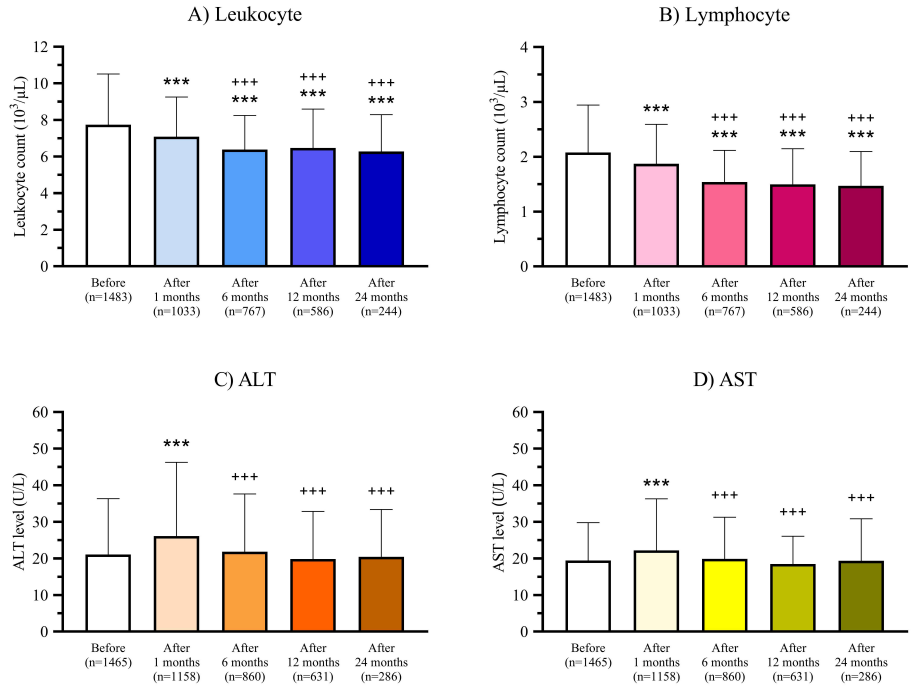


FIGURE 1
Laboratory follow up results. **(A)** Leukocyte levels, **(B)** Lymphocyte levels, **(C)** ALT levels, **(D)** AST levels. ***$p < 0.001$ compared to before DMF, $^{+++}p < 0.001$ compared to after 1 month of use of DMF. ALT, Alanine Transaminase; AST, Aspartate Transaminase.

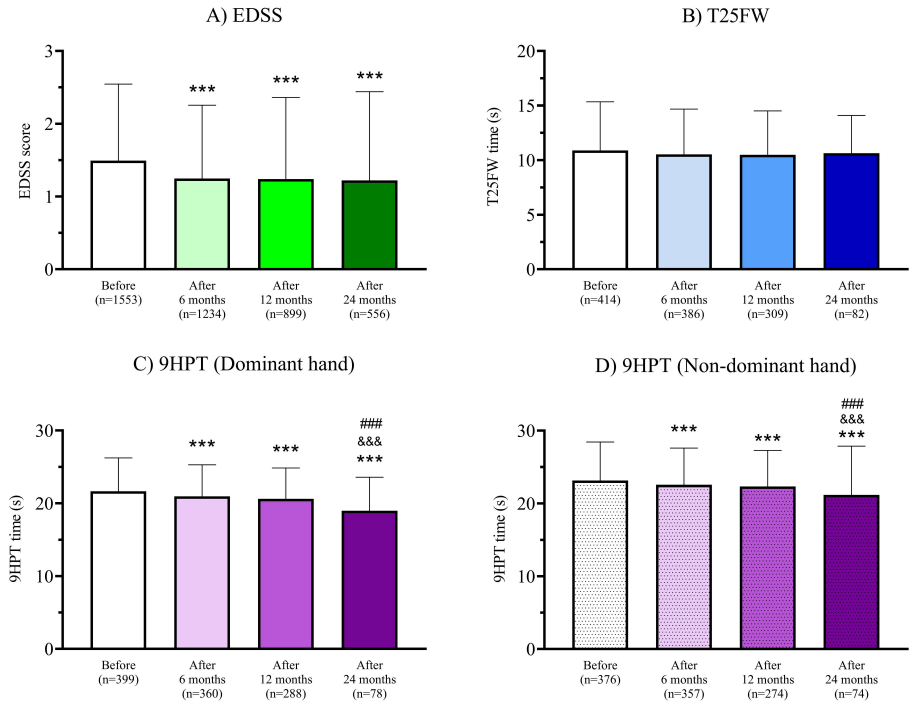


FIGURE 2
EDSS, upper and lower extremity tests. **(A)** EDSS scores, **(B)** T25FW time, **(C)** 9HPT dominant hand, **(D)** 9HPT non-dominant hand. ***$p < 0.001$ compared to before DMF, $^{\&\&\&}p < 0.001$ compared to after 6 months of use of DMF. $^{\#\#\#}p < 0.001$ compared to after 12 months of use of DMF. EDSS, Expanded Disability Status Scale; T25FW, Timed 25-Foot Walk Test; 9HPT, Nine-Hole Peg Test.

most common were gastrointestinal symptoms and flushing, with lymphopenia being the only other side effect. On the other hand, side effects lasted for an average of 37.7 days. When the demographic data of patients with side effects were analyzed, univariable analysis showed that side effects were more common in women and patients with low BMI and weight. Furthermore, since low weight was also

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TABLE 2 Factors causing side effects during dimethyl fumarate therapy.

Variable	Side effect ($n = 1,594$)		Univariable analysis ($n = 1,594$)		Multivariable analysis ($n = 1,594$)	
	Positive (+) $n = 606$	Negative (−) ($n = 988$)	OR (95% C.I.)	p	OR (95% C.I.)	p
Age (mean ± SD)	36.20 ± 10.33	36.23 ± 10.77	1.000 (0.991–1.010)	0.966	—	—
Sex (female/male; *n*)	439/167	650/338	1.367 (1.095–1.706)	**0.006**	—	—
BMI (mean ± SD)	24.54 ± 3.97	25.41 ± 4.04	1.057 (1.027–1.087)	**<0.001**	—	—
Weight, kg (mean ± SD)	67.54 ± 12.56	70.95 ± 12.52	1.023 (1.013–1.032)	**<0.001**	1.022 (1.001–1.043)	**0.038**
Smoking (*n*) Never	357	552	Ref.	0.33	—	—
Quit	87	155	1.128 (0.882–1.442) 1.159	7	—	—
Active	162	281	(0.852–1.578)	0.348	—	—
Disease duration, year (mean ± SD)	5.38 ± 5.29	4.98 ± 5.29	0.986 (0.967–1.005)	0.148	—	—
DMF use duration, year (mean ± SD)	1.76 ± 0.95	1.84 ± 1.19	1.065 (0.968–1.171)	0.198	—	—
Comorbidity (available/none; *n*)	85/513	136/860	0.952 (0.703–1.289)	0.749	—	—
EDSS (mean ± SD)	1.57 ± 1.06	1.48 ± 1.04	0.924 (0.835–1.022)	0.123	—	—
Time to reach the ETD, day (mean ± SD)	23.10 ± 8.67	22.73 ± 7.72	0.993 (0.978–1.007)	0.328	—	—

OUTCOME = Side effect positive vs negative. Multivariable logistic regression analysis was performed including age, sex, BMI, weight, disease duration, DMF use duration, and pre-treatment EDSS as covariates. Bold values indicate statistical significance ($p < 0.05$). BMI, Body Mass Index; DMF, Dimethyl fumarate; EDSS, Expanded Disability Status Scale; ETD, Effective Treatment Dose.

TABLE 3 Comparison of different doses of dimethyl fumarate with gender and side effect types.

Parameters	Doses			
	1 × 120 ($n = 258$)	2 × 120 ($n = 145$)	1 × 120 + 1 × 240 ($n = 51$)	2 × 240 ($n = 152$)
Female, side effect, *n*/total (%)	188/439 (43)	118/439 (27)	30/439 (7)	103/439 (23)
Male, side effect, *n*/total (%)	70/167 (42)	27/167 (16)*	21/167 (13)+	49/167 (29)
Side effect types, *n*				
GIS	57	60	25	59
Flushing	149	38	16	40
GIS + Flushing	32	20	3	20
Other	20	27	7	33

GIS, gastrointestinal system.
*$p = 0.006$ compared to the female 2 × 120 dose.
+$p = 0.023$ compared to the female 1 × 120 + 1 × 240 dose.

significant regarding side effects in multivariable analysis, patients with low weight may be more likely to develop side effects.

In treating multiple sclerosis, laboratory values are monitored in specific periods. A decline in lymphocyte levels is an expected finding in patients using DMF (9, 10). On the other hand, it is speculated that there may be a relationship between the development of progressive multifocal leukoencephalopathy and lymphocyte levels (11, 12). Fox et al. noted that a decrease in absolute lymphocyte count typically occurs during the first year of treatment and stabilizes (10). In this study, we observed a decline in lymphocyte levels 1 month after the onset of DMF, which further increased in the sixth month and remained stable until the end of year two. However, no severe lymphopenia was observed in any patient.

In pre-approval trials, an increased incidence of mild, transient elevations in liver aminotransferase levels was observed among participants treated with DMF (13). Moreover, according to phase III studies, abnormal liver function test results were reported in up to 50% of patients and were classified as moderate in 6% and severe in 2% (14–16). In the present study, significant elevations in liver enzymes (AST and ALT) were observed in the first month

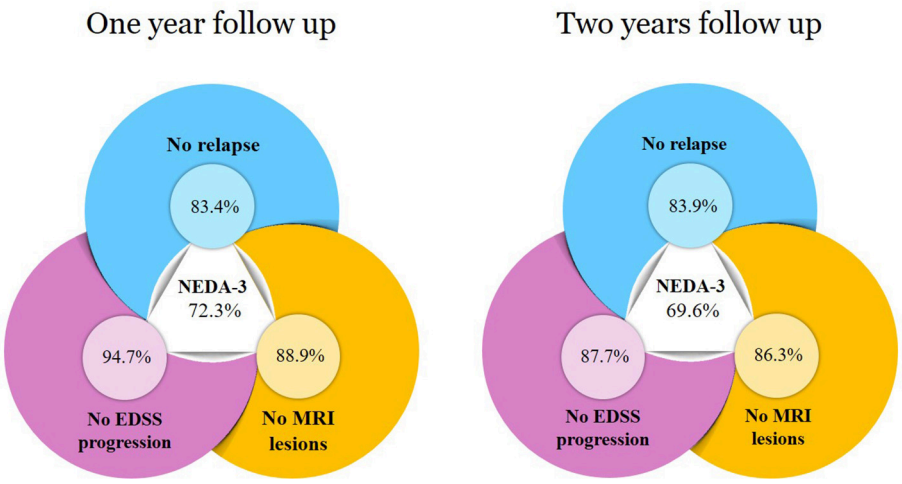


FIGURE 3
First (n = 899) and second (n = 556) year NEDA-3 (no evidence of disease activity-3) results.

after treatment initiation. However, this situation returned to pre-treatment values in the follow-up controls and indicated safe use.

Upper- and lower-extremity functions, part of the multiple sclerosis functional composite, were also evaluated to assess efficacy (17, 18). Although a statistically significant reduction in EDSS was observed during follow-up, the magnitude of this change was relatively small. Therefore, statistical significance should not necessarily be interpreted as clinical significance. Given the lack of a universally established minimal clinically important difference (MCID) for EDSS in this real-world cohort, the clinical relevance of this change should be interpreted with caution. During the 2-year follow-up, no significant change was observed in the T25FW test of lower-extremity function. However, positive changes were observed on the 9HPT test of upper-extremity function in the first and second years. The possible reason for the lack of significant changes in gait function may be that most of our patients were newly treated patients with low disability. It is possible that we did not observe an improvement in the test's effect on patients whose lower-extremity function was already impaired.

NEDA (No Evidence of Disease Activity) status was calculated for the first and second years for patients who completed these periods. Achieving NEDA status at approximately 70% indicates that DMF is used as a first-line treatment with high efficacy, especially in the MS cohort, which has many naive patients. However, NEDA data are also lower than in our study among patient groups with higher rates of switching from other first-line treatments (4, 5, 19, 20). DMF was the most effective first-line IMT according to the stepwise treatment practice implemented in the present study. The fact that the patients in our cohort who received DMF frequently consisted of patients who received this treatment as the first-line treatment option shows that it has become an accepted opinion in our country that highly effective drugs should be the primary treatment option in MS treatment. In addition, the fact that this application revealed first- and second-year NEDA-3 results of up to 70% also emphasizes the early use of higher-efficacy treatments.

Our study is one of the largest multicenter real-world studies evaluating DMF treatment in patients with MS. Nevertheless, several limitations should be acknowledged. First, the retrospective design and incomplete follow-up data may have introduced potential selection, information, and reporting biases. However, no patients were excluded based on follow-up availability, and analyses were performed using the available data at each time point. The availability of follow-up data may have introduced selection bias and could have influenced the observed efficacy and safety outcomes. Second, the absence of an untreated or comparator group and the lack of propensity score-based adjustment limit the assessment of causal relationships; therefore, the observed improvements cannot be attributed solely to DMF treatment. Third, the inclusion of data from 61 centers may have introduced inter-center variability in clinical, laboratory, MRI, and EDSS assessments, as MRI acquisition protocols and clinical assessments were not centrally standardized. Fourth, the limited number of patients with regular functional assessments restricted the evaluation of the 25-Foot Walk and 9-Hole Peg Tests. Fifth, the relatively short follow-up period may have limited the assessment of long-term efficacy and safety outcomes. Finally, functional and patient-reported outcomes were not systematically assessed in all patients, limiting the evaluation of the clinical significance of observed changes. Further prospective studies with longer follow-up, standardized assessments, and appropriate comparator groups are warranted.

In conclusion, DMF use was associated with favorable clinical outcomes, including a reduction in EDSS and approximately 70% NEDA-3 rates at 1 and 2 years. Although the reduction in EDSS was statistically significant, its relatively small magnitude warrants cautious interpretation regarding its clinical relevance. Given the observational design and the absence of a comparator group, these findings should not be interpreted as evidence of a causal treatment effect. Flushing and gastrointestinal symptoms were the most common side effects, and lower weight was independently associated with an increased likelihood of side effects. Overall, these findings provide real-world evidence on the safety, tolerability, and clinical outcomes of DMF use in patients with MS.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ondokuz Mayis University Clinical Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because patient data was obtained through retrospective file review. This data does not contain any personal or private information. Therefore, informed consent was not obtained.

Author contributions

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