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ORIGINAL RESEARCH

Effectiveness and Safety of Dimethyl Fumarate Treatment in Relapsing Multiple Sclerosis Patients: Real-World Evidence

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ABSTRACT

Introduction: Dimethyl fumarate (DMF) has been recently approved as a disease-modifying therapy for the treatment of multiple sclerosis (MS). Post-marketing studies are important to confirm what was established in clinical trials.
Objective: To evaluate effectiveness and safety of DMF and to measure the occurrence of lymphopenia in a cohort of MS patients in a clinical setting.
Methods: Using the national MS registry, we prospectively assessed relapsing MS patients who had been prescribed DMF for at least 6 months. Primary outcome measure was the proportion of relapse-free patients at last follow-up visit. Secondary outcome measures were the mean change in expanded disability status scale (EDSS) and the proportion of patients with radiological activity (gadolinium-enhancing or new T2 lesions) at the last follow-up visit. Absolute lymphocyte count (ALC) was assessed at baseline (within 6 months prior to DMF initiation) and at one or more times during DMF treatment 3 months post-initiation.
Results: Of 134 patients identified, 119 were eligible and included in the analysis. Women represented 59.7% of the studied cohort. Mean age and mean disease duration were 33.5 ± 11.1 and 8.3 ± 7 years, respectively. A total of 75.6% of the patients received prior disease-modifying therapies. Mean duration of DMF exposure was 20.5 ± 9.5 months. The proportion of relapse--free patients increased significantly from 51.2% to 89.9% ($p < 0.0001$), while the mean EDSS score decreased from 2.8 ± 1.8 at baseline to 2.3 ± 1.7 ($p < 0.058$) at last follow-up visit. The proportion of patients with MRI activity decreased significantly from 61.1% to 15.1% ($p < 0.0001$). The mean ALCs decreased from 2170 to 1430 cells/μl (34% decrease). Lymphopenia was seen in 13 (10.9%) patients, of whom 3 (2.5%) patients had grade 3 lymphopenia necessitating discontinuation of DMF. Although no serious adverse events were reported, 19.3% of patients discontinued DMF.

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Conclusion: In clinical practice, DMF appeared to be effective in reducing disease activity and progression of disability throughout the observational period. DMF was well tolerated with no serious adverse events. ALC profiles in DMF-treated patients were generally stable throughout the observational period. The proportion of patients who developed severe lymphopenia was similar to figures in clinical trials.

Keywords: Dimethyl fumarate; Kuwait; Lymphopenia; Multiple sclerosis; Safety

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease affecting more than 2.3 million people worldwide [1]. Dimethyl fumarate (DMF) has been approved as a disease-modifying therapy for the treatment of relapsing MS [2]. The proposed mechanism of action of DMF involves the activation of nuclear factor-related 2 (Nrf2) pathway resulting in augmenting the antioxidative capacities, and hence reducing inflammation [3]. Phase II and III clinical trials showed that DMF was effective in reducing both clinical and radiological disease activity [4–6]. Few adverse events were reported in phase III clinical trials that included lymphopenia (grade 3; absolute lymphocyte count <500), which developed in approximately 5% of patients [5, 6]. We aimed to prospectively assess relapsing MS patients who were treated with DMF, in terms of effectiveness, tolerability, and safety in addition to the rate of occurrence of lymphopenia in a real clinical sitting.

METHODS

We conducted a prospective study utilizing the national MS registry to evaluate relapsing MS patients who were prescribed 240 mg DMF twice a day. The registry was established in 2010 in Kuwait after combining the databases of all major hospitals [7]. All patients who were entered in the registry were followed prospectively; as per the registry protocol, patients had at least two scheduled visits per year. The treating neurologist evaluated patients at unscheduled visits if there were any new neurologic symptoms suggestive of relapse or if they had experienced side effects. Neurological examinations, including assessment of expanded disability status scale (EDSS), were performed every 6 months [8]. Magnetic resonance imaging (MRI) of the brain and cervical spine was obtained at baseline, biannually for the first year, and subsequently on an annual basis. Imaging was performed utilizing a standardized MS protocol.

Data of demographics (age, gender), clinical characteristics (course of the disease, disease duration, relapse rate, EDSS score), and treatment parameters [prior disease modifying therapies (DMTs) usage, DMF duration, adverse events (AEs)], MRI scans, and laboratory data of absolute lymphocyte count (ALC) were collected. Patients with incomplete data or progressive (primary or secondary) MS were excluded. A relapse was defined as new or recurrent neurologic symptom not associated with fever or infection that lasted for at least 24 h and was accompanied by new neurologic signs found by the examining neurologist. Disease progression was defined by an increase of at least 1 point in EDSS score in patients with EDSS less than 6 or a 0.5-point increase in those with EDSS of at least 6 [9]. Confirmed disease progression was assessed at least 6 months after the initial EDSS score. EDSS measurements within 30 days of the relapse were excluded to avoid the bias of falsely elevated EDSS scores during a relapse. MRI activity was defined as the presence of new or enlarging T2 lesions and/or gadolinium-enhancing T1 lesions in a follow-up scan.

The primary outcome was to assess the proportion of relapse-free patients at last follow-up. Secondary outcome measures included the assessment of change in confirmed disease progression measured by EDSS scores, and the proportion of patients with radiological activity (gadolinium-enhancing or new T2 lesions) at the end of the observational period. Grades of lymphopenia were assigned according to the common terminology criteria for adverse events: grade 1, ALC of 800 to the lower limit of normal; grade 2, ALC 500–799; and grade 3, ALC less than 500 [10].

All analyses were performed using SPSS 20 for Windows. Simple descriptive statistical tests (mean and standard deviation) were used to describe the numerical values of the sample. The significance of the differences of mean EDSS scores and number of relapses before and after treatment were compared by using the paired-sample Student's t test, while χ^2 tests were used for nonparametric variables (proportion of relapse-free patients and MRI activity); a p value less than 0.05 was regarded as significant. The institutional ethical committee approved the study and all patients signed the informed consent forms.

RESULTS

A total of 134 relapsing–remitting multiple sclerosis (RRMS) patients were treated with DMF were included in the registry, of whom 119 patients were included in the analysis of efficacy. Eleven patients were excluded from the efficacy analysis because of short exposure to DMF of less than 6 months, while four patients were excluded because of incomplete data. Patients' demographics are outlined in Table 1. Women represented 59.7% of the studied cohort. Mean age and mean disease duration were 33.5 ± 11 years and 8.3 ± 7 years, respectively. The indications to prescribe DMF are presented in Table 1. Most of the analyzed patients ($n = 90$; 75.6%) were exposed to prior disease-modifying therapy (DMTs).

The mean duration of DMF exposure in the cohort was 20 ± 9.5 months. The proportion of relapse-free patients increased significantly from 51.2% to 89.9% ($p < 0.0001$) at the end of observational period (Table 2). DMF was associated with a reduction of disability progression when baseline EDSS scores were compared to last follow-up visits (2.8 ± 1.8 vs. 2.3 ± 1.7; $p < 0.058$). Few patients ($n = 17$; 14.3%) had improvement of their EDSS scores, while ($n = 8$; 6.7%) showed progression of their disability. None of the patients who had improvement in their EDSS scores sustained a relapse, while five of eight patients who had EDSS worsening

Table 1 Demographic and clinical characteristics of the studied cohort ($n = 119$)

Variables	Mean ± SD/ number (%)
Gender	
Female	71 (59.7)
Male	48 (40.3)
Mean age (years)	33.5 ± 11.1
Range	16–63
Mean age of onset (years)	25.2 ± 8.4
Range	7–60
Mean disease duration (years)	8.3 ± 7
Range	1–24
Mean duration of DMF exposure (months)	20.5 ± 9.5
Range	6–44
Indication to initiate DMF	
Newly diagnosed RRMS	29 (24.4)
Relapse	28 (23.5)
Radiological activity	13 (10.9)
Tolerability	16 (13.4)
Convenience	15 (12.6)
JCV seropositivity	10 (8.4)
Adverse events to prior DMTs	8 (6.7)
Prior use of disease-modifying therapies	90 (75.6)
Interferon beta 1b SC	28 (31.1)
Interferon beta 1a IM	26 (28.9)
Interferon beta 1a SC	12 (13.3)
Fingolimod	10 (11.1)
Teriflunomide	4 (4.4)
Natalizumab	10 (11.1)

DMF dimethyl fumarate, *SD* standard deviation, *RRMS* relapsing–remitting multiple sclerosis, *JCV* John Cunningham virus, *DMTs* disease-modifying therapies

Table 2 Primary and secondary outcome measures of the studied cohort ($n = 119$)

Variables	Baseline (mean ± SD)/ number (%)	Last follow-up (mean ± SD)/ number (%)	*p* value
Primary			
Proportion of relapse-free patients	61 (51.3)	107 (89.9)	<0.0001*
Secondary			
Mean EDSS score	2.8 ± 1.8	2.3 ± 1.7	0.058
MRI activity	74 (61.1%)	18 (15.1%)	<0.0001*

SD standard deviation, *EDSS* expanded disability status scale, *MRI* magnetic resonance imaging
*Statistically significant

sustained a relapse during the observational period. The proportion of patients with MRI activity decreased significantly from 61.1% to 15.1% ($p < 0.001$) as outlined in Table 2.

The mean ALCs decreased by 34% from 2170 at baseline to 1430 cells/μl at last follow-up. Lymphopenia was seen in 13 (10.9%) patients, of whom 10 (8.4%) patients had grade 1–2 lymphopenia and 3 (2.5%) patients had persistent grade III lymphopenia necessitating discontinuation.

A total of 47 (39.5%) adverse events were registered; GI upset and flushing were the most common reported symptoms, while lymphopenia was the common most laboratory abnormality observed in the analyzed cohort (Table 3). Breakthrough disease activity was the most common reason for discontinuation. No major AEs or opportunistic infections occurred in the studied cohort.

DISCUSSION

Post-marketing studies are important to confirm what was established in clinical trials, and to assess the intermediate and long-term safety.

Table 3 Safety parameters of the study cohort ($n = 119$)

Variables	Number (%)
Adverse events	47 (39.5)
Gastrointestinal upset	15 (12.6)
Flushing	8 (6.7)
Headache	6 (5)
Lymphopenia	13 (10.9)
Elevated liver transaminases	3 (2.5)
Others	2 (1.7)
Reason for discontinuation	23 (19.3)
Disease breakthrough	14 (11.8)
Clinical relapse	12 (10.1)
MRI activity	2 (1.7)
Persistent lymphopenia (grade 3)	3 (2.5)
Gastrointestinal upset	3 (2.5)
Confirmed pregnancy	2 (1.7)
Elevated liver transaminases	1 (0.8)

SD standard deviation, *MRI* magnetic resonance imaging

We found that DMF was associated with improvements in both clinical and MRI outcome measures in patients with relapsing MS after a mean observational period of 20 months. Our results are in line with what previous phase III clinical trials, DEFINE and CONFIRM, had shown in that DMF was effective in reducing annualized relapse rate (ARR) and disease progression as measured by means of EDSS [5, 6]. The proportion of relapse-free patients in our cohort was higher than the pivotal trials of DMT. Disability progression was reduced by 14% in our cohort, slightly lower than what was observed in pivotal trials (38% in DEFINE and 21% in CONFIRM) [5, 6]. This could be explained by the fact that approximately 30% of the patients were switched to DMF because of tolerability/AEs to previous DMTs or because of convenience and willingness to initiate oral medications rather than injectable ones. Additionally, most of the patients (ca. 40%) who initiated DMF did not have any ongoing clinical disease activity, especially those who were

switched from natalizumab due to JCV seropositivity. Moreover, approximately three-quarters of our patients were exposed to prior DMTs, which is higher than the 30–40% figures in DEFINE and CONFIRM trials [5, 6].

Few post-marketing observational studies have been published so far [11, 12]. In a prospective study in a US community health center evaluating 412 patients over 3 years, 86% of patients were relapse free and 25% had activity MRI activity [11]. The proportion of relapse-free patients was similar to that in our cohort but the radiological activity was slightly higher than ours likely because of the inclusion of more natalizumab-treated patients ($n = 44$) in their cohort. A multicenter retrospective study from Germany which assessed longitudinal data of 644 MS patients treated with DMF reported a 33% reduction in ARR from 0.52 to 0.35 at 1 year [12]; this was accompanied by a 33% reduction in EDSS progression from baseline of 0.15 ± 0.49 per year to 0.10 ± 1.84 per year during DMF treatment. Again, the demographic baseline differences especially in terms of age of the studied cohort, disease duration, and proportion of naïve patients (45.2%) could explain the differences in efficacy when compared to our study.

Natalizumab discontinuation due to risk of progressive multifocal leukoencephalopathy (PML) is frequently seen in clinical practice especially after the introduction of the JC Stratify test [13]. In our cohort, of the 10 patients who were switched from natalizumab because of JCV seropositivity, three had radiological activities evident by the presence of new gadolinium-enhancing lesions, while one sustained a relapse within 4 months of initiation of DMF. This raises the potential risk of disease reactivation after transitioning from natalizumab. Several studies reported disease reactivation post-natalizumab discontinuation [14, 15]. In a retrospective study that included 54 patients, the proportion of patients who experienced relapses was 57.4%. Relapses occurred on average at 6.46 months (range 1–-11 months). The ARR increased after natalizumab suspension ($p = 0.0004$), but it was significantly lower than the pre-natalizumab level ($p = 0.0053$). Similarly, more patients had new T2 lesions and new gadolinium-enhancing lesions after discontinuation of natalizumab ($p = 0.0000$). No rebound activity was observed. The institution of alternative therapies did not influence the increase in rate of disease reactivation, but the number was small and it was therefore difficult to draw any conclusion [14]. Similar findings were reported by another retrospective study conducted at two Italian MS referral centers which assessed patients who discontinued natalizumab up to 1 year after interruption. Of the 132 included patients, 72 patients (54.5%) had relapses and 60 of 125 patients (48%), who had MRI follow-ups, had radiological reactivation. Rebound was observed in 28 of 132 patients (21.2%). Ninety-five patients (72%) were switched to other therapies after a median washout period of 5 months. A lower risk of relapses was found in patients treated with second-line therapies (fingolimod) or off-label therapy (e.g., rituximab) than in those treated with first-line therapies (IFN-beta, GA, teriflunomide, azathioprine) [16]. The duration of washout period has been consistently observed in multiple studies to be a major factor for disease reactivation [17–19]. Most experts often prefer a short washout period (4–8 weeks) in order to avoid such risk. The risk of relapse after natalizumab cessation and switch to DMF is unknown. A few studies reported data on such cohorts, but the findings were limited by the small number of patients and short follow-up durations [20, 21]. Zurawski et al. assessed 30 patients treated with natalizumab for at least 12 months and then switched to DMF at a mean of 50 days. Five patients (17%) suffered severe relapses, while 35% of patients had new lesions according to MRI activity. Relapses occurred at a mean of 3.5 months after natalizumab cessation [20]. Despite these findings, DMTs were associated with delayed long-term disability in MS patients. In an observational study on 3060 MS patients, the risks of attaining EDSS 3.0 were 94% and 73% lower in patients treated with immunomodulators and immunosuppressants, respectively, compared to untreated patients. However, the risk of attaining EDSS 6.0 was higher in patients starting immunomodulators after EDSS 3.0 than before (HR = 4.42) [22].

Thus, even in patients with longer disease duration or with neurological disabilities, there is a window of opportunity to delay disease progression in the long term.

Most of the observed AEs in our cohort were transient and managed either with dose reduction for 2–4 weeks or symptomatic therapies (e.g., aspirin for flushing). Gastrointestinal upset and flushing were the most common adverse events and these were known to be most prominent within the first few months of initiating therapy [5, 6, 11]. Although 19.3% ($n = 23$) of our patients discontinued DMF treatment, this is lower than the 30% discontinuation rates reported in the pivotal trials [5, 6] and the 29–38% discontinuation rate in other observational studies [11, 12]. Nevertheless, ongoing disease activity was the main reason for discontinuation across all studies. The rate of discontinuation due to GI upset was slightly lower in our cohort than what was reported in the pivotal studies (1.7% versus 7%) [5, 6]. Similarly, in an observational study assessing the GI tolerability in 233 patients taking DMF for up to 12 weeks, 7.3% of patients discontinued DMF because of gastrointestinal AEs [23]. The could be explained by the reporting bias since patients were prompted to report onset and offset times of any AEs including GI-related events in controlled studies. Another explanation for our low discontinuation rate secondary to GI upset is the fact that we adopted a protocol of titrating the DMF dose over 4 weeks (compared to the standard 1-week titration) and prescribed antacids and proton pump inhibitors earlier when symptoms started.

Most of the observed grade 1 and 2 lymphopenia were transient in keeping with what was reported in DEFINE and CONFIRM [5, 6]. The reported grade 3 lymphopenia in our study is consistent with figures of other post-approval studies [24–26]. Moreover, the rate of lymphopenia necessitating discontinuation of DMF in our cohort (2.5%) was similar to the 4–5% rates reported in other studies but lower than the reported 11% in the observation US study which included older patients (mean age 49 ± 12 years). Lymphopenia presumably reflects some degree of immune suppression in DMF-treated patients, and there is therefore a theoretical basis for supposing that these patients would be less likely to experience breakthrough MS activity [26]. The mechanism of DMF-induced lymphopenia is not known. In vitro studies suggest that it may induce T cell apoptosis [27].

There are several limitations in our study. First, it is an open-label with no placebo arm resulting in methodological bias. Second, more than half of the studied cohort had no disease activity when they started DMF. It should be noted that in our practice, DMF is used primarily used as a first-line therapy, mostly including newly diagnosed naïve patients or those who had tolerability issues with injectable DMTs. Patients with highly active disease (at least two relapses in 1 year) or have aggressive presentation at onset (i.e., accumulating neurological disabilities) are usually stratified to second-line therapies such as fingolimod, natalizumab, or alemtuzumab. Hence, the results should be interpreted with caution and more importantly should not be generalized. Third, most of the newly diagnosed patients in our study did not have sufficient follow-up time prior to DMF exposure as treatment is usually started within 6 months of diagnosis. Subsequently, the annual relapse rate prior to DMF initiation could not be measured in order to report post-DMF ARR. Nevertheless, our study was one of the few prospective studies and the first to be performed in a region that has a relatively adequate length of DMT exposure.

CONCLUSION

Dimethyl fumarate was associated with a significant reduction in clinical and radiological disease activity. During the observational period, DMF appeared to be safe and tolerable. Few patients developed grade 3 lymphopenia. Our results were in parallel with what was seen in pivotal trials.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Author Contributions All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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