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CLINICAL & BASIC RESEARCH

Frequency of Dimethyl Fumarate-Induced Lymphopenia among Omani Patients with Multiple Sclerosis

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abstract: ***Objectives:*** Dimethyl fumarate (DMF) is known to cause lymphopenia when used to treat patients with multiple sclerosis (MS). However, research on DMF therapy in the Arab world, especially in Oman, is scarce. This study aimed to analyse the prevalence of lymphopenia among Omani patients with MS and their reasons for discontinuing DMF therapy. ***Methods:*** In this retrospective study, the medical records of Omani patients with MS who were treated using DMF at two tertiary hospitals in Muscat, Oman, from February 2017 to February 2023 were reviewed. Their demographic, clinical and laboratory data were retrieved and analysed. Absolute lymphocyte count values at baseline and at the last follow-up, as well as the reasons for discontinuing DMF therapy, were collected. Descriptive and inferential statistical techniques were used for data analysis. Binary-logistic regression analysis was used to identify the risk factors for DMF-induced lymphopenia. ***Results:*** A total of 64 Omani patients with MS were included in this study. The majority of the study participants (n = 40; 63%) were female. All included patients started DMF therapy at the mean age of 33 ± 7.7 years. After administration of DMF, 14 (21.9%) patients developed grades 1–3 of lymphopenia. The DMF therapy was discontinued for 23 (36.0%) patients, mainly in response to adverse events or confirmed pregnancy. Female gender was the only significant predictor of DMF-induced lymphopenia (P = 0.037). ***Conclusions:*** Most Omani patients with MS had mild lymphopenia (grades 1–2). Early adverse events and pregnancy were the main reasons provided for discontinuing DMF therapy.
Keywords: Multiple Sclerosis; Dimethyl Fumarate; Lymphocyte Count; Lymphopenia; Oman.

Advances in Knowledge

- *Omani patients with multiple sclerosis (MS) on dimethyl fumarate (DMF) developed mild lymphopenia (grades 1–2), which aligns with other regional and international findings.*
- *Female gender was the only significant predictor of DMF-induced lymphopenia in the Omani patients with MS.*
- *The main reasons for DMF therapy discontinuation were early side effects (mostly gastrointestinal symptoms), hot flushes and confirmed pregnancy.*
- *To the authors' knowledge, this is the first study in Oman to investigate the frequency of lymphopenia among Omani patients with MS treated with DMF.*

Applications to Patient Care

- *Caution and monitoring shall be taken when initiating dimethyl Fumarate in Omani females with multiple sclerosis, as it may cause lymphopenia.*

Multiple sclerosis (MS) is a non-traumatic neurodegenerative disease of the central nervous system (CNS).[1] In this chronic immune-mediated disorder, auto-lymphocytes breach the blood-brain barrier and enter the CNS, where they cause local inflammation that leads to axon demyelination.[2]

Although there is no cure for MS, several disease-modifying therapies (DMTs) exist. These DMTs share similar goals but have different mechanisms of action, efficacies and safety profiles.[3] Examples of DMTs are the administration of ocrelizumab, natalizumab, fingolimod and dimethyl fumarate (DMF).[3,4] DMF is used as an oral DMT and was approved by the Food & Drug Association in 2013 to treat MS, as it demonstrated good efficacy in two randomised placebo-controlled phase 3 clinical trials: DEFINE and CONFIRM.[5,6] DMF therapy reduced expanded disability status scale scores by 38% in DEFINE and 21% in CONFIRM. Furthermore, DMF reduced the annualised relapse rate by 53% in DEFINE and 44% in CONFIRM.

Lymphopenia occurs when the patient's absolute lymphocyte count (ALC) falls below 1,000 cells/μL. The severity of lymphopenia is classified into four grades: grade 1 = 800–999 cells/μL ALC; grade 2 = 500–799 cells/μL ALC; grade 3 = 200–499 cells/μL ALC; and grade 4 = <200 cells/μL ALC. Because DMF

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reduces ALC levels by diminishing the survival rate of lymphocytes, DMF therapy should be discontinued if the patient's ALC remains below 500 cells/μL for an extended period of time.[7] In the CONFIRM trial, the mean ALC value decreased by 32% after the first year of starting DMF therapy, with 5% of patients developing grade 3 lymphopenia or higher. The DEFINE trial reported a 28% reduction in the mean ALC and a 4% incidence of grade 3 lymphopenia or higher. Both trials showed that the steepest reduction in mean ALC levels occurred in the first year of DMF therapy; the levels then plateaued and the mean values stayed within the normal limits. Additionally, the efficacy of DMF did not differ significantly between lymphopenic and non-lymphopenic patients.[5,6]

Although DMF induces lymphopenia, the lymphocytes subsets are affected differently, with the reduction of T cells—especially CD8-T cells, which are important for cell-mediated immunity against viral infections—being more significant. However, a long-term follow-up study did not report any increase in opportunistic infections.[8]

The most reported side effects of DMF therapy are flushing (35%) and gastrointestinal (GI) events (36%), such as nausea, upper abdominal pain and diarrhoea. The side effects tend to manifest in the first month of DMF administration then decrease over time.[5] The most common reason for the DMF therapy discontinuation is the lack of tolerability for the drug, which appears to be greater than that of fingolimod.[9] The time point of DMF therapy discontinuation mainly depends on the adverse events experienced by the patient.[10] The risk factors for DMF-induced lymphopenia include ethnicity, age group, body mass index (BMI) and previous DMT use.[11]

Recently, an extension study of the ENDORSE trial reported real-world data on MS patients undergoing DMF therapy with a total follow-up period of >10 years.[12] The main side effects reported were GI events (43% prevalence) and flushing (24% prevalence), both likely to manifest, as expected, early in the DMF treatment. Also reported were abnormal liver enzymes (11% prevalence) and serious infections (5% prevalence). There was no increase in the incidence of side effects over the follow-up period. Only 2.8% of the patients developed prolonged severe lymphopenia during the ENDORSE trial period.

A Kuwaiti study on 119 patients who were treated with DMF for a mean of 20 months reported that 2.5% of patients had to discontinue treatment due to persistent grade 3 lymphopenia.[13] Additionally, 7.5% of patients discontinued DMF therapy due to other commonly known side effects. According to Hauser *et al.*, assessments of efficacy and tolerability of DMTs such as DMF require long-term evidence-based data, thus necessitating more real-world studies.[3]

In the above context, data on the effect of DMF on ALC in Arab populations, particularly among Omanis, are scarce. This lack grows in significance when considering the high rates of consanguinity in the Middle East, especially in the Gulf Cooperation Council countries, including Oman and the consequent increased prevalence of genetic illnesses, including MS.[14,15]

In the absence of previous studies on DMF safety in the Omani population, this study seeks to narrow the current knowledge gap by analysing the prevalence and nature of DMF-associated lymphopenia among Omani patients with MS, as well as their reasons for discontinuing treatment with this drug.

Methods

SETTING

Most MS patients in Oman are referred to the country's two major tertiary hospitals in Muscat, where this study was conducted: Sultan Qaboos University Hospital (SQUH) and Khoula Hospital (KH). According to a study based in the two hospitals, the rate of prevalence of MS in the Omani population is 15.9 per 100,000.[16] Therefore, there are around 450 Omani patients with MS at various levels of disease progression. The decision to avail DMT is based on multiple factors, including the availability of the DMT, patient's age and gender, disease status and the treating neurologist's opinion. DMF therapy can be initiated, for example, in DMF-naïve patients to mitigate the side effects or lack of efficiency of previous DMTs. A previous study in SQUH showed that almost 50% of patients with MS were taking oral DMTs, including DMF therapy. About 3% of the patients took DMF as their initial DMT. The same study also found that Omani patients with MS could be prescribed 1–4 different DMTs during their disease course.[17]

STUDY DESIGN AND DATA COLLECTION

This research was a retrospective study conducted at SQUH and KH. The study included all the 64 Omani patients with MS who attended the neurology clinics of these two hospitals and were treated with DMF (those who later discontinued treatment were also included) from February 2017 to February 2023. The study data were extracted from the patients' electronic medical records. The demographic data collected included date of birth and gender. The clinical data included the date of MS onset, disease duration, date of starting

DMF therapy, date of discontinuing DMF therapy and duration of DMF therapy. Details such as BMI, vitamin D levels when starting DMF therapy, smoking history, DMT used before initiating DMF therapy and reasons for discontinuing DMF therapy were also retrieved from the patients' electronic records. The baseline ALC and last available ALC (at the last visit or at the time of DMF therapy discontinuation) were also noted for comparison.

DATA ANALYSIS

The data were analysed using the Statistical Package for the Social Sciences (SPSS), Version 25 (IBM Corp., Armonk, New York, USA). This study considered the lymphopenia status of Omani patients with MS and DMF therapy as the primary covariate of lymphopenia, while the socio-demographic and clinical characteristics of patients were considered the covariate of lymphopenia. Descriptive analysis was used for demographic, clinical and basic investigations. Continuous variables were represented by mean ± standard deviation (SD) and range and categorical variables were summarised as frequencies and percentages. The paired-samples t-test was used to obtain the significance of change in ALC levels associated with DMF use (P <0.05 was considered significant). To identify the risk factors for DMF-induced lymphopenia, a multiple logistic regression model was employed with lymphopenia as the binary (yes/no) outcome variable and the patients' demographic and clinical characteristics as predictors. Before fitting the regression model, data quality was checked for the presence of multicollinearity and outliers that might create a problem in the model's parameter estimation and their significance test. There was no potential outlier or collinearity problem in the data set.

ETHICAL CONSIDERATIONS

The study was conducted as per the Declaration of Helsinki, and the protocol was approved by the Medical and Research Ethics Committee of the College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman (MREC #2474).

Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

The subjects of this study were 64 Omani MS patients who were treated with DMF and followed-up at SQUH and KH during the period from February 2017 to February 2023. The majority of the patients (63%) were female. The patients' mean age was 36.2 ± 7.9 (range = 19–59) years. At baseline, most of the patients were overweight, with a mean BMI of 27.4 ± 7.2 kg/m^2. The mean age of DMF therapy initiation was 33.3 ± 7.7 years. The mean baseline vitamin D (25-OH vitamin D) and ALC levels were 87.2 ± 49.6 nmol/L and 2.1 × 10^9/L, respectively (both within their respective normal ranges). The most common DMTs used prior to DMF therapy were injectable interferons therapy, which was received by 35 (54.69%) patients. Twenty patients (31.25%) were treatment-naïve for MS [Table 1].

PREVALENCE OF LYMPHOPENIA AFTER DMF ADMINISTRATION

The prevalence of lymphopenia among the patients on DMF was 21.9% (95% confidence interval [CI] = 11.5–32.3) and was significantly higher among female patients than male patients (30.0% versus 8.3%; P <0.05). There was a 28.6% decline in the mean ALC levels, from 2.1 ± 0.77 (range = 0.40–4.70) with 95% CI = 1.86–2.25 and interquartile range (IQR) = 0.92 at baseline to 1.5 ± 0.67 (range = 0.44–3.95) with 95% CI = 1.33–1.67 and IQR = 0.89 at the last follow-up (paired-samples t-test: t = 5.6; P <0.001). As reported in the last visit, 14 (21.9%) patients developed lymphopenia after undergoing DMF therapy: 5 patients had grade 1 lymphopenia, 8 had grade 2 lymphopenia and 1 had grade 3 lymphopenia [Figures 1 and 2].

REASONS FOR DMF DISCONTINUATION

More than one-third (23; 35.9%) of the patients discontinued DMF therapy for the following main reasons: pregnancy (26%); experiencing adverse events (26%), such as gastrointestinal symptoms (13%) and hot flushes (8.7%); patients' choice/convenience (17.4%); patient noncompliance (8.7%) and allergic reactions (4.3%). Of the 6 women who stopped using DMF due to pregnancy, only 1 restarted using the drug after delivery. The others were still pregnant or lactating during our study period [Table 2].

RISK FACTORS FOR DMF-INDUCED LYMPHOPENIA

Using univariate and multiple logistic regression analysis, the crude and adjusted odds ratios of lymphopenia according to the demographic and clinical characteristics of patients were calculated. Both the univariate and multiple logistic regression analyses identified female gender as a significant predictor of DMF-induced lymphopenia. The study's female participants were found to have more than 5 times higher risk of developing lymphopenia than their male counterparts (odds ratio [OR] = 5.83; 95%

Table 1: Demographic and clinical features of Omani patients treated with dimethyl fumarate (N = 64).

Characteristics	Mean ± SD (Range)/n (%)
Gender	
Male	24 (37.5)
Female	40 (62.5)
Age in years (range)	36.2 ± 7.9 (19–59)
Age at start of DMF therapy in years	33.3 ± 7.7 (18–56)
Duration of disease in years	5.6 ± 5.6 (0–22)
Duration of DMF use in years	2.8 ± 1.6 (0–7)
Baseline BMI in kg/m^2	27.4 ± 7.2
Baseline 25-OH vitamin D in nmol/L	87.2 ± 49.6
Baseline ALC in cells × 10^9/L	2.1 ± 0.8
Smoking history	
Smokers	3 (4.7)
Non-smokers	38 (59.4)
Smoking status unknown	26 (40.6)
DMT used prior to DMF therapy	
Naïve	20 (31.2)
Injectable interferons	35 (54.7)
Interferon beta-1a (IM)	19 (29.7)
Interferon beta-1b	6 (9.4)
Interferon beta-1a (SC)	10 (15.6)
Fingolimod	6 (9.4)
Natalizumab	2 (3.1)
Teriflunomide	1 (1.6)
Lymphocyte status after initiation of DMF therapy	95% CI = 11.5–32.3%
Normal	50 (78.1)
Lymphopenia	14 (21.9)

SD = standard deviation; DMF = dimethyl fumarate; BMI = body mass index; ALC = absolute lymphocyte count; DMT = disease modifying therapies; IM = intramuscular; SC = subcutaneous; CI = confidence interval.

Table 2: Omani multiple sclerosis patients' reasons for discontinuing dimethyl fumarate therapy (n = 23).

Reason for DMF therapy discontinuation	n (%)
Patient choice/convenience	4 (17.4)
Allergic reaction	1 (4.3)
Adverse event	**6 (26.1)**
Gastrointestinal symptoms	3 (13.0)
Hot flushes	2 (8.7)
Other	1 (4.3)
Lack of efficacy	4 (17.4)
Patient noncompliance	2 (8.7)
Confirmed pregnancy	6 (26.1)

DMF = dimethyl fumarate

CI = 1.03–33.2; $P = 0.037$). Though factors such as age at diagnosis, DMF therapy duration and ALC level at start of DMF therapy also showed negative association with lymphopenia, these were not statistically significant [Table 3]. Considering the study's limited sample size, the multivariable logistic regression model should be interpreted with caution, and the authors were cautious about potential data problems such as outliers or multicollinearity. However, diagnostic tests indicated that the data was free of these problems because all the correlation coefficients between explanatory variables were <0.35 and all the variance inflation factors were <4.0 [Table 3].

Discussion

This retrospective study was conducted on Omani patients with MS attending neurology clinics at two tertiary hospitals in Oman, who were either receiving DMF therapy or had discontinued it. Their demographic distribution was similar to the internationally reported data, especially the preponderance of females and the most affected age group being 20–40 years.[18] Only Omani citizens were included in the study as the authors wanted to investigate the safety of DMF use in this specific population. Moreover, very few non-Omani patients with MS were treated at the two hospitals.

Most of the study participants were non-smokers. All the participants who were smokers were male. The mean age of starting DMF therapy was 33.3 ± 7.7 (range = 19–59) years and the mean 'current age' (age on the date of data retrieval) was 36.2 ± 7.9 (range = 18–56) years, indicating that the patients who used DMF were followed up for a period of up to 7 years, with a mean follow-up period of 2.8 ± 1.6 years.

More than two-thirds (68.8%) of the participants were exposed to other DMTs prior to starting DMF therapy,[19] compared to the 75.6% reported from Kuwait.[13] Among this study's participants, 54.7% received injectable interferons prior to DMF therapy, compared to the 73.3% in the Kuwaiti study.[13]

Table 3: The crude and adjusted odds of developing lymphopenia according to demographic and clinical characteristics of the patients using univariate and multiple logistic regression analyses.

Demographic and Clinical Characteristics	Univariate Logistic Regression		Multiple Logistic Regression	
	COR (95% CI)	*P* value	AOR (95% CI)	*P* value
Gender				
Female	4.71 (1.02–29.130)	0.041	5.83 (1.03–33.2)	0.037
Male (reference)	1.00		1.00	
Age at MS diagnosis	0.97 (0.82–1.15)	0.653	0.99 (0.84–1.18)	0.910
Age at start of DMF therapy	1.04 (0.96–1.12)	0.309	1.07 (0.93–1.23)	0.323
DMF therapy duration	0.93 (0.64–1.33)	0.656	0.92 (0.60–1.43)	0.717
BMI score	0.92 (0.80–1.05)	0.206	0.97 (0.85–1.10)	0.617
Vitamin D	1.04 (0.98–1.06)	0.073	1.02 (0.99–1.05)	0.162
Baseline ALC at start of DMF therapy	0.70 (0.31–1.62)	0.410	0.64 (0.24–1.69)	0.365
DMT used prior to DMF				
Yes	1.18 (0.32–4.32)	0.807	1.21 (0.22–6.72)	0.831
No (reference)	1.00		1.00	

COR = crude odds ratio; CI = confidence interval; AOR=adjusted odds ratio; MS = multiple sclerosis; DMF = dimethyl fumarate; BMI = body mass index; ALC = absolute lymphocyte count; DMT = disease-modifying therapies.

According to the pivotal clinical trials DEFINE and CONFIRM, MS patients receiving DMF therapy are at a higher risk of developing lymphopenia, especially in the first year of therapy.[5,6] The mean duration of DMF therapy in this study was 26.8 ± 20.3 months. This study showed a significant (28.6%) fall in the mean ALC levels. However, this was still lower than that reported by the benchmark CONFIRM (32% ALC decline) and DEFINE (28% ALC decline) studies as well as the mean fall (34% ALC decline) noted in the Kuwaiti study.[5,6,13]

The incidence of severe lymphopenia (≥ grade 3) was approximately 5% in the CONFIRM study and 4% in the DEFINE trial.[5,6] The long-term extension ENDORSE study reported a 10.6% incidence of prolonged moderate lymphopenia and 2.4% incidence of prolonged severe lymphopenia.[12] None of the participants in this study developed grade 4 lymphopenia; it is known to be rare, with a study in the USA reporting a prevalence of only 0.2%.[20] In the current study, the overall prevalence of lymphopenia was 21.9% (14 patients): grade 1 = 7.81% (5 patients),

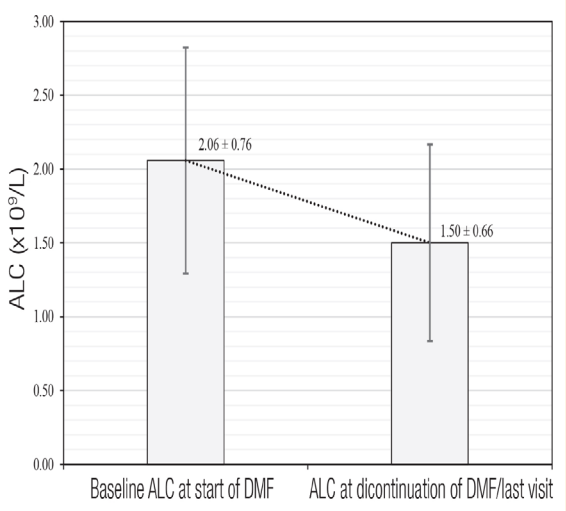

Figure 1: Changes in the absolute lymphocyte count of Omani multiple sclerosis patients after dimethyl fumarate (DMF) therapy.

ALC = absolute lymphocyte count.

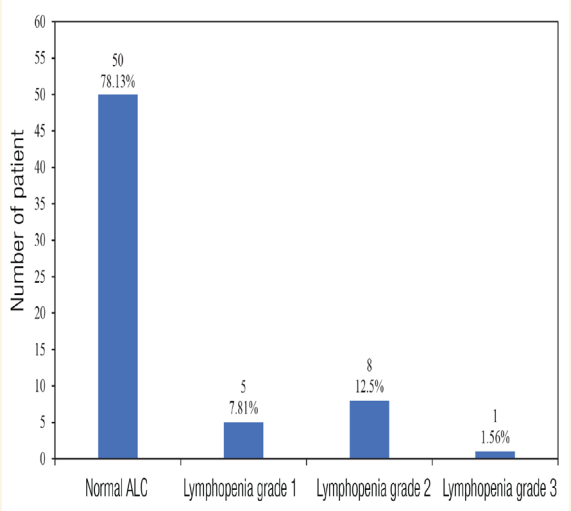

Figure 2: Prevalence of lymphopenia (grades 1, 2 and 3) among Omani multiple sclerosis patients on the date of their last visit or when dimethyl fumarate therapy was discontinued.

grade 2 = 12.5% (8 patients) and grade 3 = 1.6% (1 patient). The overall prevalence of lymphopenia in the Kuwaiti study was 10.9% (grades 1–2 = 8.4%, grade 3 = 2.5%), which is much lower than the current study.[13] A study from Italy reported an even lower lymphopenia prevalence of 2.1% (grades 1–2 = 1.2%, grade 3 = 0.9%).[21] On the other hand, a large Italian multi-centre retrospective study of 1,034 patients found 19.1% prevalence of lymphopenia, comparable with the current study's 21.9%.[22]

Several studies have reported a higher prevalence of lymphopenia than in the current study. A retrospective study of 38 patients in Italy that assessed ALC levels after 12 months of starting DMF therapy reported a lymphopenia prevalence of 25.9% (grade 1 = 6.5%, grade 2 = 12.9%, grade 3 = 6.5%).[23] Another retrospective study on 194 patients with MS in the USA reported a lymphopenia prevalence of 38% (grade 1 = 16%, grade 2 = 14%, grade 3 = 7%).[11] Most studies, including the current study, found grade 2 lymphopenia to be more prevalent than grade 1 lymphopenia. Furthermore, grade 3 lymphopenia, found in 1 patient in the current study, was also reported in other studies; however, those studies also had cases of severe lymphopenia (≥ grade 3) at frequencies that sometimes exceeded those in both the CONFIRM and DEFINE pivotal clinical trials.[5,6]

The rate of DMF therapy discontinuation in the current study was 36.0%, compared to 19.3% in the Kuwaiti study.[13] The most common reasons for DMF therapy discontinuation among the current study's participants were adverse events (9.4%) and confirmed pregnancy (9.4%). On the other hand, disease breakthrough was the most common reason (11.8%) in the Kuwaiti study.[13] The use of symptomatic drugs such as aspirin for flushing in the early stage of DMF therapy has been reported to lower the likelihood of adverse events related to DMF discontinuation.[13] However, similar documented symptomatic treatments were not provided to the current study's population.

Another possible explanation for the current study's higher frequency of DMF therapy discontinuation due to side effects is the shorter duration (1 week) of the initial titration of DMF for the study participants, as practised in the two hospitals, compared to studies that continued lower doses for longer periods of up to 2–4 weeks.[13] The multicentre prospective study of 234 patients in Italy by D'Amico *et al*. found that 26.5% of patients had DMF-induced adverse events (flushing/itching = 13.3%; GI symptoms = 9.4%), which was similar to the levels found in the two pivotal clinical trials.[5,6,21] Comparatively, the current study population had a lower prevalence of GI symptoms (4.7%) and flushing (3.1%).

The current study also found female gender to be a significant predictor of DMF-associated lymphopenia. The female patients had more than 5 times higher odds of developing lymphopenia than the male patients, contrary to some of the previous studies.[11,24,26] However, unlike many previous studies, the current study did not find any significant association between DMF-induced lymphopenia and age groups, BMI, vitamin D levels, baseline ALC status or the previous DMT used.[11,24–26] A possible reason for this is the current study's small sample size. When a study's sample size is small, a larger standard error (SE) of an estimate is usually produced, as the SE is inversely related to sample size. Conversely, when a study's sample size is large, depending on the SD of the variables, even a small observed difference may be significant. This is because SE is used as the denominator in all statistical tests. Therefore, standard deviation and sample size play important roles in statistical significance tests. However, for prevalence estimation, the current study's sample of only 64 subjects had very little implication.

A single-centre retrospective cohort study of 221 patients in the USA found that older age (>55 years of age), low baseline ALC and recent use of natalizumab were risk factors for developing moderate-to-severe lymphopenia; however, the number of DMTs taken prior to DMF therapy, ethnicity and gender were not associated with lymphopenia.[24] An Italian study by Mallucci *et al*. also found that age at the start of DMF therapy was associated with lymphopenia.[25] A retrospective study on 194 patients with MS in Israel found that older age, white ethnicity, being overweight (BMI = 25–29.9), low baseline ALC and non-smoking status were all risk factors for DMF-induced lymphopenia.[11] No significant associations with previous use of natalizumab or carbamazepine/oxcarbazepine or concomitant steroid or opiate use were found.[11] A large multicentre study on 1,089 patients with MS in Italy reported that females were less likely than males to develop lymphopenia while using DMF.[26]

In general, the risk factors for DMF-induced lymphopenia vary considerably among the studies discussed above. However, they all found older age to be a common risk factor for DMF-induced lymphopenia, which may explain the higher frequency of severe lymphopenia (≥ grade 3) in many real-world studies compared to the 2 pivotal DMF clinical trials, which excluded older age groups.[20,24]

The small sample size of this study as well as the other possible biases and random errors that may arise in interpreting odds ratios may have affected the accuracy of the results. Additionally, there were

the usual limitations of a retrospective study design type: there was no specific patient follow-up protocol, including the exact timing of follow-up after DMF therapy initiation or the timing of blood collection to assess the side effects. This prevented the authors from establishing the time gap between the initiation of DMF therapy and the manifestation of lymphopenia and other side effects.

Conclusion

The frequency of mild lymphopenia (grades 1–2) among Omani patients with MS who were treated with DMF aligned with most other regional and international findings. Only 1 of the current study's patients had severe lymphopenia (grade 3)—a lower prevalence than in many other studies. The main reason for the discontinuation of DMF therapy was related to the expected initial side effects. To improve patient compliance and reduce the therapy's discontinuation rate, the treating neurologist should ensure that the patient understands the expected side effects and how they are managed before initiating DMF therapy.

AUTHORS' CONTRIBUTION

AAA supervised and conceptualised the study and its methodology. AJ, AAA, MMI and SR did the formal analysis. AJ wrote the original draft, and AAA, MMI, SR, IR, JAK, IAZ, AAQ, HAA and ARG reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

AAA received honoraria as a speaker from Novartis, Sanofi, Biologix, Merck, Roche, Biogen and Bayer. AAA serves on the scientific advisory boards of Novartis, Merck and Roche. JAK received honoraria as a speaker from Merck, Sanofi, Novartis, Roche and Biogen. JAK serves on the scientific advisory boards of Novartis, Merck and Sanofi. JAK is participating in a phase 3 trial for Novartis. AAQ received honoraria as a speaker from Novartis and AbbVie.

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References

1. Dobson R, Giovannoni G. Multiple sclerosis – A review. Eur J Neurol 2019; 26:27–40. https://doi.org/10.1111/ene.13819.
2. Huang WJ, Chen WW, Zhang X. Multiple sclerosis: Pathology, diagnosis and treatments. Exp Ther Med 2017; 13:3163–6. https://doi.org/10.3892/etm.2017.4410.
3. Hauser SL, Cree BAC. Treatment of multiple sclerosis: A review. Am J Med 2020; 133:1380–90.e2. https://doi.org/10.1016/j.amjmed.2020.05.049.
4. Deleu D, Mesraoua B, Canibaño B, Melikyan G, Al Hail H, El-Sheikh L, et al. Oral disease-modifying therapies for multiple sclerosis in the Middle Eastern and North African (MENA) region: An overview. Curr Med Res Opin 2019; 35:249–60. https://doi.org/10.1080/03007995.2018.1476334.
5. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or Glatiramer in multiple sclerosis. N Engl J Med 2012; 367:1087–97. https://doi.org/10.1056/NEJMoa1206328.
6. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012; 367:1098–107. https://doi.org/10.1056/NEJMoa1114287.
7. Callegari I, Derfuss T, Galli E. Update on treatment in multiple sclerosis. Presse Med 2021; 50:104068. https://doi.org/10.1016/j.lpm.2021.104068.
8. Mehta D, Miller C, Arnold DL, Bame E, Bar-Or A, Gold R, et al. Effect of dimethyl fumarate on lymphocytes in RRMS: Implications for clinical practice. Neurology 2019; 92:e1724–38. https://doi.org/10.1212/WNL.0000000000007262.
9. Vollmer B, Ontaneda D, Bandyopadhyay A, Cohn S, Nair K, Sillau S, et al. Discontinuation and comparative effectiveness of dimethyl fumarate and fingolimod in 2 centers. Neurol Clin Pract 2018; 8:292–301. https://doi.org/10.1212/CPJ.0000000000000487.
10. Zecca C, Czaplinski A, Henny C, Petrini L, Beeler A, Gobbi C. SwissTecLive: Effectiveness and safety of dimethyl fumarate in the treatment of RRMS in the Swiss clinical practice setting. Heliyon 2020; 6:e05819. https://doi.org/10.1016/j.heliyon.2020.e05819.
11. Morales FS, Koralnik IJ, Gautam S, Samaan S, Sloane JA. Risk factors for lymphopenia in patients with relapsing–remitting multiple sclerosis treated with dimethyl fumarate. J Neurol 2020; 267:125–31. https://doi.org/10.1007/s00415-019-09557-w.
12. Gold R, Arnold DL, Bar-Or A, Fox RJ, Kappos L, Mokliatchouk O, et al. Long-term safety and efficacy of dimethyl fumarate for up to 13 years in patients with relapsing-remitting multiple sclerosis: Final ENDORSE study results. Mult Scler 2022; 28:801–16. https://doi.org/10.1177/13524585211037909.
13. Alroughani R, Ahmed SF, Behbehani R, Al-Hashel J. Effectiveness and safety of dimethyl fumarate treatment in relapsing multiple sclerosis patients: Real-world evidence. Neurol Ther 2017; 6:189–96. https://doi.org/10.1007/s40120-017-0080-x.
14. Islam MM. The practice of consanguineous marriage in Oman: Prevalence, trends and determinants. J Biosoc Sci 2012; 44:571–94. https://doi.org/10.1017/S0021932012000016.
15. Mohammed EMA. Multiple sclerosis is prominent in the Gulf states: Review. Pathogenesis 2016; 3:19–38. https://doi.org/10.1016/j.pathog.2016.04.001.

16. Al-Senani M, Al-Salti A, Nandhagopal R, Al-Zakwani I, Alkhabouri J, Elyas ME, et al. Epidemiology of multiple sclerosis in the Sultanate of Oman: A hospital based study. Mult Scler Relat Disord 2021; 53:103034. https://doi.org/10.1016/j.msard.2021.103034.

17. Al-Abri S, Al-Asmi A, Jose S, Gujjar AR. Initial clinical and radiological features of patients with multiple sclerosis in Oman. Mult Scler Relat Disord 2023; 75:104734. https://doi.org/10.1016/j.msard.2023.104734.

18. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: Clinical aspects. Curr Opin Neurol 2018; 31:752–9. https://doi.org/10.1097/WCO.0000000000000622.

19. Al-Asmi A, Al-Hashmi GKH, Al-Zakwani I, Al-Qassabi A, Al-Abri H, Gujjar AR. Effectiveness & safety profile of fingolimod in treating Omani patients with multiple sclerosis, single tertiary center experience. Mult Scler Relat Disord 2023; 71:104353. https://doi.org/10.1016/j.msard.2022.104353.

20. Baharnoori M, Gonzalez CT, Chua A, Diaz-Cruz C, Healy BC, Stankiewicz J, et al. Predictors of hematological abnormalities in multiple sclerosis patients treated with fingolimod and dimethyl fumarate and impact of treatment switch on lymphocyte and leukocyte count. Mult Scler Relat Disord 2018; 20:51–7. https://doi.org/10.1016/j.msard.2017.12.003.

21. D'Amico E, Zanghì A, Callari G, Borriello G, Gallo A, Graziano G, et al. Comparable efficacy and safety of dimethyl fumarate and teriflunomide treatment in relapsing-remitting multiple sclerosis: An Italian real-word multicenter experience. Ther Adv Neurol Disord 2018; 11:175628641879640. https://doi.org/10.1177/1756286418796404.

22. Lucchini M, Prosperini L, Buscarinu MC, Centonze D, Conte A, Cortese A, et al. Predictors of lymphocyte count recovery after dimethyl fumarate-induced lymphopenia in people with multiple sclerosis. J Neurol 2021; 268:2238–45. https://doi.org/10.1007/s00415-021-10412-0.

23. Marastoni D, Buriani A, Pisani A, Crescenzo F, Zuco C, Fortinguerra S, et al. Increased NK cell count in multiple sclerosis patients treated with dimethyl fumarate: A 2-year longitudinal study. Front Immunol 2019; 10:1666. https://doi.org/10.3389/fimmu.2019.01666.

24. Longbrake EE, Naismith RT, Parks BJ, Wu GF, Cross AH. Dimethyl fumarate-associated lymphopenia: Risk factors and clinical significance. Mult Scler J Exp Transl Clin 2015; 1:205521731559699. https://doi.org/10.1177/2055217315596994.

25. Mallucci G, Annovazzi P, Miante S, Torri-Clerici V, Matta M, La Gioia S, et al. Two-year real-life efficacy, tolerability and safety of dimethyl fumarate in an Italian multicentre study. J Neurol 2018; 265:1850–9. https://doi.org/10.1007/s00415-018-8916-6.

26. Mirabella M, Prosperini L, Lucchini M, Boffa L, Borriello G, Buscarinu MC, et al. Safety and efficacy of dimethyl fumarate in multiple sclerosis: An Italian, multicenter, real-world study. CNS Drugs 2018; 32:963–70. https://doi/.org/10.1007/s40263-018-0543-3.