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Frequency of Dimethyl Fumarate Induced Lymphopaenia Among Omani Patients with Multiple Sclerosis

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Abstract

Objectives: Dimethyl fumarate (DMF) is known to cause lymphopenia in treated multiple sclerosis (MS) patients. There is a dearth of research on DMF therapy in the Arab world, especially in Oman. This study aimed to analyse the prevalence of lymphopenia among Omani MS patients and the reasons for discontinuing DMF. ***Methods:*** In this retrospective study, we reviewed the medical records of Omani MS patients who were treated using DMF at two tertiary hospitals in Muscat from the period 2017 February to 2023 February. Their demographic, clinical, and laboratory data were retrieved and analysed. Absolute lymphocyte count (ALC) values at baseline and at the last follow up, as well as the reasons for discontinuing DMF 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: The study included a total of 64 MS patients and the majority (40; 63%) were female. The DMF therapy was started at mean age of 33 ± 7.7 years. After administration of DMF, 14 (21.9%) patients developed 1–3 grades lymphopenia with the following breakup: grade-1: 5/64 (7.81%) patients; grade-2: 8/64 (12.5%) patients; grade-3: 1/64 (1.6%) patient. DMF was discontinued in 23 (36.0%) patients, mainly in response to adverse events or confirmed pregnancy. Female sex was the only significant predictor of DMF-induced lymphopenia (p = 0.037). ***Conclusion:*** Most Omani MS patients had mild lymphopenia (grades 1–2), like other regional and international reports. Early adverse events and pregnancy were the main reasons provided for discontinuing DMF therapy.

***Keywords*:** Multiple Sclerosis; Dimethyl Fumarate; Absolute Lymphocyte Count; Lymphopenia; Oman

Advances in Knowledge

- Omani multiple sclerosis (MS) patients on dimethyl fumarate (DMF) developed mild lymphopenia similar to other regional and international findings.
- Female sex was the only significant predictor of DMF-induced lymphopenia in the Omani MS patients.
- To the authors' knowledge, this is the first study in Oman to study the frequency of lymphopenia among Omani MS patients treated with DMF.

Application to Patient Care

- Even though DMF causes lymphopenia, the vast majority of Omani MS patients had mild lymphopenia (grades 1–2).
- The main reasons for DMF discontinuation were early side effects mostly gastrointestinal symptoms, hot flushes and confirmed pregnancy.

Introduction

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 (BBB) and enter the CNS where they cause local inflammation, leading to demyelination of axons.[2]

There is no cure for MS but there are several disease modifying therapies (DMTs). Although they share similar goals, they have different mechanisms of action, efficacies, and safety profiles.[3] Examples of DMTs are ocrelizumab, natalizumab, fingolimod, and dimethyl fumarate (DMF).[3,4] DMF is an oral DMT, which was approved by the FDA in 2013 to treat MS, as it demonstrated good efficacy in two randomized placebo-controlled phase III clinical trials, viz., DEFINE and CONFIRM.[5,6] DMF therapy reduced expanded disability status scale (EDSS) score by 38% in DEFINE and 21% in CONFIRM trials. Furthermore, DMF reduced the annualized relapse rate (ARR) by 53% in DEFINE and 44% in CONFIRM studies.

Lymphopenia occurs when the absolute lymphocyte count (ALC) falls below 1,000 cells/μL. The severity of lymphopenia is classified into four grades: grade-1: ALC 800–999/μL; grade-2: ALC 500–799/μL; grade-3: ALC 200–499/μL; and grade-4: ALC <200/μL. Because DMF reduces ALC levels by diminishing the survival rate of lymphocytes, it should be discontinued if ALC remains below 500/μL for an extended period of time.[7] In the CONFIRM trial, the mean ALC value decreased 32% after the first year of starting DMF therapy, with 5% of the patients developing lymphopenia ≥ grade-3. The DEFINE study reported a 28% reduction in mean ALC and 4% incidence of ≥ grade-3 lymphopenia. Both the studies showed that the steepest reduction in mean ALC levels occurred in the first year of DMF therapy, which then plateaued and mean values stayed within the normal limits. In addition, 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, reduction of T cells being more significant, especially CD8-T cells which are important for cell-mediated immunity against viral infections; however, a long-term follow up study did not report any increase in opportunistic infections.[8]

The most-reported side effects of DMF 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, and then decrease over time.[5] The most common reason of DMF discontinuation is the lack of tolerability which appears to be more than that of

fingolimod.[9] The time point of DMF discontinuation mainly depends on the adverse events experienced by the patient.[10] The risk factors for lymphopenia induced by DMF 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 on DMF therapy with a total follow-up period of more than 10 years.[12] The main side effects reported were GI events (43% prevalence) and flushing (24%), both likely to manifest, as expected, early in the DMF treatment. Also reported were abnormal liver enzymes (11%) and serious infections (5%). 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 study period.

A Kuwaiti study on 119 patients who were treated with DMF for mean 20 months reported that 2.5% had to discontinue due to persistent grade 3 lymphopenia.[13] Additional 7.5% of patients discontinued DMF due to other commonly known side effects. According to Hauser & Cree (2020),[3] assessments of efficacy and tolerability of DMTs such as DMF require long-term evidence-based data, requiring more real-world studies.

In the above context, there is a paucity of data on the effect of DMF on ALC among the Arabian populations, and in particular among Omanis. This lack assumes more seriousness considering the high rates of consanguinity in the Middle East, especially in the Gulf Cooperation Countries (GCC) including Oman,[14] and the consequent increased prevalence of genetic illnesses including MS.[15]

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

Methods

Setting

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

Study design and data collection

This was a retrospective study conducted at SQUH and KH. The study included all the 64 Omani MS patients who attended neurology clinics of these two hospitals and were treated with DMF (including those who later discontinued it) from 2017 February to 2023 February. The study data was extracted from the electronic medical records of the patients. Demographic data collected included date of birth, and sex. Clinical data included the date of onset of MS, disease duration, date of starting DMF, date of discontinuation of DMF, and duration of DMF treatment. Details such as BMI, Vitamin D levels when DMF was initiated, history of smoking, the previous DMT used before initiating DMF, and the reasons for discontinuing DMF were also retrieved from the patient electronic records. The baseline ALC and last available ALC at last visitor at the time of DMF discontinuation were also noted for comparison.

Data analysis

The data was analysed using IBM SPSS Version 25 (IBM Corp., Armonk, NY). This study considered the status of lymphopenia of Omani patient with MS and DMF therapy as the primary covariate of lymphopenia, while the socio-demographic and clinical characteristics of patients as

the covariate of lymphopenia. Descriptive analysis was used for demographic, clinical, and basic investigations. Continuous variables were represented by mean ± standard deviation and range and categorical variables were summarized as frequencies and percentages. Paired sample test was used to obtain the significance of change in ALC levels associated with DMF use and $p < 0.05$ 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 presence of multicollinearity and outliers that might create a problem in parameter estimation of the model and their significance test. There was no potential outlier and collinearity problem in the data set.

Ethical considerations

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

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 May 2018 to February 2023. The majority (63%) of the patients were female. The patients' mean age was 36.2 ± 7.9 (range: 19–59) years. At baseline, most patients were overweight, with mean BMI of 27.4 ± 7.2 kg/m^2. The mean age of initiation of DMF 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 the respective normal ranges). The most common DMTs used prior to DMF were injectable interferons, received by 35/64 (54.69%) of patients. Twenty patients (31.25%) were treatment naïve for MS. Table 1 gives more demographic and clinical details of the patients.

Prevalence of lymphopenia after DMF administration

The prevalence of lymphopenia among the patients on DMF was 21.9% (95% CI: 11.5–32.3) and was significantly higher among female than male patients (30.0% vs. 8.3%; $p < 0.05$). There

was 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, interquartile range (IQR) 0.92) at baseline to 1.5 ± 0.67 (range: 0.44–3.95) with (95% CI: 1.33–1.67, IQR 0.89) at the last follow-up (paired samples test: t = 5.6; $p < 0.001$) [Figure 1]. As reported in the last visit, 14/64 (21.9%) patients developed lymphopenia after administration of DMF, of whom five patients had grade-1, eight had grade-2 lymphopenia, and one had grade-3 lymphopenia. [Figure 2].

Reasons for DMF discontinuation

More than one third (23/64; 35.9%) of the patients discontinued DMF for the following main reasons: pregnancy (26%), experiencing adverse events (26%) such as gastrointestinal symptoms (13%), hot flushes (8.7%), patients' choice/convenience (17.4%), patient noncompliance (8.7%), and allergic reactions (4.3%) [Table 2]. Of the six women who stopped using DMF due to pregnancy, only one restarted the drug after delivery. The others were still pregnant or lactating during our study period.

Risk factors for DMF-induced lymphopenia

Table 3 presents the crude and adjusted odds ratios of lymphopenia according to demographic and clinical characteristics of patients, using univariate and multiple logistic regression analysis. Both univariate and multiple logistic regression analyses identified female sex as a significant predictor of DMF-induced lymphopenia. Our female participants were found to have > 5 times higher risk of developing lymphopenia than their male counterparts with odds ratio (OR): 5.83 and 95% CI: 1.03–33.2 ($p = 0.037$). Though factors such as the age at diagnosis, DMF duration, ALC level at DMF start also showed negative association with lymphopenia, these were not statistically significant [Table 3]. However, the multivariable logistic regression model should be interpreted with caution in view of the study's limited sample size. Since we deal with a small sample in regression analysis, we 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 (VIF) were <4.0.

Discussion

This was a retrospective study among Omani MS patients, attending neurology clinics at two tertiary hospitals in Oman, who were continuing to receive DMF therapy, or had discontinued it. Their demographic distribution was similar to the internationally reported data, especially the female preponderance and the most affected age group being 20–40 years.[18] We included only Omani citizens as we wanted to study the safety of DMF in this population. In addition, very few non-Omani MS patients were treated at our centres.

Most of our participants were non-smokers. All the smokers were male; due to cultural reasons, Omani females rarely indulge in this habit. The mean age of starting DMF 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 ranging (0–7 years) with a mean follow up period of 2.8 ± 1.6 years.

More than two-thirds (68.8%) of our patients were exposed to other DMTs[19] prior to starting DMF vis-a-vis 75.6% reported from Kuwait by Alroughani *et al.* (2017).[13] Among our patients, 54.7% used injectable interferons prior to DMF compared to 73.3%in the Kuwait study.[13]

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

The incidence of severe lymphopenia (≥ grade 3) was approximately 5% in the CONFIRM[5] study and 4% in the DEFINE[6] trial. The long-term extension study, the ENDORSE trial, reported a 10.6% incidence of prolonged moderate lymphopenia and 2.4% incidence of prolonged severe lymphopenia.[12] None of our patients developed grade 4 lymphopenia. It is known to be rare; a study in the United States reported prevalence of 0.2%.[20] In our study, the overall prevalence of lymphopenia was 14/64 (21.9%), in which grade 1, grade 2 and grade 3 were 5 (7.81%), 8

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

Several studies have reported higher prevalence of lymphopenia than in our study. A retrospective study based on 38 patients in Italy which assessed ALC levels after 12 months of starting DMF reported a lymphopenia prevalence of 25.9% (grade-1: 6.5%, grade-2: 12.9%, grade-3: 6.5%).[23] Another retrospective study from the United States on 194 MS patients reported a lymphopenia prevalence of 38% in which grade-1 was 16%, grade-2 was 14%, and grade-3 was 7%.[11] Most studies including ours found grade-2 lymphopenia to be more frequent than grade-1. Furthermore, grade-3 lymphopenia, found in one patient in our study, was also reported in other studies. However, those studies also had cases of severe lymphopenia (≥ grade-3) in frequencies that sometimes exceeded those in the pivotal clinical trials of both the CONFIRM and the DEFINE studies.[5,6]

The rate of DMF discontinuation in our study was 36.0%, compared to 19.3% in the Kuwaiti study.[13] The most common reasons among our patients for discontinuation were adverse events (9.4%) and confirmed pregnancy. 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 period of DMF administration was reported to lower the likelihood of adverse events related to DMF discontinuation.[13] Similar documented symptomatic treatments were not provided to our population.

Another possible explanation for higher frequency of discontinuation due to side effects in our study is the shorter duration of one week of initial titration of DMF for our patients as practised in our centres, vis-à-vis studies which continued lower doses for longer periods, up to 2–4 weeks.[13] An Italian multi-centre prospective study by D'Amico *et al.*[21] with 234 patients found out that 26.5% of them 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] Our study population had lower prevalence of GI symptoms (4.7%) and flushing (3.1%).

We found female sex to be a significant predictor of lymphopenia associated with DMF. Our female patients had >5 times higher odds of developing lymphopenia than male patients, a finding congruent with most previous studies.[18] However, unlike many studies, we did not find any significant association between lymphopenia caused by DMF with age groups, BMI, vitamin D level, baseline ALC status, or the previous DMT used. A reason for this might be the small sample size of our study. If the sample size is small, usually it produces a larger standard error (SE) of an estimate, because SE is inversely related to sample size. As a result, if the sample size is large, even a small observed difference could be significant, depending on the standard deviation of the variables, because in all statistical tests SE is used as the denominator. Standard deviation and sample size play important role in statistical significance test. However, for prevalence estimation, our sample of only 64 subjects have very little implication.

A single-centre cohort retrospective study in the United States on 221 patients 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, ethnicity, or sex were not associated with lymphopenia.[24] Mallucci *et al.*[25] also found in their Italian study that age at the start of DMF therapy was associated with lymphopenia. A retrospective study in Israel on 194 MS patients found that older age, white ethnicity, overweight (BMI 25–29.9), low baseline ALC, and non-smoking status were risk factors for DMF-induced lymphopenia.[11] There was no significant association with previous use of natalizumab or carbamazepine/oxcarbazepine or concomitant steroid or opiate use.[11] Contrary to most studies including ours, a large Italian multicentre study on 1,089 MS patients reported that females were less likely than males to develop lymphopenia while using DMF.[26]

In general, the risk factors for DMF-induced lymphopenia have varied considerably among the above real-world studies. However, they all found older age as 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 two pivotal clinical trials of DMF which excluded older age groups.[20,24]

Limitations

The small sample size may have affected the accuracy of our results as well as the other possible biases and random errors when it comes to interpreting odds ratios. In addition, there were the usual limitations of a retrospective study design type. There was no specific protocol to follow-up the patients, including the exact timing of follow-up after initiation of DMF, or the timing of blood collection to assess the side effects. This prevented us from establishing the time gap between starting DMF therapy and manifestation of lymphopenia and other side effects.

Conclusion

The frequency of mild lymphopenia (grades 1–2) among Omani MS patients who were treated with DMF was similar to most other regional and international findings. Only one of our patients had severe lymphopenia (grade-3), a lower prevalence than in many other studies. The main reason for discontinuation of DMF was related to the expected initial side effects. Before initiating DMF treatment, the treating neurologist should ensure that the patient understands the expected side effects and how they are managed, for better patient compliance and reduced discontinuation rate.

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Conflicts of Interest

AA-A received honoraria as a speaker from Novartis, Sanofi, Biologix, Merck, Roche, Biogen and Bayer. He serves on the scientific advisory boards of Novartis, Merck, and Roche. JA-K received honoraria as a speaker from Merck, Sanofi, Novartis, Roche and Biogen. He serves on

the scientific advisory boards of Novartis, Merck, and Sanofi. He is participating in phase 3 trial for Novartis. AA-Q received honoraria as a speaker from Novartis and AbbVie.

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Authors' Contribution

AJ did the formal analysis and writing of the original draft. AA-A did the supervision, conceptualization, methodology, formal analysis and reviewed and editing the manuscript. MMI was involved in the formal analysis and reviewed and editing the manuscript. SR contributed to the formal analysis and reviewed and editing the manuscript. IR, JA-K, IA-Z, AA-Q, HA-A and ARG reviewed and editing the manuscript. All authors approved the final version of the manuscript.

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: 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 D L, 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–e38. 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 2021; 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: 752–759. 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. doi: 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. doi: 10.1007/s40263-018-0543-3.

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

Sex:	
Male	24 (37.5%)
Female	40 (62.5%)
Age in years, (range)	36.2 ± 7.9 (19–59)
Age at DMF start in years, (range)	33.3 ± 7.7 (18–56)
Duration of disease in years, (range)	5.6 ± 5.6 (0–22)
Duration of DMF use in years (range)	2.8 ±1.6 (0–7)
Baseline BMI	27.4 ± 7.2
Baseline 25-OH vitamin D (nmol/L)	87.2 ± 49.6
Baseline ALC ($\times 10^9$/L)	2.1 ± 0.8
Smoking history:	
Smokers	3 (4.7%)
Non-smokers	38 (59.4%)
Smoking status unknown	26 (40.6%)
DMT use prior to DMF	
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 DMF initiation	
Normal	50 (78.1%)
Lymphopenia	14 (21.9%), 95% CI: 11.5% -32.3%

Note. *ALC: absolute lymphocyte count; DMT: disease modifying therapies; SD: standard deviation.*

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

Reason for DMF discontinuation	Number of patients	Percentage *(based on n = 23)*
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
Noncompliance of the patient	2	8.7
Confirmed pregnancy	6	26.1
Total	23	100

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

Demographic and clinical characteristics	Univariate logistic regression		Multiple logistic regression	
	COR[a] (95% CI)	p-value	AOR[b] (95% CI)	p-value
Sex				
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 diagnosis	0.97 (0.82 – 1.15)	0.653	0.99 (0.84–1.18)	0.910
Age at DMF start	1.04 (0.96 – 1.12)	0.309	1.07 (0.93–1.23)	0.323
DMF 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 DMF start	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	

Note. [a]*COR*: *crude odds ratio*; [b]*AOR=adjusted odds ratio*; ***significant; B: regression coefficient; CI: confidence interval; BMI: body mass index; DMT: disease-modifying therapies; SE: standard error; ALC: absolute lymphocyte count.*

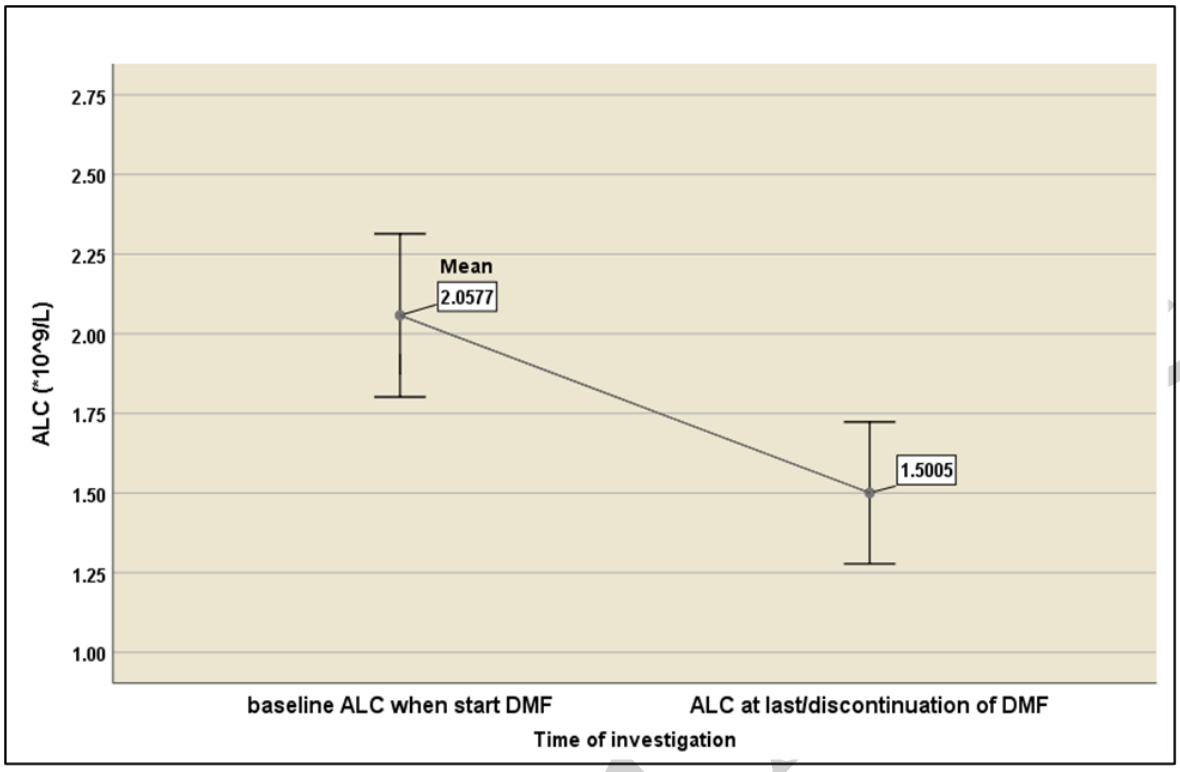

Figure 1: Changes in the absolute lymphocyte count of Omani MS patients after DMF administration

Note. *MS: multiple sclerosis*; *ALC: absolute lymphocyte count; DMF: dimethyl fumarate*.

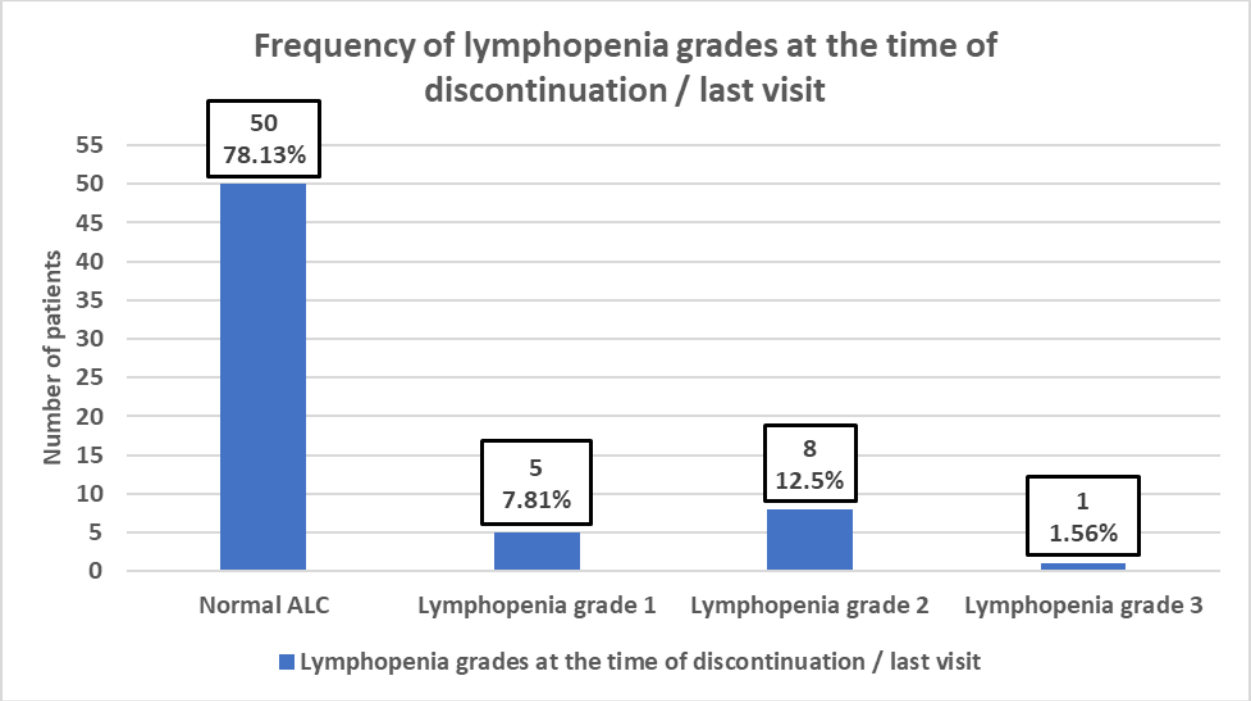

Figure 2: Prevalence of lymphopenia grades 1, 2, and 3 among Omani multiple sclerosis patients on the date of last visit or when dimethyl fumarate was discontinued.