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Risk factors for development of lymphopenia in dimethyl fumarate-treated patients with multiple sclerosis☆,☆☆

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ABSTRACT

Background: Dimethyl fumarate (DMF, Tecfidera®) is a first-line disease-modifying therapy for relapsing-remitting multiple sclerosis. Lymphopenia is a frequent reason for discontinuation in fumarate-treated patients. Management strategies to minimize risk of lymphopenia are warranted.
Objective: The aims of this study were to investigate the correlation of body mass index (BMI), baseline absolute lymphocyte count (ALC), age and sex with risk of DMF-induced lymphopenia in MS patients.
Methods: The study was a retrospective cohort study of 452 MS patients who had been prescribed DMF at six clinics in two Danish regions between May 2014 and September 2017. Data on lymphocyte counts, BMI, age, sex, and reason for discontinuation of DMF were collected through the Danish Multiple Sclerosis Registry, with follow- up to two years after treatment start.
Results: 28.5% of patients had lymphopenia grade II or higher at some time in the first two years of DMF treatment. Increased risk of lymphopenia was observed in patients with baseline ALC of 1.00–1.49×10^9 cells/L (odds ratio, OR 5.48, $p<0.0001$) and 1.50–1.99×10^9 cells/L (OR 2.08, $p = 0.0009$). Reduced risk of lymphopenia was observed in patients with ALC of 2.00–2.49×10^9 cells/L (OR 0.51, $p< 0.01$) and ≥ 2.50×10^9 cells/L (0.12, $p<0.0001$). Patients aged ≥ 56 years had an increased risk of lymphopenia (OR 3.58, $p<0.001$), and patients with BMI ≥ 30 kg/m^2 had a decreased risk of lymphopenia (OR 0.53, p value = 0.03).
Conclusion: Low baseline ALC and older age were risk factors for DMF-induced lymphopenia, while BMI ≥ 30 kg/m^2 and high baseline ALC were protective factors for developing lymphopenia in MS patients treated with DMF.

1. Introduction

Fumaric acid esters (FAE) have been investigated since 1959 and have been used (as Fumaderm®) in Germany and the Netherlands since 1994 for the treatment of psoriasis (Schweckendiek, 1959; Mrowietz and Asadullah, 2005). Dimethyl fumarate (DMF) is a first-line disease-modifying therapy (DMT) in the treatment of relapsing-remitting multiple sclerosis (MS). It was marketed for treatment of MS in 2013 (Tecfidera®) and of psoriasis in 2017 (Skilarence®) in the US and Europe (Mrowietz et al., 2017; Fox et al., 2012; Gold et al., 2012). Currently more than 445,000 patients have been treated, generating safety data on more than 875,000 treatment years (Gold et al., 2020).

Based on this experience with DMF, diroximel fumarate (DRF) and monomethyl fumarate (MMF) recently also received FDA approval for use in MS. DRF and MMF were developed with the aim of achieving similar efficacy as DMF but with fewer gastrointestinal adverse events (AEs), presumably due to less accumulation of methanol in the gut (Jonasson and Sejbaek, 2020; Naismith et al., 2019; Naismith et al., 2020; Palte et al., 2019). Trials of DRF and MMF have demonstrated similar declines in absolute lymphocyte count (ALC) after initiating

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treatment, but MMF trials have been of shorter duration and have focused on pharmacokinetics and bioavailability of MMF (Jonasson and Sejbaek, 2020; Naismith et al., 2019; Naismith et al., 2020; Lategan et al., 2021; Wynn et al., 2020).

The summary of product characteristics for DMF was updated in 2015, and the frequency of monitoring for ALCs was increased from two to four times a year. The update also stated that physicians should consider interruption of DMF treatment in patients with grade III lymphopenia that persisted for more than six months. Since then, few cases of progressive multifocal leukoencephalopathy (PML) have been reported, and the 19 first cases of PML post-DMF treatment demonstrated persistent grade III lymphopenia (0.5–0.2 $\times$ 10^9/L) prior to the PML (Gieselbach et al., 2017). In view of the available data on 875,000 treatment years, the risk is considered very low (Gold et al., 2020; Diebold et al., 2019).

Risk factors for DMF-induced lymphopenia has previously been studied in mainly smaller cohorts where approximately one in four patients had registered lymphopenia grade II or more (Sainz de la Maza et al., 2019; Lucchini et al., 2021; Sierra Morales et al., 2020; Boffa et al., 2020; Longbrake et al., 2015).

The aim of the current study was to investigate whether body mass index, pre-treatment absolute lymphocyte count, age or sex were associated with increased risk of developing DMF-induced lymphopenia in patients with multiple sclerosis.

2. Materials and methods

2.1. Study design and inclusion criteria

The study was designed as a multicenter, retrospective cohort study. We included patients who had a diagnosis of multiple sclerosis according to the McDonald Criteria (Thompson et al., 2018) and were treated with DMF as part of standard clinical practice. Data on age, sex, and body mass index and blood sample results were collected. Reason for discontinuation of DMF was extracted from the Danish Multiple Sclerosis Registry (DMSR).

This study was approved by the Danish Patient Safety Authority (case #3-3013-622/1) and the Danish Data Protection Agency (Journal No. #16/11931).

2.2. Data collection

It is mandatory for Danish physicians treating MS patients to report clinical data on these patients to DMSR, and data quality is ensured locally by the treating physicians as well as the data coordinator at DMSR using patient health records (Magyari et al., 2021).

The study data consisted of patients who initiated treatment with DMF from March 2014 to September 2017 at six multiple sclerosis clinics located in two of the five regions in Denmark – Region of Southern Denmark with a catchment area of 1,218,000 citizens and Region Zealand with a catchment area of 834,740 citizens, giving a total of 2,052,740 citizens. Data were collected from September 2017 to October 2017. Laboratory results were retrieved from the respective IT service in each region, and body mass index was registered at the time of the visit or by phone/e-mail. To check that phone-collected height and weight estimates were reliable, we compared height and weight values collected at physical examination in the outpatient clinic with values collected by phone interview in a subgroup of patients from Roskilde University Hospital (n = 54). Clinical data from DMSR and patients' records were transferred to EpiData®.

2.3. Study population

Of the initial 475 patients, 23 were excluded due to missing data (5 patients did not respond to phone and e-mail inquiries about height and weight, laboratory results were not available for 9 patients, and a further 9 patients had missing baseline lymphocyte counts).

After these exclusions, the study cohort consisted of 452 patients (see Fig. 1).

2.4. Lymphopenia—definition and data collection

The lowest reported absolute lymphocyte count (ALC) defined the grading of lymphopenia for each patient. Patients were considered to have lymphopenia (grade II–IV) if the (ALC) was $< 0.8 \times 10^9$/L at any time during DMF treatment. Grades of lymphopenia were assigned according to the common terminology criteria for adverse events (U.S. Department of Health and Human Services, 2017), defining grade I lymphopenia as lower level of normal to 0.8 10^9 cells/L, grade II lymphopenia as <0.8–0.5 10^9 cells/L, grade III lymphopenia as <0.5–2 10^9 cells/L and lastly grade IV lymphopenia as <0.2 10^9 cells/L. Lymphocyte counts after treatment discontinuation were not included in the data analysis.

2.5. Statistical analysis

All statistical analyses were performed using the software GraphPad Prism version 9.2.0 for Windows.

Patient demographics are described using means and standard deviations, and the reason for DMF discontinuation is described by proportions. Body mass index (BMI) was calculated based on height and weight (weight/height^2 = kg/m^2).

Baseline ALC and patient age were both divided into five subgroups, and BMI was divided into four subgroups for analysis. For the analysis of significance, the α-level was 0.05 and Fisher's exact test was used. Odds ratios were calculated with 95% confidence intervals.

3. Results

3.1. Demographic profile

The study cohort comprised 452 MS patients with a total of 897 treatment years, corresponding to an average treatment length of 1.98 years per patient.

As depicted in Table 1, 71% were female, the mean age was 40.8 years (SD 10.6 years), mean BMI was 25.4 kg/m^2 (SD 5.1 kg/m^2), and

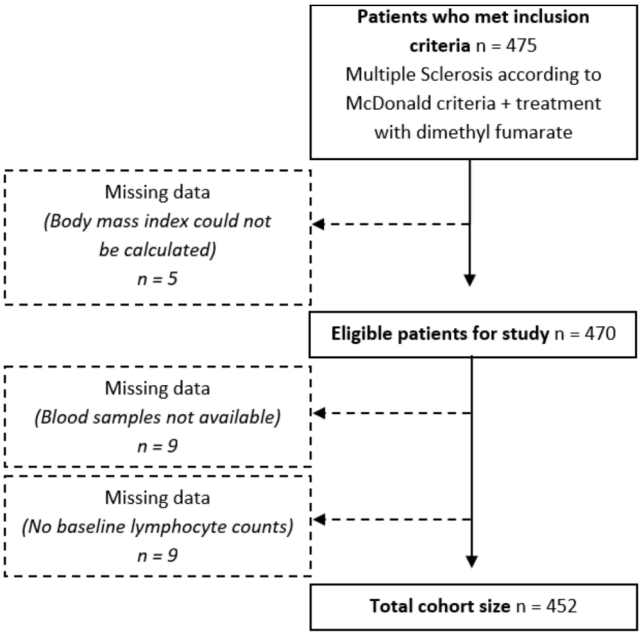

Fig. 1. Flow chart depicting recruitment for the cohort.

Table 1
Odds ratio refers to risk of lymphopenia within the given subgroup.

Table 1	n / Total[a]	Proportion (%)	Odds ratio (95% CI)	P value
Sex				
Female	93 / 322	28.9	1.06 (0.67–1.67)	0.82
Male	36 / 130	27.7	0.94 (0.60–1.50)	0.82
Age (years)				
≤ 25	8 / 40	20.0	0.60 (0.28–1.30)	0.27
26–35	17 / 104	16.6	0.41 (0.23–0.72)	0.0018**
36–45	46 / 154	29.9	1.10 (0.73–1.68)	0.66
46–55	40 / 122	32.8	1.32 (0.85–2.04)	0.24
≥ 56	18 / 32	56.3	3.58 (1.79–7.62)	0.0008***
BMI (kg/m^2)				
≤ 18.5	4 / 15	26.7	0.91 (0.31–2.65)	> 0.99
18.6–24.9	64 / 240	26.7	0.82 (0.54–1.25)	0.35
25–29.9	43 / 124	34.7	1.57 (0.99–2.41)	0.06
≥ 30	19 / 74	25.7	0.53 (0.30–0.92)	0.03*
Baseline ALC (10^9 cells/L)				
≥ 2.5	7 / 111	6.3	0.12 (0.05–0.27)	< 0.0001****
2.0–2.49	25 / 123	22.7	0.51 (0.31–0.81)	0.0049**
1.5–1.99	50 / 134	39.6	2.08 (1.34–3.22)	0.0009***
1.0–1.49	40 / 70	61.4	5.48 (3.17–9.19)	< 0.0001****
≤ 0.99	7 / 14	50.0	2.59 (0.96–6.92)	0.13

Statistically significant values are marked by: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.0001$. ALC = absolute lymphocyte count, BMI = body mass index.

[a] n refers to number of patients with lymphopenia, total is the total amount of patients in the given subgroup.

mean baseline ALC was 2.09×10^9cells/L (SD 0.67×10^9cells/L).

3.2. Discontinuation rates

A total of 146 patients (32.3%) discontinued DMF treatment, giving a mean treatment duration in Region of Southern Denmark of 566.4 days (SD ± 327.8 days) and in Region Zealand of 362.4 days (SD ± 249.0 days).

The reasons for discontinuation are illustrated in Fig. 2. DMF was discontinued in 31 patients (21.2%) due to lymphopenia, 31 patients (21.2%) due to gastrointestinal adverse effects, 5 patients (3.4%) due to depression/low energy (MS fatigue), 23 patients (15.8%) due to flushing, 36 patients (24.7%) due to planning of pregnancy or pregnancy, and 20 patients (13.7%) due to 'other' reasons including low patient adherence, leg cramps, dizziness, trigeminal neuralgia, patient's wishes, and anaphylaxis.

3.3. Absolute lymphocyte count

Data on lymphocyte count were collected at baseline (before treatment with DMF) and during treatment with DMF at the following timepoints: month$_3$ (m) ($n = 381$), m$_6$ ($n = 325$), m$_9$ ($n = 289$), m$_{12}$ ($n = 284$), m$_{18}$ ($n = 266$), and m$_{24}$ ($n = 282$).

We collected lymphocyte counts when patients had baseline ALC and one or more ALC during treatment with DMF at the following timepoints: month$_3$ (m) ($n = 381$), m$_6$ ($n = 325$), m$_9$ ($n = 289$), m$_{12}$ ($n = 284$), m$_{18}$ ($n = 266$) and m$_{24}$ ($n = 282$).

Compared to mean baseline ALC, we found a decline in subsequent ALCs throughout the treatment period: m$_3$: 1.65 (± 0.64) x 10^9/L; m$_6$: 1.40 (± 0.58) x 10^9/L; m$_9$: 1.34 (± 0.66) x 10^9/L; m$_{12}$: 1.30 (± 0.60) x 10^9/L; m$_{18}$: 1.30 (± 0.61) x 10^9/L; m$_{24}$: 1.29 (± 0.63) x 10^9/L.

Lymphopenia grade 2 or higher with ALC equal to or below 0.8 × 10^9 cells/L occurred in 129 patients (28.5%). Of these, 29 patients (22.5%) had grade 3 lymphopenia with ALC of 0.2–0.5 × 10^9 cells/L, 25. A single patient (0.2%) had grade 4 lymphopenia with ALC below 0.2 × 10^9 cells/L.

3.4. Age, BMI, and sex as risk factors

We found age above 56 years to be a risk factor for DMF-induced lymphopenia with an odds ratio (OR) of 3.58 (CI 1.79–7.62, $p = 0.0008$), see Table 1. Age between 26 and 35 years of age was shown to be a protective factor against lymphopenia with an OR of 0.41 (CI 0.23–0.72, $p = 0.0018$). No significant risk association was found between ALC and age below 25 years, age between 36 and 45 years, and age between 46 and 54 (p value of 0.27, p value of 0.66 and p value 0.24, respectively, see Table 1 for odds ratios and standard deviations).

We found an association between BMI above 30 and lower risk of lymphopenia with an OR of 0.53 (CI=0.30–0.92), $p = 0.03$. Apart from this no association was found between lymphopenia and BMI.

Sex was not associated with DMF-induced lymphopenia ($p = 0.82$).

The odds ratios are depicted as a forest plot in Fig. 3.

3.5. Baseline lymphocyte count

Overall, we found a significant higher risk of developing lymphopenia in patients with baseline ALC equal to or below 1.99×10^9cells/L, while a baseline ALC above 2.00×10^9cells/L decreased the risk of lymphopenia during treatment with DMF (see Table 2).

There was a statistically significant correlation between baseline ALC above 2.5 × 10^9 cells/L and a reduced likelihood of developing lymphopenia with an OR of 0.12 (CI = 0.05–0.27), $p = <0.0001$.

For the patient group with baseline ALC between 2.0–2.49×10^9 cells/L, the OR was 0.51 (CI = 0.31–0.81), $p = 0.0049$. For the patient group with baseline ALC between 1.5–1.99×10^9 cells/L, the OR was 2.08 (CI = 1.34 – 3.22), $p = 0.0009$. For the patient group with baseline ALC between 1.00–1.49×10^9cells/L, the OR was 5.48 [CI = 3.17–9.19], p=<0.0001. We found no significant risk for developing lymphopenia in

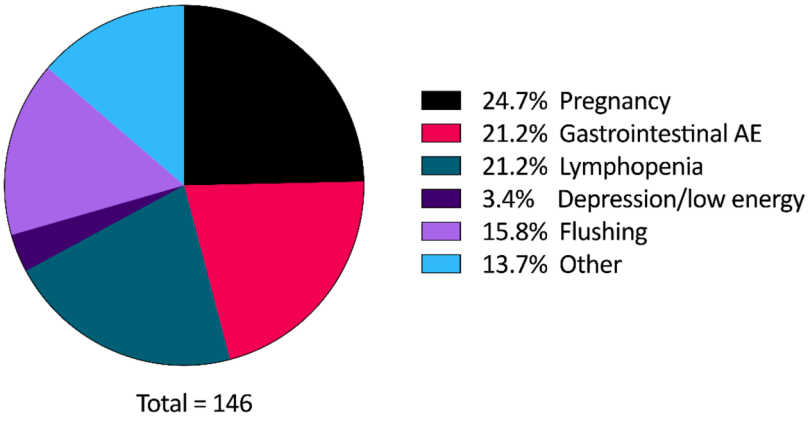

Fig. 2. Pie chart of reason for discontinuation of treatment with DMF. Gastrointestinal AE = gastrointestinal adverse effects.

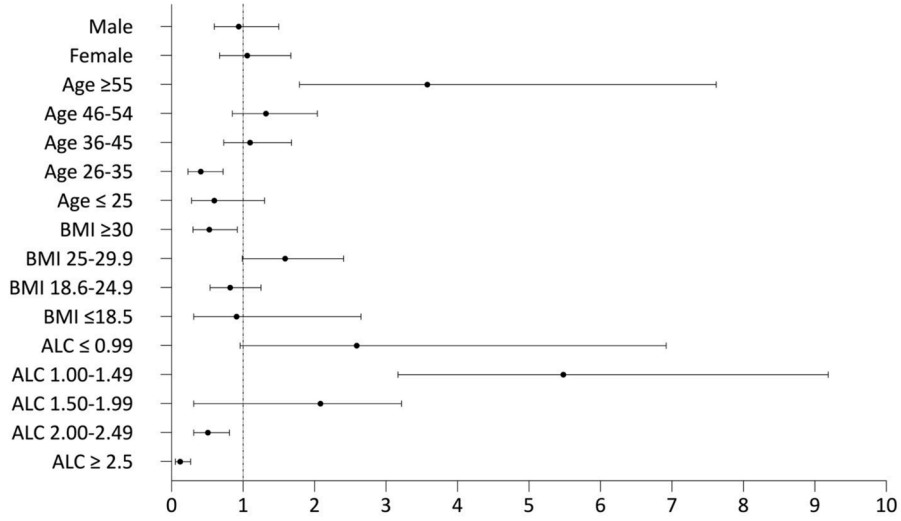

Fig. 3. Forest plot of risk factors.
ALC = baseline absolute lymphocyte count.
Age in years, BMI in kg/m^2, blood ALC in 10^9cells/L.

patients with baseline ALC equal to or below 0.99×10^9cells/L ($n = 14$), but a trend was observed. The odds ratios are depicted in the forest plot show in Fig. 3.

4. Discussion

In this cohort of 452 patients treated with DMF, we examined risk factors for lymphopenia and found that baseline ALC $< 2 \times 10^9$ cells/L and age $\geq$56 years were associated with DMF-induced lymphopenia. Patients with baseline ALC levels between $1.0–1.49\times10^9$ cells/L had an odds ratio of 5.48 for development of lymphopenia, and those with $1.5–1.99\times10^9$ cells/L had an odds ratio of 2.08, while patients aged $\geq$ 56 years had an odds ratio of 3.58 for development of lymphopenia. In contrast, baseline ALC $> 2 \times 10^9$ cells/L and age $\leq$ 36 years were protective against development of lymphopenia during treatment with DMF. This is similar to results of previous studies (Baharnoori et al., 2018; EE Longbrake et al., 2015) and supports that low baseline ALC and age above 56 years are significant risk factors that clinicians need to be aware of when initiating treatment with DMF. We also observed a trend in patients with baseline ALC $<1.0 \times 10^9$ cells/L regarding development of lymphopenia, however not statistically significant. This could be explained by the low sample size ($n = 14$) in this subgroup and thereby lack of statistically power. Another explanation could be previous DMTs prior to initiation of DMF. Only one patient in this subgroup was treatment naïve and the rest of patients had a treatment history with glatirameracetat ($n = 3$), fingolimod ($n = 1$), interferon beta 1a/b ($n = 8$) and teriflunomide ($n = 1$).

When we examined the association between lymphopenia and BMI, we found a borderline significant ($p = 0.03$) odds ratio of 0.53 in patients with BMI $\geq$ 30, suggesting that obesity could be protective against development of lymphopenia in DMF-treated patients. This is the first study to demonstrate a protective effect of obesity, however, and the results should be interpreted with caution. A previous study examining BMI in DMF-treated MS patients found that BMI between 25 and 30 kg/m^2 is a risk factor for lymphopenia. That study included 194 patients with MS who were treated for more than 12 months (Morales et al., 2020). Our study included 452 patients who were treated on average for 24 months and found an odds ratio of 1.57, but with a borderline significant p-value ($p = 0.06$). We could therefore not reproduce the finding that BMI between 25 and 30 kg/m^2 is a risk factor for development of lymphopenia.

We also examined the relationship between development of lymphopenia and sex and found no correlation. One study from 2015 found that sex was a not a risk factor (Longbrake and Cross, 2015), whereas a more recent study suggested that females were more likely to develop lymphopenia (Mirabella et al., 2018). We could not reproduce these findings.

A recent study found differences regarding suppression of ALC and subsets of CD8+ T-cells in patients with MS who were treated with DMF or monoethyl fumarates, suggesting different response in levels of lymphocytes. Our study only examined response to DMF treatment, and it is uncertain whether the findings can be transferred to novel fumarate agents such as diroximel fumarate or monomethyl fumarate.

4.1. Limitations and sources of error

Our study is not without limitations. We had to exclude 4.8% ($n = 23$) of our cohort due to missing data. We do not believe that the results or interpretation are affected by these missing data, however. Our study did not examine ethnicity, which could be a confounder for development of lymphopenia (Morales et al., 2020). The relatively small proportion of non-Caucasians in Denmark may make it difficult to examine the association between ethnicity and DMF-induced lymphopenia.

In summary, this study found that baseline ALC $< 2 \times 10^9$ cells/L and age $\geq$ 56 years were associated with DMF-induced lymphopenia, and these factors should be considered before DMF treatment is initiated, especially in patients with ALC $< 1.5 \times 10^9$ cells/L. In contrast, a body mass index above 30 kg/m^2 was protective against development of lymphopenia, as were age under 36 years and baseline ALC $>2 \times 10^9$ cells/L. Sex was not associated with lymphopenia in DMF-treated MS patients.

Disclosures

J Ravn, HB Jensen and PB Andersen have nothing to disclose.

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Author contributions

J Ravn, HB Jensen, M Kant, PB Andersen, MK Góra, T Sejbaek all

contributed to study design

J Ravn, HB Jensen, M Kant, PB Andersen, MK Góra, T Sejbaek all contributed to patient recruitment and patient data

J Ravn and T Sejbaek contributed to sample processing

J Ravn, HB Jensen, M Kant, PB Andersen, MK Góra, T Sejbaek all contributed to analysis/interpretation of results

J Ravn, HB Jensen, M Kant, PB Andersen, MK Góra, T Sejbaek all were part of drafting/revising the paper

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