Time course of lymphocyte repopulation after dimethyl fumarate-induced grade 3 lymphopenia: contribution of patient age

Myriam Briner, Maud Bagnoud, Andrei Miclea, Christoph Friedli, Lara Diem, Andrew Chan, Robert Hoepner (iD) **and Anke Salmen**

Abstract

Background: Dimethyl fumarate (DMF) is licensed for treatment of relapsing–remitting multiple sclerosis (RRMS). DMF can induce lymphopenia, which is assumed to increase the risk for opportunistic infections like progressive multifocal leukoencephalopathy. Our goal for this work was to estimate the frequency of grade 3 lymphopenia in DMF-treated patients with RRMS and to characterize patient-sided factors influencing the time course of lymphocyte repopulation after DMF withdrawal.

Material and methods: A single-center retrospective data analysis was performed at University Hospital Bern, Switzerland. Patients with DMF treatment were analyzed for lymphocyte counts. Demographic factors were statistically analyzed in grade 3 lymphopenic patients.

Results: We estimated a grade 3 lymphopenia frequency of 11/246 (4.5%), corroborating previous studies. In all patients, lymphocytes recovered to values ⩾800/μl within 0.5 years. Multivariate linear regression analysis unmasked older age as being associated with a longer duration of repopulation.

Conclusion: Considering the aging population, our findings warrant further investigations of DMF-induced lymphopenia.

Keywords: adverse event, age, fumarate, multiple sclerosis, lymphocytes, white blood cells

Correspondence to:
Myriam Briner
Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Freiburgstrasse, CH-3010 Bern, Switzerland
myriam.briner@insel.ch

Maud Bagnoud
Andrei Miclea
Christoph Friedli
Lara Diem
Andrew Chan
Robert Hoepner
Anke Salmen
Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland

Introduction

Dimethyl fumarate (DMF; Tecfidera®, Biogen Idec, Cambridge, MA, USA) was labelled to treat relapsing–remitting multiple sclerosis (RRMS), after two randomized placebo-controlled phase III clinical trials had demonstrated a favorable risk–benefit ratio.[1,2] In a recent review, 19 cases of progressive multifocal leukoencephalopathy (PML) were reported in patients treated with DMF or other oral fumarate formulations (5 RRMS; 14 psoriasis).[3] Since 13 of these patients showed grade 3 lymphopenia prior to PML diagnosis, high-grade lymphopenia was considered as a risk factor for PML development during fumarate therapy.[3] Consequently, recommendations for monitoring DMF in RRMS were changed and medication withdrawal is recommended in patients with an absolute lymphocyte count below 500/μl.[4] The frequency of ⩾ grade 1 lymphopenia was reported to occur in approximately 16.5% of DMF-treated patients[5] and between 2.4–7% of the patients develop grade 3 lymphopenia (200 to <500/μl).[1,2,6,7] Recently, a small case series of five patients with RRMS showed that even after DMF withdrawal, severe lymphopenia can persist for at least half a year.[8] Thus, studies focusing on lymphocyte repopulation after DMF withdrawal are urgently needed. In addition, patient-related factors predisposing for a longer duration of post-DMF lymphopenia are not yet described. We therefore aimed to characterize the time course and patient-related factors for lymphocyte repopulation in patients with RRMS after DMF withdrawal due to grade 3 lymphopenia.

Materials and methods

We performed a single-center (Inselspital, Bern University Hospital, Switzerland) retrospective data analysis, which was approved by the cantonal ethics committee (KEK-BE 2017-01369).

Electronic patient records were searched for patients with RRMS treated with DMF for at least 1 month using the following search terms: 'dimethyl fumarate', 'Tecfidera' and 'relapsing–remitting multiple sclerosis'. We identified 246 patients with RRMS with DMF treatment. The 'Common Terminology Criteria for Adverse Events (version 3.0)' definition of grade 3 lymphopenia (200 to <500 per µl) was used in this study.[9] Lymphocyte counts of patients with grade 3 lymphopenia were evaluated from DMF withdrawal until reaching lymphocyte counts ≥800/µl, which was defined as lymphocyte repopulation. We did not include patients with an infection around the time point of blood sampling.

Statistical analysis included comparative statistic as well as multiple linear regression analysis and was performed using SPSS (IBM, Armonk, NY, USA).

Results

A total of 11 of 246 DMF-treated (240 mg twice daily) patients with RRMS developed grade 3 lymphopenia after a mean of 501.9 days of treatment [95% confidence interval (CI) 288.4–715.4; range 172–1064]. No grade 4 lymphopenia was observed. There was no statistically significant difference between sex distribution in the grade 3 lymphopenic group compared with the whole DMF-treated population (female-to-male ratios: grade 3 lymphopenia: 2.8:1 versus whole population 2.2:1, Chi-square: $p = 0.81$).

Of the 11 patients, 4 developed lymphopenia within the first year of treatment, 5 within the second year and 2 after the second year. None of the patients received pretreatment with cell-depleting immunotherapies; the most frequently used drug before DMF was interferon-β (4/11; Table 1). Overall, two patients had co-medication potentially alleviating leuko- or lymphopenia (one clozapine, one carbamazepine; Supplementary Table 1). Lymphocytes recovered after DMF withdrawal in all of the 11 patients within half a year (mean 71.2 days, 95% CI 24.5–117.8, range 9–180; Figure 1). Multiple linear regression analysis adjusted for sex and duration of DMF treatment identified age at withdrawal of DMF as an independent predictor for a longer duration until reaching lymphocyte repopulation (regression coefficient: 4.07 (95% CI 1.26–6.87), $p = 0.01$). After lymphocyte recovery, 9 of the 11 patients were re-exposed to an immunotherapy (see Supplementary Table 2). All patients ($n = 2$) directly re-exposed with DMF 240 mg twice daily re-experienced lymphopenia (Supplementary Table 2).

Discussion

In our retrospective analysis, the frequency of grade 3 lymphopenia in DMF-treated patients with RRMS (4.5%) corroborates previous findings.[1,2,6,7] In contrast with phase III clinical trials, where lymphocytes especially declined during the first year of treatment and remained stable thereafter,[1,2] we demonstrated that, compared with the first treatment year, grade 3 lymphopenia occurred more frequently afterwards (first year 4/11 versus ≥second year 7/11). This highlights the importance of regular full blood counts independent of DMF treatment duration. For lymphocyte recovery in our retrospective analysis, we demonstrated that older age was associated with a longer recovery phase. Only a small case series investigated recovery of lymphopenia after DMF withdrawal. Here, applying our definition of lymphocyte recovery, none of five patients recovered over a period of at least 6 months.[8] In our study, lymphocytes did recover after DMF withdrawal in all of the 11 patients within half a year (Figure 1). After recovery of lymphopenia, five patients were re-exposed to DMF. Of these, two patients re-exposed with DMF 240 mg twice daily re-experienced lymphopenia whereas three patients continuing with reduced DMF dosage did not (one of the three patients was switched to a full dose after 12 months on reduced dosage; Supplementary Table 2).

Reasons for a longer recovery in older patients are speculative. However, immunosenescence leading to profound changes in the immune system is likely to be causative.[10] In our aging population, there is thus an unmet need for future research to focus on age-associated treatment effects in this vulnerable patient cohort. Limitations of our data analysis are the monocentric and retrospective nature of our observational study. Therefore, findings should be re-evaluated prospectively with a larger patient population.

Table 1. Characteristics of DMF-treated and lymphopenic (grade 3) patient cohort (*n* = 11). Multiple linear regression analysis (MVreg) for the outcome variable 'duration until reaching lymphocyte recovery in days' was run. Lymphocyte recovery was defined as lymphocyte count ⩾800/μl. MVreg was adjusted for sex and duration of DMF treatment (days). R^2 (MVreg): 0.69, *n* = 11.

	Mean (95% CI)	Range
Age (years)	49.8 (40.4–59.3)	22.7–71.8
Duration of DMF treatment (days)	501.9 (288.4–715.4)	172–1064
Dosage of DMF (mg)	480 (480–480)	480–480
Time until lymphocyte counts ⩾800 μl (days)	71.2 (24.5–117.8)	9–180
	N	%
Diagnosis (RRMS)	11/11	100
Sex (female)	8/11	72.7
Immunotherapy prior to DMF		
None	6/11	54.5
Interferon	4/11	36.4
Natalizumab	1/11	9.1
	Coefficient (95% CI)	*p* value
Multiple Linear Regression Analysis		
Age at DMF withdrawal (years)	4.07 (1.26–6.87)	0.01

CI, confidence interval; DMF, dimethyl fumarate; MVreg, multiple linear regression analysis; *N*, number of observations; RRMS, relapsing–remitting multiple sclerosis.
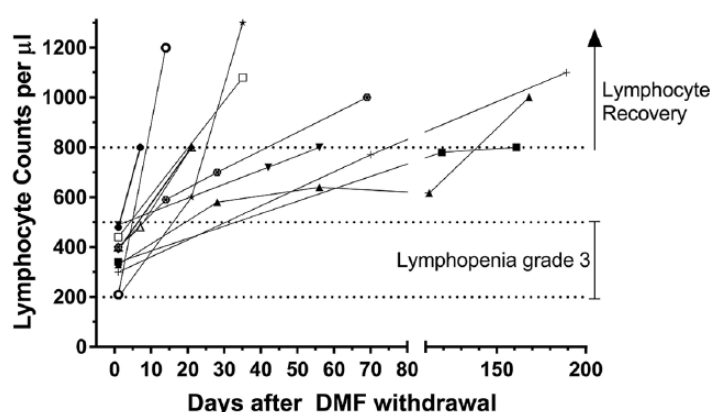

Figure 1. Time course of lymphocyte counts/μl after DMF withdrawal. Each line represents an individual patient with DMF-induced grade 3 lymphopenia (*n* = 11). Definition of grade 3 lymphopenia followed CTCAE recommendations.[9] Individual lines start at the date of DMF withdrawal of each patient (set as day 0).
CTCAE, Common Terminology Criteria for Adverse Events; DMF, dimethyl fumarate.

ORCID iD
Robert Hoepner [iD] https://orcid.org/0000-0002-0115-7021

Supplemental material
Supplemental material for this article is available online.

References

1. Gold R, Kappos L, Arnold DL, *et al*. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; 367: 1098–1107.

2. Fox RJ, Miller DH, Phillips JT, *et al*. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; 367: 1087–1097.

3. Mills EA, Ogrodnik MA, Plave A, *et al*. Emerging understanding of the mechanism of action for dimethyl fumarate in the treatment of multiple sclerosis. *Front Neurol* 2018; 9: 5.

4. European Medicine Agency. Tecfidera: EPAR - product information, www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002601/WC500162069.pdf (2014, accessed 28 August 2018).

5. Mirabella M, Prosperini L, Lucchini M, *et al*. Safety and efficacy of dimethyl fumarate in multiple sclerosis: an Italian, multicenter, real-world study. *CNS Drugs*. 2018; 32: 963–970.

6. Sejbaek T, Nybo M, Petersen T, *et al*. Real-life persistence and tolerability with dimethyl fumarate. *Mult Scler Relat Disord* 2018; 24: 42–46.

7. Fox RJ, Chan A, Gold R, *et al*. Characterizing absolute lymphocyte count profiles in dimethyl fumarate–treated patients with MS Patient management considerations. *Neurol Clin Pract* 2016; 6: 220–229.

8. Zecca C, Antozzi CG, Torri Clerici V, *et al*. Severe multiple sclerosis reactivation during prolonged lymphopenia after dimethyl fumarate discontinuation. *Acta Neurol Scand* 2018; 137: 623–625.

9. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v3.0 (CTCAE), ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf#search=%22Common Terminology Criteria for Adverse Events Version 3.0 %22 (2006, accessed 28 August 2018).

10. Nikolich-Zugich J. The twilight of immunity: emerging concepts in aging of the immune system. *Nat Immunol* 2018; 19: 10–19.