Delayed and recurrent dimethyl fumarate induced-lymphopenia in patients with Multiple Sclerosis

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Background and aims

Early lymphopenia is a known side effect of dimethyl fumarate (DMF), with increasing risk of Progressive Multifocal Leucoencephalopathy (PML) when it is severe and prolonged. However, the long-term effects of DMF on immune response and its impact on lymphocyte count when another disease-modifying treatment (DMT) is introduced, remain unknown. To better understand these specific aspects, we reviewed cases that developed prolonged grade 2 to 4 lymphopenia under DMF in Lausanne MS clinic.

Method

Retrospective analysis of the 12 patients (10.1 % out of 119 patients) who discontinued DMF because of prolonged lymphopenia. During DMF therapy, and within a timeframe of up to 18 months after switching to another DMT, we reviewed demographics, clinical, biological and MRI characteristics, as well as lymphocyte subsets in a subgroup of patients.

Results

Table 1. Clinical and biological characteristics of the patients under DMF. Compared to non-lymphopenic patients, lymphopenic patients were older at DMF initiation and the majority were male.

	Non L-DMF (n=107)	L-DMF (n=12)	*P**
Age, years (mean [(± SD), min-max])	40 [(± 12), 19-70]	51 [(± 13), 37-75]	**0.0003**
EDSS score (median [(IQR), min-max])	1.5 [(1.5-2.5), 1.5-6.5]	2.0 [(1.5-2.5), 1.5-4]	0.258
Disease duration, years (mean [(± SD), min-max])	6.5 [(± 7), 0.01-31.7]	9 [(± 10), 0.1-34]	0.483
Sex, F/M (n)	83/24	6/6	**0.037**
Duration of DMF exposure, months (mean [(± SD), min-max])	30 [(± 18), 2.5-66]	28 [(± 15), 6-53]	0.054
Previous DMT (1 to 4 per patient) (number of patients and %)	60 (56%)	8 (67%)	0.482
- beta-interferon	51 (48%)	7 (58%)	0.483
- glatiramer acetate	10 (9%)	0	0.268
- teriflunomide	3 (3%)	1 (8%)	0.313
- natalizumab	5 (5%)	2 (17%)	0.094
- fingolimod	22 (21%)	1 (8%)	0.309
- others	3 (3%)	0	0.556
ALC at treatment onset, x10^9 cells/L (mean [(± SD), min-max])	1.99 [(± 0.69), 0.83-4.33]**	1.77 [(± 0.88), 1.03-4.04]	0.589

RRMS, relapsing-remitting multiple sclerosis; DMF, dimethyl fumarate; SD, standard deviation; EDSS, expanded disability status scale; IQR, interquartile range; F, female; M, male; DMT, disease-modifying therapy; ALC, absolute lymphocyte count.
*Mann-Whitney U or χ2 test for continuous and categorical variables, respectively
**Data available for 98 patients.

Figure 1. Lymphocyte count obtained before DMF introduction (T0), at the lowest value under DMF treatment (T1), after its discontinuation (T2) and after the switch to another DMT not associated with a T lymphopenia (T3). Note the lymphopenia relapse in T3 under new DMT.

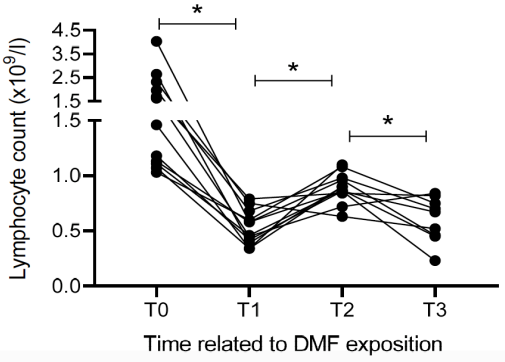


Figure 2. Peripheral blood total lymphocyte count in the 3 patients who developed late lymphopenia (up to 3 years) during DMF treatment.

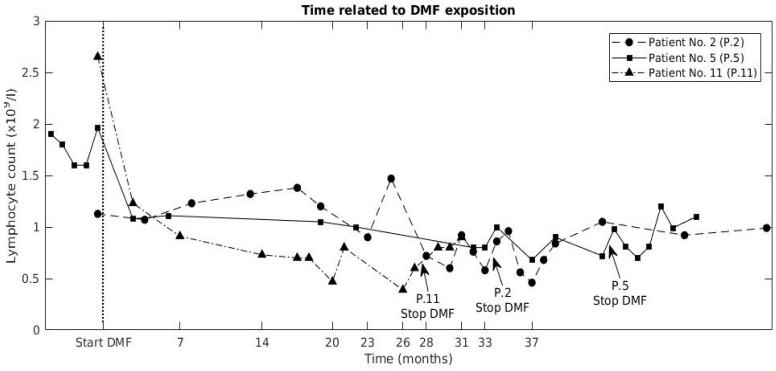
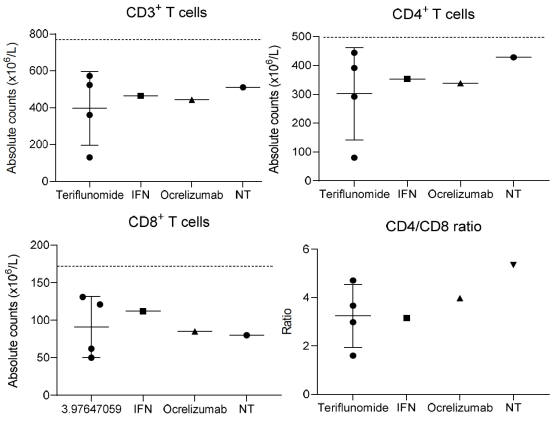


Figure 3. Lymphocyte subsets after the introduction of a new DMT. All patients showed a decrease in CD3+ T cells with, on average, CD4+ and CD8+ T cells below the lower normal value. CD8+ T cell counts especially decreased with a disproportionately high CD4+/CD8+ ratio.



Conclusions

- DMF has a long-term impact on lymphocyte biology, even after its discontinuation.
- Sustained reduction in CD8+ T cells associated with recurrent lymphocyte decrease may increase opportunistic infection (e.g. PML) risk, even after DMF discontinuation.
- These effects should be taken in consideration when switching therapies after DMF, especially in older patients.

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