Title: Incidence of persistent lymphopenia in people with multiple sclerosis on dimethylfumarate

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Abstract

Background

Dimethyl fumarate (DMF) is a disease modifying therapy (DMT) used in the management of Multiple Sclerosis (MS). Lymphopenia occurs in approximately 30% of people receiving this medication. The recently revised Summary of Product Characteristics (SPC) recommends increased monitoring or cessation of this medication in the context of persistent lymphopenia, because of an increased risk of Progressive Multifocal Leukoencephalopathy (PML). It is therefore important for clinicians and patients to be aware of the frequency of persistent, moderate-severe lymphopenia in order to make informed decisions regarding drug choice and safety monitoring.

Methods

We reviewed medical records of 156 people with MS (PwMS) started on DMF between 2014-2020, who received at least 6 months of treatment, in order to identify the incidence and duration of persistent lymphopenia.

Result

Ten were excluded due to missing data. In 146 patients, treated for 30.7 months (mean), 16 (11%) were found to experience persistent moderate lymphopenia (0.5-0.7x10^9/L) and 5 (3%) experienced persistent severe lymphopenia (<0.5 x 10^9/L). Of the 5 patients with persistent severe lymphopenia, 3 discontinued DMF. Two cases stopped directly due to SPC recommendations and after 6-months no further DMTs were initiated. Treatment was withdrawn in a further case due to lack of efficacy. Two cases remained on DMF as their persistent severe lymphopenia predated SPC revision. Mean times to persistent moderate and severe lymphopenia were 10.6 months and 25.5 months respectively. Increased age was a predictor for persistent lymphopenia (B=0.071, p=0.004) while sex, and previous DMT were not.

Conclusion

Persistent, moderate-severe lymphopenia is relatively common in people on DMF. More robust guidelines regarding risk/benefit discussion and future DMT sequencing are required to further guide individualised care.

Introduction

In the last 10-15 years, there has been considerable expansion in the availability of disease modifying therapies (DMTs) that reduce relapses and accumulation of disability in people with multiple sclerosis (MS). Dimethyl fumarate (DMF) is a tablet DMT licensed by the European Medicines Agency for use in 2014 for individuals with active relapsing-remitting MS. It has become a popular choice in many settings as a result of its convenient route of administration, relatively favourable safety profile and moderate efficacy. Lymphopenia occurs in approximately 30% of people with MS (PwMS) exposed to DMF within the first year (1). However, in 2020 the Summary of Product Characteristics (SPC) for DMF was changed to reflect reports of 11 confirmed cases of PML associated with use of the product (2). The association between PML and more profound and durable lymphopenia in those using DMF led to new recommendations to undertake enhanced surveillance or discontinuation of the drug in those who experience moderate or severe lymphopenia with duration of >6 months. These recommendations will require additional resource and raise uncertainties about appropriate sequencing of DMTs in people who are required to discontinue DMF in the context of lymphopenia. Understanding the patterns, risk factors for and incidence of persistent moderate-severe lymphopenia will inform counselling of patients considering this drug, together with service design.

Methods

We reviewed records from the MS Clinic at University Hospital of Wales, a regional neuroinflammatory centre in the UK, to identify all PwMS who commenced DMF between 2014 – 2020. We reviewed the medical records of all those who remained on DMF for at least 6 months and had laboratory information available from treatment start to date completed treatment, or last clinical follow-up if remaining on treatment. Additional notes review (primary and secondary care records) was undertaken for all people who experienced persistent, moderate-severe lymphopenia in order to identify infections, antibiotic prescribing and hospitalisations.

We used laboratory data from routine blood monitoring to identify patients who were detected to have persistent lymphopenia (lasting > 6 months) during treatment. Lymphopenia was defined as: mild (<1.0x10^9/L); moderate (0.5 - 0.7 x 10^9/L); severe (< 0.5 x 10^9/L) (1). We recorded date of onset and eventual outcome of the longest period of lymphopenia in each case. Outcomes of persistent moderate or severe lymphopenia included: (i) stayed on drug vs. discontinued drug, and (ii) lymphopenia improved vs. persisted vs. worsened. Time to lymphopenia was evaluated using Kaplan Meier survival analysis, where cases were censored at the onset of persistent lymphopenia or at the time of their last recorded follow-up. Cox regression analysis was used to determine whether age, sex or line of treatment (first vs. subsequent lines) were predictors of developing moderate or severe lymphopenia (composite outcome). The South-East Wales Ethics Committee approved the study (reference number 05/WSE03/111).

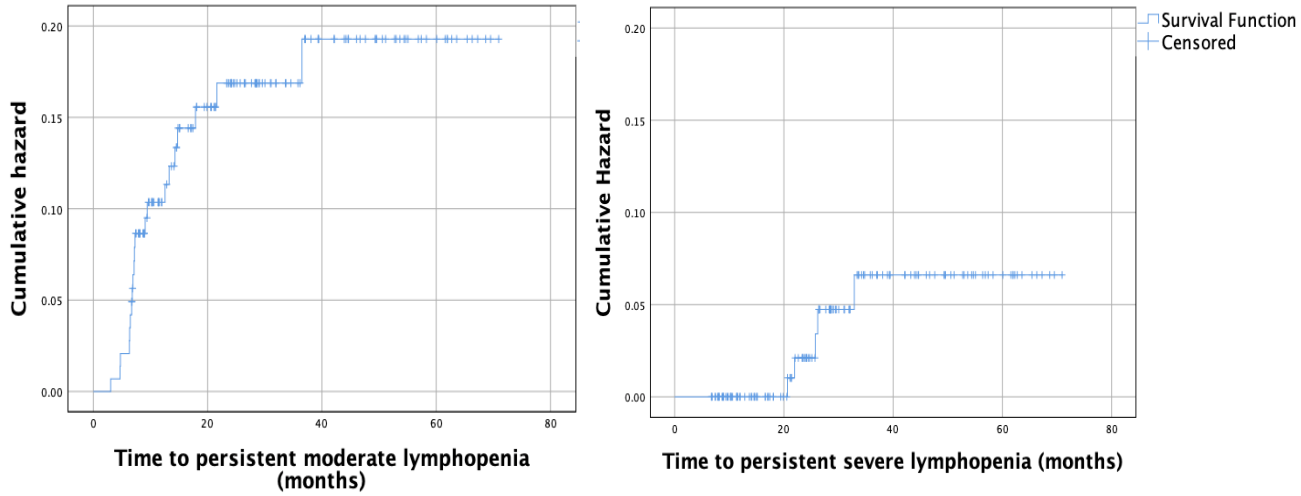
Results

Of 196 people commencing DMF at our centre between 2014-2020, 156 patients remained on treatment for >6 months (40 people either stopped DMF after <6 months or remained on treatment but duration was <6 months at the time of data collection). Ten patients were excluded because of incomplete laboratory information. Of the remaining 146 patients, 102 (70%) were female, 44 (30%) were male, and mean age at DMF initiation was 42.7 years. 49 people had received prior DMT, 97 received DMF first-line. At time of analysis, 32 out of 146 (22%) had discontinued DMF and 114 (78%) remained on treatment. Mean time on treatment at the time of analysis was 30.7 months (range 6.7-70.9). Reasons for discontinuation were adverse events (16), lack of efficacy (13), drug holiday (1), planning pregnancy (1) and poor compliance (1). According to the SPC, the full blood count (FBC) should be measured at baseline and monitored every 3 months during DMF treatment. However, this was relaxed to 6-monthly in the United Kingdom during the COVID-19 pandemic, if the most recent lymphocyte count was >0.5 (3). In this real-world cohort, baseline FBC was available in

144/146 (99%) and mean interval of FBC analysis was 3.4 months. Baseline lymphocyte count was normal (>1x10^6/L) in 141/144 cases (0.9 in two cases; 0.5 in one case). All patients experiencing persistent, moderate-severe lymphopenia had normal baseline lymphocytes.

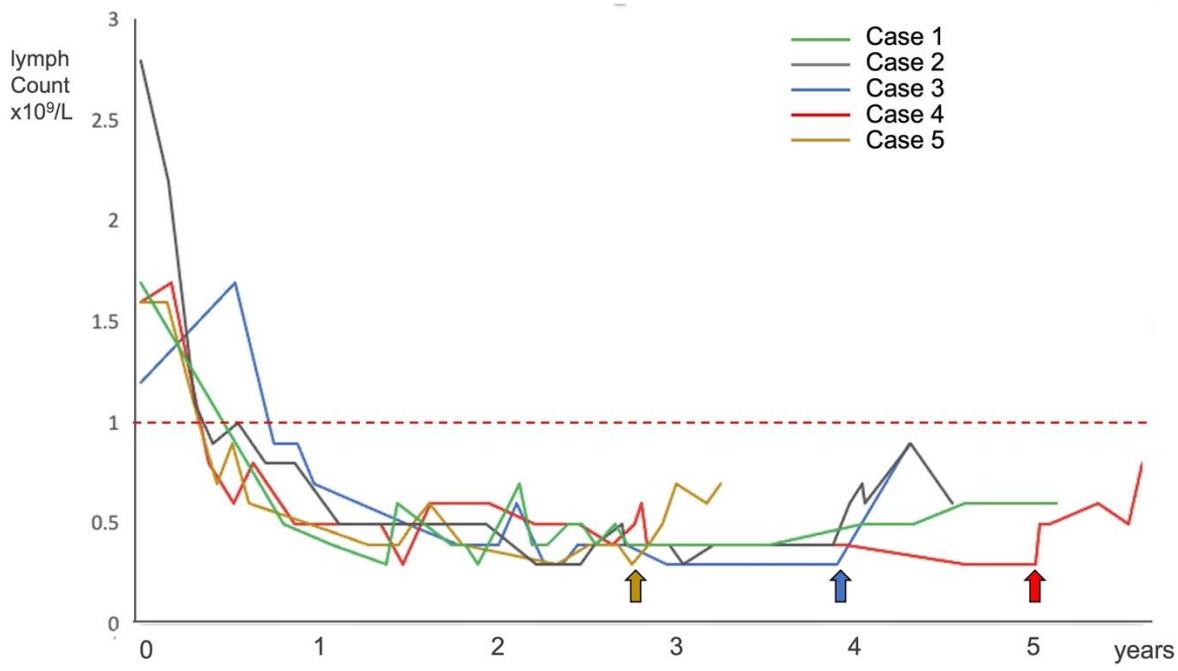
108 of 146 (75%) in the cohort experienced no persistent lymphopenia. The remaining 38 (25%) experienced some degree of persistent lymphopenia, which was mild in 17 (12%), moderate in 16 (11%) and severe in 5 (3%). Time to onset of persistent, moderate and severe lymphopenia was 10.6 (range 3.0-36.5) and 25.5 (range 20.7-32.9) months respectively. Estimated median survival time from drug start to the onset of persistent, moderate and severe lymphopenia was 60.8 (95% confidence interval (CI) 56.8-64.8), and 68.0 (95% CI 65.6-70.5) months respectively (Figure 1).

Figure 1 – Estimated median survival time from DMF start to onset of persistent moderate or severe lymphopenia



The 5 PwMS who developed persistent, severe lymphopenia had already experienced at least 6 months of moderate lymphopenia (Figure 2). Increased age was a risk factor for developing moderate/severe lymphopenia (B=0.071, p=0.004) while sex, and previous DMT were not.

Figure 2 – Graph illustrating change in lymphocyte count from time of dimethyl fumarate (time = 0) in 5 cases who experienced persistent severe lymphopenia. Vertical arrows indicate cessation of treatment in 3 cases.



In the 21 PwMS who experienced persistent, moderate lymphopenia, 20 (95%) continued DMF and one stopped due to lack of efficacy. In those 20 people who continued DMF, 5 subsequently developed severe lymphopenia, 2 improved to mild lymphopenia and the other 13 remained moderately lymphopenic after a mean follow-up of 19.6 months. Notes review found that of all 21 PwMS who experienced persistent, moderate-severe lymphopenia, 4/21 (19%) had documented infection during the lymphopenia (3 urinary tract infections and one case of COVID-19), of whom 2/21 had antibiotics prescribed, but there were no hospitalisations.

In the 5 PwMS who experienced persistent, severe lymphopenia, Cases 1 and 2 continued DMF and lymphopenia improved to moderate after 9.5/19.9 months (Figure 2). In the remaining 3 cases, DMF was stopped after 11.4-24.1 months. In two cases this was in response to SPC revision and had 6 month follow up by date of data capture; FBCs monitored every 1-2 months after cessation had shown lymphopenia to resolve to moderate by 6 months, but neither had yet commenced another DMT. DMF was stopped in one other individual with severe persistent lymphopenia prior to SPC revisions, due to lack of efficacy; natalizumab was initiated one month later.

Discussion

Dimethyl fumarate is a popular disease modifying therapy for PwMS and has a relatively low risk of PML. However, associations between PML and persistent lymphopenia in people receiving DMF have prompted the manufacturer to urge caution in people experiencing moderate/severe lymphopenia lasting more than 6 months. The new SPC guidelines recommend that DMF should be discontinued in people with prolonged severe lymphopenia for more than 6 months, and in those with sustained moderate lymphopenia, the benefit/risk of treatment should be re-assessed (2). Other reports have suggested that severe lymphopenia (of any duration) occurs in ~ 5% exposed to DMF (4, 5), and that prolonged (>12 months) lymphopenia of any degree occurs in ~ 15% (6). To our knowledge this is the first real-world cohort where rates of ***persistent*** (>6 months), graded lymphopenia have been reported. This will guide clinicians and patients about the likelihood of persistent lymphopenia, with specific relevance to recent changes to the SPC.

In our cohort of 146 PwMS remaining on DMF for greater than 6 months, 14% experienced persistent moderate/severe lymphopenia. Mean time to develop severe, persistent lymphopenia (25.5 months) was twice as long as moderate, persistent lymphopenia (10.6 months). We found that

older age was a risk factor for persistent moderate-severe lymphopenia but in this cohort sex and previous DMT did not appear to predict likelihood.

All individuals with persistent, severe lymphopenia had previously experienced persistent, moderate lymphopenia. None of the 21 individuals who experienced persistent, moderate lymphopenia stopped the drug as a direct consequence. Overall, 5% of those with persistent, moderate lymphopenia later developed persistent, severe lymphopenia. Given the relatively high incidence of persistent, moderate lymphopenia, more nuanced recommendations for the clinician decision-making in this group would be valuable. Two of five individuals with severe lymphopenia stopped dimethyl fumarate as a direct consequence, however, only after a minimum of 11 months (prompted in both cases by SPC revision, which occurred in 2020). Both experienced at least 6 months without DMT, during which time lymphopenia improved to moderate. DMF was stopped in another individual with severe persistent lymphopenia due to lack of efficacy, and alternative DMT was commenced one month later. Others have shown that lymphopenia on DMF usually recovers within 6 months but in a minority it persists beyond 12 months, posing potential delays in commencing alternative DMTs (7).

Limitations of our study included relatively low rates of moderate/severe lymphopenia, which limits the ability to model predictors. The SPC recommends surveillance for lymphopenia, with lymphocyte monitoring every 3 months. Our cohort were slightly below this frequency of monitoring (mean interval of 3.4 months). More frequent blood monitoring may have resulted in a greater detection of prolonged lymphopenia, however, since this is a real-world cohort, it is likely to reflect frequency of monitoring in other centres. We did not systematically record adverse events. Notes review was undertaken for those with persistent lymphopenia but comparison data is unavailable for those without persistent lymphopenia.

Conclusion

The new SPC recommendations for DMF suggest the need for a risk/benefit discussion in those experiencing persistent, moderate lymphopenia, and treatment cessation in individuals with persistent, severe lymphopenia due to the increased incidence of PML in these subgroups. We found a persistent, moderate-severe lymphopenia occurred in 14% of our cohort. Older age was a risk factor for its development. Only two people stopped treatment directly due to persistent lymphopenia, but both experienced treatment delays to next DMT. More robust guidelines regarding risk/benefit discussion and future DMT sequencing are required to further guide individualised care.

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