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Dimethyl Fumarate Associated Lymphopenia in Clinical Practice

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Keywords

Dimethyl fumarate; multiple sclerosis; lymphopenia

Dimethyl fumarate (DMF) was approved in the United States for the treatment of relapsing multiple sclerosis in March, 2013. Grade 3 lymphopenia (absolute lymphocyte count (ALC) <500) developed in approximately 5% of patients in the phase III clinical trials (1, 2). With the approval of the Washington University Human Research Protection Office, we conducted a retrospective chart review of all patients prescribed DMF at our Center from March 2013 to August 2014 (n=144) to assess the prevalence of grades 2 (ALC 500–799) and 3 lymphopenia in a real world setting.

Approximately 6% (9/144) of the total cohort developed grade 3 lymphopenia and 14% (20/144) developed grade 2 or 3 lymphopenia. Lymphopenia usually developed after patients had been taking DMF for at least 4 months. Thus, by 4–6 months post-initiation, 10% of patients (4/40) had grade 3 lymphopenia. At >12 months, 28.6% (4/14) had ALC <500; this was significantly higher than the predicted frequency of 5%. Once lymphocyte counts fell, they remained stably low or continued to drop; recovery into the normal range was not observed.

Patients over 55 years old were significantly more likely to develop grade 3 lymphopenia compared to younger patients (p=0.034, Fisher's exact test), which is notable because older patients were excluded from the phase 3 trials of DMF. No clear trends linked lymphopenia to prior treatment with any specific DMT. Sex and race were not significant predictors of lymphopenia.

This retrospective study had insufficient numbers and intensity of surveillance to reliably detect any increased incidence of infection in lymphopenic patients. In the group of patients with grade 1 lymphopenia (ALC 800–1000), one developed an infection with HSV-1, and one had shingles. Both recovered fully. Of patients with grades 2–3 lymphopenia, one developed cellulitis. Otherwise, no infections were reported to the treating neurologists.

The practical significance of lymphopenia due to DMF has yet to be elucidated. Opportunistic infections, including JC virus infection leading to progressive multifocal leukoencephalopathy (PML), are a known complication of lymphopenia. PML has been

described in patients with idiopathic CD4 lymphopenia (3) in addition to those with known risk factors such as HIV or natalizumab therapy. It is unknown whether DMF-induced lymphopenia predisposes to PML. No cases have been reported, but DMF has been in widespread use for only about two years. Moreover, a few cases of PML have occurred in lymphopenic patients who were prescribed older fumarates (4, 5). Guidelines for these older fumarates recommend following blood counts every 3 months and discontinuing the drug if grade 3 lymphopenia develops. However, current prescribing information for DMF simply recommends checking CBC every 6–12 months and does not offer guidelines about when to discontinue therapy.

The present study is limited by its retrospective nature and the small number of patients with long-term follow up. Nevertheless, it raises important questions regarding the mechanism and possibly the safety of DMF, particularly in older patients, and suggests that more frequent monitoring may be needed. Further study is needed to guide clinicians in the management of patients who develop low ALCs on DMF.

ADDENDUM

Since acceptance of this letter, a 54 year old patient treated with DMF for 54 months has died from PML. This patient had been persistently lymphopenic (ALC 290-580) for about 3.5 years prior to her diagnosis with PML.

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