Dimethyl fumarate (DMF) has an associated risk of lymphopenia in relapsing remitting multiple sclerosis (RRMS) patients, affecting primarily CD8+ T-lymphocytes. These lymphocytes may play an important role in the containment of JC virus, the etiologic agent of progressive multifocal leukoencephalopathy (PML). Identifying patients who are at risk for lymphopenia may allow better determination of MS patients to treat with DMF and of appropriate discontinuation of DMF for prevention of PML. Other studies showed lymphopenia occurs more readily in patients previously treated with natalizumab, with advanced age, and with low baseline ALC. We examined additional risk factors or exposures that influence risk of lymphopenia such as carbamazepine, smoking, steroids, opiates, and vitamin D.

**OBJECTIVES**

1. To identify risk factors for DMF-induced lymphopenia.
2. To characterize the impact of DMF on T-lymphocyte subsets in MS patients.

**METHODS**

- We performed a retrospective analysis of 196 DMF-treated MS patients at BIDMC since 2013.
- We captured ethnic background, prior medication history, complete blood counts, vitamin D levels and T lymphocyte subsets.
- Possible lymphopenia risk factors examined included age, BMI (Body Mass Index), baseline ALC (Absolute Lymphocyte Count), prior natalizumab exposure, vitamin D levels, and exposure to carbamazepine, opiates, tobacco or steroids while on DMF. Vitamin D levels were corrected for seasonal variation.
- Lymphopenia was defined as grade 1: absolute lymphocytes count (ALC) 800-999/ul; grade 2: ALC 500-799/ul; grade 3: ALC 200-499/ul and grade 4: ALC <200/ul.
- We calculated the cumulative incidence of lymphopenia using standard Kaplan-Meier analysis.
- Using lymphocyte nadir data, we utilized Fisher exact test model to determine which variables were associated with the development of grade 1-3 or grade 2-3 lymphopenia.
- We conducted paired analysis for CD4 and CD8 counts at baseline and nadir using t tests.

**RESULTS**

- Low baseline ALC, BMI 25-30, and white race were significantly associated with differences in cumulative risk of lymphopenia.
- Figure 3. There was a trend for significance with smoking at reduced risk of developing grade 1-3 lymphopenia and high average Vit D at higher risk of lymphopenia grade 2-3.

- Gender, prior exposure to natalizumab, steroids, carbamazepine were NOT associated with cumulative risk of lymphopenia. These results differ from previous studies that showed natalizumab affects DMF-related lymphopenia.

**CONCLUSIONS**

1. Grade 2-3 lymphopenia occurs in 21% and grade 3 lymphopenia occurs in 8% of DMF-treated MS patients.
2. Patients with lowest quartile baseline ALC, with BMI 25 to 30, who were older than 40 years old, or with white race had a significantly higher incidence of lymphopenia.
3. Increased vigilance in lymphocyte monitoring is particularly warranted in patients with these characteristics.
4. Lymphopenia in DMF-treated MS reduces CD8+ more than CD4+ T-cells.
5. Higher vitamin D levels above 30ng/ml appear to increase risk of DMF related lymphopenia.
6. If DMF-induced lymphopenia occurs, vitamin D dosing may need to be reduced to prevent further reductions in lymphocytes.