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Predictors of hematological abnormalities in multiple sclerosis patients treated with fingolimod and dimethyl fumarate and impact of treatment switch on lymphocyte and leukocyte count

M. Baharnoori[a], C.T. Gonzalez[a], A. Chua[a], C. Diaz-Cruz[a], B.C. Healy[a], J. Stankiewicz[a], H.L. Weiner[a], T. Chitnis[a,*]

[a] Partners MS Center, Brigham and Women's Hospital (BWH), Harvard Medical School, Brookline, Boston, MA United States

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ABSTRACT

Background: There is limited data regarding the predictors of hematological abnormalities in multiple sclerosis (MS) patients treated with dimethyl fumarate (DMF) or fingolimod (FNG), and the impact of treatment switch on lymphocyte and leukocyte count

Methods: We identified 405 patients on DMF and 300 patients on FNG (treatment duration: at least 12 month) within a large prospective study of MS patients conducted at the Partners MS Center, Brigham and Women's Hospital (CLIMB study) between Jan 2011 to Feb 2016. Patients had complete blood counts with differentials at baseline and every 6 months while on treatment. Most participants had a clinical visit with complete neurologic examinations every 6 months and brain MRI scan every 12 months. T cell subset profile was available for subgroup of patients (n = 116).

Results: In the FNG group, the risk of developing lymphopenia grade 4 (< 200) was higher in female patients (p = 0.0117) and those who were previously treated with natalizumab (p = 0.0116), while the risk of lymphopenia grade 3b+4 (< 350) was higher in female patients (p = 0.0009). DMF treated patients with lower baseline lymphocyte count had a higher chance of developing lymphopenia grade 2 (< 800) (p < 0.0001) or 2+3 (< 500) (p < 0.0001). We examined the effect of treatment switch between DMF and FNG. No significant recovery in lymphocyte and leukocyte count was observed after treatment switches. Reduced dosing of FNG in patients with lymphopenia led to increase in lymphocyte count but also increased disease activity in 25% of patients.

Conclusion: Female sex and prior exposure to natalizumab increased the probability of lymphopenia on FNG, while low absolute lymphocyte count was associated with increased risk of lymphopenia on DMF. Parallel switch did not lead to recovery from hematological abnormalities. Long-term studies with larger number of patients are required to confirm our findings and to establish guidelines for prediction and management of hematological abnormalities.

1. Introduction

Fingolimod (FTY720/Gilenya, FNG) is the first oral medication approved for treatment of multiple sclerosis in 2010. Its primary mechanism of action is via modulation of Sphingosine 1-phosphate (S1P) signaling pathway (Luo et al., 1999). Acting as S1P receptors1 ($S1P_1$) agonist, FNG can cause lymphopenia by preventing egress of lymphocytes from secondary lymphoid organs such as lymph nodes and thymus (Mandala et al., 2002; Matloubian et al., 2004) resulting in redistribution of T and B lymphocytes. Two phase III clinical trials reported that lymphocyte count was reduced by 73% (TRANSFORMS) and 70% (FREEDOMS) within a month after treatment and remained stable afterward (Cohen et al., 2010; Kappos et al., 2010). Reduction in peripheral lymphocyte count is related to redistribution of circulating B and T lymphocytes and not to their permanent depletion. Two fatal infections (disseminated primary varicella zoster and herpes simplex encephalitis) occurred in patients receiving a higher than FDA approved dose, 1.25 mg daily (Cohen et al., 2010). With the exception of lower respiratory tract infections, the rate of infections was comparable between placebo and treatment arms (Kappos et al., 2010). Despite the rarity of serious infections in clinical trials, there have been increasing reports of opportunistic fungal (e.g. disseminated cryptococcus)

* Corresponding author.
E-mail address: tchitnis@partners.org (T. Chitnis).

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(Huang, 2015; Seto et al., 2016; Grebenciucova et al., 2016; Achtnichts et al., 2015; Forrestel et al., 2016) and viral (e.g. progressive multifocal encephalopathy, PML) infections (Gyang et al., 2016; Baharnoori et al., 2016; Rosenkranz et al., 2015; Lehmann-Horn et al., 2016; Nieuwkamp et al., 2015) in MS patients treated with FNG. The majority occurred in the presence of a substantial decrease in lymphocyte or white blood cell counts.

Dimethyl fumarate (Tecfidera, DMF) was the second oral disease modifying therapy approved by the FDA in 2013. Its purported mechanism of action is via activation of the nuclear factor (erythroid-derived 2)-like 2 (NRF2) pathway, an endogenous cellular defense system against inflammatory and oxidative stress (Linker et al., 2011; Scannevin et al., 2012). In addition, DMF serves as an inhibitor of NF-kB translocation. T cell survival is dependent on NF-kB activation (Gillard et al., 2015). Phase III clinical trials reported that white-cell count and lymphocyte count were decreased over the first year and then plateaued. There have been several reports of PML with the use of DMF and similar compound fumaric acid esters in patients with psoriasis (Williamson and Berger, 2015). No additional signal for serious infections has been reported in patients with substantial decrease in lymphocyte counts (Fox et al., 2012; Gold et al., 2012). The current US label recommends that treatment interruption should be considered if absolute lymphocyte counts (ALC) less than 500 persist for more than 6 months, although the most recent case of PML with DMF occurred when lymphocyte count less that 500 was present for less than 6 months (Lehmann-Horn et al., 2016).

There are currently 14 approved drugs for multiple sclerosis in the US. Oral medications are an attractive option for MS patients considering their high efficacy and easy administration. An important challenge facing MS clinicians is the optimization of the benefit/risk ratio. Identifying a potential predisposition to lymphopenia may help in developing a successful risk mitigation strategy. In the current study, we studied the probability and predictors of various hematologic abnormalities commonly seen in patients treated with FNG or DMF. We also compared lymphocyte subset profiles in lymphopenic and non lymphopenic patients, and studied changes in lymphocyte counts when transitioning from one therapy to the other.

2. Material and methods

2.1. Participants

This was a nested cohort of MS patients enrolled in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital (CLIMB) and Partners MS Center prospective study. We only included patients who had been on FNG or DMF for at least 12 months. Most participants had a clinical visit with complete neurologic examination every 6 months and brain MRI scan every 12 months. Four hundred five patients on DMF and three hundred patients on FNG were included in this study. Fifty one patients on DMF and sixty five patients on FNG had T cell subset profile available.

2.2. Standard protocol approvals, registrations, and patient consents

Ethical approval for this study was obtained from the Partners Healthcare Human Research Committee Institutional Review Board. Patients provide informed consent upon enrolling in the CLIMB Study.

2.3. Lymphopenia and leukopenia grading

Lymphopenia and leukopenia grading defined as; Lymphopenia grade 1 (< lower limit normal (LLN)-800/mm3), grade 2 (500–800/mm3), grade 3 (200–500/mm3), grade 3b (< 350/mm3) and grade 4 (< 200/mm3). Leukopenia grading defined as; grade 1 (< LLN- 3000/mm3), grade2 (WBC: 2000–3000/mm3), grade 3 (WBC: 1000–2000/mm3) and grade 4 (< 1000/ mm3) (grading modified from https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14QuickReference_5x7.pdf).

2.4. Statistical analysis

Data analysis was performed using the statistics package SAS. Univariate analyses were performed using a logistic regression model to assess the association between sex, age at treatment start, disease duration, prior MS medication, baseline absolute lymphocyte count (ALC), body mass index (BMI), Vitamin D level (ng/ml) and binary outcomes of lymphopenia and leukopenia grades. Variables with $p < 0.20$ from the univariate models were included in a multivariate logistic regression model to identify the predictors associated with lymphopenia and leukopenia in the respective DMF and FNG samples. Significance levels evaluated at an alpha level of 0.05 in the multivariate model. In the lymphocyte subset analysis, binary outcomes of lymphopenia grades were used in the univariate logistic regression analysis of percentage of CD19, CD56 and CD3-positive cells and log transformed absolute number of CD4, CD8, and CD4/CD8 ratio.

3. Results

3.1. FNG

A total of 300 patients on FNG were included (demographics provided in Table 1).

Over the course of the study 17% (n = 51) developed lymphopenia grade 4, 59% (n = 176) had lymphopenia grade 3b ± 4% and 26% (n = 77) had leukopenia grade 2+3. Details on the annual occurrence of

Table 1
Demographic characteristics of FNG and dimethyl fumarate (DMF).

Variable	FNG	DMF
N	300	405
Female (%)	221 (73.6)	295 (72.8)
RRMS (%)	284 (94.6)	310 (76.5)
Age (years, mean ± SD)	40.8 ± 10.2	45.3 ± 11.3
Disease duration (years, mean ± SD)	12.2 ± 6.9	11.3 ± 7.7
Treatment duration (years, mean ± SD)	3.3 ± 1.4	2.4 ± 0.6
EDSS at treatment initiation (mean ± SD)	2.0 ± 1.5	2.1 ± 1.9
£ Baseline BMI (mean ± SD)	23.5 ± 5.9	23.4 ± 5.8
⅄ Baseline Vitamin D level (mean ± SD)	52 ± 17.7	44.5 ± 19.1
Baseline absolute lymphocyte count (mean ± SD)	1.9 ± 0.76	1.8 ± 1.3
Baseline white blood cell count (mean ± SD)	6.0 ± 2.0	6.9 ± 2.0
¥ JCV + status (%)	148 (49.3)	172 (42.4)
No previous MS treatments (%)	85 (28.4)	140 (34.5)
Previous treatments (%)		
Glatiramer Acetate	64 (21.4)	109 (27)
Interferon	85 (28.4)	95 (23.5)
Natalizumab	34 (11.3)	22 (5.5)
DMF	8 (2.6)	NA
FNG	NA	15 (3.7)
Monthly steroid	11 (3.6)	7 (1.7)
Cyclophosphamide	7 (2.3)	6 (1.4)
Other	6 (2)	11(2.7)
Lymphopenia Grade 1+2 (%)	41(13.5)	234 (57.7)
Lymphopenia Grade 2 (%)	37 (12.3)	69 (17)
Lymphopenia Grade 2+3 (%)	125 (41)	43 (11)
Lymphopenia Grade 3b+4 (%)	176 (59)	7 (1.7)
Lymphopenia Grade 4 (%)	51 (17)	1 (0.2)
Leukopenia Grade 2+3 (%)	77 (26)	8 (1.9)
T Cell Subset - Lymphopenia Grade 2+3 (%)	54 (83)	5 (10)
T Cell Subset - Leukopenia Grade 2+3 (%)	18 (28)	1 (1.9)
T Cell Subset - Lymphopenia Grade 3b+4 (%)	46 (71)	2 (3.9)
T Cell Subset - Lymphopenia Grade 4 (%)	13 (20)	0 (0)

Legend: DMF: Dimethyl Fumarate; EDSS: Expanded Disability Status Scale; SD: Standard Deviation. NA: not applicable. £ Baseline BMI is missing for 191 patients on FNG and 163 patients on DMF. ⅄ Baseline Vitamin D level is missing for 97 patients on FNG and 87 patients on DMF. ¥ JC virus status missing for 82 patients on FNG and 113 patients on DMF.