SOMATO PUBLICATIONS

Current Research in Neurology and Neurosurgery

Research Article

Relapses in MS Patients Treated with DMF with no Variation in Lymphocyte Counts

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Received: 25 February 2019; **Accepted:** 03 April 2019; **Published:** 04 April 2019

Citation of this article: Fjeldstad-Pardo, C., Reyna, T., Smith, J., Sharp, T., Pardo, G. (2019) Relapses in MS Patients Treated with DMF with no Variation in Lymphocyte Counts. Curr Res Neurol Neurosurg, 2(1): 030-032.

ABSTRACT

Background: Dimethyl fumarate (DMF, Tecfidera®) has proven to be effective in reducing clinical relapses and MRI activity in relapsing multiple sclerosis. In the phase 3 clinical trials the proportion of patients with a relapse over 2 years was 29%. Participants experienced a 30% drop of the mean absolute lymphocyte counts (ALC), with the majority remaining above the lower limit of normal (LLN) of 900mm^3. A drop in ALC to <500 mm^3 was identified in 6% of participants. Although a low lymphocyte count is potentially associated with an increased risk for infections, it is not required for clinical efficacy as determined by analysis of those with lymphocytes above the LLN. No reports of the response for individuals with no change in ALC exist to date as it has only been reported for the cohort with and without lymphopenia with the latter just being defined as above the LLN.

Objective: To evaluate the clinical characteristics of a cohort of patients that did not have any change in their ALC while on DMF to identify a possible therapeutic role of any decrease in ALC.

Methods: One hundred and sixty three individuals (mean age 46.1±2.4, 76% females) participated in this study. DMF treatment duration ranged from 6 to 30 months (mean 19.2±2.4). Disease duration was 9.4±1.2 years. Lymphocyte counts were evaluated prior to starting therapy and every six months after the first dose.

Results: The mean baseline ALC was 2130 mm^3 and the nadir 1210 mm^3. The mean decrease of ALC for the entire cohort was 920 mm^3±60, representing a 43% drop. A total of 17 patients (10.4%) did not experience any change in lymphocyte count throughout, defined as less than 10% from baseline. In the cohort with unchanged ALC, 3 individuals had a clinical relapse during follow up, representing 17.6% of this subgroup.

Conclusion: Our cohort had a higher proportional drop in ALC than what was identified in the pivotal clinical trials. The proportion of patients with a relapse in the group with no change in the ALC was similar to the one reported in those trials, suggesting that a decrease in circulating lymphocytes is not a conditioning factor for DMF clinical efficacy.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS). There is no cure for MS, but many drugs have been used to help decrease the frequency of clinical exacerbations and reduce physical disability progression. These disease-modifying therapies have mechanisms of action that involve the reduction of immune activation, which could potentially lead to lymphopenia [1].

Dimethyl fumarate (DMF, Tecfidera®) was approved in 2013 for treatment of relapsing forms of MS based on the efficacy and safety results of two phase 3 trials, DEFINE and CONFIRM. DMF's mechanism of action responsible for the clinical benefit in MS is not fully known but it acts at different stages and modulates different cells involved in the immune cascade [2]. Some of these effects include activation of the nuclear factor-like (Nrf2) pathway to protect against oxidative stress-induced cellular injury and loss in neurons and astrocytes [3], induction of apoptosis of activated T cells [4] with a

particular decrease of $CD8^+$ T cells [5], creating a Th1 to Th2 shift [2], and reducing dendritic cell maturation [6].

In DEFINE and CONFIRM the proportion of patients on DMF 240 mg bid who experienced a clinical relapse over 2 years was 27% and 29% respectively [7,8]. These trials identified a 30% decrease in the mean absolute lymphocyte count (ALC) from baseline, with a majority of participants remaining above 900 mm^3 which is the lower limit of normal (LLN). Although no difference in efficacy was identified between those with ALC below or above the LLN, no analysis has ever been done of individuals in which there was no change in the ALC.

The objective of this study was to evaluate the relapse rate of a cohort of patients that did not have any change in their ALC while on DMF to identify a possible therapeutic role of a decrease in ALC, even if not below the LLN.

Methods

Subjects

A retrospective chart review of all 163 individuals (mean age 46.1±2.4, 76% females) that began treatment with DMF at the Oklahoma Medical Research Foundation Multiple Sclerosis Center of Excellence between April 2013 and May 2015 was performed. DMF treatment duration ranged from 6 to 30 months (mean 19.2±2.4). Disease duration was 9.4±1.2 years. Hematology assessments including hemoglobin, hematocrit, red blood cell count, white blood cell count with differential to include ALC, and platelet count were performed prior to starting therapy and every six months following the first dose. Clinical relapses were defined as a new or worsening neurological dysfunction that persisted for over 24 hours in absence of fever or an infection and with a new objective finding on examination, as assessed by a neurologist specializing in MS.

Statistical analyses

Data analyses were conducted using R 3.1.1 (2014), Vienna, Austria. Average reductions in total leukocytes, eosinophils, lymphocytes, and neutrophils were computed for each patient. Linear mixed models were used to estimate the average trajectory of each of these variables over time and p values were used to determine whether each slope significantly differed from zero. Statistical significance was defined at P≤.05.

The collection of samples and the review of data were approved by the OMRF Institutional Review Board, Oklahoma City, OK.

Results

The entire cohort of 163 identified individuals was suitable for analysis. The mean baseline ALC was 2130 mm^3 and the mean nadir 1210 mm^3. The mean decrease of ALC for the entire group was 920 mm^3±60, representing a 43% drop.

A total of 146(89.6%) (mean age 46.16±11.11; 77% females) individuals experienced a decrease in lymphocyte count. The changes over time for the different cell types were modeled using linear mixed models (Figures 1-4). Patients experienced statistically significant drops in leukocytes, eosinophils, and lymphocytes (p<.001) over the course of treatment.

A total of 17 patients (10.4%) (mean age 44.29±10.80; 71% females) did not experience any change in ALC, defined as less than 10% from baseline. In the group with unchanged ALC, 3 individuals (mean age 39.67±13.32; 33% females) had a clinical relapse during follow up, representing 17.6% of this subgroup (Table 1).

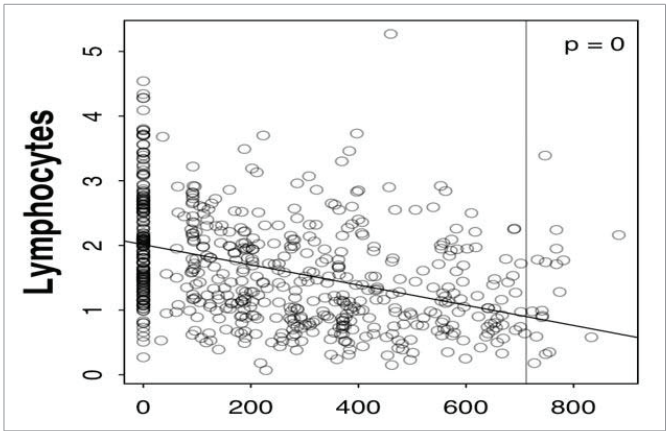

Figure 1: Linear mixed model depicting lymphocyte absolute count ($10^3/mm^3$) over time.

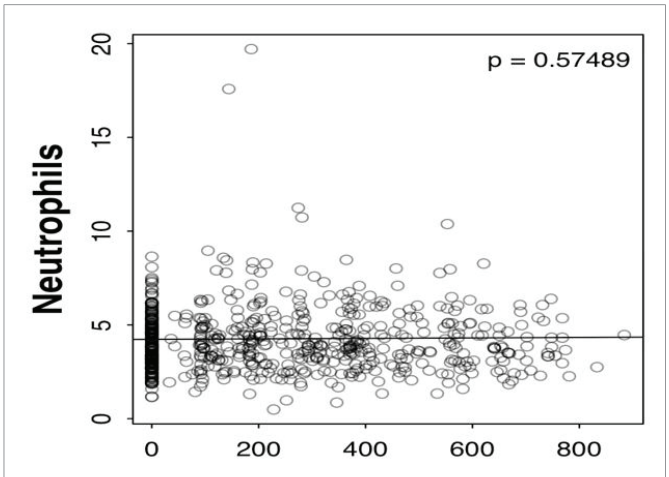

Figure 2: Linear mixed model depicting neutrophils count ($10^3/mm^3$) over time.

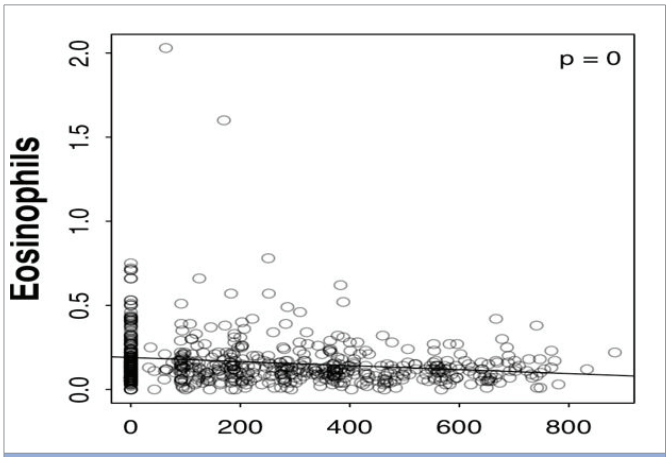

Figure 3: Linear mixed model depicting eosinophil count ($10^3/mm^3$) over time

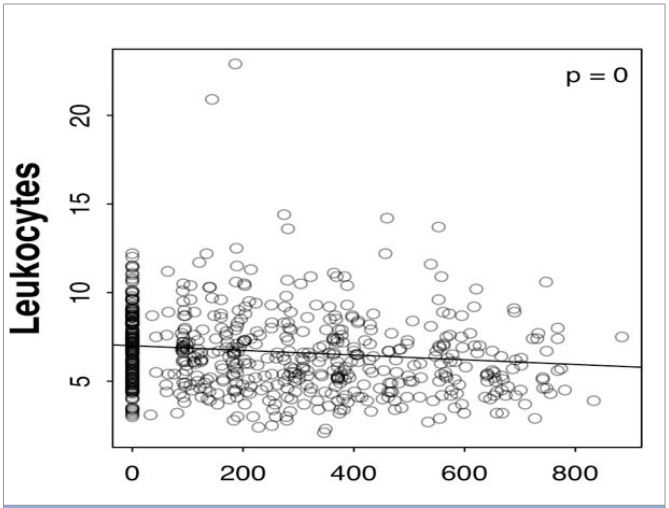

Figure 4: Linear mixed model depicting leukocyte count ($10^3/mm^3$) over time.

Table 1: Demographics of individuals with no change in ALC who experienced a relapse.

Patient	Age (yrs)	Duration of disease (yrs)	Prev DMTs/ type	Time on DMF at relapse (months)
1 (male)	50	13	1 / fingolimod	8
2 (female)	24	8	1/ glatiramer	10
3 (male)	41	17	1 / interferon beta 1a	12

No serious or opportunistic infections were identified.

Discussion

Analysis of pooled data of the phase 2b study (NCT00168701), the two phase 3 trials, and an ongoing long-term extension of DEFINE/CONFIRM (ENDORSE) showed a mean baseline ALC of 1980 mm^3 with a decrease of approximately 30% during the first year of treatment, remaining above the LLN throughout the observation period. A proportion of patients experienced actual lymphopenia with 9% having grade 1 (800-910 mm^3), 21% grade 2 (500-799 mm^3), 7% grade 3 (200-499 mm^3) and <1% grade 4 (<200 mm^3) at least at one time point during the duration of the trials [9]. Other studies have also identified lymphopenia in association with DMF use. A real-world setting review of 221 individuals identified grade 2 lymphopenia in 12% and grade 3 in 6%of the entire cohort, with a different rate for those over 55 years old which as a group experienced grade 3 lymphopenia in excess of 20% and combined grade 2 and 3 in 40% [10]. Analysis of annualized relapse rate in the phase 3 trials showed a non-significant difference with reduction of 52.8% in those with lymphopenia and 45.3% in those without [9], with the latter group including individuals that might have had a drop in lymphocytes but remained above the LLN. Likewise, real-world analysis have found no differential rate of relapses for lymphopenic and non-lymphopenic patients [10].

Even though analyzing the data this way suggests lymphopenia does not appear to have an effect on efficacy, it does not take into account that the group without lymphopenia still had a decrease in the number of circulating lymphocytes, and an effect of any such decrease in lymphocytes might still be responsible for the identified clinical benefit.

We evaluated our cohort to determine the relapse incidence in individuals treated with DMF that had experienced no change in lymphocyte counts. In doing so, we found that the proportion of patients in this group that had a relapse was 17.6%, which is lower than the 27-29% identified in the DMF phase 3 trials. This type of analysis has not been performed in any of the reported trials. Caveats include shorter length of use with a mean in our group of 19 months, smaller cohort, and a retrospective single center design.

Conclusion

Our cohort had a higher drop in ALC than the one identified in phase 3 clinical trials at 43% vs 30%. The proportion of patients with a relapse in the group with no change in the ALC was lower than the one reported for the entire cohort in the pivotal trials, suggesting that any decrease in circulating lymphocytes is not a conditioning factor for the clinical efficacy of DMF.

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