1. ABSTRACT

Title

A Retrospective, Multi-Center, Observational Study to Assess the Effect of Tecfidera® Delayed-Release Capsules on Lymphocyte Subsets in Subjects with Relapsing Forms of Multiple Sclerosis (REALIZE)

Keywords

Tecfidera, dimethyl fumarate, multiple sclerosis, lymphocytes

Rationale and background

The Phase 2 and Phase 3 clinical development program of dimethyl fumarate (DMF) established the risk-benefit profile, and led to the marketing authorization of DMF with the brand name of Tecfidera. During this development it was found that mean lymphocyte counts decreased by approximately 30% during the first year of treatment with DMF and then plateaued with mean counts remaining within normal limits. However, it is unknown whether $CD4^+$ and $CD8^+$ counts are differentially affected by DMF treatment, or if there is a correlation between decline in ALC and decline in lymphocyte subtypes. While a clinical relevance has not been observed, several small independent observational studies in related compounds and Tecfidera indicate an effect on T-cells, with a preferential impact on $CD8^+$ T cells in particular [Gross 2016; Khatri 2015; Spencer 2015].

This retrospective study aimed to evaluate lymphocyte subtypes (focusing on $CD4^+$ and $CD8^+$ T cells) as related to ALC after initiation of DMF treatment in patients with relapsing multiple sclerosis (MS), observe changes to lymphocyte counts post-discontinuation of Tecfidera, and assess the incidence of serious infections and/or opportunistic infections, and MS relapses.

Research question and objectives

The primary objective of the study was to retrospectively investigate changes in lymphocyte counts and lymphocyte subtypes, with a focus on $CD4^+$ and $CD8^+$ T cells, in patients on Tecfidera therapy for at least 6 months.

The secondary objective was to investigate changes in lymphocyte subtypes other than $CD4^+$ and $CD8^+$ T cells.

The exploratory objectives were as follows:

- To assess the incidence of opportunistic infections and serious infections
- To assess the incidence of relapses requiring hospitalization, outpatient care, or steroid use
- To measure lymphocyte and subtypes (if available) recovery following Tecfidera discontinuation

Study design

This study was conducted as a retrospective, observational study of patients with relapsing forms of MS who received Tecfidera for at least 6 months in routine clinical practice. The study consisted of a retrospective medical chart abstraction, conducted at a single time point for each patient, with no required study visits or procedures. Data were collected for each patient from up to 6 months prior to Tecfidera initiation through at least 6 months of continuous Tecfidera treatment. In patients who discontinued Tecfidera, up to 6 months of data after Tecfidera discontinuation were collected.

Setting

The study was conducted at 9 sites (4 neurology, 2 MS-specific, and 3 medical centers) located in the United States (U.S.). These centers were selected as they had conducted additional lymphocyte subtype monitoring as part of their center's standard of care.

Patients and study size, including dropouts

This study was conducted in patients with relapsing forms of MS, who initiated Tecfidera treatment for the first time (treatment naïve) on or after 27 March 2013 under routine clinical care. For inclusion in the study, patients' charts must have had a baseline measurement for absolute lymphocyte count (ALC) and absolute $CD4^+$ or $CD8^+$ count within 6 months prior to Tecfidera initiation, and at least 1 measurement for ALC and absolute $CD4^+$ or $CD8^+$ count while on Tecfidera treatment for at least 6 months. For patients who discontinued Tecfidera, data was collected for up to 6 months following Tecfidera discontinuation.

Detailed eligibility criteria are described in Section 9.3.

The study enrolled 483 patients from 9 sites in the U.S.

Variables and data sources

The following were collected for all patients:

- Assessment of eligibility
- Documentation of written informed consent, if required
- Demographic characteristics
- Relevant medical history and comorbidities
- MS disease history
- Prior and current MS treatment
- Concomitant medications and therapies, including immunomodulatory and immunosuppressive treatment
- Tecfidera prescription information
- MS relapse information

- Laboratory values (ALC, lymphocyte subset count [i.e., $CD4^+$ and $CD8^+$, as well as any additional lymphocyte subsets if available], absolute leukocyte count)
- Serious and opportunistic infections
- Malignancies

Data were collected retrospectively and directly from information already recorded in the patient's medical record and other source documents available at the clinical sites. All data were entered into an electronic case report form (eCRF).

Results

A total of 483 patient charts were abstracted for the study, and 476 patients were included in the Full Analysis Population; 7 enrolled patients were excluded from the Full Analysis Population because they did not have values critical for analysis (see Section 10.1). The majority of patients were female (73%), of white race (73%), and were characterized as 'Not Hispanic or Latino' (72%). On average, patients were approximately 49 years of age at the time of medical record abstraction. Nearly all patients (94%) had relapsing-remitting MS (RRMS) and had been diagnosed with MS for an average of 12 years prior to initiating Tecfidera. Over two thirds of patients (72%) had been previously treated with an MS therapy prior to initiating Tecfidera; of these, 29% received Tysabri® (natalizumab). Almost all patients (99%) received a non-MS medication at any time, most commonly colecalciferol (39%) and baclofen (27%). Of the patients whose charts were abstracted based on the eligibility criteria, a total of 114 had discontinued treatment after being on Tecfidera for an average of 1.329 years; the most common reasons for discontinuation were adverse events (AEs) and Investigator decision. Demographic characteristics, medical history, and treatment history did not differ substantially between the overall population and those who discontinued Tecfidera or by study center.

Mean ALC, $CD4^+$, and $CD8^+$ declined over the study period following Tecfidera initiation from baseline to Month 6 and Month 12. For the overall population, the mean baseline ALC (2.23×10^9/L), $CD4^+$ (1.06×10^9/L), and $CD8^+$ (0.50×10^9/L) decreased by approximately 39%, 37%, and 47%, respectively, through 6 months and 44%, 42%, and 53%, respectively, through 12 months. The largest declines were shown through the first 6 months, with slower rates of decline through Month 18. The majority of patients (55%) remained above lower limit normal (LLN) at their lowest ALC regardless of their baseline value.

To better understand the differences in the percentage of ALC decline that had been observed in the controlled studies and given that a third of patients in this study were previously treated with Tysabri, post-hoc analyses were performed to compare ALC, $CD4^+$, and $CD8^+$ decreases in patients previously treated with Tysabri to patients who had not received prior Tysabri treatment. At Month 6 and 12, respectively, the ALC decrease was approximately 32% and 36% in patients with no prior Tysabri use compared to 51% and 58% in patients with prior Tysabri use. In the subset of patients with prior Tysabri use, the mean baseline ALC was 2.90×10^9/L compared to a mean baseline ALC of 1.97×10^9/L in patients without prior Tysabri use; Tysabri is known to increase the number of circulating lymphocytes and therefore a reduction in lymphocyte

counts after discontinuation of Tysabri is expected due to its pharmacodynamic effects. At Month 6 and Month 12, respectively, the $CD4^+$ decrease was approximately 33% and 37% in patients with no prior Tysabri use compared to 46% and 52% in patients with prior Tysabri use. At Month 6 and Month 12, respectively, the $CD8^+$ decrease was approximately 40% and 46% in patients with no prior Tysabri use compared to 57% and 65% in patients with prior Tysabri use.

ALC dynamics were correlated with $CD4^+$ and $CD8^+$ counts, with low ALC correlated with low $CD4^+$ and $CD8^+$ at both baseline and Month 9 through Month 15. Overall, the pattern of lymphocyte decline was generally similar across age groups through 6 months of treatment. In this population with a median age of 51 years (range 24 to 78), at Month 12, older age (≥50 years) was associated with a higher percent reduction in median ALC, $CD4^+$, and $CD8^+$ compared to patients <50 years. In addition, at Month 12 older age (≥50 years) was associated with a higher proportion of patients with ALC and $CD8^+$ <LLN compared to patients <50 years.

Analyses of lymphocyte counts following Tecfidera discontinuation were conducted in the Tecfidera Discontinued Population (n=114). Of the 114 patients in the Tecfidera Discontinued Population, 58 patients (51%) had an available ALC value post-discontinuation. Generally, ALC and lymphocyte subset values increased following Tecfidera discontinuation. Few patients reached their baseline (n=6) or normal (n=18) values within 6 months following Tecfidera discontinuation. Among the patients who recovered to baseline and normal values, the median time to recovery was approximately 2 to 3 months.

Few patients experienced a possible opportunistic or serious infection in the 6 months prior to Tecfidera treatment (n=7, 1%), during Tecfidera treatment (average duration 1.303 years) [n=38, 8%], or in the 6 months post-Tecfidera (n=6, 5%) treatment, respectively, as reported by the healthcare provider or designated personnel performing chart abstraction. However, based on the clinical information available it was not possible to confirm the infections as either opportunistic or serious (see Section 10.4.3.2.1). Fourteen percent (n=65), 25% (n=117), and 7% (n=8) of patients had at least 1 MS relapse in the 6 months prior to Tecfidera treatment, during Tecfidera treatment, or 6 months post-Tecfidera treatment, respectively. No association was observed between WBC, ALC, $CD4^+$, and $CD8^+$ and the occurrence of possible opportunistic or serious infections as well as MS relapse.

Discussion

This retrospective, observational chart review study provides valuable information to better understand changes in lymphocyte counts and specifically the impact on lymphocyte subsets in patients treated with Tecfidera in routine clinical practice. This study captured data routinely recorded in medical records from patients with relapsing forms of MS in the U.S. and evaluated changes in lymphocytes and lymphocyte subsets following Tecfidera initiation and discontinuation. The results of this study suggest that ALC dynamics over the first year of Tecfidera treatment were comparable to those seen in clinical trials and small observational studies. ALC was correlated with $CD4^+$ and $CD8^+$ counts. There was no association between lymphopenia and the incidence of serious infections and/or possible opportunistic infections. While some patients had low

$CD4^+$ and $CD8^+$ counts, there was no evidence of a clinically relevant impact. ALCs values did recover after treatment discontinuation in some patients although analyses of recovery post-Tecfidera treatment were limited by small sample size and limited number of assessments available after discontinuation. There was some evidence that after 12 months of treatment with Tecfidera, the incidence of ALC <LLN was higher in patients ≥50 years versus patients <50 years. However, regardless of age there were declines in ALC below the LLN. Given the limitations of this study, the clinical relevance of this observation is unclear. These results continue to support ALC monitoring during Tecfidera treatment as an effective means to identify patients with reductions in ALC who may be at subsequent risk of prolonged moderate to severe lymphopenia.

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