Multiple Sclerosis and Related Disorders 24 (2018) 11–19

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Natalizumab treatment shows low cumulative probabilities of confirmed disability worsening to EDSS milestones in the long-term setting

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ARTICLE INFO

Keywords:
Disability worsening
Natalizumab
Relapsing-remitting multiple sclerosis
EDSS milestones

ABSTRACT

Background: Though the Expanded Disability Status Scale (EDSS) is commonly used to assess disability level in relapsing-remitting multiple sclerosis (RRMS), the criteria defining disability progression are used for patients with a wide range of baseline levels of disability in relatively short-term trials. As a result, not all EDSS changes carry the same weight in terms of future disability, and treatment benefits such as decreased risk of reaching particular disability milestones may not be reliably captured. The objectives of this analysis are to assess the probability of confirmed disability worsening to specific EDSS milestones (i.e., EDSS scores ≥3.0, ≥4.0, or ≥6.0) at 288 weeks in the Tysabri Observational Program (TOP) and to examine the impact of relapses occurring during natalizumab therapy in TOP patients who had received natalizumab for ≥24 months.

Methods: TOP is an ongoing, open-label, observational, prospective study of patients with RRMS in clinical practice. Enrolled patients were naive to natalizumab at treatment initiation or had received ≤3 doses at the time of enrollment. Intravenous natalizumab (300 mg) infusions were given every 4 weeks, and the EDSS was assessed at baseline and every 24 weeks during treatment.

Results: Of the 4161 patients enrolled in TOP with follow-up of at least 24 months, 3253 patients with available baseline EDSS scores had continued natalizumab treatment and 908 had discontinued (5.4% due to a reported lack of efficacy and 16.4% for other reasons) at the 24-month time point. Those who discontinued due to lack of efficacy had higher baseline EDSS scores (median 4.5 vs. 3.5), higher on-treatment relapse rates (0.82 vs. 0.23), and higher cumulative probabilities of EDSS worsening (16% vs. 9%) at 24 months than those completing therapy. Among 24-month completers, after approximately 5.5 years of natalizumab treatment, the cumulative probabilities of confirmed EDSS worsening by 1.0 and 2.0 points were 18.5% and 7.9%, respectively (24-week confirmation), and 13.5% and 5.3%, respectively (48-week confirmation). The risks of 24- and 48-week confirmed EDSS worsening were significantly higher in patients with on-treatment relapses than in those without relapses. An analysis of time to specific EDSS milestones showed that the probabilities of 48-week confirmed transition from EDSS scores of 0.0–2.0 to ≥3.0, 2.0–3.0 to ≥4.0, and 4.0–5.0 to ≥6.0 at week 288 in TOP were 11.1%, 11.8%, and 9.5%, respectively, with lower probabilities observed among patients without on-treatment relapses (8.1%, 8.4%, and 5.7%, respectively).

Conclusions: In TOP patients with a median (range) baseline EDSS score of 3.5 (0.0–9.5) who completed 24 months of natalizumab treatment, the rate of 48-week confirmed disability worsening events was below 15%;

Abbreviations: CP, cumulative probability; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TOP, Tysabri Observational Program

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https://doi.org/10.1016/j.msard.2018.04.020
Received 27 September 2017; Received in revised form 24 April 2018; Accepted 30 April 2018

after approximately 5.5 years of natalizumab treatment, 86.5% and 94.7% of patients did not have EDSS score increases of ≥1.0 or ≥2.0 points, respectively. The presence of relapses was associated with higher rates of overall disability worsening. These results were confirmed by assessing transition to EDSS milestones. Lower rates of overall 48-week confirmed EDSS worsening and of transitioning from EDSS score 4.0–5.0 to ≥6.0 in the absence of relapses suggest that relapses remain a significant driver of disability worsening and that on-treatment relapses in natalizumab-treated patients are of prognostic importance.

1. Introduction

In relapsing-remitting multiple sclerosis (RRMS), patients undergo clearly defined acute episodes of neurological deficits known as relapses followed by periods of full or partial recovery, with no increases in disability observed between attacks (Lublin et al., 2014b). Incomplete recovery from such relapses has been shown to lead to sustained accumulation of disability over time (Hirst et al., 2008; Lublin et al., 2003).

Disease progression is commonly assessed using the Expanded Disability Status Scale (EDSS) and is frequently used as an endpoint in clinical trials of RRMS therapies (Lublin et al., 2014a; Polman et al., 2006). EDSS worsening is typically defined in clinical studies as a 1.0-point increase in EDSS score (or a 0.5-point increase from an EDSS score ≥6.0) confirmed at 12 or 24 weeks. However, these criteria are used for patients with a wide range of baseline levels of disability in relatively short-term trials. As the EDSS is nonlinear, a 0.5- or 1.0-point increase may correspond with varying levels of impairment or disability increase. Thus, the traditional definition of confirmed disability worsening may not capture clinically meaningful treatment benefits, such as a reduction in the risk of reaching particular disability milestones. Furthermore, disability assessments based on 12- to 24-week confirmed EDSS worsening may include reversible disability changes, overestimating the accumulation of permanent disability by up to 30% (Kalincik et al., 2015).

Natalizumab (Tysabri, Biogen, Cambridge, MA, USA) is a selective α4-integrin blocker that ultimately prevents migration of peripheral blood lymphocytes into the central nervous system and is used to treat patients with RRMS (Rudick and Sandrock, 2004). In the phase 3 AFFIRM study in RRMS patients, natalizumab treatment reduced the cumulative probability of 12-week confirmed EDSS worsening at 2 years by 42%, with worsening observed in 17% of natalizumab-treated patients and 29% of placebo-treated patients (Polman et al., 2006). Natalizumab treatment was also associated with a reduction in the severity of relapses and residual disability. The probability of complete recovery from relapse increased by 55%–67% in natalizumab-treated patients compared with placebo-treated patients (Lublin et al., 2014a). Further analysis of AFFIRM data showed that natalizumab treatment over 2 years was associated with a 67% decrease in patients' progressing to an EDSS score ≥4.0 and a 70% reduction in patients' progressing to an EDSS score ≥6.0 (Weinstock-Guttman et al., 2012).

While the AFFIRM trial established the initial safety and efficacy of natalizumab, the Tysabri Observational Program (TOP) was designed to evaluate the effects of long-term natalizumab treatment in a clinical practice setting (Butzkueven et al., 2014). In the 5-year interim analysis of TOP patients, the cumulative probability of 24-week confirmed EDSS worsening with natalizumab treatment was 14% (Butzkueven et al., 2014).

The analysis presented here assesses the probability of 24- and 48-week confirmed worsening to specific EDSS milestones at up to 288 weeks (approximately 5.5 years) in TOP patients who had been treated for ≥24 months. It also includes a sensitivity analysis of confirmed disability worsening sustained at the last available EDSS assessment and examines the influence of relapses occurring during treatment on disability outcomes.

2. Materials and methods

2.1. Study design

The methodology for TOP (ClinicalTrials.gov trial NCT00493298), an ongoing, prospective, observational, 10-year, open-label study of patients with RRMS in clinical settings in Europe, Australia, Argentina, and Canada, has previously been published (Butzkueven et al., 2014). The study protocol was approved by each center's independent ethics committee. A complete list of investigators and the countries in which they practice is included in the Supplementary material. The TOP study was designed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and all enrolled patients provided written informed consent.

Patients enrolled in TOP were required to be natalizumab naive or to have received ≤3 doses of natalizumab in their lifetime at the time of enrollment. Enrolled patients received an intravenous infusion of natalizumab 300 mg every 4 weeks.

2.2. Assessments

EDSS scores were assessed at baseline and every 24 weeks during natalizumab treatment. An initial analysis compared baseline characteristics, relapse rates, and the cumulative probability of EDSS worsening in patients with ≥24 months (i.e., ≥96 weeks) of natalizumab treatment (24-month completers) and in patients who had discontinued after <24 months of treatment (discontinuers). Discontinuers were further subdivided based on whether they had reported discontinuation because of lack of efficacy or for any other reason. Subsequent analyses included only patients with ≥24 months of treatment data.

The cumulative probability of confirmed EDSS worsening (defined as either a ≥ 1-point or ≥2-point increase in EDSS score from baseline that was confirmed 24 or 48 weeks later) at up to 288 weeks in TOP was evaluated. The cumulative probability of 24- and 48-week confirmed worsening to specific EDSS milestones was also evaluated in each of the following three patient subgroups: patients with baseline EDSS scores of 0.0–2.0 (inclusive), who were evaluated for an EDSS score increase to a milestone of ≥3.0; patients with baseline EDSS scores of 2.0–3.0 (inclusive), who were evaluated for an EDSS score increase to a milestone of ≥4.0; and patients with baseline EDSS scores of 4.0–5.0 (inclusive), who were evaluated for an EDSS score increase to a milestone of ≥6.0. Finally, the cumulative probability of 24- and 48-week confirmed EDSS worsening at 288 weeks was evaluated in patients either with or without reported on-treatment relapses during the study. On-treatment relapses were defined as new or recurrent neurological symptoms that were not associated with fever, lasted for ≥24 h, and were followed by a period of 30 days of stability or improvement. Sensitivity analyses excluded patients whose worsening was not confirmed at the last available EDSS assessment.

2.3. Statistical analysis

Baseline characteristics of TOP patients are presented using summary statistics. The Kaplan-Meier method was used to estimate the cumulative probability of EDSS worsening at 96 weeks for the analysis of early discontinuers or at 288 weeks for analyses of 24-month completers.