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.

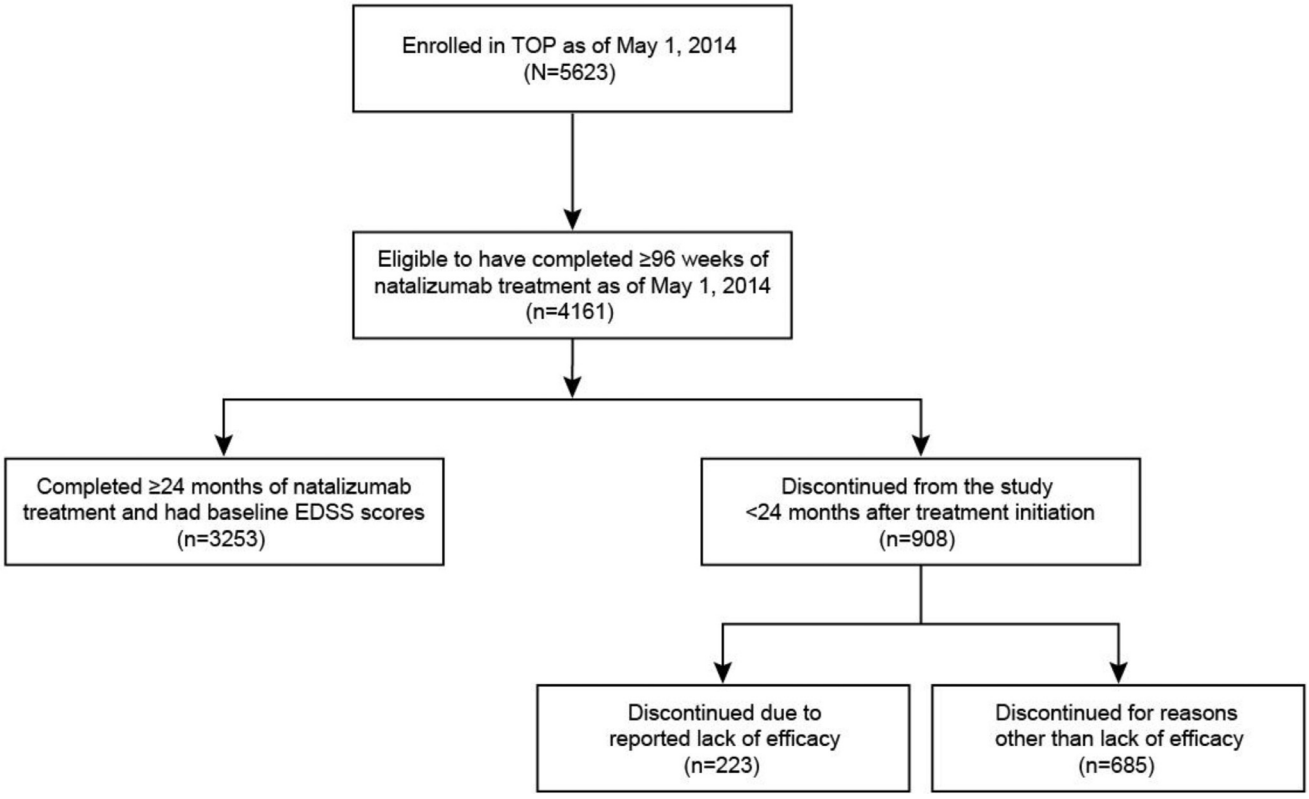

Fig. 1. Patient flow.

p-values and hazard ratios (HRs) comparing patients with and without reported on-treatment relapses were based on the Cox proportional-hazards model. The mean adjusted annualized relapse rate was calculated using descriptive statistics for prenatalizumab rates. For on-natalizumab mean adjusted annualized relapse rates, a negative binomial regression was used to account for overdispersion of the relapse count data. Relapses occurring between the 24- and 48-week confirmation evaluations were neither excluded from nor specially handled during the statistical analysis. Analyses were conducted using SAS/STAT software (version 9.3, SAS Institute, Cary, NC, USA)

3. Results

3.1. Study population

Of the 5623 patients enrolled in TOP as of May 1, 2014, 5587 (99.4%) had baseline EDSS scores recorded; 3253 (58.2%) of these patients had completed ≥24 months of natalizumab (Fig. 1). In this analysis, >85% of visits had recorded EDSS assessments. Of the 908 patients who discontinued natalizumab treatment, 685 indicated reasons other than lack of efficacy for discontinuation, while 223 discontinued due to a reported lack of efficacy.

All baseline characteristics appeared similar between groups, except that patients who had discontinued treatment within the first 24 months due to a reported lack of efficacy had a higher mean baseline EDSS score (4.4) than patients who had completed ≥24 months of continuous natalizumab treatment (3.4) or had discontinued for reasons other than lack of efficacy (3.6) (Table 1). Patients who completed ≥24 months of natalizumab had received a mean of 42.1 doses of natalizumab at the time of this analysis, while patients who discontinued treatment within the first 24 months due to a reported lack of efficacy and for reasons other than lack of efficacy had received a mean of 12.6 and 12.1 doses, respectively.

While no difference in the probability of 24-week confirmed EDSS worsening at week 96 was observed between 24-month completers and discontinuers for reasons other than lack of efficacy, discontinuers who cited lack of efficacy had a higher rate of EDSS worsening (Fig. 2). In the first year of treatment, 24-month completers had a significantly lower mean adjusted annualized relapse rate than discontinuers for reasons other than lack of efficacy (0.23 vs. 0.31; $p < 0.001$), and both groups had a lower rate than the group that discontinued due to lack of efficacy (0.82; $p < 0.001$; Fig. 3). A similar trend was observed in the proportions of patients who were relapse free at 1 year: 80.9% of 24-month completers and 82.9% of discontinuers for reasons other than lack of efficacy were relapse free, compared with 61.4% of discontinuers who reported lack of efficacy.

3.2. EDSS worsening at 5.5 years confirmed at 24 and 48 weeks

Among 24-month completers with available baseline EDSS scores, the cumulative probabilities of 24- and 48-week confirmed worsening were 18.5% and 13.5%, respectively, when worsening was defined as an increase in EDSS score of ≥1.0 point (Table 2). When worsening was defined as an increase of ≥2.0 points, the cumulative probabilities were 7.9% and 5.3%, respectively.

A similar pattern was observed in the sensitivity analysis. When confirmed worsening events that later reverted were excluded, the overall risks of ≥1.0- or ≥2.0-point worsening were consistently lower (15.6% and 6.8%, respectively, for 24-week confirmed worsening and 12.1% and 4.9%, respectively, for 48-week confirmed worsening; Table 2) than in the primary analysis, which potentially overestimated the accumulation of more permanent disability by 53% (18.5% vs. 12.1%) and 61% (7.9% vs. 4.9%) for 24-week confirmed worsening of ≥1.0 and ≥2.0 points, respectively, and by 12% (13.5% vs. 12.1%)

Table 1
Characteristics of 24-month completers versus discontinuers.

Characteristic	Completed ≥24 months of treatment (n = 3253)	Discontinued after <24 months for reasons other than lack of efficacy (n = 685)	Discontinued after <24 months due to reported lack of efficacy (n = 223)
Age at baseline, mean (SD), years	36.9 (9.7)	38.6 (9.6)	38.8 (9.3)
Female, n (%)	2314 (71.1)	524 (76.5)	160 (71.7)
Relapses in year prior to natalizumab initiation, mean (SD)	2.01 (1.03)	1.93 (1.00)	2.03 (1.04)
Relapses in year prior to natalizumab initiation, n (%)			
≤1	1125 (34.6)	260 (38.0)	77 (34.5)
>1	2128 (65.4)	425 (62.0)	146 (65.5)
≥1	3216 (98.9)	681 (99.4)	221 (99.1)
Baseline EDSS score			
Mean (SD)	3.4 (1.6)	3.6 (1.7)	4.4 (1.5)
Median (range)	3.5 (0.0–9.5)	3.5 (0.0–8.0)	4.5 (1.0–8.0)
Disease duration at baseline, median (range), years	7.1 (0–43.9)	8.7 (0–40.2)	8.3 (0.3–31.9)
Prior DMTs, n (%)			
0	280 (8.6)	55 (8.0)	15 (6.7)
1	1554 (47.8)	280 (40.9)	82 (36.8)
≥2	1419 (43.6)	350 (51.1)	126 (56.5)
Treatment duration prior to natalizumab initiation, years			
Mean (SD)	4.1 (3.6)	4.2 (3.9)	4.1 (3.8)
Median (range)	3.1 (0–21.8)	3 (0–24.2)	2.8 (0–17.3)
Number of natalizumab doses received at time of this analysis			
Mean (SD)	42.1 (14.2)	12.6 (7.3)	12.1 (6.2)
Median (range)	40 (4–90)	12 (1–24)	11 (1–24)

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; SD = standard deviation.

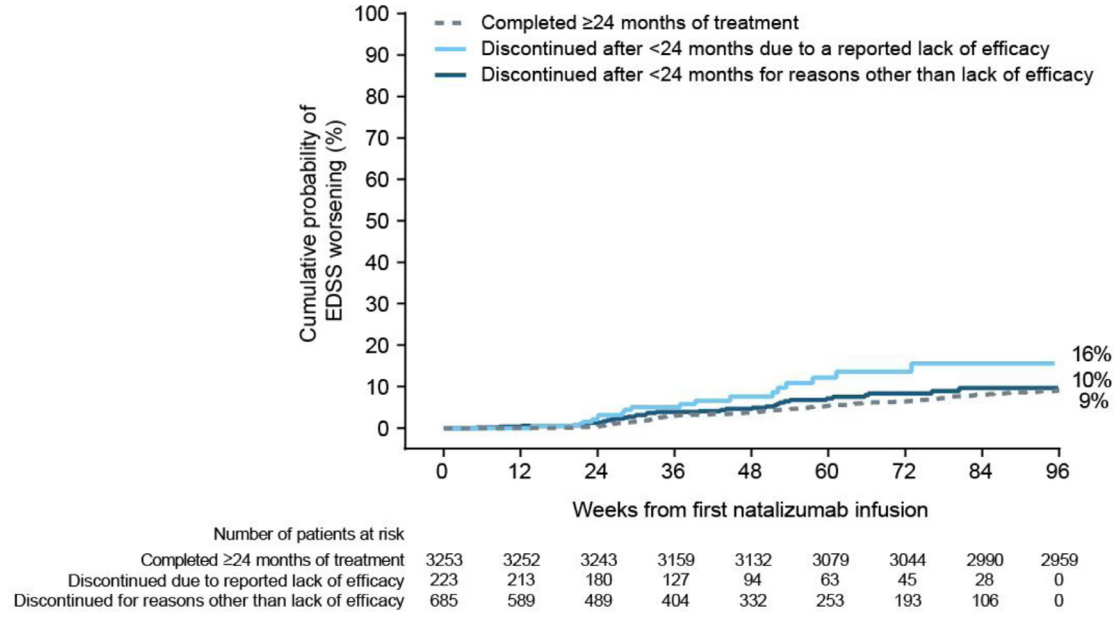

Fig. 2. Kaplan-Meier analysis of 24-week confirmed EDSS worsening in 24-month (i.e., 96-week) completers and discontinuers. Log-rank *p*-value: 0.004; pairwise comparison *p*-values: completed ≥24 months vs. discontinued due to lack of efficacy: 0.005; completed ≥24 months vs. discontinued for reasons other than lack of efficacy: 0.157; discontinued due to a lack of efficacy vs. discontinued for reasons other than lack of efficacy: 0.917.

and 8% (5.3% vs. 4.9%) for 48-week confirmed worsening of ≥1.0 and ≥2.0 points, respectively.[3]

[3] Derived from Table 2; based on the assumption that more permanent accumulation of disability is best reflected by 48-week confirmed data from the sensitivity analysis, the percentages of potential overestimation were calculated using Table 2 values from the least stringent criteria in the primary analysis (24-week confirmed) compared with the sensitivity analysis confirmed at 48 weeks and at end of follow-up.

3.3. Confirmed EDSS worsening at 5.5 years by relapse status

Among 24-month completers, cumulative probabilities of 24- and 48-week confirmed EDSS worsening of either ≥1.0 or ≥2.0 points were significantly higher in patients with on-treatment relapses than in those without relapses (Table 2 and Fig. 4A–D). When the sensitivity analysis criteria were used to analyze the risk of worsening, similar differences were observed between patients with and without on-treatment relapses (Table 2).

When 24-week and 48-week confirmed EDSS worsening rates in all

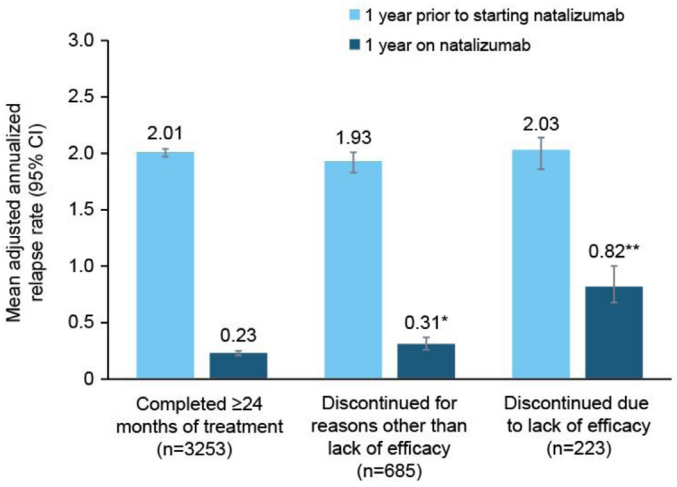

Fig. 3. Mean adjusted annualized relapse rates in the year prior to starting natalizumab and after 1 year on natalizumab in 24-month completers and discontinuers. *$p < 0.001$ for comparison with patients who completed ≥24 months of treatment; **$p < 0.001$ for comparison with patients who completed ≥24 months of treatment and with patients who discontinued for reasons other than lack of efficacy.

Table 2
Cumulative probability of 24- and 48-week confirmed EDSS worsening at 288 weeks.

			24-week confirmed worsening				48-week confirmed worsening			
CP, %	24-week confirmed worsening overall (n = 3253)	48-week confirmed worsening overall (n = 3253)	Patients without relapses (n = 2020)	Patients with relapses (n = 1233)	HR (95% CI)	*p*-value	Patients without relapses (n = 2020)	Patients with relapses (n = 1233)	HR (95% CI)	*p*-value
Primary analysis										
Worsening of EDSS score by ≥1.0 point	18.5	13.5	15.0	23.6	1.67 (1.39–2.01)	<0.001	10.8	17.7	1.79 (1.45–2.22)	<0.001
Worsening of EDSS score by ≥2.0 points	7.9	5.3	5.6	11.2	1.83 (1.32–2.52)	0.001	3.2	8.3	2.01 (1.36–2.97)	0.001
Sensitivity analysis[a]										
Worsening of EDSS score by ≥1.0 point	15.6	12.1	12.6	20.0	1.69 (1.38–2.07)	<0.001	9.5	16.0	1.81 (1.44–2.26)	<0.001
Worsening of EDSS score by ≥2.0 points	6.8	4.9	5.0	9.3	1.64 (1.15–2.34)	0.007	3.0	7.3	1.77 (1.17–2.67)	0.007

CI = confidence interval; CP = cumulative probability; EDSS = Expanded Disability Status Scale; HR = hazard ratio.
[a] Excluded worsening events that later reverted.

patients (primary analysis) were compared with 48-week confirmed EDSS worsening rates in patients who had not reverted at the last available EDSS assessment (sensitivity analysis), potential overestimations were observed in patients with and without on-treatment relapses, similar to observations not stratified by relapse status.

3.4. Confirmed worsening to EDSS milestones at 5.5 years

In the overall population of 24-month completers, 898 patients had a baseline EDSS score of 0.0–2.0 (inclusive). Among these patients, the cumulative risk of 48-week confirmed transition to an EDSS score ≥3.0 was 11.1% (Table 3). Using sensitivity analysis criteria, assessing the risk of reaching an EDSS score ≥3.0 was 9.9%. The risk of 48-week confirmed EDSS worsening to a score ≥3.0 was significantly higher in patients with on-treatment relapses than in patients without on-treatment relapses (HR = 1.92 [95% confidence interval (CI): 1.20–3.08]; $P = 0.006$; Table 3 and Fig. 5A).

Among the 686 patients with a baseline EDSS score of 2.0–3.0 (inclusive), the cumulative risk of 48-week confirmed transition to an EDSS score of ≥4.0 was 11.8% (Table 3). Using sensitivity analysis criteria, the risk of reaching an EDSS score ≥4.0 was 9.6%. The risk of 48-week confirmed EDSS worsening to a score ≥4.0 was significantly higher in patients with on-treatment relapses than in patients without on-treatment relapses (HR = 1.90 [95% CI: 1.17–3.07], $P = 0.009$; Table 3 and Fig. 5B).

For the 821 patients with a baseline EDSS score of 4.0–5.0, inclusive, the cumulative risk of 48-week confirmed transition to an EDSS score of ≥6.0 was 9.5% (Table 3). A similar risk (9.1%) was observed when the sensitivity criteria were used. The risk of 48-week confirmed EDSS worsening to a score ≥6.0 was not significantly different among patients with and without on-treatment relapses (HR = 1.63 [95% CI: 0.96–2.76], $P = 0.068$; Table 3 and Fig. 5C), although a strong trend was observed, suggesting that the low event rate led to an underpowered analysis. For each milestone, similar results were observed for

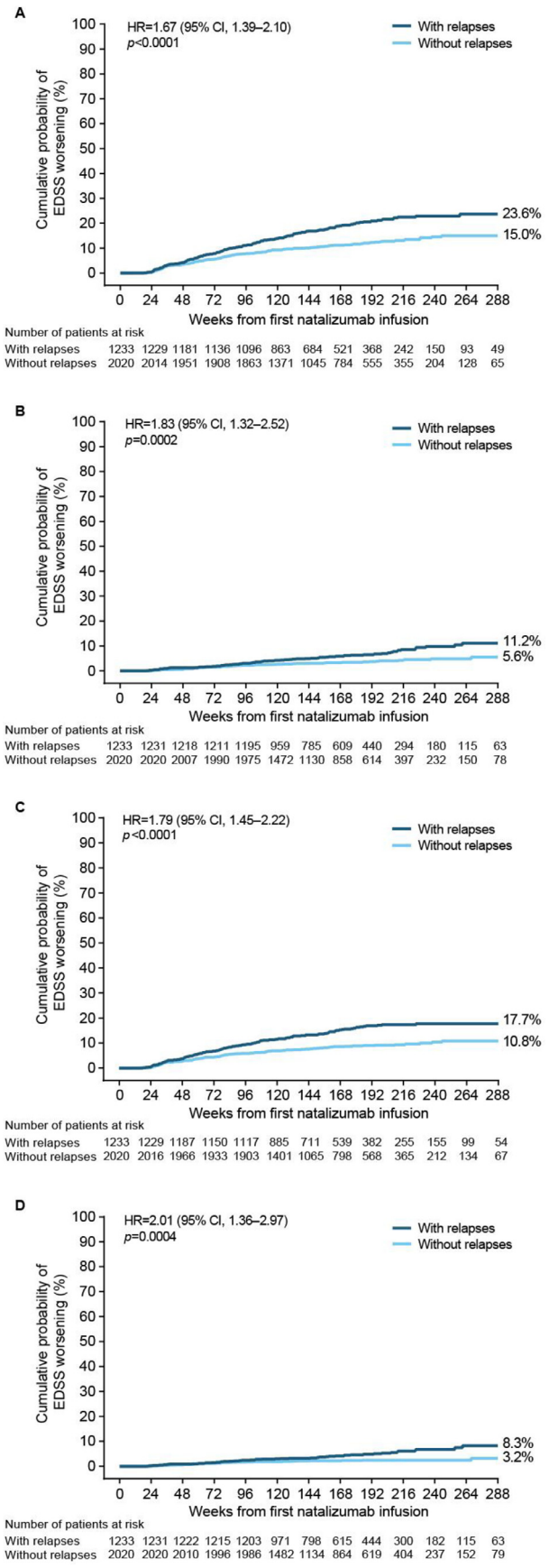

Fig. 4. Cumulative probability of EDSS worsening by relapse status. Kaplan–Meier plots of the cumulative probability of 24-week confirmed EDSS worsening of (A) ≥1.0 or (B) ≥2.0 points by on-treatment relapse status and 48-week confirmed EDSS worsening of (C) ≥1.0 or (D) ≥2.0 points by on-treatment relapse status. EDSS = Expanded Disability Status Scale; HR = hazard ratio.

the cumulative risk of 24-week confirmed worsening (Table 3).

When rates of confirmed worsening in all patients (primary analysis) were compared with rates of confirmed worsening in patients who had not reverted on the last available EDSS assessment (sensitivity analysis), the 24-week confirmed disability worsening in the primary analysis potentially overestimated the accumulation of permanent disability by 46% (14.5% vs. 9.9%) for transition to EDSS ≥3.0 from baseline scores of 0.0–2.0, by 89% (18.1% vs. 9.6%), for transition to EDSS ≥ 4.0 from baseline scores of 2.0–3.0, and by 35% (12.3% vs. 9.1%) for transition to EDSS ≥6.0 from baseline scores of 4.0–5.0, whereas the 48-week confirmed worsening in the primary analysis potentially overestimated the accumulation of permanent disability by only 12% (11.1% vs. 9.9%), 23% (11.8% vs. 9.6%), and 4% (9.5% vs. 9.1%), respectively (Table 3).[4] Similar potential overestimations were observed in patients with and without on-treatment relapses.

4. Discussion

In AFFIRM, the cumulative probability of disability worsening (defined as an increase of ≥1.0 point in EDSS score from a baseline score of ≥1.0 or an increase of ≥1.5 points from a baseline score of 0.0, sustained for 12 weeks) over 2 years was 17% for natalizumab versus 29% for placebo (Polman et al., 2006). The TOP study was designed to evaluate the outcomes of long-term natalizumab therapy in terms of safety but also on disability worsening over a longer time period. In the analysis of the TOP study presented in this paper, for all tested EDSS-based disability worsening outcomes, the probability of 48-week confirmed EDSS worsening by either 1.0 or 2.0 points after approximately 5.5 years of natalizumab treatment remained low (13.5% and 5.3%, respectively). The cumulative probability of 48-week confirmed worsening in TOP was consistently lower than that of 24-week confirmed worsening, suggesting that confirmation of disability at 24 weeks identifies many EDSS changes that are not sustained at 48 weeks. A sensitivity analysis excluding patients with confirmed worsening events that no longer met worsening criteria at the last available EDSS assessment further decreased the probabilities of potentially irreversible worsening events but was similar to crude 48-week confirmed EDSS worsening for all endpoints. These results indicate that 48-week confirmed worsening is a robust outcome measure that may reliably capture irreversible disability worsening; these results are consistent with prior work suggesting that the most important determinant of disability worsening stability is the length of the confirmation period (Kalincik et al., 2015).

The results reported here extend those of the 5-year analysis of the overall TOP population, which demonstrated the effectiveness of natalizumab as assessed by relapse rate and probability of disability worsening (Butzkueven et al., 2014). That publication also evaluated the safety of long-term natalizumab treatment, which should be considered along with its treatment benefits. In particular, longer natalizumab treatment duration, especially beyond 2 years, is associated with a risk of progressive multifocal leukoencephalopathy (PML), a serious brain infection (Bloomgren et al., 2012). Several other factors can also

[4] Derived from Table 3; based on the assumption that more permanent accumulation of disability is best reflected by 48-week confirmed data from the sensitivity analysis, the percentages of potential overestimation were calculated using Table 3 values from the least stringent criteria in the primary analysis (24-week confirmed) compared with the sensitivity analysis confirmed at 48 weeks and at end of follow-up.

Table 3
Cumulative probabilities of 24-week or 48-week confirmed worsening to specific EDSS milestones at 288 weeks.

	Overall		Patients without relapses		Patients with relapses		HR (95% CI)	*p*-value[a]
	n	CP, %	n	CP, %	n	CP, %		
24-week confirmed worsening								
Primary analysis								
From EDSS score of 0.0–2.0 to ≥3.0	898	14.5	619	10.7	279	21.8	1.96 (1.31–2.95)	0.001
From EDSS score of 2.0–3.0 to ≥4.0	686	18.1	426	14.8	260	23.1	1.56 (1.04–2.33)	0.032
From EDSS score of 4.0–5.0 to ≥6.0	821	12.3	453	8.7	368	16.2	1.55 (0.98–2.45)	0.066
Sensitivity analysis[a]								
From EDSS score of 0.0–2.0 to ≥3.0	898	12.1	619	9.2	279	17.6	1.83 (1.17–2.88)	0.009
From EDSS score of 2.0–3.0 to ≥4.0	686	14.4	426	12.2	260	17.7	1.49 (0.95–2.34)	0.085
From EDSS score of 4.0–5.0 to ≥6.0	821	11.6	453	8.7	368	14.7	1.35 (0.84–2.16)	0.218
48-week confirmed worsening								
Primary analysis								
From EDSS score of 0.0–2.0 to ≥3.0	898	11.1	619	8.1	279	16.7	1.92 (1.20–3.08)	0.006
From EDSS score of 2.0–3.0 to ≥4.0	686	11.8	426	8.4	260	16.9	1.90 (1.17–3.07)	0.009
From EDSS score of 4.0–5.0 to ≥6.0	821	9.5	453	5.7	368	13.4	1.63 (0.96–2.76)	0.068
Sensitivity analysis[b]								
From EDSS score of 0.0–2.0 to ≥3.0	898	9.9	619	7.3	279	14.7	1.88 (1.14–3.10)	0.013
From EDSS score of 2.0–3.0 to ≥4.0	686	9.6	426	7.0	260	13.6	1.87 (1.12–3.14)	0.017
From EDSS score of 4.0–5.0 to ≥6.0	821	9.1	453	5.7	368	12.6	1.47 (0.86–2.51)	0.162

CI = confidence interval; CP = cumulative probability; EDSS = Expanded Disability Status Scale; HR = hazard ratio.
[a] For comparison between patients with and without relapses.
[b] Excluded worsening events that later reverted.

be used to evaluate a patient's PML risk, including prior immunosuppressant use and anti-JC virus antibody index (Ho et al., 2017), allowing individualized assessment of PML risk. Continued monitoring of patients in TOP will provide further information about the longer-term benefits and safety profile of natalizumab treatment.

A major limitation of the current study, as with most long-term studies, is the lack of information about the patients discontinuing therapy and withdrawing from the study. Indeed, attrition bias, caused by unequal loss of participants, introduces systematic errors that distort the balance of confounders between study groups. However, patients in TOP who discontinued treatment within 24 months for reasons other than lack of efficacy (16.4%) did not differ in baseline characteristics or disability worsening at 96 weeks from 24-month completers. Thus, these patients were likely to have been experiencing treatment benefits. Moreover, discontinuers who reported a lack of efficacy comprised only 5.4% of the patient population and are therefore unlikely to have substantially affected the results. These patients had higher baseline EDSS scores, higher on-treatment relapse rates, and higher rates of 24-week confirmed EDSS worsening at 96 weeks, consistent with the reported lack of efficacy. Ongoing additional analyses of patients discontinuing natalizumab will provide valuable information on outcomes in this subset of patients.

Among ≥ 24-month completers, probabilities of 48-week confirmed transition from EDSS scores of 0.0–2.0 to ≥3.0, from 2.0–3.0 to ≥4.0, and from 4.0–5.0 to ≥6.0 at week 288 in TOP were low (11.1%, 11.8%, and 9.5%, respectively). The 5.5-year cumulative probability of transition from an EDSS score of 4.0–5.0 to ≥6.0 (9.5%) appears particularly low when compared with a natural history cohort of RRMS patients in which worsening from an EDSS score of 4.0 to 6.0 occurred within 5.7 years in 50% of patients (Confavreux et al., 2000).

Probabilities of EDSS worsening and of transition to significant disability milestones (i.e., EDSS scores of ≥3.0, ≥4.0, and ≥6.0) were consistently lower in relapse-free patients than in patients who experienced on-treatment relapses. The interaction between persistent relapse activity and increased probability of EDSS worsening was significant for the lower EDSS milestones (scores ≥3.0 and ≥4.0), but not for a transition to an EDSS score ≥6.0. This finding is consistent with a previous study that showed a negative correlation between prerelapse EDSS score and postrelapse residual disability (Lublin et al., 2003).

These data also indicate that relapses may play less of a role in EDSS worsening in natalizumab-treated patients with higher EDSS scores. These patients may have transitioned from RRMS to secondary progressive multiple sclerosis (SPMS), characterized as the gradual worsening of disability with or without relapses (Lublin et al., 2014b). Although the exact definition of SPMS has not been established, it is often viewed as starting when patients reach an EDSS score of approximately 4.0 and continue to experience disability progression independent of relapse activity (Lorscheider et al., 2016). Conversion from RRMS to SPMS occurs within 20 years of disease onset in more than half of patients and within 30 years in 75% of patients (Tremlett et al., 2008). The low 5.5-year cumulative probability of 48-week confirmed EDSS worsening in the absence of relapse identified in this analysis (10.8%) indicates limited accumulation of disability progression independent of relapses. Furthermore, the low 5.5-year cumulative probabilities of 48-week confirmed worsening from an EDSS score of 2.0–3.0 to ≥4.0 (11.8% overall and 8.4% in relapse-free patients) and from an EDSS score of 4.0–5.0 to ≥6.0 (9.5% overall and 5.7% in relapse-free patients) suggests a low level of conversion to SPMS in patients treated with natalizumab beyond 2 years. However, as TOP is a single-arm observational study, interpretation of these results is limited by the lack of a control group for comparison.

Overall, these results support the long-term, real-world effectiveness of natalizumab in preventing disease worsening as assessed by transition to major EDSS milestones. These results also contribute valuable information to the benefit-risk assessment of natalizumab when multiple treatment options are considered.

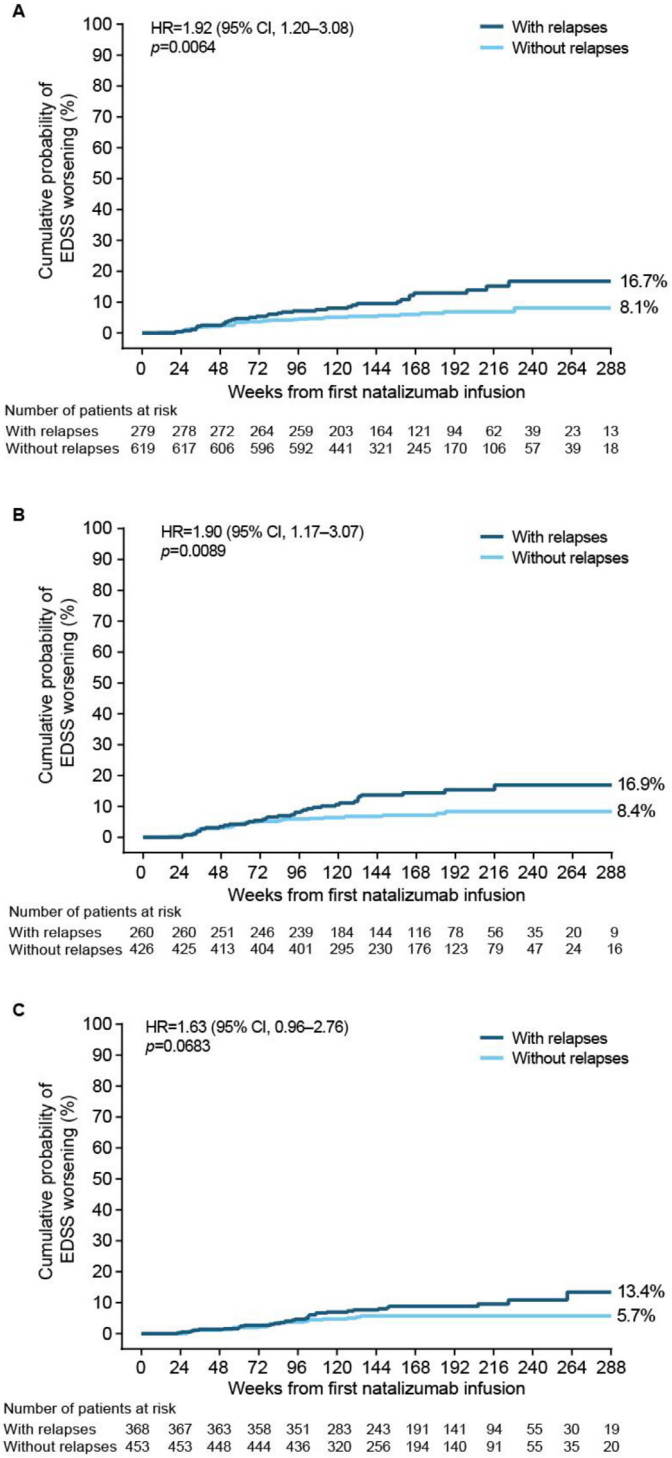

Fig. 5. Kaplan-Meier plots of the cumulative probability of 48-week confirmed worsening to EDSS milestones of (A) ≥3.0 from a baseline EDSS score of 0.0–2.0, (B) ≥4.0 from a baseline EDSS score of 2.0–3.0, and (C) ≥6.0 from a baseline EDSS score of 4.0–5.0. EDSS = Expanded Disability Status Scale; HR = hazard ratio.

Acknowledgments

This study was supported by Biogen.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript and take responsibility for the integrity of the work as a whole. Biogen provided funding for medical writing support in the development of this manuscript; Edwin Thrower, PhD, and Alison Adams, PhD, from Ashfield Healthcare Communications (Middletown, CT, USA), based on input from authors, wrote the first draft and revised subsequent drafts of the manuscript, and Joshua Safran from Ashfield Healthcare Communications copyedited and styled the manuscript per journal requirements. Biogen reviewed and provided feedback on the manuscript to the authors. The authors had full editorial control of the manuscript, and provided their final approval of all content.

Conflict of interest

Dr. Trojano has served on scientific advisory boards for Biogen, Merck Serono, and Novartis; received speaker honoraria from Biogen,

Merck Serono, Novartis, Sanofi, and Teva; and received research grants from Biogen, Merck Serono, and Novartis.

Dr. Butzkueven has received compensation for consulting from Biogen, Merck, Novartis, and Teva and research support from Biogen, Merck, and Novartis.

Dr. Kappos's institution (University Hospital Basel) has received research support from Actelion, Addex, Bayer Health Care, Biogen, Biotica, CSL Behring, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Roche, Sanofi, Santhera, Siemens, Teva, UCB, Xenoport, the European Union, the Roche Research Foundation, the Swiss MS Society, and the Swiss National Research Foundation.

Dr. Wiendl has received honoraria from AbbVie, Actelion, Alexion, Biogen, Cognomed, Evgen, F. Hoffmann-La Roche Ltd, MedDay, Merck Serono, Novartis, Roche Pharma AG, Sanofi-Genzyme, and Teva; and received research support from Biogen, GlaxoSmithKline GmbH, Pfizer, Roche Pharma AG, and Sanofi-Genzyme.

Dr. Spelman has received honoraria for consultancy and funding for travel from Biogen and Novartis.

Dr. Pellegrini is an employee of and holds stock and/or stock options in Biogen.

Dr. Chen was an employee of Biogen at the time of this analysis and is now an employee of Shire, which was not in any way associated with this study.

Dr. Dong was an employee of Biogen at the time of this analysis.

Drs. Koendgen and Belachew were employees of Biogen at the time of this analysis. They are now employees of F. Hoffmann–La Roche Ltd., which was not in any way associated with this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2018.04.020.

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