Characteristics of Real-world Disability Improvement in Relapsing-Remitting Multiple Sclerosis Patients Treated with Natalizumab in the TYSABRI® Observational Program

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Conclusions

- This analysis is the first to quantify the timing, magnitude, and duration of confirmed disability improvement (CDI) events, which occurred in 23.5% (1204 of 5119) of natalizumab-treated patients in the TYSABRI Observational Program (TOP).
  - CDI was defined as a decrease in Expanded Disability Status Scale (EDSS) score of ≥1.0 point in patients with a baseline score ≥2.0 (n=5119), confirmed ≥24 weeks later, and duration was assessed as time to return to baseline EDSS score.
  - CDI was more likely to occur in the first year of natalizumab treatment than in later years, and most patients with CDI exhibited a confirmed EDSS improvement of ≥1.5 points.
  - Improvement in EDSS score was maintained over 7 years in the majority of CDI patients who were continuously on natalizumab therapy. Maintenance of CDI was more likely for those with a greater magnitude of improvement than for those with a lesser magnitude of improvement.
- Data do not support the hypothesis that earlier CDI events have different characteristics and underlying mechanisms from later CDI events.
  - Baseline characteristics did not predict which patients would have earlier versus later CDI, and the probability of maintaining improvement did not differ based on the timing of CDI.
  - While patients with earlier CDI were likely to achieve a higher magnitude of improvement, the data overall suggest that meaningful improvements can occur both during and after the first year of natalizumab treatment.
- The potential for substantial, long-lasting disability improvement with natalizumab treatment may be an additional factor in its overall efficacy profile to be considered when making treatment decisions.

Introduction

- Reductions in EDSS scores have been observed with high-efficacy multiple sclerosis (MS) therapies,[1-5] suggesting that disability improvement may be an important functional outcome in the treatment of MS.
- In the 2-year AFFIRM clinical trial, natalizumab treatment was associated with an estimated probability of 12-week CDI of 29%.[2] In real-world settings included in TOP, the cumulative probability of 24-week CDI for natalizumab-treated patients was 34% over 10 years.[6]
- Patients initiating natalizumab shortly after onset of MS symptoms have exhibited a higher probability of CDI than patients initiating treatment later in the disease course (49% vs 26%–38%), confirming the benefits of earlier treatment and highlighting the potential for natalizumab to improve neurological function throughout the disease course.[7]
- This analysis is the first examination of the timing, magnitude, and duration of CDI during long-term natalizumab treatment in the real world, which may help to establish disability improvement as a valuable measure of treatment efficacy.

Objectives

- To characterize the timing, magnitude, and duration of CDI in patients participating in TOP.
- To test the hypothesis that improvement events occurring sooner after treatment initiation may have different characteristics than those occurring later in the disease course, consistent with earlier events representing more acute reductions in inflammation.

Methods

- TOP is an ongoing 10-year observational study of patients with RRMS initiating natalizumab in real-world clinical practice settings.[1]
  - As of November 1, 2016, 5993 patients were enrolled in TOP.
- This analysis included patients with CDI, defined as a decrease of ≥1.0 point from a baseline EDSS score of ≥2.0 confirmed at ≥24 weeks.
- Kaplan-Meier time-to-event analyses were used to evaluate the magnitude and duration (time from EDSS improvement to return to baseline level or worse) of CDI.
  - In this investigation, 1 year was defined as a 48-week period.
- CDI magnitude and duration were analyzed in all TOP patients with CDI and in subgroups who experienced CDI ≤1 year after starting natalizumab or >1 year after starting natalizumab.
- Cox models were used to determine the baseline characteristics that predicted the timing of improvement.

Results

- Of the 5119 patients in TOP with baseline EDSS scores of ≥2.0, 1204 (23.5%) had CDI (Table 1).
- The cumulative probability of CDI was 35.5% at 8.5 years. The probability of CDI was 14.0% during year 1, 8.4% during year 2, 4.2% during year 3, 2.5% during year 4, and 4.0% over years 5–7.

Timing of improvement

- Among patients with CDI, 642 (53.3%) had CDI ≤1 year after starting natalizumab and 562 (46.7%) had CDI >1 year after starting natalizumab (Table 1).
- Baseline characteristics (age, EDSS score, disease duration, number of relapses in the prior year, and presence of gadolinium-enhancing [Gd+] lesions) did not predict whether CDI would occur during the first year of treatment or later (data not shown).

Magnitude of improvement

- Among CDI patients, more than half exhibited an EDSS score improvement >1.0 point, and more than one-third exhibited an EDSS score improvement ≥2.0 points (Figure 1).
  - A significantly greater proportion of patients with CDI ≤1 year after natalizumab initiation exhibited a CDI of ≥1.5 or ≥2.0 points than of patients with later CDI.
- Over 7 years, the adjusted likelihoods of CDI ≥1.5 and ≥2.0 points were 63.7% and 40.6%, respectively.

Duration of improvement

- The adjusted likelihood of maintaining improvement (ie, EDSS score remaining below baseline) over 7 years after the CDI event was 58.9%.
- Overall, 903 patients (75.0%) maintained CDI (Figure 2).
  - For patients whose EDSS score returned to baseline, CDI was maintained for a mean (SD) of 2.48 (1.39) years, and a minimal change from baseline EDSS score through follow-up was observed (mean change [SD], −0.01 [1.15]).
- Maintenance of CDI was more likely in patients with greater than lesser magnitude of CDI and was less likely in older than younger patients (Figures 3 and 4). No other baseline characteristics were significant predictors of CDI duration (Figure 3).

Figure 1. Percentage of patients with CDI ≥1.5 or ≥2.0 points in the overall CDI population and stratified by CDI timing

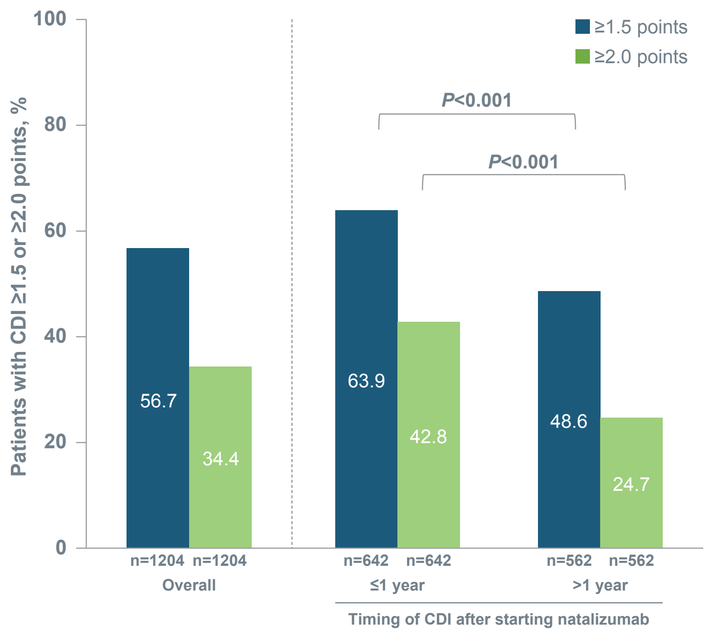
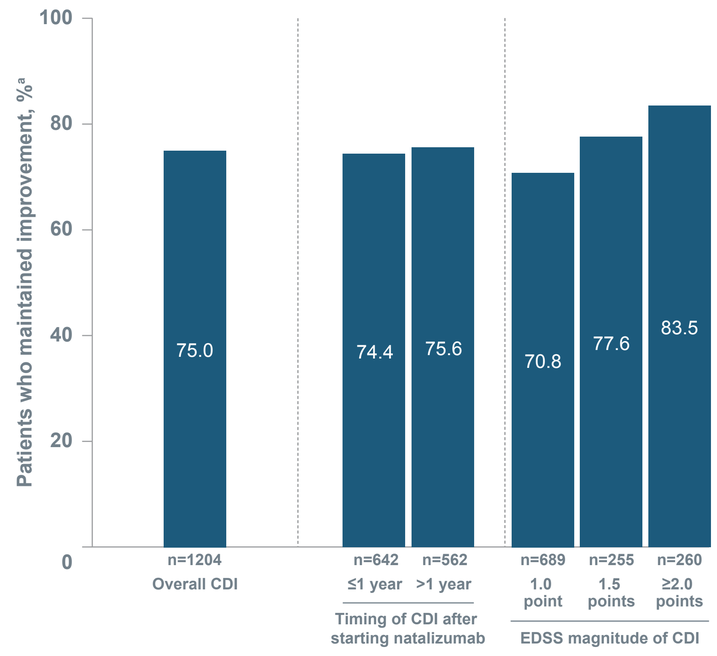
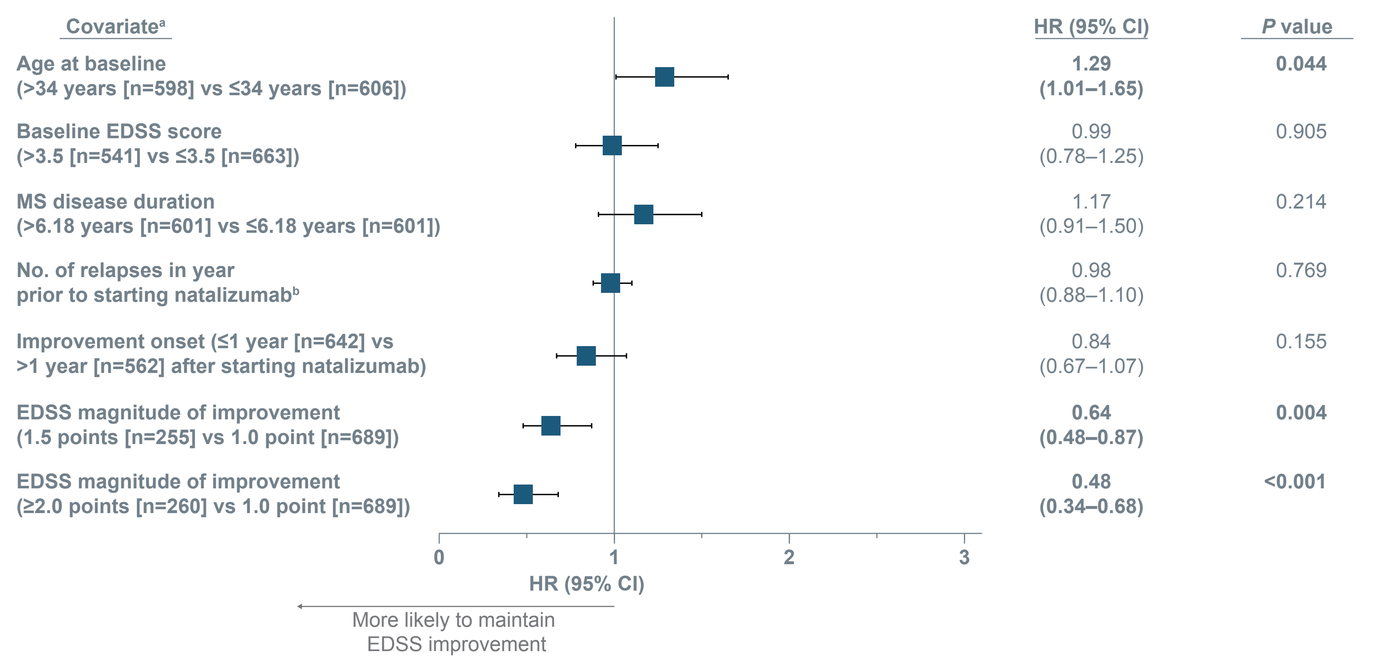


Figure 2. Proportion of patients who maintained EDSS improvement in the overall CDI population and stratified by timing and magnitude of CDI



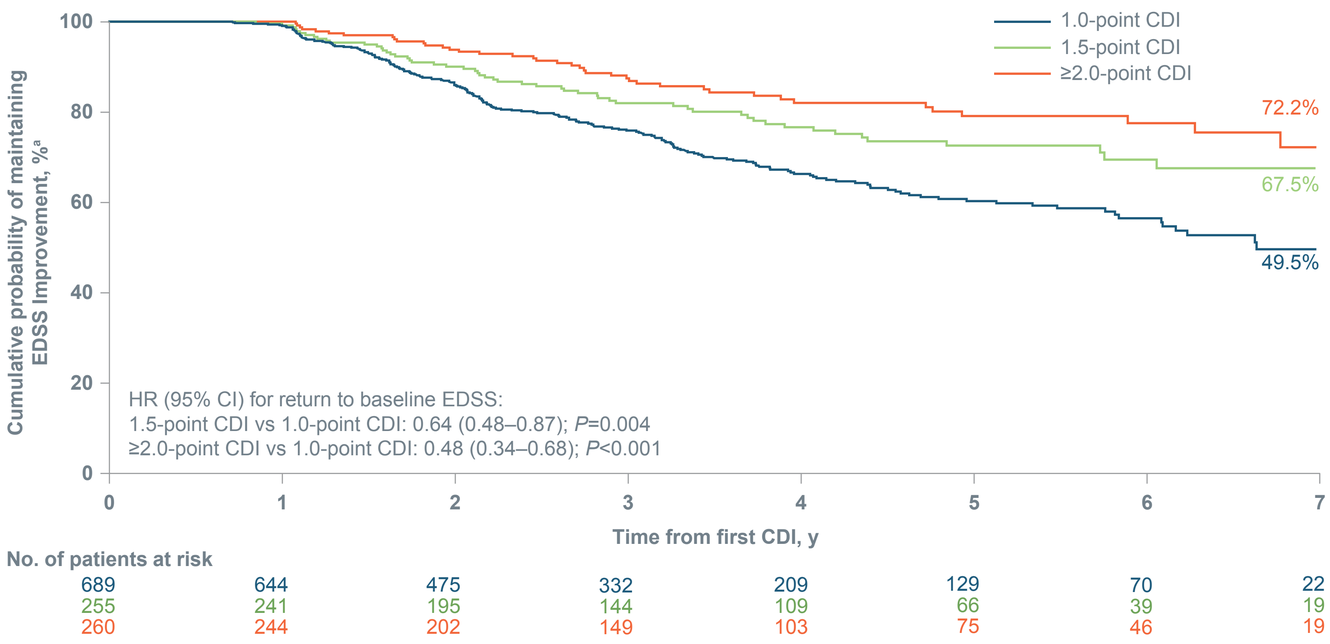
[a]Maintenance of EDSS improvement was defined as EDSS score remaining below baseline.

Figure 3. Predictors of maintaining EDSS improvement following CDI



CI=confidence interval. Hazard ratio (HR) is for the likelihood of return to baseline EDSS score following CDI. Statistically significant values are shown in bold.
[a]For categorical variables (all except number of relapses in year prior to starting natalizumab), tested variables are listed in parentheses; the reference group is listed second.
[b]Relapses in the year prior to natalizumab initiation were analyzed as a continuous variable (N=1204).

Figure 4. Cumulative probability of maintaining EDSS improvement by magnitude of first improvement



Cox model adjusted for covariates (age, baseline EDSS score, number of prior relapses, MS disease duration, timing of improvement, and magnitude of improvement).
[a]Maintenance of EDSS improvement was defined as EDSS score remaining below baseline.

Table 1. Baseline characteristics of TOP RRMS patients with CDI

Characteristic	All patients with CDI (N=1204)	Patients with CDI ≤1 year after natalizumab start (n=642; 53.3% of patients with CDI)	Patients with CDI >1 year after natalizumab start (n=562; 46.7% of patients with CDI)
Age, mean (SD), y	35.1 (9.31)	35.0 (9.39)	35.2 (9.24)
Female, n (%)	854 (70.9)	451 (70.2)	403 (71.7)
MS duration, mean (SD), y	7.8 (6.51)	7.6 (6.31)	7.9 (6.72)
EDSS score, mean (SD)	3.8 (1.30)	3.9 (1.32)[a]	3.6 (1.27)[a]
EDSS score ≥3.0, n (%)	898 (74.6)	506 (78.8)[a]	392 (69.8)[a]
Relapses in prior year, mean (SD)	2.1 (1.06)	2.2 (1.08)	2.1 (1.05)
Patients with Gd+ lesions at baseline, n (%)	577 (66.5)[b]	320 (67.9)[b]	257 (64.7)[b]
Prior DMTs used, n (%)			
0	152 (12.6)	74 (11.5)	78 (13.9)
1	582 (48.3)	317 (49.4)	265 (47.2)
≥2	470 (39.0)	251 (39.1)	219 (39.0)

DMT=disease-modifying therapy. [a]Statistically significant difference between patients with CDI ≤1 year and >1 year after natalizumab initiation ($P<0.01$). *P* value is based on a Wilcoxon rank-sum test for mean EDSS score and a chi-square test for EDSS score ≥3.0 vs <3.0. [b]Data were available for 868 patients with CDI, 471 patients with CDI ≤1 year after natalizumab start, and 397 patients with CDI >1 year after natalizumab start.

References 1. Butzkueven H, *et al. J Neurol Neurosurg Psychiatry*. 2014;85:1190-1197; 2. Phillips JT, *et al. Mult Scler*. 2011;17:970-979; 3. Giovannoni G, *et al. Mult Scler*. 2016;22(suppl 3):671-672. P1270; 4. Coles AJ, *et al. Neurology*. 2017;89:1117-1126; 5. Lublin F, *et al. Int J MS Care*. 2016;18(suppl 1):42-43. DX34; 6. Biogen. Data on file; 7. Spelman T, *et al. Neurology*. 2017;88(suppl):P6.350. **Disclosures** This study was supported by Biogen. HW: honoraria from AbbVie, Actelion, Alexion, Biogen, Cognomed, Evgen, F. Hoffmann–La Roche, MedDay, Merck Serono, Novartis, Roche Pharma AG, Sanofi Genzyme, Teva; research support from Biogen, GlaxoSmithKline GmbH, Roche Pharma AG, Sanofi Genzyme. HB: compensation for consulting from Biogen, Merck Serono, Novartis; research support from Biogen, Merck Serono. LK: in last 3 years, institution (University Hospital Basel) received and used exclusively for research support: steering committee, advisory board, consultancy fees from Actelion, Addex, Bayer HealthCare, Biogen, Biotica, Eli Lilly, Genzyme, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB, Xenoport; speaker fees from Bayer HealthCare, Biogen, Merck, Novartis, Sanofi, Teva; support of educational activities from Bayer HealthCare, Biogen, CSL Behring, the European Union, Genzyme, Merck, Novartis, Sanofi, Teva; grants from Bayer HealthCare, Biogen, F. Hoffmann–La Roche, Merck, Novartis, the Roche Research Foundations, the Swiss Multiple Sclerosis Society, the Swiss National Research Foundation. TS: honoraria for consultancy and funding for travel from Biogen, Novartis. MT: compensation for consulting from Biogen, Merck Serono, Novartis; speaker honoraria from Biogen, Merck Serono, Novartis, Sanofi, Teva; research grants from Biogen, Merck Serono, Novartis. QD: employee of Biogen at the time of this analysis. NC, P-RH, SL: employees of and own stock and/or stock options in Biogen. **Acknowledgments** All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this poster and take responsibility for the integrity of the work as a whole. Biogen provided funding for medical writing and editorial support in the development of this poster; Alison Adams, PhD, of Ashfield Healthcare Communications (Middletown, CT, USA) wrote the first draft of the poster based on input from authors, and Mary Kacillas and Joshua Safran of Ashfield Healthcare Communications copyedited and styled the poster per congress requirements. Biogen reviewed and provided feedback on the poster to the authors. The authors had full editorial control of the poster and provided their final approval of all content.