ECTRIMS 2015
Biogen Presentations: natalizumab
Introduction

The 2-year, phase 3 AFFIRM trial demonstrated the efficacy of natalizumab (TYSABRI®) in patients with relapsing-remitting multiple sclerosis (RRMS).

Methods

Study design

- TOP is an ongoing, open-label, 10-year prospective study planned for up to 6000 patients with RRMS in clinical settings in Europe, Australia, Argentina and Canada.

- Prior DMTs are permitted, but prior natalizumab use was restricted to 3 doses or fewer before start of treatment.

- Participating patients receive intravenous natalizumab 300 mg every 4 weeks.

- Baseline characteristics were summarised using descriptive statistics and were compared between the Canadian and non-Canadian populations.

- EDSS scores were evaluated at baseline and every 6 months thereafter.

Statistical analyses

- Baseline characteristics were summarised using descriptive statistics and were compared between the Canadian cohort and the non-Canadian population using the Wilcoxon rank-sum test and Chi-Square test for categorical variables.

- Within the Canadian and non-Canadian populations, annualised relapse rates at baseline and on treatment, as well as their percentage reductions, were compared using a robust Poisson regression model.

Results

- As of 1 November 2014, 339 patients were enrolled in TOP in Canada and 5352 were enrolled in the rest of the world.

- At baseline, the Canadian cohort was similar to the non-Canadian cohort in terms of proportion of women, MS disease duration, EDSS score, Multiple Sclerosis Severity Score (MSSS) value and lower percentage of DMT use in that year (Table 1).

- Compared with the rest of the world, at baseline, the Canadian population was slightly older, had experienced fewer relapses in the year leading up to natalizumab treatment, and had a lower percentage of DMT use in that year (Table 1).

- In this interim analysis of data from >4 years, Canadian patients reported slightly fewer relapses prior to initiating natalizumab and were in their treatment course compared with the rest of the world.

- Despite these differences, similar significant reductions in annualised relapse rates were observed in the Canadian-specific cohort and the rest of the global TOP population, regardless of baseline disability status, indicating long-term efficacy with sustained continued therapy.

- Natalizumab treatment resulted in stabilized EDSS scores over time.

- Overall safety data from Canadian were consistent with the known safety profile for natalizumab and with safety data from outside of Canada.

Conclusions

- In this interim analysis of data from >4 years, Canadian patients reported slightly fewer relapses prior to initiating natalizumab and were in their treatment course compared with the rest of the world.

- Despite these differences, similar significant reductions in annualised relapse rates were observed in the Canadian-specific cohort and the rest of the global TOP population, regardless of baseline disability status, indicating long-term efficacy with sustained continued therapy.

- Natalizumab treatment resulted in stabilized EDSS scores over time.

- Overall safety data from Canadian were consistent with the known safety profile for natalizumab and with safety data from outside of Canada.

Acknowledgments

Medical writing assistance was provided by Cheng Zigrand, with editorial support by STA Communications. Their work was funded by Biogen Canada Inc.

Supported by Biogen Canada Inc.

FJ: honoraria from several pharmaceutical companies for clinical trials.

Figure 1: Baseline and on-treatment annualised relapse rates in the overall Canadian and non-Canadian TOP populations

Figure 2: Baseline and on-treatment annualised relapse rates in the Canadian and non-Canadian TOP populations by baseline EDSS score

Figure 3: EDSS scores over time for the Canadian TOP population

Table 1: Baseline and on-treatment annualised relapse rates in the overall Canadian and non-Canadian TOP populations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Canadian Population</th>
<th>Non-Canadian Population</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, years SD</td>
<td>35.18±7.7</td>
<td>37.39±7.8</td>
<td>0.0093</td>
</tr>
<tr>
<td>MS duration, year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>4.0 (1.0–11.0)</td>
<td>3.1 (1.0–18.0)</td>
<td>0.0378</td>
</tr>
<tr>
<td>Relapses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.0 (0–6)</td>
<td>2.0 (0–10)</td>
<td>0.0007</td>
</tr>
<tr>
<td>≤1 relapse, year prior to natalizumab start, n (%)</td>
<td>169 (49.9)</td>
<td>1821 (34.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;1 relapse, year prior to natalizumab start, n (%)</td>
<td>170 (50.1)</td>
<td>1821 (34.0)</td>
<td>0.8981</td>
</tr>
<tr>
<td>EDSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.2±2.2</td>
<td>3.2±2.0</td>
<td>0.5253</td>
</tr>
<tr>
<td>MSSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>8.62 (5.0–9.4)</td>
<td>8.64 (5.0–9.0)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Table 2: Incidence of serious adverse events reported in the Canadian TOP population that were deemed related or possibly related to natalizumab (TYSABRI) and with safety data from outside of Canada.

<table>
<thead>
<tr>
<th>Event</th>
<th>Canadian patients</th>
<th>Non-Canadian patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis relapse</td>
<td>1/339 (0.3%)</td>
<td>1/5352 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Immune reconstitution inflammatory syndrome</td>
<td>1/339 (0.3%)</td>
<td>1/5352 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Herpes zoster disseminated</td>
<td>1/339 (0.3%)</td>
<td>1/5352 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>
| Incidence calculated, a patient is counted once per one-time adverse event or preferred term.

References

Natalizumab for Relapsing-Remitting Multiple Sclerosis: Interim Data from the Ireland Tysabri Observational Program (ITOP)


*St Vincent’s University Hospital, Dublin, Ireland; Cork University Hospital, Cork, Ireland; *Adelaide and Meath Hospital, incorporating the National Children’s Hospital, Tallaght, Dublin, Ireland; *Academic Unit of Neurology, School of Medicine, Trinity College Dublin, Dublin, Ireland; Departments of Clinical Immunology and Neurology, *St Vincent’s University Hospital (SVUH) and *Cork University Hospital (CUH), University College, *UC, Institute of Neurology, London, UK.

**Sin Seuca Hospital, College Road, Cork, Ireland; **St James General Hospital, Sligo, Ireland; **St Boniface UK and Ireland

**EP1462

INTRODUCTION

- The prevalence of multiple sclerosis (MS) in the Republic of Ireland varies from 283 per 100,000 people in Donegal to 127.8 per 100,000 people in Dublin.1
- Registry studies from several countries2 suggest that natalizumab is an effective and well-tolerated disease-modifying therapy (DMT) for highly active relapsing-remitting multiple sclerosis (RRMS).
- Data on the efficacy and safety of natalizumab in RRMS in Ireland are limited.

OBJECTIVE

- To assess the safety and efficacy of natalizumab in RRMS patients in routine neurological practice in the Republic of Ireland.

METHODS

Study design

- The Ireland Tysabri Observational Program (ITOP) is a multicentre retrospective and prospective observational study.
- Patients could enrol in ITOP at any stage during natalizumab treatment. Patient demographics and disease characteristics were collected at enrolment. Patients were followed for 36 months. The study closed to new enrolment in May 2015.
- Ethics committee approvals were obtained as per local regulations.

Analysis

- An interim analysis was performed in December 2013, 2 years after the first patient’s first visit. The interim data are summarised by frequency distributions for discrete endpoints and by summary statistics for continuous endpoints.
- Annually reduced relapse rates (ARRs) before and after natalizumab treatment were compared using negative binomial regression or Poisson regression for repeated data.

RESULTS

Demographics and disease presentation

- Data on patient demographics and disease characteristics were available for 112 of 117 patients enrolled at 6 centres in the ITOP.
- At the time of this interim analysis, the 112 ITOP patients that were included had received a mean (standard deviation [SD]) of 47.9 (21.6) months of natalizumab treatment since diagnosis (range: 0–114 months).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>35.6 (12.7)</td>
</tr>
<tr>
<td>Gender, %</td>
<td>51 (49)</td>
</tr>
<tr>
<td>MS disease duration at enrolment, years#</td>
<td>3.9 (2.4)</td>
</tr>
<tr>
<td>MS disease status at enrolment, year*</td>
<td>2012 (2003, 2015)</td>
</tr>
<tr>
<td>EDSS score at enrolment*</td>
<td>2.5 (1.8)</td>
</tr>
<tr>
<td>EDSS score prior to natalizumab treatment*</td>
<td>2.8 (1.6)</td>
</tr>
<tr>
<td>EDSS score at initiation of natalizumab treatment*</td>
<td>2.3 (1.3)</td>
</tr>
<tr>
<td>Duration of natalizumab treatment since enrolment, months#</td>
<td>36.2 (26.0)</td>
</tr>
<tr>
<td>MS disease duration at enrolment, years#</td>
<td>3.9 (2.4)</td>
</tr>
<tr>
<td>MS disease status at enrolment, year*</td>
<td>2012 (2003, 2015)</td>
</tr>
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<td>2.8 (1.6)</td>
</tr>
<tr>
<td>EDSS score at initiation of natalizumab treatment*</td>
<td>2.3 (1.3)</td>
</tr>
</tbody>
</table>

Table 2. Number of patients in ITOP reporting SAs

<table>
<thead>
<tr>
<th>SAs</th>
<th>n (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

Safety and tolerability

- In ITOP, of 117 patients (7.7%) experienced ≥1 serious adverse event (SAE) (Table 2).
- No cases of progressive multifocal leukoencephalopathy (PML), other opportunistic infections, or malignancy were observed, and no patients discontinued natalizumab due to an SAE.
- A total of 31 patients discontinued natalizumab for the following reasons: disability progression or possible lack of efficacy (n=7), desire to become pregnant (n=3), medication break (no rationale provided; n=1), concerns about the risk of PML (n=2).

Table 3. Hospitalisations due to relapses

<table>
<thead>
<tr>
<th>Hospitalisations due to relapses</th>
<th>n (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The percentage of patients with hospitalisations due to MS relapse decreased from 26% to 12% per year post natalizumab treatment (Table 3).</td>
<td></td>
</tr>
<tr>
<td>The durations of follow-up before and after initiation of natalizumab varied in this study, potentially influencing the number of days hospitalisation and introducing bias.</td>
<td></td>
</tr>
<tr>
<td>Although no impact on overall duration of hospitalisation was observed post natalizumab initiation, the reduced number of hospitalisation events may potentially result in economic benefits.</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS

- Compared with populations in other observational studies of natalizumab-treated patients, the mean time since diagnosis in the ITOP population (4.9 years) and the mean duration of prior DMT (2.3 years) was lower,10 suggesting that most patients start natalizumab therapy relatively early in their MS course.
- The significant reduction in ARR of 23% during the study compared with the special period to natalizumab treatment is in keeping with other phase IV observational studies.11,21-23 Significant reductions in ARR occurred irrespective of baseline EDSS score or prior DMT treatment.
- The overall safety profile of natalizumab in this study is consistent with the safety profile from clinical studies and in the post-marketing setting.24
- The rate of duration of follow-up before natalizumab treatment was 2 years, and nearly half of patients were positive for JCV antibodies at baseline. Therefore, no significant reductions occurred due to JCV status or patient consent in PML risk.
- Natalizumab was associated with a reduction in natalizumab discontinuations compared with the 2-year period prior to natalizumab treatment. Further analyses and a prospective study will be needed to confirm this finding.

DISCLOSURES

No authorship fees were paid. Biogen funded medical writing and editorial communications. Biogen also funded Tracy Willmott, TW1 Healthcare Consulting (project management) and Medivents (logistical support).

Natalizumab was administered in accordance with the clinical guidelines at the site of enrolment. No specific funding was sought or obtained for this study.

For an extensive version of this paper please visit: www.sgi.com/ITOP

REFERENCES

INTRODUCTION

- ASCEND is a randomized, double-blind, placebo-controlled phase 3b study evaluating natalizumab treatment in patients with secondary progressive multiple sclerosis (SPMS).
- Previous analyses of the baseline characteristics of ASCEND patients examined the relationship between particular patient-reported and objective measures of disability. Most correlations were found between the MS Walking Scale (MSWS-12) and the Timed 25-Foot Walk (T25FW) (rho: 0.39) and between the ABILHAND questionnaire and the 9-Hole Peg Test (9HPT) (rho: dominant hand, -0.37; nondominant hand, -0.31).

OBJECTIVE

- To evaluate the correlations between patient-reported impairment (ambulation and upper extremity function), as well as the physical impact of MS on daily life, and objective measures of disability in the ASCEND population at baseline.

METHODS

Study Design

- The primary end point in ASCEND is a composite of 3 objective disability measures: the Expanded Disability Status Scale (EDSS), the T25FW, and the SHFT. Progression was defined as meeting 2 of the following 3 components:
  - EDSS score increase of ≥1.0 point from a baseline score of 0.0;
  - ≥1.5 points from a baseline score of 0.0;
  - ≥1.5 points from a baseline score of 0.0.

- The following patient-reported measures of disability were also evaluated:
  - MSWS-12: range 0–100; higher scores indicate more ambulatory impairment.1
  - The 67-item ABILHAND questionnaire: range 0–100; higher scores indicate less difficulty with everyday manual activities.
  - MS Impact Scale (MSIS-29) physical score: range 0–100; higher scores indicate greater impact of MS on daily life.

- Short Form 36 Health Survey (SF-36) Physical Component Score (PCS): range 0–100; higher scores indicate better physical health-related quality of life.

Statistical Analysis

- Of the composite endpoint measures, only those with continuous scales (T25FW and 9HPT) were analyzed.
- For each analyzed measure, patients were grouped into quartiles by <25th percentile, 25th to <50th percentile, 50th to <75th percentile, and ≥75th percentile.
- Relationships between baseline objective and patient-reported measures were evaluated by trend test across quartiles and Spearman rank correlation coefficient (rho).

RESULTS

- Objective baseline measures of disability in the SPMS patients enrolled in ASCEND are shown in Table 1.

Table 1. Perceived baseline EDSS scores, T25FW times, and SHFT times among all ASCEND patients.

Table 3. Baseline MSIS-29 physical scores and SF-36 PCS scores for each T25FW and SHFT quartile.

Analysis of Baseline T25FW and SHFT Quartiles

- Patients were grouped into quartiles based on objective disability measures. Baseline characteristics are shown for the T25FW quartiles and the SHFT dominant hand quartiles (Table 2).

Table 2. Baseline characteristics.

- Characteristics of the SHFT nondominant hand quartiles are generally similar to characteristics of the SHFT dominant hand quartiles.

CONCLUSIONS

- At baseline, ASCEND patients with longer T25FW times had greater perceived impairment of ambulatory function than patients with shorter times, and patients with longer 9HPT times reported greater impairment of upper extremity function than patients with shorter times.
- Objective measures of disability were more correlated with patient-reported measures specifically designed to capture the impact of MS (MSWS-12 and MSIS-29) than with a general measure of health-related quality of life (SF-36).
- This analysis supports the use of the 9HPT and SHFT as components of the primary composite endpoint in the ongoing ASCEND study of natalizumab in secondary progressive MS.

Acknowledgments

- Funding for the publication of this poster was provided by Biogen, Novartis, and Genentech, Inc. M.M.K. is supported by a fellowship from the Muscular Dystrophy Association. The authors thank the ASCEND investigators for their contributions to the study and to this poster. The authors also acknowledge the ongoing ASCEND study of natalizumab in secondary progressive MS.

Disclosures

- Biogen, Cambridge, MA, USA; [1] Heinrich-Heine University, Düsseldorf, Germany; [2] National Hospital for Neurology & Neurosurgery, London, United Kingdom; [3] Danish Multiple Sclerosis Center, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

References

6. Ware JE. Medical Outcomes Trust, Boston, MA. 1996. Medical Outcomes Trust, Boston, MA.
Patients with multiple sclerosis (MS) report a lower quality of life (QoL) than the general population10 or patients with other chronic diseases.10

- Disease-specific QoL in MS can be evaluated using the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS).10

The occurrence of relapses has been correlated with reduced QoL in MS patients.10

- Treatment with natalizumab has been shown to improve QoL.11,12

MS registry data and previous real-world studies suggest that treatment with natalizumab results in a lower relapse rate compared with other disease-modifying therapies.4

To compare relapse rates and QoL between MS patients treated with natalizumab and those treated with one of the platform therapies.

Study design

- Data were identified from the Adelphi Multiple Sclerosis Disease-Specific Programme (DSP), an observational, cross-sectional study including neurologists and MS patients in the United States, France, Germany, Italy, Spain, and the United Kingdom. Full DSP methodology has been published previously.4

- Patients included in these analyses were being treated with either natalizumab or a platform therapy (any of the approved formulations of interferon beta or glatiramer acetate) and had been on their current therapy for >12 months.

Assessments

- Physicians reported any relapses that occurred in the previous 12 months.

- Patients assessed as a part of the study were patients treated with either natalizumab or a platform therapy (any of the approved formulations of interferon beta or glatiramer acetate) and had been on their current therapy for >12 months.

Baseline characteristics were analyzed using categorical variables or Kruskal-Wallis tests for nonparametric data. P-values were calculated using chi-squared tests for categorical variables or Kruskal-Wallis tests for nonparametric data.

- Average treatment effects (ATEs) were estimated and adjusted utilizing a propensity score generated using Expanded Disability Status Scale score at initiation of current treatment, age, sex, body mass index (BMI), duration of current treatment, line of therapy, time since diagnosis, and number of comorbid conditions.

- Estimated treatment effects were generated using regressions weighted by propensity scores (inverse-probability-weighted regression adjustment [IPWRA]).11

- IPWRA estimators have the desirable property of double-robustness.

Data for physician-reported relapses were available for 739 patients, while HAQUAMS data were available for 278 patients.

- Baseline characteristics are shown in Table 1. Patients on natalizumab had significantly more years since diagnosis with MS than patients treated with platform therapies.

- Significant differences between patients on natalizumab and platform therapies were not observed for the HAQUAMS subscales assessing fatigue and thinking (P=0.380), upper limb mobility (P=0.083), or social function (P=0.551).

- MS patients treated with natalizumab reported significantly less overall impairment of QoL, as measured by the total HAQUAMS score, than patients treated with platform therapies (ATE: −0.19; 95% CI: −0.35, −0.03) (Figure 2).

- Patients treated with natalizumab reported significantly better mood and lower limb function than patients treated with platform therapies (ATE: −0.25; 95% CI: −0.49, −0.02) (Figure 2).

- Natalizumab-treated patients reported significantly less mood impairment than patients on platform therapies (ATE: −0.25; 95% CI: −0.49, −0.02) (Figure 2).

- Compared with patients on platform therapies, patients treated with natalizumab reported significantly less impairment of mobility and lower limb function (ATE: −0.42; 95% CI: −0.59, −0.24) (Figure 2).

- Consistent with previous studies showing improvements in physical and psychological health-related quality of life after natalizumab treatment, natalizumab-treated patients reported significantly better mood and lower limb function than patients treated with platform therapies (ATE: −0.19; 95% CI: −0.35, −0.03) (Figure 2).

REFERENCES

1. Naoshy S, Pike J, Jones E, Watson C. Relapse Rates and Quality of Life among Patients Receiving Disease-Modifying Therapy for Multiple Sclerosis. 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis 7-10 October, 2015 Barcelona, Spain.
INTRODUCTION

• Clinically active relapsing-remitting multiple sclerosis (RRMS) is defined by the occurrence of relapses, episodes of neuropsychologic dysfunction followed by full or partial recovery.1,2 Many RRMS patients eventually develop secondary progressive MS (SPMS), characterized by disability progression with or without relapses.1,2

• As per recently revised definitions of the clinical course of MS, disability “worsening” describes increasing disability in RRMS patients, with “progression” referring to the disability accumulation unrelated to relapses in progressive forms of MS.3

• The Expanded Disability Status Scale (EDSS), the endpoint typically used to assess disability increase in RRMS clinical trials, may not be sensitive enough to identify disability progression unrelated to relapses.

• In addition, studies enrolling clinically active RRMS patients may include patients who experience disability regressing, especially in the first year, possibly due to recovery from the qualifying clinical event.

• An initial decrease in EDSS score after treatment initiation at baseline makes it more difficult to characterize subsequent events of disability worsening or progression.

• This study explores the use of a roving EDSS reference to enable, between two time points, the capture of worsening and progression unrelated to relapse as well as confirmed worsening events that occur after regression and that do not meet worsening criteria using the study baseline reference.

OBJECTIVE

• To evaluate exploratory analyses of EDSS worsening to capture disability progression unrelated to relapses using data on disability changes occurring over a period of approximately 3.5 years in the TYSABRI® Observation Program (TOP).

METHODS

• TOP is an ongoing, global, open-label, 10-year prospective study of natalizumab-treated patients with RRMS. Patients received intravenous infusions of 300 mg natalizumab every 4 weeks.4

• EDSS scores were assessed at regular clinical visits every 24 weeks. EDSS worsening was defined as increases in EDSS score of 0.5 points from a score of 0.0, 2.0 or 3.5 points from a score of 5.5, or 5.0 points from a score of 12.0, confirmed at ≥24 weeks.5

• EDSS increase was assessed using either the conventional study baseline EDSS score as a reference or a roving EDSS reference, approximately 60% of overall EDSS worsening events were defined as confirmed worsening using the roving EDSS reference (sensitivity analysis).

• A roving EDSS reference value, overall EDSS increase occurring between time points with EDSS progression unrelated to a concurrent relapse (defined as a relapse that was recorded from ≤30 days prior to the reference EDSS assessment to ≤12 weeks post progression assessment) was calculated (Figure 2).

• Sensitivity analyses compared progression events that were recorded based on an EDSS reference score that was lower than study baseline and that was not ≥21-week confirmed.

RESULTS

• As of May 1, 2014, 562 of 562 enrolled patients had baseline EDSS scores and were included in the analysis.

• The mean (standard deviation) baseline EDSS score was 3.5 (1.6).

• Enrolled patients had received natalizumab treatment for a median (range) of 108.3 weeks (1 day to 360.6 weeks).

• Disability Worsening and Progression Unrelated to Relapse Using Roving EDSS Reference

• When the baseline EDSS score was used as a fixed reference, the cumulative probability of confirmed overall EDSS worsening ≥24 weeks apart was 23.3%.

• EDSS progression unrelated to relapse (excluding events with a concurrent relapse) represented approximately 50% of overall EDSS worsening events (Table 1).

• The probabilities of both confirmed overall EDSS worsening and progression unrelated to relapse were higher in patients treated with natalizumab compared to those in the 242-weeks-apart analysis.

• Disability Worsening and Progression Unrelated to Relapse Using a Roving EDSS Reference

• Using a roving EDSS reference value, the cumulative probability of confirmed EDSS worsening between assessments ≥24 weeks apart appeared similar to that between assessments 24 weeks apart (Table 1).

• In the primary analysis, the probabilities of confirmed EDSS progression unrelated to relapse between assessments 24 weeks apart were 39% to 35% of forms of low EDSS progression events unrelated to relapse, and 50% more EDSS worsening events overall, than defining the study baseline EDSS score as a fixed reference (Table 1).

CONCLUSIONS

• Using a roving EDSS reference captured more events of confirmed EDSS increase than using the study baseline EDSS score as a fixed reference. The roving EDSS reference was not reflective of an emerging relapse.

• Although further validation is needed, the use of a roving EDSS reference rather than conventional study baseline EDSS score reference may represent a sensitive measure to capture disability progression in a long-term observational MS data set.

Table 1. Cumulative probabilities (Kaplan-Meier analysis) at 288 weeks in TOP of confirmed EDSS worsening or progression unrelated to relapse using a study baseline or roving EDSS reference (n=562)

<table>
<thead>
<tr>
<th>Study baseline reference</th>
<th>Overall confirmed EDSS worsening</th>
<th>Confirmed EDSS progression unrelated to relapsea</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS assessments ≥24 weeks apart</td>
<td>20.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Roving EDSS reference</td>
<td>19.5</td>
<td>9.7</td>
</tr>
<tr>
<td>EDSS assessments ≥24 weeks apart</td>
<td>31.7</td>
<td>24.5</td>
</tr>
<tr>
<td>Roving EDSS reference</td>
<td>31.4</td>
<td>21.4</td>
</tr>
<tr>
<td>EDSS assessments ≥48 weeks apart</td>
<td>34.9</td>
<td>21.7</td>
</tr>
<tr>
<td>Roving EDSS reference</td>
<td>34.7</td>
<td>17.3</td>
</tr>
<tr>
<td>EDSS assessments ≥12 weeks apart</td>
<td>23.7</td>
<td>17.6</td>
</tr>
<tr>
<td>Roving EDSS reference</td>
<td>23.5</td>
<td>16.6</td>
</tr>
</tbody>
</table>

Figure 1. Schematic of the roving EDSS reference system

Figure 2. Schematic of a roving EDSS reference system

Figure 3. Cumulative probability (Kaplan-Meier analysis) at 288 weeks in TOP of 24-week confirmed EDSS worsening or progression unrelated to relapse occurring between EDSS assessments ≥24 weeks apart

References


Acknowledgments

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Progression to Disability Milestones in Multiple Sclerosis With Long-term Natalizumab Treatment
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31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis 7-10 October, 2015 Barcelona, Spain

INTRODUCTION

• Relapsing-remitting multiple sclerosis (RRMS) patients are frequently characterized by relapse and relapse-related feared health consequences.
• Relapses in prior year, n (%) 2214 (71.1) 160 (71.7) 524 (76.5) 4.10 (1.15–2.34) 0.032
• Relapses in prior year, n (%) 2214 (71.1) 160 (71.7) 524 (76.5) 4.10 (1.15–2.34) 0.032

METHODS

Study Design
• This was a population comprised those patients with available baseline EDSS scores who had completed ≥24 months of continuous natalizumab treatment or patients that patients who discontinued treatment within the first 24 months.
• Characteristics of patients who discontinued treatment during the first 24 months were also assessed.

EDSS scores were assessed at baseline and every 24 weeks during treatment.
• The Kaplan-Meier method was used to estimate the cumulative probabilities of 24-week confirmed worsening to specific EDSS milestones at 288 weeks (Table 1).
• Sensitivity analyses excluded patients with EDSS values: completed ≥24 months vs discontinued due to lack of efficacy: 0.005; completed ≥24 months vs discontinued due to reasons other than lack of efficacy: 0.218

Table 1. Characteristics of patients at baseline and during follow-up.

Primary analysis

Worsening of EDSS score from 2.0–3.0 to ≥4.0 (n=3253)

P value

HR (95% CI)

1.90 (1.17–3.07) 0.009
1.83 (1.17–2.88) 0.009
1.35 (0.84–2.16) 0.218
1.20 (0.75–2.00) 0.495
1.38 (0.85–2.26) 0.175
1.44 (0.96–2.16) 0.072
1.39 (0.85–2.26) 0.175
1.36 (0.85–2.16) 0.203

Results

As of May 2014, 3335 patients had completed ≥24 months of continuous natalizumab treatment, receiving a median (range) of 40 (4–90) infusions (Table 1).
• The mean adjusted annualised relapse rate was calculated using logistic regression (proportional hazards) and negative binomial regression (on-natalizumab rates).

Statistical Analysis
• The Kaplan-Meier method was used to estimate the cumulative probability of worsening of 24 weeks for the following patient subgroups:

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

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

CONCLUSIONS

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

Worsening of EDSS score from 2.0–3.0 to ≥4.0

P value

HR (95% CI)

Figure 1. Kaplan-Meier graph of 24-week confirmed EDSS worsening of ≥1.0 point at week 56 in patients who completed ≥24 months of natalizumab treatment compared with discontinuers.

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9. MT: scientific advisory boards for Biogen, Merck Serono, Novartis; speaker honoraria from Biogen, Merck Serono, Novartis, Sanofi, Teva; research grants from Biogen, Merck Serono, Novartis. HB: honoraria from Bayer, Biogen, Medac, Merck Serono, Novo Nordisk, Xenoport, the European Union, the Roche Research Foundation, the Swiss MS Society, the Swiss National Research Foundation. HW: honoraria from Bayer, Biogen, Medac, Merck Serono, Novo Nordisk, Xenoport, the European Union, the Roche Research Foundation, the Swiss MS Society, the Swiss National Research Foundation. TS: honoraria for consultancy and funding for travel from Biogen, Novartis. FP, YC, QD, HK, SB: employees of Biogen.

Acronyms and abbreviations

All authors were involved in TOP (Multiple Sclerosis With Long-term Natalizumab Treatment) Study Group. JN, SP, EM, AD, and HL were involved in the design of the study and the conduct of the TOP Study. PM, BT, JC, AN, and RZ were involved in the data collection. PM, SP, EM, and AD were involved in the data analysis. PM, SP, EM, AD, and BT were involved in the interpretation of data. PM, SP, EM, AD, and BT were involved in the drafting of the manuscript. PM, SP, EM, AD, and BT were involved in the final approval of the version to be published. PM, SP, EM, AD, and BT were involved in the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Figure 1. Kaplan-Meier graph of 24-week confirmed EDSS worsening of ≥1.0 point at week 56 in patients who completed ≥24 months of natalizumab treatment compared with discontinuers.

Worsening of EDSS score from 2.0–3.0 to ≥4.0

P value

HR (95% CI)

1.56 (1.04–2.33) 0.032
1.38 (0.85–2.16) 0.203
1.44 (0.96–2.16) 0.072
1.36 (0.85–2.16) 0.203

1.83 (1.17–2.88) 0.009
1.80 (1.17–2.88) 0.009
1.77 (1.17–2.67) 0.007
}

• In TOP patients treated with natalizumab for 62 years, we observed low probabilities of 48-week confirmed EDSS worsening (13.5% for worsening of ≥1.0 point) and transition to significant disability milestones (<12%) after approximately 5.5 years of follow-up.

• Discontinuation of confirmed worsened EDSS worsening and of EDSS milestones were generally lower in relapse-free patients than in patients who had experienced relapses.

• Differences observed in the results of the sensitivity analysis, excluding patients with events that no longer met worsening criteria, suggested that the primary analysis was more robust to the outcome measure that may more reliably capture irreversible disability worsening than 24-week confirmed progression.
INTRODUCTION

- Natalizumab has been commercially available for ≥48 months
- In addition, the majority of natalizumab-treated patients had risk factors, histology, treatment, and causality were also assessed.

OBJECTIVE

- To compare cumulative malignancy reporting rates in natalizumab-treated patients to rates in the US general population.

METHODS

- A search of the natalizumab global safety database was conducted, including data from November 23, 2004, to February 7, 2015.

RESULTS

- Overall Cumulative Review of Malignancies

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<th>Site/Type</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
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<th>Female</th>
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<td>578</td>
<td>1240</td>
<td>526</td>
<td>1160</td>
<td>536</td>
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<td>111</td>
<td>127</td>
<td>100</td>
<td>114</td>
<td>90</td>
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<tr>
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<td>14</td>
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<tr>
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CONCLUSIONS

- More recent epidemiological data from the UK’s Malignancy Registry for Multiple Sclerosis (UKMRS) reports an age-adjusted standardized incidence rate (SIR) of 2 per 100,000 person-years in the adult UK population.

Acknowledgments

P1094

No Evidence of an Increased Risk for Malignancy Associated with Natalizumab Therapy in 9 Years of Postmarketing Surveillance

Carroll-Infante C, Gheuens S, Wenten M, Ho PR, Koulkina I, Richman S

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Table 1. Comparison of cumulative reporting rates of HCP-confirmed malignancies in natalizumab-treated patients to SEER incidence rates

Table 2. Characteristics of natalizumab-treated patients with gonadal testicular cancer

- The ages of 2 patients were not reported.
- Two cases included in the reporting rate were misdiagnosed as MS and received 1–2 infusions of natalizumab before diagnosis was made. Brain cancer predated natalizumab use in these cases.
- Four cases with CNS lymphoma included in the reporting rate were misdiagnosed as MS and received 1–3 infusions of natalizumab before diagnosis was made. CNS lymphoma predated developing leukemia.
- 41.51

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7-10 October, 2015
Barcelona, Spain

For an electronic version of this poster, please see...

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5. HCP-confirmed events

6. The overall cumulative rate of HCP-confirmed malignancies in natalizumab-treated patients was 363.89 (95% confidence interval [CI], 345.45–382.91) per 100,000 PYs, which is lower than the overall SEER rate of 468.19 malignancies per 100,000 PYs. Malignancies in natalizumab-treated patients were similar in type and frequency to those in the general population, with breast, prostate, and pancreatic cancer being the most frequently reported malignancies in both genders (Table 1).

7. The ages of 2 patients were not reported.

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