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The STRIVE study of natalizumab in patients with early MS: baseline characteristics

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BACKGROUND

- Results from the TYSABRI® Observational Program (TOP) showed that natalizumab treatment was most effective in treatment-naive patients and in patients with lower Expanded Disability Status Scale (EDSS) scores[1]; however, the use of natalizumab in early multiple sclerosis (MS) has not been systematically studied.
- Natalizumab treatment is associated with a risk of progressive multifocal leukoencephalopathy (PML), an infection of the central nervous system caused by the JC virus (JCV).[2]
- Since the presence of anti-JCV antibodies is a known risk factor for PML,[2] the benefit/risk profile of natalizumab is enhanced when natalizumab is used to treat patients who test negative for anti-JCV antibodies.
- The baseline characteristics of patients who were enrolled in the Study of TYSABRI in Early Relapsing-Remitting MS in Anti-JCV Antibody Negative Patients (STRIVE) as of January 17, 2014, are presented.

OBJECTIVES

- The primary objective of STRIVE is to determine baseline and yearly response factors that may predict overall freedom from measured disease activity (FMDA) status at months 12 and 24 and freedom from measured clinical disease activity status at months 36 and 48 in patients with relapsing-remitting MS (RRMS) who are being treated with natalizumab.
  - FMDA status was defined as no 24-week confirmed EDSS progression, no relapses, no gadolinium-enhancing (Gd+) lesions, and no new or enlarging T2-hyperintense lesions.
  - Freedom from measured clinical disease activity status was defined as no 24-week confirmed EDSS progression and no relapses.

METHODS

Study design

- STRIVE is a phase 4, prospective, multicenter, single-arm, 4-year observational study conducted in the United States in patients initiating treatment with natalizumab.
  - Enrollment began in December 2011.
  - Planned enrollment is approximately 300 patients at 60 US centers.
- Patients received natalizumab 300 mg intravenously every 4 weeks.
  - The initial natalizumab infusion could be given any time after the baseline assessments were completed. It was preferred that the first natalizumab infusion be administered on the same day as the baseline visit or within 2 weeks after the baseline visit date.
- Key inclusion criteria are as follows:
  - Age 18–65 years, with an RRMS diagnosis of ≤3 years' duration;
  - EDSS score ≤4.0;
  - Negative test results for anti-JCV antibodies ≤6 months prescreening or at baseline (with patients who converted to anti-JCV antibody positive status during the course of the study allowed to continue on natalizumab at the discretion of the treating neurologist);
  - Prior treatment with disease-modifying therapy (DMT) for ≤36 months total before the date of informed consent or treatment-naive status with respect to DMTs, which included, but were not limited to, intramuscular interferon beta-1a (IM IFNβ-1a), subcutaneous (SC) IFNβ-1b, SC IFNβ-1a, glatiramer acetate (GA), and fingolimod;
  - The decision to treat with natalizumab having preceded enrollment;
  - Patient satisfaction of the approved therapeutic indications for natalizumab.
- Key exclusion criteria include the following:
  - Any prior treatment with natalizumab;
  - Anti-JCV antibody positive status at any time point;
  - Contraindications to treatment with natalizumab as described in the US prescribing information;
  - A history of PML or other opportunistic infections or an increased risk for such infections;
  - A history of diagnoses of primary progressive MS and/or secondary progressive MS;
  - Current treatment with immunomodulatory or immunosuppressive therapy or a prior history of immunosuppressive use.

Study endpoints

- The primary endpoints are as follows:
  - The proportion of patients who have FMDA status at months 12 and 24;
  - The proportion of patients who have freedom from measured clinical disease activity at months 36 and 48.
- Additional endpoints include the following:
  - Identification of prognostic factors at baseline that predict overall FMDA status at month 12 and yearly factors that predict overall FMDA status at month 24;
  - Identification of prognostic factors at baseline that predict freedom from measured clinical disease activity at month 12 and yearly clinical factors that predict clinical disease-free status (measured by relapses and EDSS) in subsequent years at months 24, 36, and 48;
  - Freedom from measured clinical disease activity status, annualized relapse rate, confirmed EDSS progression and improvement (sustained over 24 weeks), and magnetic resonance imaging measures (T2, T1, T1 with Gd+, and brain atrophy) annually at months 12, 24, 36, and 48;
  - Retinal nerve fiber layer (RNFL) thickness (measured by optical coherence tomography [OCT]) and low-contrast visual acuity at months 24 and 48 and change from baseline in a subset of 100 patients;
  - Patient-reported outcomes annually at months 12, 24, 36, and 48 and change from baseline; outcomes include cognitive impairment (Symbol Digit Modalities Test), capacity for work (Work Productivity and Activity Improvement questionnaire), and quality of life (Multiple Sclerosis Impact Scale-29).

Analyses of baseline characteristics

- This interim analysis represents data collected as of January 17, 2014.
- The following baseline data were summarized by descriptive statistics:
  - Demographics and clinical characteristics;
  - MS disease history;
  - Past medical conditions;
  - Disease characteristics;
  - MS treatment history;
  - OCT results.

RESULTS

- As of January 17, 2014, 166 patients had been enrolled.
- Twenty patients had discontinued treatment; the most common reasons for discontinuation were investigator decision (3%) and compliance issues (3%).
- Baseline demographic and clinical characteristics for the enrolled population are presented in Table 1.

Table 1: Baseline demographics (all enrolled patients)

Demographic and clinical characteristics	N=166
Age, mean (SD)	33.0 (8.40)
Gender, n (%)	
Female	124 (74.7)
Male	42 (25.3)
Race, n (%)	
Asian	2 (1.2)
Black or African American	29 (17.5)
White	126 (75.9)
Other	9 (5.4)

SD=standard deviation.

- Past medical conditions most commonly reported by patients were categorized as neurological (67 patients [40.4%]), psychosocial (49 patients [29.5%]), allergy (44 patients [26.5%]), endocrine/metabolic (43 patients [25.9%]), genitourinary (42 patients [25.3%]), and musculoskeletal (33 patients [19.9%]).
- Mean time from first symptoms of MS was 1.9 years; mean time from MS diagnosis was 0.6 years (Table 2).

Table 2: MS disease history (all enrolled patients)

Disease history	N=166
Time from first MS symptom, years	
Mean (SD)	1.9 (2.58)
Median (min, max)	1 (0, 15)
Time from diagnosis of MS, years	
Mean (SD)	0.6 (0.76)
Median (min, max)	0 (0, 3)
Total number of relapses experienced within the past year	
Mean (SD)	1.4 (1.16)
Median (min, max)	1 (0, 12)
Total number of relapses experienced within the past 2 years	
Mean (SD)	1.7 (1.33)
Median (min, max)	1 (0, 12)

- The mean (SD) baseline EDSS score, MS Severity Score (MSSS), and T1 and T2 lesion volumes are presented in Table 3.

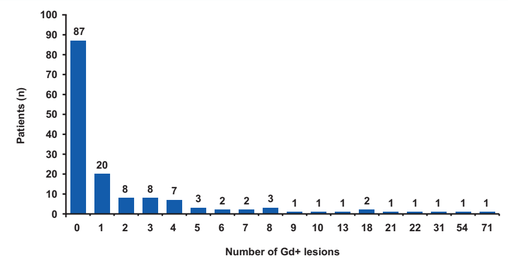
Table 3: Baseline disease characteristics (all enrolled patients)

Baseline disease characteristic	N=166
EDSS score[a]	
Mean (SD)	2.1 (1.15)
Median (min, max)	2.0 (0.0, 5.4)
MSSS[b]	
Mean (SD)	5.0 (2.59)
Median (min, max)	5.0 (0, 9.1)
T1 lesion volume, mL[c]	
Mean (SD)	2.1 (4.05)
Median (min, max)	1 (0, 30)
T2 lesion volume, mL[c]	
Mean (SD)	8.1 (10.95)
Median (min, max)	4 (0, 73)

[a]n=163; [b]n=161; [c]n=147.

- Slightly more than half of all patients (87 of 166 [52.4%]) had no Gd+ lesions at baseline (Figure 1).

Figure 1: Distribution of Gd+ lesions at baseline (all enrolled patients)



- Seventy-seven patients (46.4%) received prior treatment with a DMT; the mean (SD) treatment duration of all prior MS treatment was 283 (232.8) days (with total duration calculated by adding all treatment durations) (Table 4).
  - Of the patients who received prior treatment, most had received GA (38 patients) and/or IM IFNβ-1a (25 patients).

Table 4: Prior MS treatment history (all enrolled patients)

MS treatment	n (%)	Duration, median (min, max), days
Prior MS treatment		
Yes	77 (46.4)	230 (3, 1145)[a]
No	89 (53.6)	NA
Prior treatment by DMT		
IM IFNβ-1a	25 (15.1)	234 (8, 1065)
SC IFNβ-1b	5 (3.0)	256 (92, 365)
SC IFNβ-1a	14 (8.4)	230 (5, 547)
GA	38 (22.9)	195 (4, 1145)
Teriflunomide	2 (1.2)	219 (151, 287)
Other	4 (2.4)	6.5 (3, 275)

[a]Total duration calculated by adding all treatment duration.
NA=not applicable.

- Baseline OCT was conducted on 55 of 166 patients (33.1%) (stratus=6; Spectralis®=19 [Heidelberg Engineering, Carlsbad, CA]; cirrus=30) to examine RNFL thickness and macular volume (Table 5).

Table 5: Optical coherence tomography summary

	Right eye (OD)	Left eye (OS)
RNFL average thickness, µm		
n	52	52
Mean (SD)	96.7 (25.67)	97.1 (27.31)
Total macular volume, mm^3		
n	55	55
Mean (SD)	28.1 (113.7)	28.6 (116.9)

CONCLUSIONS

- The anti-JCV antibody negative patients enrolled in STRIVE have a relatively short disease duration and relatively low levels of disability, allowing for systematic examination of natalizumab use in early MS.
- This study will provide data on patient characteristics that most reliably predict FMDA status in anti-JCV antibody negative patients over 2–4 years.
- OCT and visual acuity data will assess the structure and function of the visual pathway to evaluate MS pathophysiology over time in patients being treated with natalizumab.
  - The RNFL is an ideal structure to evaluate neurodegeneration in MS; several studies have demonstrated correlations between RNFL thinning and visual loss.[3]
  - In this population, the mean baseline RNFL values were within the range of normal values for a healthy population.[4]
- This information may help to optimize treatment decisions for anti-JCV antibody negative patients with early RRMS.

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