Long-term safety and effectiveness of natalizumab redosing and treatment in the STRATA MS Study

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ABSTRACT

Objectives: Report long-term safety and effectiveness of natalizumab over 240 weeks in the prospective, observational, open-label Safety of TYSABRI Re-dosing and Treatment (STRATA) Study.

Methods: Patients (N = 1,094) previously enrolled in natalizumab multiple sclerosis clinical trials received natalizumab 300 mg IV every 4 weeks, up to 240 weeks. Serious adverse events, Expanded Disability Status Scale (EDSS) scores, and annualized relapse rates were analyzed.

Results: At data cutoff (February 9, 2012), natalizumab exposure was 3,460 patient-years; a median of 56 (range 1–70) infusions were received. Serious adverse events, including progressive multifocal leukoencephalopathy, were consistent with natalizumab's known profile. Upon natalizumab re-exposure, rates of anti-natalizumab antibodies and hypersensitivity reactions were 3% and 5% overall, and 40% and 24% among patients with 1 to 2 prior natalizumab doses. Patients originally randomized to placebo/another disease-modifying therapy vs natalizumab in previous studies had significantly higher EDSS scores at STRATA baseline; this difference persisted over 240 weeks. EDSS scores generally remained stable. Patients initially randomized to natalizumab had lower annualized relapse rates over 240 weeks.

Conclusions: Serious adverse events were consistent with natalizumab's known safety profile; short exposure with a gap before redosing was associated with higher incidences of anti-natalizumab antibodies and hypersensitivity reactions. Stability of EDSS scores and consistently low relapse rates over 5 years of natalizumab treatment are consistent with its known efficacy profile.

Classification of evidence: This study provides Class III evidence that in patients with relapsing-remitting multiple sclerosis, natalizumab stabilizes EDSS scores, decreases relapse rates, and is associated with an increased risk of progressive multifocal leukoencephalopathy. *Neurology*® 2014;83:78–86

GLOSSARY

EDSS = Expanded Disability Status Scale; **IFNβ-1a** = interferon β-1a; **JCV** = JC virus; **MS** = multiple sclerosis; **PML** = progressive multifocal leukoencephalopathy; **RRMS** = relapsing-remitting multiple sclerosis; **STRATA** = Safety of TYSABRI Re-dosing and Treatment; **TOUCH** = TYSABRI Outreach: Unified Commitment to Health; **TYGRIS** = TYSABRI Global Observation Program in Safety.

Natalizumab (Tysabri; Biogen Idec Inc.) is a humanized monoclonal antibody that specifically binds to the α4 subunit of α4β1 integrin, preventing leukocyte migration into the brain and reducing inflammation.^{1,2} In phase 3 studies, natalizumab showed efficacy in reducing relapse rates and disability progression in patients with relapsing-remitting multiple sclerosis (RRMS).^{3,4} Post hoc analyses showed that more natalizumab-treated than placebo-treated patients remained free of measured disease activity,⁵ results confirmed in clinical practice by the TYSABRI Observational Program.⁶

Supplemental data
at [Neurology.org](#)

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The occurrence of progressive multifocal leukoencephalopathy (PML) in 3 natalizumab-treated patients in clinical studies resulted in temporary withdrawal of natalizumab from the market in 2005–2006.^{7–10} Upon natalizumab reapproval, eligible patients already enrolled in multiple sclerosis (MS) clinical trials at the time of the drug's withdrawal were invited to participate in the open-label, prospective, multinational, single-arm Safety of TYSABRI Re-dosing and Treatment (STRATA) Study. Three risk factors for PML in natalizumab-treated patients were subsequently identified: positive anti-JC virus (JCV) antibody status, prior immunosuppressant use, and longer duration of natalizumab therapy, especially >24 months.^{11,12}

STRATA includes a unique cohort with longer lifetime exposure than the >100,000

patients with MS receiving natalizumab in clinical settings. Although reflecting a relatively small number of patients, results from the STRATA cohort are relevant to long-term safety and effectiveness of natalizumab use in clinical practice.^{13–16} We summarize 240-week STRATA data on the safety and effectiveness of natalizumab as of February 9, 2012.

METHODS Study design. STRATA was initiated under 2 protocols to evaluate the safety of natalizumab monotherapy after re-exposure to natalizumab in patients with MS who participated in previous natalizumab studies (figure 1).

STRATA was originally planned for 48 weeks in North America and the rest of the world, but the study outside of North America was extended for up to a total of 480 weeks to observe long-term safety and effectiveness. The US portion of the North American study was stopped between 24 and 48 weeks; patients in the Canadian portion could transfer to the ongoing study outside of North America after 48 weeks. All US patients continuing

Figure 1 STRATA Study flow diagram

Eligible patients previously participated in a natalizumab multiple sclerosis clinical feeder study. (Some patients from these studies were enrolled in a safety extension study before STRATA started.) The safety extension and STARS studies were prematurely terminated when natalizumab dosing was voluntarily suspended. While the ROW patients entered the first 48 weeks of STRATA and subsequent extension period (still ongoing), US STRATA patients had the option to enroll in TOUCH once the STRATA Study was closed in the United States; some of these patients were also enrolled in TYGRIS (US STRATA/TYGRIS). Red dashed lines indicate that some patients did not participate in the safety EXT study, but went directly into STRATA from the feeder studies. Data are shown as of February 9, 2012. ^aAll US patients who continued on treatment beyond week 48 were enrolled in TOUCH (as per US requirements); TYGRIS patients remained part of TOUCH. Enrollment in these programs was simultaneous. ^bAt week 240 or have not reached week 240 yet. EXT = extension; FU = follow-up; GA = glatiramer acetate; IFNβ-1a = interferon β-1a; ROW = rest of world; SC = subcutaneous; STRATA = Safety of TYSABRI Re-dosing and Treatment; TOUCH = TYSABRI Outreach: Unified Commitment to Health; TYGRIS = TYSABRI Global Observation Program in Safety; US = United States.

natalizumab treatment enrolled in the mandatory TOUCH (TYSABRI Outreach: Unified Commitment to Health) prescribing program. Some US TOUCH patients also concurrently enrolled in the ongoing, voluntary TYSABRI Global Observation Program in Safety (TYGRIS).

Standard protocol approvals, registrations, and patient consents. The protocols (ClinicalTrials.gov identifier number NCT00306592 for North America, NCT00297232 for the rest of the world) were approved by the relevant institutional review boards/ethics committees. All participants gave written informed consent.

Primary research question. These analyses of data from the STRATA Study were conducted to evaluate the safety of natalizumab monotherapy after re-exposure to natalizumab in patients with MS who participated in previous natalizumab studies and to evaluate the long-term impact of natalizumab monotherapy on disability measured by Expanded Disability Status Scale (EDSS) changes over time, as well as on the frequency of relapses.

Classification of evidence. This study provides Class III evidence that in patients with RRMS, natalizumab stabilizes EDSS scores, decreases relapse rates, and is associated with an increased risk of PML.

Patients. Eligible patients with RRMS previously participated in a natalizumab “feeder” study: AFFIRM (natalizumab monotherapy vs placebo)³; SENTINEL (natalizumab + interferon β -1a [IFN β -1a] vs IFN β -1a alone [given with placebo])⁴; GLANCE (natalizumab + glatiramer acetate alone [given with placebo])¹⁷; or STARS (natalizumab vs subcutaneous IFN β -1a vs placebo, Biogen Idec, data on file). Most patients who received placebo, or placebo and/or another disease-modifying therapy (hereafter referred to as “placebo”) in feeder studies, continued into a safety extension study, during which they received natalizumab until dosing was suspended. Fifty-seven feeder-study patients remained naive to natalizumab at STRATA baseline (figure 1).

Patients entering the STRATA Study were required to discontinue concomitant immunosuppressive or immunomodulatory treatment for the study’s duration.

Exclusion criteria included persistently positive anti-natalizumab antibodies; compromised immune system; prior natalizumab discontinuation because of a related allergic reaction or serious adverse event; malignancy history; or any major disease precluding recombinant humanized immunomodulatory antibody use.

The study was conducted in accordance with local regulations and the International Conference on Harmonisation of Good Clinical Practice Guideline.

Safety assessments. Serious adverse events were monitored. Serum anti-natalizumab antibodies were determined at month 6 using an ELISA; patients who tested positive were retested approximately 6 to 8 weeks later for confirmation. After the initial scheduled collection, samples for anti-natalizumab antibodies were not collected unless the investigator suspected persistently positive antibodies. Infusion/hypersensitivity reactions were monitored for the initial (first 48 weeks) STRATA period.

Effectiveness assessments. EDSS scores were recorded at screening, then every 24 weeks. A relapse was defined objectively as new or recurrent neurologic symptoms, not associated with fever, lasting for ≥ 24 hours and following a period of improvement or stabilization of symptoms of ≥ 30 days. Unadjusted annualized relapse rates were calculated from reports of MS relapse.

Statistical analyses. Data included in analyses came from several sources, including the initial North America and rest-of-world STRATA protocols, the extension of the rest-of-world protocol, and the TYGRIS protocol for US patients previously enrolled in STRATA (US STRATA). References to STRATA data in this report include US STRATA/TYGRIS data wherever possible (i.e., STRATA + US STRATA/TYGRIS) (figure 1) and are referred to as STRATA data. Data are based on the February 9, 2012, cutoff, when most ongoing patients should have reached week 240. With the exception of PML data, no data beyond week 240 are included. Where appropriate, data from feeder studies and the safety extension study were included in analyses of effectiveness. Analyses were based only on observations obtained at each assessment, without imputing missing data. Descriptive statistics calculated using SAS statistical software (SAS Institute, Cary, NC) are presented. Because STRATA is an extension study for patients previously enrolled in other studies, sample size was not based on statistical considerations.

RESULTS Patients. A total of 1,094 patients enrolled in STRATA: 356 from North America and 738 from other countries (figure 1). As of February 9, 2012, 245 patients (22%) had discontinued study treatment and 217 (20%) had completed the initial 24 to 48 weeks but did not continue into the STRATA extension. Patients continuing beyond the initial study period were reconsented if they continued into long-term treatment in STRATA. Main reasons for discontinuing natalizumab study treatment included voluntary withdrawal/withdrawal of consent (92 patients; 8%), adverse events (51 patients; 5%), other reasons (49 patients; 4%), lost to follow-up/noncompliance/relocation (15 patients; 1%), lack of efficacy (13 patients; 1%), persistent anti-natalizumab antibodies (11 patients; 1%), principal investigator withdrew from program (11 patients, 1%), or death (3 patients; $<1\%$). As of February 9, 2012, the adverse events most frequently cited as reasons for discontinuation of study treatment were infections and infestations (14 events, including 8 cases of PML); immune system disorders (9 events, including anaphylactic reactions, hypersensitivity reactions, and immune reconstitution syndrome); and benign, malignant, and unspecified neoplasms (8 events). The fatal events reported in the 3 patients who died while receiving study treatment were pulmonary embolism, suicide, and myocardial infarction.

Overall, mean age was 41.4 years, 69% were women, and median time since initial MS diagnosis was 8.0 years. Median time between last natalizumab infusion before STRATA (in patients who received natalizumab in feeder studies or safety extension) and first infusion in STRATA was 85.0 weeks. Baseline characteristics appeared similar across subgroups of patients who remained on treatment, withdrew at any stage before week 240, or completed only the initial period (table 1). Feeder study baseline

Table 1 Baseline demographic and disease characteristics at entry into the STRATA Study

Characteristic	Entire STRATA population (N = 1,094)	STRATA subgroups		
		Remained in STRATA at wk 240 (n = 632)	Completed initial STRATA period, did not enter STRATA extension (includes US STRATA/TYGRIS) (n = 217) ^a	Discontinued study (n = 245)
Mean age, y, $\pm$ SD	41.4 $\pm$ 8.1	40.4 $\pm$ 8.2	43.0 $\pm$ 7.4	42.4 $\pm$ 8.2
Sex, % female	69	67	73	71
Median (range) EDSS score ^b	2.5 (0.0–8.0)	2.5 (0.0–8.0)	2.5 (0.0–8.0)	3.0 (0.0–7.5)
Median disease duration since diagnosis, y (range)	8 (4–34), n = 1,088	7 (4–28), n = 628	8 (4–31), n = 217	9 (4–34), n = 243
Median no. of relapses (range) ^b	1 (0–8), n = 1,088	1 (0–5), n = 628	1 (1–8), n = 217	1 (0–4), n = 243
Median exposure to natalizumab, no. of doses (range) ^c	32.0 (0–41)	34.0 (0–41)	31.0 (0–40)	16 (0–39)
Median time since last natalizumab infusion, wk (range)	85 (57–157)	85 (57–157)	85 (57–105)	86 (57–148)

Abbreviations: EDSS = Expanded Disability Status Scale; STRATA = Safety of TYSABRI Re-dosing and Treatment; TYGRIS = TYSABRI Global Observation Program in Safety.

Unless otherwise indicated, values are from STRATA Study baseline (not feeder studies).

^a Of these patients, at least 160 are confirmed to have remained on natalizumab treatment after STRATA.

^b Relapse and EDSS data were not systematically collected between the last previous natalizumab infusion and the start of STRATA. Therefore, data for the year before participation in feeder studies are provided.

^c During feeder and/or safety extension studies (before STRATA).

characteristics were compared for patients who enrolled in STRATA and those who did not enroll (table e-1 on the *Neurology*[®] Web site at Neurology.org). A higher percentage of patients who did not enroll in STRATA were female and had less prior exposure to natalizumab, i.e., a higher proportion had been randomized to placebo in feeder studies.

At the time of this analysis, natalizumab exposure was 3,460 patient-years, and patients had received a median of 56 (range 1–70) infusions in STRATA. The median lifetime number of natalizumab infusions was 90 (range 4–104) in patients originally randomized to natalizumab in feeder studies and 55 (range 2–77) in patients originally randomized to placebo.

Safety. Anti-natalizumab antibodies. In the first 24 weeks, 31 patients (3%) were persistently positive for anti-natalizumab antibodies (including 15 patients [1.4%] testing positive for anti-natalizumab antibodies at last sample collection with no subsequent retest result). A high incidence of anti-natalizumab antibodies was seen in those with 1 to 2 prior natalizumab doses before dose interruption: 21 of 52 evaluable patients (40%).

Infusion and hypersensitivity reactions. In the first 48 weeks, 55 of 1,094 patients (5%) experienced an infusion reaction, defined as any reaction that occurred within 2 hours after start of natalizumab infusion. Reactions occurred most frequently in patients with previous exposure to 1 to 2 natalizumab infusions (13 of 55 patients with 1–2 prior natalizumab infusions; 24%). The most common infusion-related

reactions were headache and hypersensitivity. Forty-two percent of patients with ≥ 1 positive anti-natalizumab antibody result had an infusion reaction, compared with 4% of antibody-negative patients (figure e-1). Eight natalizumab-related hypersensitivity-like reactions were reported ($< 1\%$), including 3 severe and 4 in patients with 1 to 2 prior infusions.

Serious adverse events. One hundred seventy-one patients (16%) reported at least one serious adverse event (excluding MS relapse). No single serious adverse event was seen in $\geq 2\%$ of patients. The most common system organ classes in which serious adverse events were reported included infections and infestations (4%), gastrointestinal disorders (2%), and neoplasms (2%) (table 2). The incidence and profile of serious adverse events were consistent with previous reports.^{11,12}

Progressive multifocal leukoencephalopathy. As reported in table 2, as of February 9, 2012, there were 8 confirmed cases of PML in STRATA. As of August 23, 2013, there were 14 confirmed cases of PML in STRATA. All 14 cases were anti-JCV antibody positive at all available time points at least 6 months before PML diagnosis, compared with 67% of the STRATA population that had at least one anti-JCV antibody-positive test result. Five of the 14 patients with PML (36%) previously received immunosuppressant therapy compared with 7% of the overall STRATA cohort. Patients with PML received between 33 and 91 natalizumab infusions since reintroduction in STRATA before PML diagnosis; lifetime exposure ranged from 34 to 111 infusions. PML

Table 2 Incidence of serious adverse events (excluding MS relapse) occurring in at least 5 patients over 240 weeks

System organ class	No. (%)
Patients dosed	1,094 (100)
Patients with at least one serious adverse event	171 (16)
Infections and infestations	44 (4)
Urinary tract infections	9 (<1)
Progressive multifocal leukoencephalopathy ^a	8 (<1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	25 (2)
Basal cell carcinoma	5 (<1)
Gastrointestinal disorders	21 (2)
Injury, poisoning, and procedural complications	18 (2)
Psychiatric disorders	14 (1)
Nervous system disorders, excluding MS relapse	12 (1)
Musculoskeletal and connective tissue disorders	12 (1)
Respiratory, thoracic, and mediastinal disorders	9 (<1)
Cardiac disorders	8 (<1)
Reproductive system and breast disorders	8 (<1)
Hepatobiliary disorders	7 (<1)
Immune system disorders	7 (<1)
Renal and urinary disorders	6 (<1)
Vascular disorders	6 (<1)

Abbreviation: MS = multiple sclerosis.

Includes data as of February 9, 2012, database lock. Terms are presented throughout by descending incidence. A patient was counted only once within each group of serious adverse events.

^a See text discussion of progressive multifocal leukoencephalopathy for information on cases reported after week 240; as of August 23, 2013, there were 14 total patients with progressive multifocal leukoencephalopathy (those shown here and those reported after week 240).

incidence estimates by treatment epoch for the STRATA cohort compared with natalizumab-treated patients in the postmarketing setting are shown in figure e-2; Kaplan-Meier estimates of postmarketing and STRATA cumulative PML probability are shown in figure e-3.

Effectiveness assessments. Expanded Disability Status Scale.

Mean baseline EDSS scores in STRATA were higher ($p = 0.027$) in patients randomized to placebo vs natalizumab in feeder studies (3.13 vs 2.90). While placebo and natalizumab groups had similar mean EDSS scores at feeder study start (2.36 vs 2.38), EDSS scores for those randomized to placebo worsened during feeder studies (2.69 vs 2.36) and both groups worsened during the treatment gap. Over 240 weeks, mean EDSS scores remained stable in both groups; the difference between placebo and natalizumab (3.15 vs 2.79) at week 240 remained significant ($p = 0.024$) (figure 2A).

In long-term, single-arm studies, bias can result from selective dropout of more severely affected patients, erroneously suggesting long-term treatment

benefit. Therefore, sensitivity analyses explored the extent to which informative censoring may contribute to the unusually stable EDSS scores observed in this natalizumab-treated population:

1. Patients who completed only the initial 24 to 48 STRATA weeks are not classified as withdrawals, because discontinuation was related to protocol changes, not clinical decisions. Nineteen percent of those originally randomized to placebo and 20% of those originally randomized to natalizumab completed only the initial STRATA period. Available data from this period show no difference between patients who discontinued after the initial period vs those who remained on treatment.
2. EDSS scores for patients remaining in STRATA at week 240 ($n = 632$) were compared with scores of those who withdrew ($n = 245$) (figure 2B). Mean scores for those who withdrew were already worse at STRATA baseline (3.36 vs 2.87) and remained worse throughout STRATA (mean = 3.45 vs 2.92 at last available on-treatment time point, median of 3.00 vs 2.50). Of 385 patients originally randomized to placebo, 49% remained in STRATA at week 240; 32% had withdrawn. Of 709 prior natalizumab patients, 63% remained in STRATA at week 240; 17% had withdrawn. Therefore, both original treatment assignment and disease activity pre-STRATA entry appear to have influenced disease activity during STRATA and in some cases subsequent withdrawal.
3. Mean EDSS score change from STRATA baseline was 0.05 at the last available on-treatment time point for patients remaining in STRATA vs 0.07 for those who withdrew; median change was 0.00 in all subgroups across all visits.
4. In patients who withdrew, the mean last available on-treatment EDSS score was 3.45, after a median of 13 years (range 5–38) since first MS symptoms. For those who remained, it was 2.92 after a median of 14 years (range 7–42).

Annualized relapse rate. Overall, the unadjusted annualized relapse rate remained low at 0.17 (figure 3A) and even lower beyond 48 weeks. Patients originally randomized to natalizumab had a lower annualized relapse rate vs patients originally randomized to placebo (0.15 vs 0.22), but reduction beyond 48 weeks was seen in both groups. A statistical difference between groups was noted during the first year ($p < 0.01$) and during the overall study period ($p < 0.01$) but not during other individual years. Annualized relapse rate was higher during feeder studies and during STRATA for those who withdrew vs those remaining in STRATA, but both groups had an overall reduction beyond 48 weeks (figure 3B).

Figure 2 EDSS scores over time

STRATA EDSS data, assessed every 24 weeks in the study, are plotted by 48-week intervals in the figure. (A) By original treatment assignment in feeder studies. Includes all available on-treatment EDSS score data during STRATA. ^a $p < 0.0001$ for comparison between scores pre- and postnatalizumab treatment gap (among patients who had at least one natalizumab dose prenatizumab treatment gap). ^b $p < 0.001$ for comparison between original assignment to placebo vs original assignment to natalizumab. ^cIncludes data on patients dosed with natalizumab. ^d $p < 0.05$ for comparison between original assignment to placebo vs original assignment to natalizumab; ^e $p < 0.01$ for comparison between original assignment to placebo vs original assignment to natalizumab. (B) By continuation of treatment status in STRATA (completed 240 weeks vs discontinued treatment before week 240). Includes all available on-treatment EDSS score data for natalizumab and placebo groups combined. Patients who only completed the initial 24- to 48-week period ($n = 217$) are not included in panel B. ^fIncludes data on patients dosed with natalizumab. EDSS = Expanded Disability Status Scale; LOCF = last observation carried forward; STRATA = Safety of TYSABRI Re-dosing and Treatment.

DISCUSSION STRATA data provide valuable information about responses to long-term natalizumab treatment; 58% of patients remained in STRATA up to week 240. Of those patients who did not continue in STRATA beyond the initial treatment

period, it is known that most patients continued natalizumab treatment.

Safety data in STRATA are consistent with natalizumab's known safety profile. There was a low overall incidence of anti-natalizumab antibodies. The risk of

Figure 3 Annualized relapse rates over time

(A) By original treatment assignment in feeder studies. Reflects all available on-treatment relapse data during the STRATA Study. ^a $p < 0.0001$ for comparison between original assignment to placebo vs original assignment to natalizumab. ^bIncludes data on patients dosed with natalizumab. ^c $p < 0.01$ for comparison between original assignment to placebo vs original assignment to natalizumab. ^d $p < 0.001$ for comparison between original assignment to placebo vs original assignment to natalizumab. (B) By continuation of treatment status in STRATA (at or have not yet reached week 240 vs discontinued treatment before week 240). Includes all available on-treatment relapse data for natalizumab and placebo groups in STRATA combined. ^bIncludes data on patients dosed with natalizumab. STRATA = Safety of TYSABRI Re-dosing and Treatment.

infusion reactions and hypersensitivity on natalizumab redosing was low. This was expected, because prior anti-natalizumab antibodies and hypersensitivity reactions were exclusionary to STRATA enrollment. Of note, it was confirmed that natalizumab redosing after an extended treatment gap was not

associated with a change in immunogenic response for most patients. However, the incidence of infusion reactions and anti-natalizumab antibodies was higher in patients with only 1 to 2 prior doses, suggesting that brief exposure followed by an extended period without treatment contributed to a higher risk for

anti-natalizumab antibodies and infusion-related adverse events on re-exposure.^{17,18}

All patients with confirmed PML diagnoses had detectable anti-JCV antibodies at least 6 months prediagnosis and after at least 2 years of natalizumab exposure; both are known risk factors for PML development. It is unknown whether the dosing interruption had any impact on PML incidence. The STRATA population is relatively small, limiting the ability to perform a detailed analysis of PML stratified by all known risk factors. A comparison of PML incidence estimates in STRATA vs the overall postmarketing setting¹⁹ by treatment epoch suggests generally similar incidences. However, 95% confidence intervals around PML risk in STRATA are broad because of the small sample size; therefore, a higher incidence of PML in STRATA cannot be excluded. Another limitation is that the STRATA population is a closed cohort, while the natalizumab postmarketing population is dynamic and may have changed in response to expanding knowledge of PML risk factors. Additional confounding factors may include potential differences in PML risk profile because patients enrolled in STRATA have longer lifetime natalizumab exposures than patients in clinical practice.

Annualized relapse rate remained low throughout STRATA, which was expected based on prior data.^{3,4} Of note, the relapse rate during the first year was significantly lower in patients originally randomized to natalizumab vs placebo, and EDSS scores were significantly lower at every time point up to week 240 in patients originally randomized to natalizumab vs placebo. Although differences between patients originally randomized to natalizumab and those originally randomized to placebo at STRATA baseline may preclude unbiased comparison, these observations suggest that earlier treatment initiation may provide a persistent advantage compared with later treatment and that earlier suppression of inflammatory activity may have important clinical benefits.^{20–22}

While data from prospective follow-up studies such as STRATA can be highly relevant to long-term treatment in clinical practice, selection bias and informative censoring are recognized limitations and were therefore carefully evaluated:

- Demographic/disease characteristics were not meaningfully different between patients entering STRATA and those who did not.
- However, the proportion of patients who entered STRATA was smaller in those who previously received placebo compared with those who previously received natalizumab.
- Characteristics do not appear different between those who did and those who did not continue into the STRATA extension beyond week 48.

- For patients who withdrew from STRATA for other reasons, “lack of efficacy” was rarely cited. Although these patients had a slightly higher EDSS score before and at STRATA baseline and their annualized relapse rate had already been slightly higher in feeder studies, their last available EDSS score in STRATA was similar to STRATA baseline. The main reason cited for discontinuation was concern about PML risk. Patients who withdrew had stable EDSS scores, although higher than those who remained in STRATA.
- Because PML risk may have led patients with a more benign MS prognosis to choose an alternative therapy, it is unlikely that this would introduce bias favoring natalizumab.
- The proportion of patients remaining in the study throughout week 240 was higher in those previously randomized to natalizumab vs placebo, suggesting that prior treatment allocation had a significant effect on STRATA enrollment and retention.

While it can be contended that informative censoring and bias were unlikely, it cannot be definitively determined whether patients with a better or worse disease course or prognosis chose not to enter or continue on in STRATA, whether those who withdrew would have remained stable on therapy, or whether patients may have remained stable without natalizumab therapy. These considerations around potential confounding factors as well as the absence of a control arm limit the conclusions that can be drawn from this observational study. STRATA provides evidence that redosing after short exposure followed by a long gap leads to increased immunogenicity. The safety profile in STRATA is consistent with the known safety profile of natalizumab, and known risks, including PML, require continued vigilance.

AUTHOR CONTRIBUTIONS

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