Efficacy of Natalizumab Therapy in Patients of African Descent With Relapsing Multiple Sclerosis

Analysis of AFFIRM and SENTINEL Data

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Background: Patients with multiple sclerosis (MS) who are of African descent experience a more aggressive disease course than patients who are of white race/ethnicity. In phase 3 clinical trials (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis [AFFIRM] and Safety and Efficacy of Natalizumab in Combination With Interferon Beta-1a in Patients With Relapsing Remitting Multiple Sclerosis [SENTINEL]), natalizumab use significantly improved clinical and magnetic resonance imaging outcomes over 2 years in patients with relapsing MS. Because patients of African descent may be less responsive to interferon beta treatment than patients of white race/ethnicity, the efficacy of natalizumab therapy in this population is clinically important.

Objective: To evaluate the efficacy of natalizumab use in patients of African descent with relapsing MS.

Design: Post hoc analysis.

Setting: Academic research.

Patients: Patients of African descent with relapsing MS who received natalizumab or placebo in the phase 3 AFFIRM study and those who received natalizumab plus intramuscular interferon beta-1a or placebo plus intramuscular interferon beta-1a in the phase 3 SENTINEL study.

Main Outcome Measure: Efficacy of natalizumab use in patients of African descent with relapsing MS who participated in the AFFIRM or SENTINEL trial.

Results: Forty-nine patients of African descent participated in AFFIRM (n=28) or SENTINEL (n=21). Demographic and baseline disease characteristics were similar between patients treated with natalizumab (n=21) or placebo (n=28). Natalizumab therapy significantly reduced the annualized MS relapse rate by 60% (0.21 vs 0.53 in the placebo group, P=.02). Compared with placebo use, natalizumab therapy also significantly reduced the accumulation of lesions observed on magnetic resonance imaging over 2 years: the mean number of gadolinium-enhancing lesions was reduced by 79% (0.19 vs 0.91, P=.03), and the mean number of new or enlarged T2-weighted lesions was reduced by 90% (0.88 vs 8.52, P=.008).

Conclusion: Natalizumab therapy significantly improved the relapse rate and accumulation of brain lesions in patients of African descent with relapsing MS.

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Patients of African descent who participated in the AFFIRM or SENTINEL trial were included in this post hoc analysis; the inclusion criteria for these phase 3 studies were previously published. In the AFFIRM trial, the study population was randomized 2:1 to receive natalizumab (300 mg) or placebo by intravenous infusion once every 4 weeks plus intramuscular interferon beta-1a (30 µg) once weekly for up to 116 weeks. Analyses were performed among patients with screening identified their racial/ethnic origin as “black.”

To achieve adequate patient numbers for analysis, data from the 2 studies were combined. Hence, the placebo group consists of patients randomized to placebo in AFFIRM and to placebo plus intramuscular interferon beta-1a in SENTINEL, while the natalizumab-treated group consists of patients randomized to natalizumab monotherapy in AFFIRM and to natalizumab plus intramuscular interferon beta-1a in SENTINEL. “Study” was excluded as a stratification factor for analyses because sample sizes were too small to investigate differences in results between the 2 trials.

Treatment effects on the following efficacy end points at 2 years were assessed: annualized relapse rate (ARR), time from first dose to first relapse, number of new or enlarged T2-weighted lesions, number of gadolinium-enhancing lesions, changes in T1-weighted and T2-weighted lesion volumes, change in Expanded Disability Status Scale (EDSS) score from baseline, and time from first dose to sustained disability progression (defined as a ≥1.0-point increase in EDSS from a baseline EDSS of ≥1.0 or a ≥1.5-point increase in EDSS from a baseline EDSS of 0, sustained for 12 weeks or 24 weeks). Magnetic resonance imaging measurements were assessed at the Central MRI Analysis Center at the Institute of Neurology, University College London, London, England.

The following statistical analysis methods were used for each endpoint. The statistical models included the same covariates as were used in the previous analyses. The ARR was analyzed using Poisson regression with overdispersion adjusted for the number of relapses in the year before study enrollment, baseline EDSS (≥3.5 vs >3.5), presence of gadolinium-enhancing lesions at baseline, and age (<40 vs ≥40 years). The time from first dose to first relapse was analyzed using a Cox proportional hazards model adjusted for the number of relapses in the year before study enrollment. A rank-based analysis of covariance was used to compare changes in T2-weighted and T1-weighted lesion volume over 2 years, number of new or enlarged T2-weighted lesions over 2 years, number of gadolinium-enhancing lesions at 2 years, and change in EDSS from baseline at 2 years. Each model was adjusted for the corresponding baseline value. Missing data were not imputed. The time from first dose to sustained (12 week and 24 week) disability progression was analyzed using a Cox proportional hazards model adjusted for baseline EDSS and age (<40 vs ≥40 years).

One of us (A.L.P.) performed the statistical analysis using commercially available software (SAS Institute Inc, Cary, North Carolina). Biogen Idec provided files containing all data described herein to the UCSF Multiple Sclerosis Center. Another of us (B.A.C.C.) verified the results by performing a replication statistical analysis with this data set using a different software program (STATA, version 9.0; StataCorp LP, College Station, Texas).
Forty-nine patients of African descent participated in either study: 6 patients from the AFFIRM study and 22 patients from the SENTINEL study were in the placebo arms, and 4 patients from the AFFIRM study and 17 patients from the SENTINEL study were in the natalizumab-treated arms. Of 49 patients, 36 patients (73%) completed the studies; 13 patients (27%) withdrew (7 from the placebo arm and 6 from the natalizumab-treated arm). Two patients (1 from each treatment arm) discontinued the study drug but completed the study follow-up. Demographic and baseline disease characteristics are given in Table 1. Overall, the 2 study arms were fairly well matched at baseline, but some slight imbalances caused by randomization were not stratified by race/ethnicity. Patients in the placebo arm showed a trend toward more relapses in the year before study enrollment than participants in the natalizumab-treated arm. Placebo patients also had a higher median baseline T1-weighted hypointense lesion volume. Because important baseline factors were included in the statistical models to assess treatment effect, all inferences were adjusted for baseline imbalances.

EFFECT OF NATALIZUMAB USE ON RELAPSES

Natalizumab therapy significantly reduced the ARR over 2 years compared with placebo. The unadjusted ARR was 63% lower in the natalizumab-treated group (0.80 vs 0.30, \( P = .01 \)). After adjusting for baseline covariates, the treatment effect remained significant (Figure 1A). Natalizumab therapy also significantly reduced the risk of first relapse by 68% over 2 years compared with placebo (Figure 1B).

EFFECT OF NATALIZUMAB USE ON MAGNETIC RESONANCE IMAGING OUTCOMES

Natalizumab therapy had a significant effect on magnetic resonance imaging outcomes over 2 years in patients of African descent (Table 2). Natalizumab use significantly reduced the mean number of new or enlarged T2-weighted lesions over 2 years by 90% and the mean number of gadolinium-enhancing lesions at 2 years by 79% compared with placebo. Natalizumab therapy also significantly reduced changes in T2-weighted and T1-weighted lesion volume over 2 years compared with placebo (Figure 2).

COMPARISON OF AFRICAN WITH NONAFRICAN DESCENDED PATIENTS

In Table 3, the relative effects of natalizumab use on relapses and magnetic resonance imaging outcomes in...
participants of African descent vs non-African descent are compared among the present study, AFFIRM, and SENTINEL. Similar results were found when the participants of non-African descent were restricted to those of white race/ethnicity (data not shown).

**EFFECT OF NATALIZUMAB USE ON DISABILITY**

Statistically significant benefits of natalizumab use on disability were not found in this data set. The mean (median) changes in EDSS at 2 years were 0.03 (0.0) for natalizumab and 0.60 (0.50) for placebo ($P = .22$). The estimated hazard ratios were 0.789 (95% confidence interval, 0.283-2.199; $P = .65$) for time to 12-week sustained disability progression and 0.578 (95% confidence interval, 0.105-3.170; $P = .53$) for time to 24-week sustained disability progression. The large confidence intervals and nonsignificant $P$ values do not allow any definite conclusions about an effect on disability over 2 years and are anticipated owing to the small sample size.

**DEVELOPMENT OF ANTIBODIES TO NATALIZUMAB THERAPY**

One patient in the natalizumab-treated group was persistently positive for antinatalizumab antibodies during the course of treatment. This patient experienced disability progression (at 12 weeks and at 24 week), had the largest change in EDSS at 2 years (3.0 points), and demonstrated the most relapses (n=4), gadolinium-enhancing lesions (n=3), and new or enlarged T2-weighted lesions (n=10) among patients of African descent in the natalizumab-treated group over 2 years.

**SAFETY**

Among 49 patients, 100% (28 of 28) of placebo and 95% (20 of 21) of natalizumab-treated patients reported at least 1 adverse event. Blurred vision was reported by 29% (6 of 21) of natalizumab-treated patients vs no placebo patients. Table 4 gives adverse events experienced by at least 5 patients in either study group. The overall incidence of adverse events among this subpopulation was similar to that among the overall study populations.$^8$-$^{10}$

**COMMENT**

Patients of African descent typically exhibit a more aggressive course of MS characterized by rapid progression of disability, more frequent relapses, and worse postrelapse recoveries. Little research on treatment in this population has been reported. The limited available data suggest that this patient population does not seem to respond to treatment with interferon beta as robustly as their counterparts of white race/ethnicity; however, it is unclear whether the observed reduced response is due to a treatment effect or differences in the natural history of the disease.$^3$
A limitation of the present study is that race/ethnicity was self-identified. Patients of African descent with MS in the United States and Europe are often an admixed population, and genetic determination of the extent of admixture could not be used in this study because DNA was not collected from the study participants. The extent of African-origin HLA DNA and the presence of the null mutation of HLA-DRB3 are associated with more severe disability outcomes in African Americans with MS. Therefore, it is possible that these genetic factors are uncontrolled confounders in our study and could bias the observations if they were disproportionately represented in the placebo group.

The present post hoc analysis included patients with MS of African descent who participated in the pivotal AFFIRM and SENTINEL trials. The pooling of data in this meta-analysis allowed for adequate numbers for assessment, and the inclusion of data from the SENTINEL trial seemed reasonable, especially because patients of African descent might be less responsive to treatment with interferon beta-1a. However, assuming that interferon beta-1a has at least some efficacy in patients of African descent, the inclusion of many patients who were actively receiving interferon beta-1a in the placebo group would be expected to attenuate the differences between the placebo and natalizumab-treated groups and could result in underestimation of the effect of natalizumab use on disease activity in this data set. To our knowledge, this is the first study to examine and demonstrate efficacy of an MS disease-modifying therapy among this population in the context of placebo-controlled trials.

This analysis demonstrated statistically significant reductions in relapses and magnetic resonance imaging lesion activity with natalizumab treatment. Although analyses of disability progression did not show statistically significant differences between the placebo and natalizumab-treated groups (possibly owing to the small sample size), the positive trend seen for change from baseline in EDSS, along with a similar effect on time to sustained disability progression, is encouraging and should be explored further. Because patients of African descent tend to have more severe disease and may be less responsive to interferon treatment, the findings from this study are relevant to clinicians who treat patients with MS.

In clinical practice, natalizumab is used primarily as a second-line therapy in patients who have had ongoing disease activity, despite treatment with interferons or glatiramer acetate, or in patients who cannot tolerate these medications. The results of the present study provide support for evidence that natalizumab has beneficial effects in patients of African descent with MS. We believe that this information will be clinically helpful for neurologists who are contemplating the use of natalizumab in this patient population. Studying the effects of medications among patients of different racial/ethnic backgrounds raises ethical and technical challenges. Despite these challenges, the authors recommend further research with the goal of characterizing the efficacy of natalizumab treatment, as well as other disease-modifying therapies, in patients from various racial/ethnic backgrounds.

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