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Effects of Natalizumab on Relapses and MRI Outcomes in Hispanic Patients with Relapsing Multiple Sclerosis

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BACKGROUND

- In the pivotal AFFIRM and SENTINEL clinical studies, natalizumab (TYSABRI®) was effective both as a monotherapy and in combination with interferon beta (IFNβ)-1a in patients with relapsing multiple sclerosis (MS)
  - In AFFIRM, natalizumab monotherapy significantly reduced annualized relapse rate (ARR) by 68% ($P < .001$) and the risk of sustained disability progression by 42%–54% ($P < .001$) over 2 years compared with placebo[1]
  - In SENTINEL, natalizumab added to IFNβ-1a significantly reduced ARR by 55% ($P < .001$) and the risk of sustained disability progression by 24% over 2 years compared with placebo added to IFNβ-1a[2]
- In recent subgroup analyses of data from AFFIRM and SENTINEL, natalizumab demonstrated efficacy in patients of African descent that was comparable to its efficacy in the overall study populations[3]
- The effects of MS therapies in Hispanic patients have not been well studied
- We retrospectively analyzed the effects of natalizumab treatment on relapse rates, disability, and magnetic resonance imaging (MRI) outcomes in Hispanic patients who participated in AFFIRM and SENTINEL

OBJECTIVE

- To evaluate the efficacy of natalizumab in Hispanic patients with relapsing MS who participated in the AFFIRM or SENTINEL studies

METHODS

Patients

- Inclusion criteria for AFFIRM and SENTINEL have been published previously[1,2]
- Patients included in this analysis indicated "Hispanic" as their ethnic origin at screening

Study Design

- AFFIRM and SENTINEL were randomized, double-blind, placebo-controlled, phase 3 clinical studies
- In AFFIRM, patients received natalizumab 300 mg or placebo (2:1) by intravenous (IV) infusion once every 4 weeks for up to 116 weeks
- In SENTINEL, patients received natalizumab 300 mg IV or placebo once every 4 weeks added to intramuscular (IM) IFNβ-1a 30 µg once weekly (1:1) for up to 116 weeks
- Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted ≥ 24 hours and were accompanied by new neurologic signs found by the examining neurologist
- Progression of disability was defined as an increase of ≥ 1.0 point in the Expanded Disability Status Scale (EDSS) score from a baseline score of at least 1.0 or an increase of ≥ 1.5 points in the EDSS score from a baseline score of 0 (progression could not be confirmed during a relapse)
- Contiguous, 3-mm-thick axial slices through whole brain were acquired. MRI analysis was performed by experienced raters unaware of treatment assignment

Analyses

- Post-hoc analyses were performed on Hispanic patients who participated in AFFIRM and SENTINEL
- Data from comparator (placebo in AFFIRM and placebo + IFNβ-1a in SENTINEL) groups were combined, and data from the natalizumab monotherapy group in AFFIRM were combined with data from the natalizumab + IFNβ-1a group in SENTINEL

RESULTS

Patients

- A total of 35 patients who participated in AFFIRM (n = 13) and SENTINEL (n = 22) identified themselves as Hispanic
  - Overall, 20 patients received natalizumab and 15 received comparator
- Demographic and baseline disease characteristics for Hispanic patients in AFFIRM and SENTINEL are shown in Table 1
  - The majority of patients (83%) were female, and the mean patient age was 34.5 years
  - Patients in the natalizumab group showed a trend toward more gadolinium-enhancing (Gd+) lesions (3.35 ± 5.75) than patients in the comparator group (1.27 ± 2.34), but this difference was not statistically significant
  - Important baseline factors were included in the statistical models for assessing treatment effects; hence all inferences were adjusted for any baseline imbalances

TABLE 1. Demographic and Baseline Disease Characteristics of Hispanic Patients in AFFIRM and SENTINEL

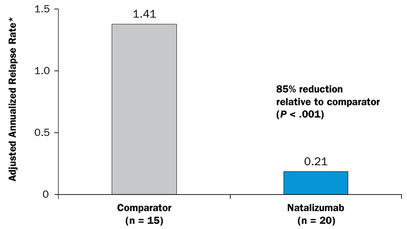
	Comparator (n = 15)	Natalizumab (n = 20)	*P* Value
Age, years, mean ± SD	34.7 ± 5.3	34.3 ± 8.7	.886
Female, n (%)	12 (80)	17 (85)	1.000
EDSS score, mean ± SD	2.67 ± 1.35	2.23 ± 1.09	.292
No. of relapses in prior year, mean ± SD	1.67 ± 0.82	1.75 ± 1.55	.839
Median duration of disease, years	8.0	6.0	.402
No. of Gd+ lesions, mean ± SD	1.27 ± 2.34	3.35 ± 5.75	.138
≥ 9 T2 lesions, n (%)	15 (100)	17 (85)	.244
Median T2 lesion volume, mm^3	3868.4	3965.3	.777
Median T1 hypointense lesion volume, mm^3	414.9	683.7	.677
BPF, mean ± SD	0.825 ± 0.014 (n = 15)	0.823 ± 0.016 (n = 19)	.719

BPF = brain parenchymal fraction; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhancing; SD = standard deviation.

Effect of Natalizumab on Relapses

- In Hispanic patients, natalizumab significantly reduced ARR over 2 years, relative to comparator (Figure 1)
  - After adjusting for baseline characteristics, ARR was 85% lower in the natalizumab group than in the comparator group
- Natalizumab significantly reduced the risk of relapse over 2 years by 76% relative to comparator (hazard ratio [HR] = 0.24; 95% confidence interval [CI]: 0.08, 0.70; $P = .009$) (Figure 2)
  - The 2-year cumulative probability of relapse was 26.2% for patients treated with natalizumab and 80.0% for patients who received comparator

FIGURE 1. Annualized Relapse Rate over 2 Years

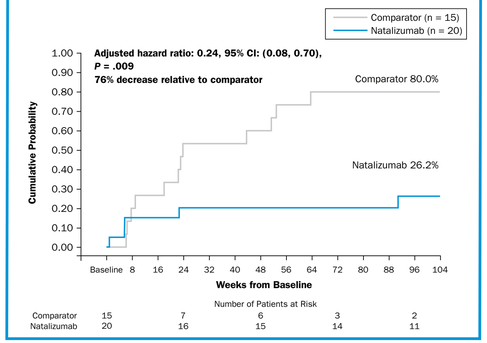


*Estimated from Poisson regression, adjusted for number of relapses in one year prior to study entry, baseline EDSS score (≤ 3.5 vs > 3.5), presence of Gd+ lesions at baseline, and age in years (< 40 vs ≥ 40).

Effect of Natalizumab on Disability Progression

- Natalizumab reduced the risk of disability progression sustained for 12 and 24 weeks by 69% and 86% over 2 years relative to comparator. However, this effect did not reach statistical significance
  - At 2 years, the cumulative probability of disability progression sustained for 12 weeks was 16.9% in the natalizumab group and 51.3% in the comparator group (HR = 0.31; 95% CI: 0.08, 1.24; $P = .098$)
  - At 2 years, the cumulative probability of disability progression sustained for 24 weeks was 5.0% in the natalizumab group and 38.7% in the comparator group (HR = 0.14; 95% CI: 0.02, 1.26; $P = .080$)

FIGURE 2. Cumulative Probability of Relapse over 2 Years



Effect of Natalizumab on MRI Outcomes

- In Hispanic patients, natalizumab significantly reduced the mean number of Gd+ lesions by 100% at 2 years relative to comparator ($P = .021$, from rank-based analysis of covariance [ANCOVA], adjusted for presence of Gd+ lesions at baseline) (Table 2)
- Natalizumab significantly reduced the mean number of new or enlarging T2 lesions by 95% over 2 years relative to comparator ($P = .013$, from rank-based ANCOVA, adjusted for baseline number of T2 lesions [< 9 vs ≥ 9]) (Table 2)
- During the second year of study, other differences in MRI outcomes emerged between treatment groups. However, the differences over 2 years did not reach statistical significance (Table 2)
  - From year 1 to year 2, the mean number of new T1 lesions was significantly lower in the natalizumab-treated group than in the comparator group (0.36 ± 1.08 vs 2.73 ± 4.96, respectively; $P = .012$)
  - From year 1 to year 2, mean percentage change in brain parenchymal fraction (BPF) was significantly lower in the natalizumab-treated group than in the comparator group (–0.078 ± 0.704 vs –0.668 ± 0.604, respectively; $P = .021$)
- Changes in volume of T1 lesions and T2 lesions over 2 years by treatment group are shown in Figure 3

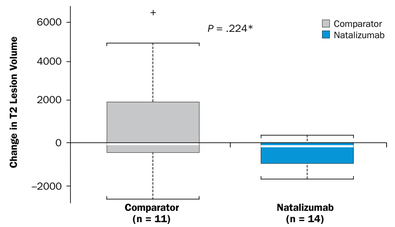
TABLE 2. MRI Outcomes at Year 2

	Comparator (n = 11)	Natalizumab (n = 14)	*P* Value
No. of Gd+ lesions, mean ± SD	1.55 ± 3.62	0.00 ± 0.00	.021[a]
No. of new or enlarged T2 lesions, mean ± SD	11.64 ± 17.53	0.57 ± 1.65	.013[a]
No. of all new T1 lesions, mean ± SD	5.73 ± 9.85	2.00 ± 2.00	.339[b]
Percentage change in BPF from baseline, mean ± SD	–1.16 ± 0.72 (n = 10)	–0.68 ± 0.78 (n = 15)	.072[a]

[a]From rank-based ANCOVA, adjusted for baseline values.
[b]From rank-based ANOVA.

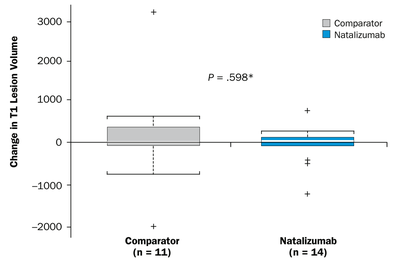
FIGURE 3. Change in Volume of T2 (A) and T1 (B) Lesions over 2 Years

A.



*From rank-based analysis of covariance, adjusted for baseline T2 lesion volume.

B.



*From rank-based analysis of covariance, adjusted for baseline T1 lesion volume.

CONCLUSIONS

- Hispanic patients with relapsing MS treated with natalizumab in AFFIRM and SENTINEL experienced significant reductions in relapses and MRI lesion activity relative to patients who received comparator
- The efficacy of natalizumab on relapses and MRI lesions in Hispanic patients was similar to its efficacy in the overall study populations of AFFIRM and SENTINEL[1,2]
- The finding that natalizumab reduced the proportion of patients experiencing sustained progression of disability over 2 years is consistent with the relapse outcome. Although statistical significance was not reached, patient numbers were small
- These findings, along with those of other subgroup analyses,[3] confirm the efficacy of natalizumab is maintained across ethnic subgroups

References

1. Polman CH, O'Connor PW, Havrdova E, et al. *N Engl J Med.* 2006;354:899–910.
2. Rudick RA, Stuart WH, Calabresi PA, et al. *N Engl J Med.* 2006;354:911–923.
3. Cree B, Stuart W, Tornatore C, et al. Poster presented at: 61st Annual Meeting of AAN; April 25–May 2, 2009; Seattle, WA. P06.143.

Disclosures

Author disclosures

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