ORIGINAL ARTICLE

Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis

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ABSTRACT

BACKGROUND

Interferon beta is used to modify the course of relapsing multiple sclerosis. Despite interferon beta therapy, many patients have relapses. Natalizumab, an α_4 integrin antagonist, appeared to be safe and effective alone and when added to interferon beta-1a in preliminary studies.

METHODS

We randomly assigned 1171 patients who, despite interferon beta-1a therapy, had had at least one relapse during the 12-month period before randomization to receive continued interferon beta-1a in combination with 300 mg of natalizumab (589 patients) or placebo (582 patients) intravenously every 4 weeks for up to 116 weeks. The primary end points were the rate of clinical relapse at 1 year and the cumulative probability of disability progression sustained for 12 weeks, as measured by the Expanded Disability Status Scale, at 2 years.

RESULTS

Combination therapy resulted in a 24 percent reduction in the relative risk of sustained disability progression (hazard ratio, 0.76; 95 percent confidence interval, 0.61 to 0.96; P=0.02). Kaplan–Meier estimates of the cumulative probability of progression at two years were 23 percent with combination therapy and 29 percent with interferon beta-1a alone. Combination therapy was associated with a lower annualized rate of relapse over a two-year period than was interferon beta-1a alone (0.34 vs. 0.75, P<0.001) and with fewer new or enlarging lesions on T_2-weighted magnetic resonance imaging (0.9 vs. 5.4, P<0.001). Adverse events associated with combination therapy were anxiety, pharyngitis, sinus congestion, and peripheral edema. Two cases of progressive multifocal leukoencephalopathy, one of which was fatal, were diagnosed in natalizumab-treated patients.

CONCLUSIONS

Natalizumab added to interferon beta-1a was significantly more effective than interferon beta-1a alone in patients with relapsing multiple sclerosis. Additional research is needed to elucidate the benefits and risks of this combination treatment. (ClinicalTrials.gov number, NCT00030966.)

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*The Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) Investigators are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

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THE ADHESION MOLECULE $\alpha_4\beta_1$ INTEGRIN is a key initiator of the inflammatory cascade involved in the pathogenesis of multiple sclerosis.[1-4] Natalizumab (Tysabri, Biogen Idec and Elan Pharmaceuticals) is the first α_4 integrin antagonist in a new class of selective adhesion-molecule inhibitors for the treatment of multiple sclerosis. Natalizumab binds to α_4 integrin on the surface of leukocytes, inhibiting their migration into the brain and thereby reducing inflammation.

Current disease-modifying therapies for relapsing–remitting multiple sclerosis (interferon beta and glatiramer acetate) are only partially effective,[5-8] and most patients with multiple sclerosis have breakthrough disease activity despite therapy with these agents. Hence, there is a need for additional treatment options in multiple sclerosis. Natalizumab is an attractive therapy to add to current disease-modifying therapies in patients with breakthrough disease because preliminary efficacy[9] and safety[10] data have been favorable and because the mechanism of action of natalizumab may complement those of other disease-modifying therapies.[11-17]

The Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) study was a two-year, phase 3 clinical trial designed to determine whether natalizumab, when added to interferon beta-1a, has efficacy in addition to that associated with interferon beta-1a alone. The trial was also designed to confirm the safety of natalizumab when added to interferon beta-1a.

METHODS

PATIENTS

One hundred twenty-four clinical centers in Europe and the United States enrolled 1196 patients beginning on January 14, 2002. All patients gave written informed consent. The study protocol was developed by the investigator advisory committee and the sponsors and was approved by central and local ethics committees, and the study was overseen by an independent safety-monitoring committee. Data were collected by the investigators and an independent organization (PPD International) and were held and analyzed by Biogen Idec and Elan Pharmaceuticals. During the study, the investigator advisory committee and representatives of Biogen Idec met at least monthly to review and manage the study. The manuscript was written by Drs. Rudick and Panzara, with input from each of the other authors; all the authors vouch for the veracity and completeness of the data and analyses.

Eligible patients were 18 to 55 years of age; had a diagnosis of relapsing–remitting multiple sclerosis,[18] a score on the Expanded Disability Status Scale (EDSS) (possible scores range from 0 to 10, with higher scores indicating more severe disease) between 0 and 5.0,[19] and a magnetic resonance imaging (MRI) scan revealing lesions consistent with a diagnosis of multiple sclerosis; had received treatment with interferon beta-1a for at least 12 months before randomization; and had had at least one relapse during the 12-month period before randomization. Patients were ineligible if they had primary progressive, secondary progressive, or progressive relapsing multiple sclerosis[20]; if they had had a relapse within 50 days before randomization; or if they had been treated with an approved disease-modifying therapy other than interferon beta-1a intramuscularly once weekly within the 12-month period before randomization.

STUDY DESIGN AND RANDOMIZATION

This study was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial. Data from 1171 of the 1196 patients enrolled were analyzed, because a single center with 25 patients was excluded before unblinding owing to irregularities in data. Patients were randomly assigned, in a 1:1 ratio, to receive 300 mg of natalizumab (589 patients) or placebo (582 patients) intravenously every 4 weeks in addition to interferon beta-1a (Avonex, Biogen Idec) at a dose of 30 μg intramuscularly once weekly for up to 116 weeks. Randomization was stratified according to study site in blocks of four (two active and two placebo) with the use of a computer-generated schedule and a multidigit identification number, implemented by way of an interactive voice-response system. All study personnel, patients, sponsor personnel involved in the conduct of the study, and members of the investigator advisory committee were blinded to the treatment assignments throughout the study.

STUDY PROCEDURE AND END POINTS

Each site designated primary and backup examining neurologists and treating neurologists. The

examining neurologists performed the EDSS and neurologic examinations but were otherwise not involved in the patients' medical care. The treating neurologists were responsible for all patient care, including the management of adverse events and relapses of multiple sclerosis.

Clinical visits every 12 weeks included assessment of relapses, EDSS evaluation, blood chemical and hematologic tests, assessment of any adverse events, and immunogenicity studies. Patients were also seen by a treating neurologist during unscheduled visits within 72 hours after the development of new symptoms so that they could be assessed for possible relapses or adverse events. If a relapse was suspected, the patient was evaluated by the examining neurologist. Relapses were defined as the development of new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new, objective neurologic findings. At the discretion of the treating neurologist, relapses were treated with intravenous methylprednisolone at a dose of 1000 mg per day for three or five days. Patients who had disability progression that was sustained for 12 weeks were asked to provide consent to continue study participation and were given the option of adding an available multiple sclerosis treatment as rescue medication, according to protocol, while continuing to receive the study drug. Patients who discontinued the study drug were strongly encouraged to remain in the study for follow-up assessments, and all patients who continued to participate in the study were evaluated (according to the intention-to-treat principle).

Proton-density, T_2-weighted MRI scans and gadolinium-enhanced T_1-weighted MRI scans of the brain were obtained at baseline and at weeks 52 and 104. Forty contiguous, 3-mm-thick axial slices were acquired. MRI analyses were performed centrally at the MS-MRI Evaluation Center (Basel, Switzerland) by blinded raters. The scans were checked for artifacts, compliance with scanning requirements, and repositioning.

The primary efficacy end point was the rate of clinical relapse at one year. Secondary end points at one year were the number of new or enlarging T_2-hyperintense lesions, the number of gadolinium-enhancing lesions, and the proportion of patients free of relapse. The primary efficacy end point at two years was the cumulative probability of sustained disability progression, defined as an increase by at least 1.0 point in the EDSS score from a baseline score of at least 1.0 or an increase by at least 1.5 points in the EDSS score from a baseline score of 0, sustained for 12 weeks; progression could not be confirmed during a relapse. Secondary end points at two years were the rate of clinical relapse, the volume of T_2-hyperintense lesions, the number of new T_1-hypointense lesions, and disability as measured by the Multiple Sclerosis Functional Composite.[21] This report presents data pertaining to primary end points and key secondary efficacy end points, as well as safety data. Results pertaining to additional secondary end points and tertiary end points are not included in this report.

Binding antibodies against natalizumab were assessed with use of an enzyme-linked immunosorbent assay. Positive samples (0.5 μg per milliliter) were further tested in a flow-cytometry assay to determine whether these antibodies interfered with the binding of natalizumab to α_4 integrin.

STATISTICAL ANALYSIS

The sample size was estimated, on the basis of data from previous trials of natalizumab[9] and interferon beta-1a,[6] with the use of two-sided tests with an experiment-wise alpha of 0.05. The annualized rate of relapse among patients receiving combination therapy at one year was predicted to be 0.6, as compared with 0.9 among patients receiving interferon beta-1a alone. For the annualized relapse rate, the likelihood-ratio test was used to determine the sample size with half the patients receiving active drug and half receiving placebo. With an assumed dropout rate of 17 percent, rounding, a type I error rate of 2.5 percent, and a type II error rate of 90 percent, the number of patients needed was estimated to be 1200. To power the study for the two-year end point of disability progression, we assumed a progression rate of 34.9 percent at the end of two years in the group assigned to interferon beta-1a alone and a progression rate of 22.7 percent at the end of two years (a 35 percent improvement) in the combination-therapy group. Simulations of the log-rank test were run with 60 percent of the accrual in the first 24 weeks and the remainder in the next 24 weeks. With an assumed dropout rate of 20 percent, the sample size of 1200 provided at least 92 percent power with a Bonferroni adjustment for multiple end points and with the type I error rate maintained at 5 percent.

The baseline characteristics of the patients were analyzed with the use of a t-test, with the exceptions of sex, race, and diagnosis of multiple sclerosis (based on the McDonald criteria[18]), which were analyzed with the use of a chi-square test. The time to the onset of disability progression sustained for 12 weeks was used to determine the cumulative probability of disability progression estimated by the Kaplan–Meier method. The Cox proportional-hazards model, adjusted for the baseline EDSS score, was used to compare the Kaplan–Meier curves. The annualized relapse rate was calculated by Poisson regression and adjusted for the number of relapses in the year before randomization; data pertaining to relapses that occurred after rescue treatment was initiated (per protocol) were censored. Additional baseline factors were tested for inclusion in each of the models: EDSS score (≤3.5 or >3.5), gadolinium-enhancing lesions (present or absent), the number of T_2-hyperintense lesions (<9 or ≥9), and age (<40 or ≥40 years).[22-24] Each covariate was tested in the model for statistical significance by a backward-selection procedure, and only statistically significant covariates (P≤0.10) were included in the final models. No additional covariates were included in the analysis of disability progression. Three additional covariates (baseline EDSS score, the presence or absence of gadolinium-enhancing lesions at baseline, and age) were included in the analysis of relapse rate.

A sensitivity analysis of disability progression (based on the change in EDSS score) sustained for 24 weeks was also conducted. For the annualized rate of relapse, sensitivity analyses were performed with and without censoring, as well as with and without adjustment for significant covariates. The unadjusted rate of relapse was calculated as the total number of relapses divided by the total number of subject-years of follow-up in each treatment group. The Hochberg procedure[25] for multiple comparisons was used in the analysis of the two primary end points; hence, the significance level was set such that if the higher of the P values for the analyses of these end points was less than or equal to 0.05, then both end points were considered to be statistically significant; otherwise, the lower of the P values was tested at a significance level of 0.025.

Secondary efficacy end points were ranked-ordered, and a closed testing procedure was used such that if statistical significance was not achieved for a given end point, then end points of a lower rank were considered not statistically significant. Secondary efficacy end points were analyzed by logistic regression with a term for treatment group and with their respective baseline values as covariates; missing values were imputed by using the mean in the study population.

Adverse events were analyzed with use of the chi-square test, and serious adverse events were analyzed with use of Fisher's exact test. Poisson regression was used to calculate the difference between the rates of infection in each treatment group.

All analyses followed the intention-to-treat principle. All reported P values are two-tailed. The date on which the database was locked for the two-year analyses was May 31, 2005, and as a result there were 2528 patient-years of observation and 1222 patient-years of exposure to natalizumab.

RESULTS

PATIENTS

SENTINEL was stopped approximately one month early, on February 28, 2005, because of two reports of progressive multifocal leukoencephalopathy (PML). Of the 1171 patients, a total of 1003 (86 percent) completed the 120-week study; 168 patients (14 percent overall; 12 percent of the group assigned to interferon beta-1a plus natalizumab and 16 percent of the group assigned to interferon beta-1a alone) withdrew from the study (Fig. 1). Sixty-four patients discontinued the study drug but completed follow-up (5 percent overall; 5 percent of the combination-therapy group and 6 percent of the group assigned to interferon beta-1a alone). There were no significant differences in demographic or disease-related characteristics at baseline between the two treatment groups, with the exception of the duration of disease (median, seven years in the combination-therapy group and eight years in the group assigned to interferon beta-1a alone; P=0.02) (Table 1).

The SENTINEL data represent 28 percent of the placebo-controlled experience with natalizumab (in terms of patient-years of exposure) in both multiple sclerosis and Crohn's disease and 44 percent of the overall experience in multiple sclerosis.

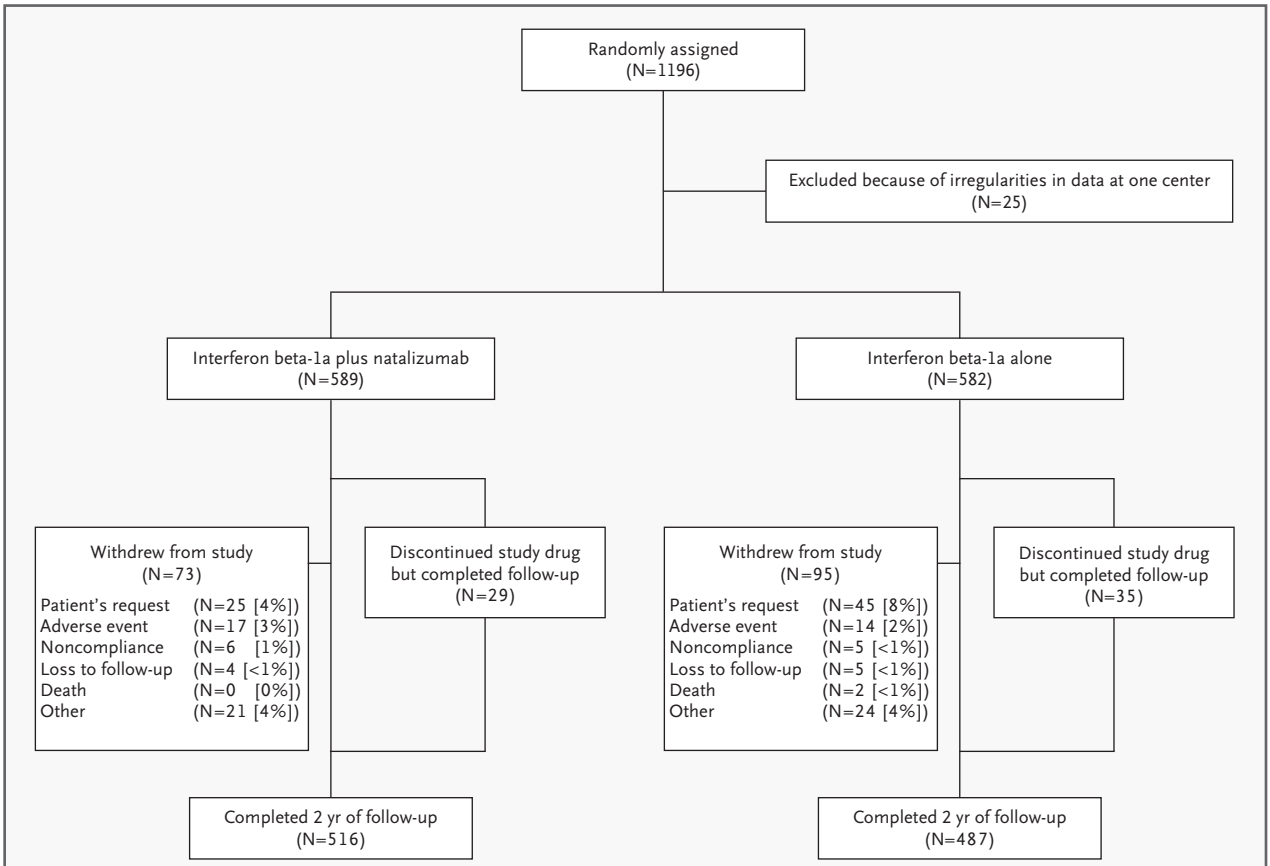

Figure 1. Disposition of Patients during the Two-Year SENTINEL Study.

EFFICACY

Kaplan–Meier estimates of the cumulative probability of sustained disability progression at 2 years were 23 percent with combination therapy and 29 percent with interferon beta-1a alone (Fig. 2 and Table 2). Combination therapy resulted in a 24 percent decrease in the risk of sustained disability progression (hazard ratio, 0.76; 95 percent confidence interval, 0.61 to 0.96; P=0.02). In the sensitivity analysis of the risk of disability progression sustained for 24 weeks, estimates of the cumulative probability of progression by 2 years were 15 percent for combination therapy and 18 percent for interferon beta-1a alone (representing an 18 percent reduction with combination therapy); however, this difference was not statistically significant (P=0.17).

Combination therapy reduced the annualized rate of relapse at one year, which was 0.82 with interferon beta-1a alone, to 0.38 (P<0.001) — a 54 percent reduction (Table 2). This difference was maintained at two years, at which time the rate was 0.75 with interferon beta-1a alone and 0.34 with combination therapy (a 55 percent reduction with combination therapy, P<0.001). Subgroup analyses (according to relapse history, EDSS score, age, sex, the presence or absence of gadolinium-enhancing lesions, and the number of T_2-hyperintense lesions) and a sensitivity analysis of relapse rate showed consistent results. The proportion of patients who were relapse-free at two years was 54 percent in the combination-therapy group, as compared with 32 percent in the group assigned to interferon beta-1a alone (P<0.001). The risk of relapse was 50 percent lower with combination therapy (hazard ratio, 0.50; 95 percent confidence interval, 0.43 to 0.59; P<0.001).

The number of new or enlarging T_2-hyperintense lesions over the two-year period was re-

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