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A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis

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ABSTRACT

BACKGROUND

Oral fingolimod, a sphingosine-1-phosphate–receptor modulator that prevents the egress of lymphocytes from lymph nodes, significantly improved relapse rates and end points measured on magnetic resonance imaging (MRI), as compared with either placebo or intramuscular interferon beta-1a, in phase 2 and 3 studies of multiple sclerosis.

METHODS

In our 24-month, double-blind, randomized study, we enrolled patients who had relapsing–remitting multiple sclerosis, were 18 to 55 years of age, had a score of 0 to 5.5 on the Expanded Disability Status Scale (which ranges from 0 to 10, with higher scores indicating greater disability), and had had one or more relapses in the previous year or two or more in the previous 2 years. Patients received oral fingolimod at a dose of 0.5 mg or 1.25 mg daily or placebo. End points included the annualized relapse rate (the primary end point) and the time to disability progression (a secondary end point).

RESULTS

A total of 1033 of the 1272 patients (81.2%) completed the study. The annualized relapse rate was 0.18 with 0.5 mg of fingolimod, 0.16 with 1.25 mg of fingolimod, and 0.40 with placebo ($P<0.001$ for either dose vs. placebo). Fingolimod at doses of 0.5 mg and 1.25 mg significantly reduced the risk of disability progression over the 24-month period (hazard ratio, 0.70 and 0.68, respectively; $P=0.02$ vs. placebo, for both comparisons). The cumulative probability of disability progression (confirmed after 3 months) was 17.7% with 0.5 mg of fingolimod, 16.6% with 1.25 mg of fingolimod, and 24.1% with placebo. Both fingolimod doses were superior to placebo with regard to MRI-related measures (number of new or enlarged lesions on T_2-weighted images, gadolinium-enhancing lesions, and brain-volume loss; $P<0.001$ for all comparisons at 24 months). Causes of study discontinuation and adverse events related to fingolimod included bradycardia and atrioventricular conduction block at the time of fingolimod initiation, macular edema, elevated liver-enzyme levels, and mild hypertension.

CONCLUSIONS

As compared with placebo, both doses of oral fingolimod improved the relapse rate, the risk of disability progression, and end points on MRI. These benefits will need to be weighed against possible long-term risks. (ClinicalTrials.gov number, NCT00289978.)

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Fingolimod (FTY720) is an oral sphingosine-1-phosphate–receptor modulator[1] that is currently being evaluated for the treatment of multiple sclerosis. There is evidence that fingolimod acts by preventing lymphocyte egress from lymph nodes.[2,3] This leads to a reduced infiltration of potentially autoaggressive lymphocytes into the central nervous system.[4,5] Preclinical findings also suggest that fingolimod may promote neuroprotective and reparative processes within the central nervous system through modulation of sphingosine-1-phosphate receptors expressed on neural cells.[6-12]

A 6-month, phase 2, placebo-controlled study[13] and its open-label extension study[14] showed sustained suppression, for up to 5 years, of both relapse and inflammatory activity in patients receiving fingolimod. Furthermore, in a recently completed, 12-month, phase 3 study involving patients with relapsing–remitting multiple sclerosis (TRANSFORMS [Trial Assessing Injectable Interferon vs. FTY720 Oral in RRMS]; ClinicalTrials.gov number, NCT00340834), reported elsewhere in this issue of the *Journal*, fingolimod reduced the relapse rate and disease activity as measured with the use of magnetic resonance imaging (MRI), as compared with a once-weekly, intramuscular injection of interferon beta-1a at a dose of 30 μg.[15]

In our phase 3, double-blind, placebo-controlled study, called FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis), we investigated the effects of daily fingolimod treatment for 24 months on the relapse rate, disability progression, and MRI measures of inflammation, burden of disease, and tissue destruction in patients with relapsing–remitting multiple sclerosis.

Methods

Study Oversight

Steering-committee members (listed in the Supplementary Appendix, available with the full text of this article at NEJM.org) collaborated with the sponsor, Novartis Pharma, to develop the protocol and monitor the ongoing study. Data were collected by the investigators and analyzed by the sponsor. All the authors had access to the data, participated in the data analysis and interpretation, and wrote the manuscript. All authors vouch for the accuracy and completeness of the data and the statistical analysis. All authors participated in the writing of the manuscript and approved the final manuscript before submitting it for publication.

Patients

Key eligibility criteria were an age of 18 to 55 years; a diagnosis of multiple sclerosis, according to the revised McDonald criteria[16]; a relapsing–remitting course[17]; one or more documented relapses in the previous year or two or more in the previous 2 years; and a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS; which ranges from 0 to 10, with higher scores indicating greater disability).[18] Key exclusion criteria were relapse or corticosteroid treatment within 30 days before randomization, active infection, macular edema, diabetes mellitus, immune suppression (drug- or disease-induced), or clinically significant systemic disease. Interferon-beta or glatiramer acetate therapy had to have been stopped 3 or more months before randomization.

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice[19] and the Declaration of Helsinki.[20] The protocol was approved by each site's institutional review board; patients gave written informed consent before any study-related procedures were performed.

Study Design and Randomization

Patients were randomly assigned, in a 1:1:1 ratio, to receive oral fingolimod capsules in a dose of 0.5 mg or 1.25 mg or matching placebo, once daily for 24 months. Randomization was performed centrally, with the use of a validated system and stratification according to site, with a block size of six within each site.

To ensure that all assessments remained unbiased regarding the study-group assignments (i.e., unaffected by awareness of them), an independent, specially trained and certified[21] examining neurologist determined all the EDSS scores; this examining neurologist or a trained technician administered the Multiple Sclerosis Functional Composite (MSFC; comprising the average of the scores on the timed 25-foot walk, the 9-hole peg test, and the paced auditory serial-addition test with a 3-second interstimulus interval, with each converted to a z score [with the combined study population at baseline as the reference population], with higher scores representing improve-

ment).[22] Another independent physician monitored patients for 6 or more hours after administration of the first dose of the study drug. MRI scans were analyzed at a central MRI evaluation center by radiologists who were unaware of the study-group assignments, and an independent data and safety monitoring board evaluated the safety and overall benefit–risk profiles.

STUDY PROCEDURES AND END POINTS

Clinical assessments were performed at screening and at randomization (baseline), and study visits, including safety assessments, were scheduled at 2 weeks and 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 months after randomization. The EDSS score was determined every 3 months, and the MSFC z score every 6 months. Standardized MRI scans were obtained at the screening visit and at 6, 12, and 24 months and were analyzed centrally at the Multiple Sclerosis–MRI Evaluation Center at the University Hospital in Basel, Switzerland.

The primary end point was the annualized relapse rate, defined as the number of confirmed relapses per year. Relapses were verified by the examining neurologist within 7 days after the onset of symptoms. To constitute a confirmed relapse, the symptoms must have been accompanied by an increase of at least half a point in the EDSS score, of one point in each of two EDSS functional-system scores, or of two points in one EDSS functional-system score (excluding scores for the bowel–bladder or cerebral functional systems).

The key secondary end point was the time to confirmed disability progression, defined as an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.

Other secondary end points included the time to a first relapse, time to disability progression (confirmed after 6 months), changes in the EDSS score and MSFC z score[23] between baseline and 24 months, number of gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing lesions, number of new or enlarged lesions on T_2-weighted MRI scans, proportion of patients free from new or enlarged lesions on T_2-weighted scans, volumes of hyperintense lesions on T_2-weighted scans and hypointense lesions on T_1-weighted scans, change in brain volume between baseline and 24 months, and safety and tolerability measures. Specifications of the adverse-event monitoring procedure, as defined in the study protocol, were the same as those in TRANSFORMS and are detailed in the Supplementary Appendix, which also provides other methodologic details.

STATISTICAL ANALYSIS

For the primary end point, on the basis of data from a phase 2 study of fingolimod,[13,24] the expected annualized relapse rate was 0.7 for the group receiving placebo and 0.42 for the group receiving 1.25 mg of fingolimod, with a common standard deviation of 1.06. We calculated that a sample of 1250 patients would provide 95% statistical power to detect a relative reduction of 40% or more in the annualized relapse rate with fingolimod as compared with placebo, after 24 months. With this sample size, using a log-rank test and a two-sided α level of 0.05 (assuming a study-discontinuation rate of 25%[13]), we calculated that the study would have a statistical power of more than 90% to detect an absolute difference between the two groups of 12% in the proportion of patients with disability progression (confirmed after 3 months) at month 24, which was expected to be approximately 30% in the placebo group.

Both the intention-to-treat population and the safety population included all patients who had undergone randomization. The study tested two null hypotheses: that there were no differences in the annualized relapse rate between the group receiving fingolimod at a dose of 1.25 mg and the group receiving placebo or between the group receiving fingolimod at a dose of 0.5 mg and the group receiving placebo. The aggregate annualized relapse rate was estimated by means of a negative binomial regression model with adjustment for study group, country, number of relapses within 2 years before baseline, and EDSS score at baseline. The time to relapse or progression was estimated with the use of the Kaplan–Meier method.[25] The times to disability progression (confirmed after 3 or 6 months) were compared in the main analysis by means of the log-rank test and in the supportive analysis by means of a Cox proportional-hazards model with adjustment for study group, country, baseline EDSS score, and age. To control for a type I statistical error, a prospectively planned, hierarchical testing procedure was used to compare fingolimod with placebo re-

garding the primary and key secondary end points, in the following order: the annualized relapse rate, first in association with 1.25 mg of fingolimod and next in association with 0.5 mg of fingolimod, and then the time to disability progression (confirmed after 3 months), first with 1.25 mg of fingolimod and next with 0.5 mg of fingolimod. Each test was performed with a significance level of 0.05. However, the next test was performed only when the preceding test was statistically significant. Missing data were not imputed.

Safety analyses were summarized by means of descriptive statistics; inferential significance testing was not performed. Statistical details for other end points are provided in the Supplementary Appendix.

RESULTS

STUDY POPULATION

From January 2006 through August 2007, a total of 1272 patients were randomly assigned to a study group (Fig. 1) at 138 centers in 22 countries (see the Supplementary Appendix for a list of the centers and principal investigators). Baseline characteristics were similar across the three study groups (Table 1). In total, 1033 patients (81.2%) completed the 24-month study, with 945 (74.3%) still receiving the assigned study drug. The study drug was discontinued in proportionately fewer patients in the group receiving 0.5 mg of fingolimod (18.8%) than in the group receiving 1.25 mg of fingolimod (30.5%) or in the placebo group (27.5%). Reasons for study-drug discontinuation are listed in Figure 1.

EFFICACY

All clinical and MRI-related efficacy end points significantly favored both doses of fingolimod over placebo, and there were no significant differences in efficacy between the two fingolimod doses (Table 2).

Relapse

The aggregate annualized relapse rate (the primary end point) was lower with fingolimod at a dose of 0.5 mg (0.18) and fingolimod at a dose of 1.25 mg (0.16) than with placebo (0.40), representing relative reductions of 54% and 60%, respectively, in the annualized relapse rate (Table 2). As compared with placebo, both doses of fingolimod reduced the annualized relapse rate among patients who had not previously received disease-modifying treatment as well as among those who had been treated previously ($P<0.01$ for all comparisons). In the fingolimod groups as compared with the placebo group, the time to a first relapse was longer (Fig. 2A), the risk of relapse was reduced, and proportionately more patients remained free of relapse during the 24-month period (Table 2).

Disability

The time to disability progression, with confirmation either after 3 months (the key secondary end point) or after 6 months, was longer with both fingolimod doses than with placebo (Fig. 2B and Table 2). Fingolimod reduced the risk of disability progression, confirmed after 3 months, over the 24-month study period (hazard ratios, 0.68 for the 1.25-mg dose and 0.70 for the 0.5-mg dose). The cumulative probability of disability progression (confirmed after 3 months) was 17.7% for 0.5 mg of fingolimod, 16.6% for 1.25 mg of fingolimod, and 24.1% for placebo. Regarding disability progression that was confirmed after 6 months, the risk was also reduced with fingolimod over the 24-month study period (hazard ratio, 0.60 with the 1.25-mg dose and 0.63 for the 0.5-mg dose), and the cumulative probability of progression was 12.5% for 0.5 mg of fingolimod, 11.5% for 1.25 mg of fingolimod, and 19.0% for placebo. During the study period, the EDSS scores and MSFC z scores remained stable or improved slightly in the fingolimod groups and worsened in the placebo group (Table 2).

MRI-Related End Points

Patients in either fingolimod group had significantly fewer gadolinium-enhancing lesions than those in the placebo group at 6, 12, and 24 months, as well as fewer new or enlarged lesions on T_2-weighted MRI scans at 24 months (Table 2). Proportionately more patients in the fingolimod groups than in the placebo group were also free from gadolinium-enhancing or new or enlarging lesions at these time points (Table 2 and Fig. 2C). The median volume of lesions on T_2-weighted scans decreased between baseline and month 24 with fingolimod but increased with placebo.

During the 24-month study period, changes in the volume of hypointense lesions on T_1-weight-

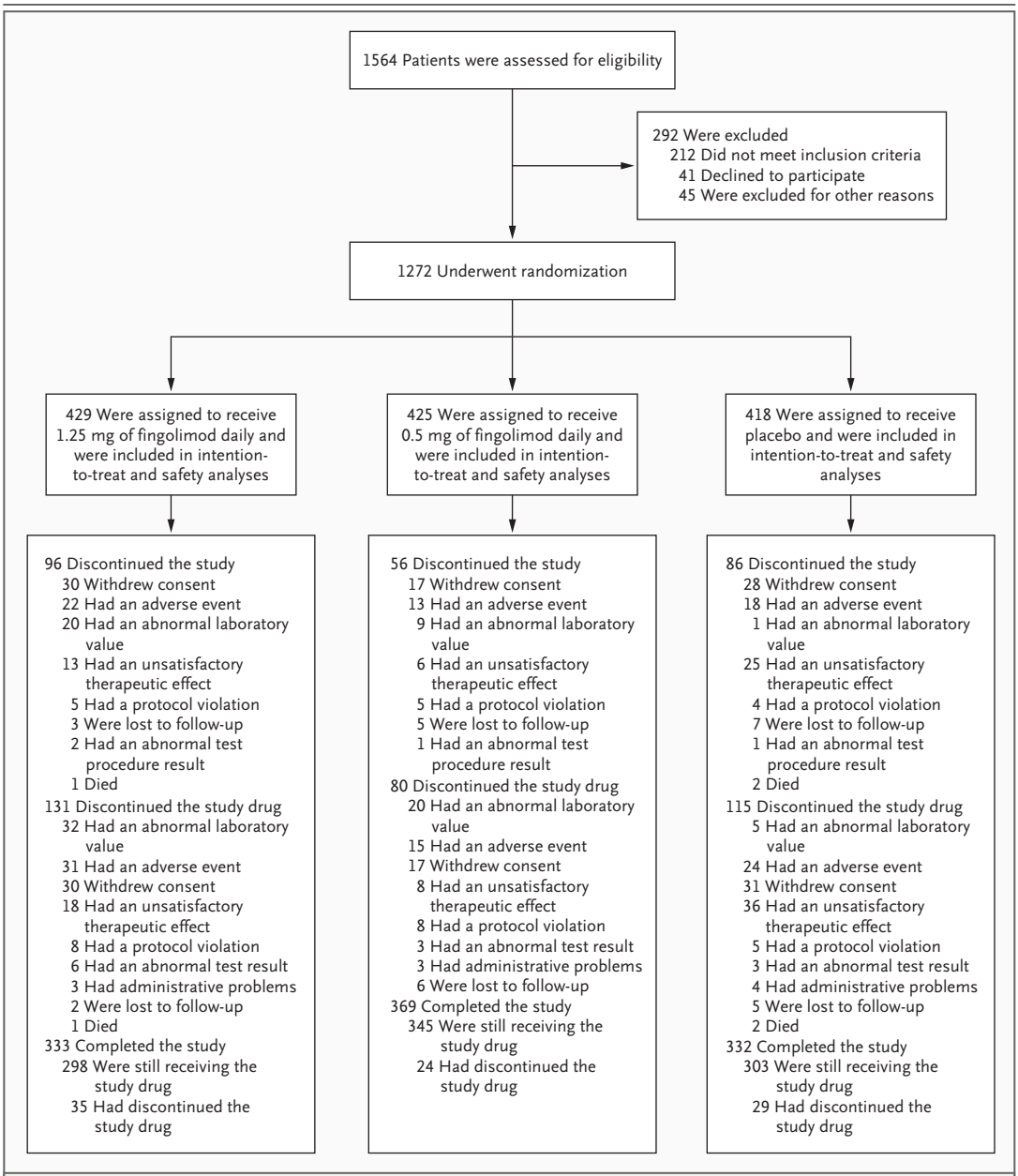

Figure 1. Enrollment, Randomization, and Follow-up of Study Patients.

Among the 292 patients who were assessed for eligibility but were not enrolled, some were excluded for more than one reason. For one patient receiving 1.25 mg of fingolimod daily who completed the study while receiving the study drug, the status was incorrectly recorded by the investigator as having discontinued the study while still receiving the study drug. Patients who discontinued the study drug include those who discontinued the study; the correct status is shown here.

ed scans favored both doses of fingolimod over placebo (Table 2). In addition, reductions in brain volume were smaller with fingolimod.

ADVERSE EVENTS

Similar proportions of patients (93 to 94%) in the three study groups were reported to have adverse events (Table 3); the events were mild to moderate in severity in 82% of patients receiving 0.5 mg of fingolimod, 77% of those receiving 1.25 mg of fingolimod, and 77% of those receiving placebo. Adverse events that led to discontinuation of the study medication (including abnormal laboratory-test results) were more common with fingolimod

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