ORIGINAL ARTICLE

Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis

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ABSTRACT

BACKGROUND

Teriflunomide is a new oral disease-modifying therapy for relapsing forms of multiple sclerosis.

METHODS

We concluded a randomized trial involving 1088 patients with multiple sclerosis, 18 to 55 years of age, with a score of 0 to 5.5 on the Expanded Disability Status Scale and at least one relapse in the previous year or at least two relapses in the previous 2 years. Patients were randomly assigned (in a 1:1:1 ratio) to placebo, 7 mg of teriflunomide, or 14 mg of teriflunomide once daily for 108 weeks. The primary end point was the annualized relapse rate, and the key secondary end point was confirmed progression of disability for at least 12 weeks.

RESULTS

Teriflunomide reduced the annualized relapse rate (0.54 for placebo vs. 0.37 for teriflunomide at either 7 or 14 mg), with relative risk reductions of 31.2% and 31.5%, respectively ($P<0.001$ for both comparisons with placebo). The proportion of patients with confirmed disability progression was 27.3% with placebo, 21.7% with teriflunomide at 7 mg ($P=0.08$), and 20.2% with teriflunomide at 14 mg ($P=0.03$). Both teriflunomide doses were superior to placebo on a range of end points measured by magnetic resonance imaging (MRI). Diarrhea, nausea, and hair thinning were more common with teriflunomide than with placebo. The incidence of elevated alanine aminotransferase levels (≥1 times the upper limit of the normal range) was higher with teriflunomide at 7 mg and 14 mg (54.0% and 57.3%, respectively) than with placebo (35.9%); the incidence of levels that were at least 3 times the upper limit of the normal range was similar in the lower- and higher-dose teriflunomide groups and the placebo group (6.3%, 6.7%, and 6.7%, respectively). Serious infections were reported in 1.6%, 2.5%, and 2.2% of patients in the three groups, respectively. No deaths occurred.

CONCLUSIONS

Teriflunomide significantly reduced relapse rates, disability progression (at the higher dose), and MRI evidence of disease activity, as compared with placebo. (Funded by Sanofi-Aventis; TEMSO ClinicalTrials.gov number, NCT00134563.)

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Teriflunomide, the active metabolite of leflunomide, is being investigated as a new oral disease-modifying therapy for relapsing forms of multiple sclerosis.[1] Although the two drugs are related in structure, teriflunomide has a distinct profile.[2] It reversibly inhibits dihydroorotate dehydrogenase, a key mitochondrial enzyme involved in new pyrimidine synthesis for DNA replication. Consequently, the drug reduces T- and B-cell activation, proliferation, and function in response to autoantigens. However, teriflunomide preserves the replication and function of slowly dividing cells that use exogenous supplies of pyrimidine nucleotides through the so-called salvage pathway.[3-5]

Teriflunomide has been shown to delay the onset of disease, reduce relapses, and improve neurologic findings in studies of experimental autoimmune encephalomyelitis.[6] In a phase 2 study involving patients with relapsing multiple sclerosis, once-daily oral treatment with teriflunomide, at a dose of 7 mg or 14 mg, significantly reduced disease activity as measured by magnetic resonance imaging (MRI) and improved clinical outcomes.[7,8] The Teriflunomide Multiple Sclerosis Oral (TEMSO) trial, a phase 3, randomized, double-blind, placebo-controlled, parallel-group study, was designed to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients who had relapsing multiple sclerosis.

Methods

Patients

Patients eligible for enrollment were 18 to 55 years of age, met the McDonald criteria for a diagnosis of multiple sclerosis,[9] and had a relapsing clinical course, with or without progression. They were required to have a score of 5.5 or lower on the Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating greater disability) and at least two clinical relapses in the previous 2 years or one relapse during the preceding year, but no relapses in the 60 days before randomization. Patients were excluded if they had other systemic diseases, were pregnant, or planned to conceive during the trial period.

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by central and local ethics committees and each site's institutional review board; patients gave written informed consent before entering the study. The study protocol and statistical analysis plan are available with the full text of this article at NEJM.org.

Study Oversight

The study protocol was developed by the sponsor (Sanofi-Aventis), with guidance from a steering committee of international experts on multiple sclerosis. The study was overseen by an independent data-monitoring committee. Data were collected by the investigators and analyzed by the sponsor. The authors were assisted by an independent medical-writing-services agency paid by the sponsor. The first draft of the manuscript was developed by the two lead academic authors, with input from the sponsor. The two lead academic authors made the decision to submit the manuscript for publication, in concert with the other authors. All authors vouch for the accuracy and completeness of the data, the statistical analysis, and the fidelity of the study to the trial protocol. During the study, the investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data.

Study Design and Randomization

After a screening phase of up to 4 weeks, eligible patients were randomly assigned (in a 1:1:1 ratio) to receive a once-daily oral dose of placebo, 7 mg of teriflunomide, or 14 mg of teriflunomide for 108 weeks. Randomization was stratified according to the baseline EDSS score (≤3.5 or >3.5) and according to trial site, with a block size of 6. Participants who completed the study could enter an ongoing, long-term, blinded extension study, in which those who had received placebo were randomly assigned to either dose of teriflunomide; an interim analysis showed continuing safety and efficacy in patients treated with teriflunomide (for details, see the Supplementary Appendix, available at NEJM.org).

Study Procedures

A treating neurologist at each site was responsible for evaluating patient eligibility, supervising the administration of study medication, recording and managing adverse events, assessing relapses, and monitoring safety assessments. An independent, specially trained and certified examining neurolo-

gist determined all the EDSS scores and performed all assessments of functional systems. Both treating and examining neurologists were unaware of treatment assignments; only the treating neurologist was aware of any side effects that could potentially be related to active therapy. EDSS scores were determined at the time of screening, at the baseline visit, every 12 weeks after the baseline visit, and at unscheduled visits when patients returned to the clinic for assessment of potential relapse. MRI scans were obtained according to the study protocol at baseline and weeks 24, 48, 72, and 108; imaging data were collected at the MRI facilities of the participating clinical sites and sent to the central MRI Analysis Center in Houston for processing and data extraction.[10-12]

Patients were required to visit the study site within 7 days after the onset of a suspected relapse, for assessment by the examining neurologist. Suspected and confirmed relapses could be treated with intravenous glucocorticoids at the treating neurologist's discretion.

Safety was evaluated on the basis of adverse events reported by study participants or investigators. Laboratory tests were performed at the time of screening, at baseline, every 2 weeks for the first 24 weeks, and then every 6 weeks until study completion. Physical and neurologic examinations were performed at week 12 and then every 24 weeks. An abdominal ultrasonographic examination to assess for pancreatic abnormalities was performed before the study and then every 24 weeks, because of previous infrequent reports of pancreatitis associated with leflunomide use.[13] Patients who withdrew from the study or did not participate in the extension study underwent an 11-day elimination period, during which they received cholestyramine or activated charcoal.[14]

STUDY END POINTS

The primary objective of the study was to determine the efficacy of teriflunomide in reducing the annualized relapse rate (defined as the number of confirmed relapses per patient-year). A relapse was defined as the appearance of a new clinical sign or symptom, or clinical worsening of a previous sign or symptom that had been stable for at least 30 days and that persisted for a minimum of 24 hours in the absence of fever. Confirmed relapses required an increase of 1 point in each of two EDSS functional-system scores or of 2 points in one EDSS functional-system score (excluding bowel and bladder function and cerebral function) or an increase of 0.5 points in the EDSS score from the previous clinically stable assessment.

The key secondary objective was to determine the efficacy of teriflunomide in delaying the progression of disability over the study period, as assessed on the basis of changes in the EDSS score. Sustained disability progression was defined as an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks. The key prespecified MRI end point was total lesion volume.[10] Other MRI end points included the number of gadolinium-enhancing lesions on T_1-weighted images, the volume of hypointense lesion components on T_1-weighted images, the number of unique active lesions (defined as the number of gadolinium-enhancing lesions on T_1-weighted images or new or enlarged lesions on T_2-weighted images, without double counting), and brain atrophy. Patient-reported fatigue, assessed with the use of the Fatigue Impact Scale (FIS, which ranges from 0 to 160, with higher scores indicating greater fatigue), was an additional secondary end point.

STATISTICAL ANALYSIS

A sample of 360 randomly assigned patients per group was required to provide 95% statistical power to detect relative risk reductions of 25% in the annualized relapse rate after 2 years, assuming an annualized relapse rate of 0.74 for the group receiving placebo and a standard deviation of 0.626.[15] All analyses were performed according to a modified intention-to-treat principle. The modified intention-to-treat population comprised patients who underwent randomization and were exposed to study medication for at least 1 day. All inferential analyses were performed at the two-sided 5% level of significance.

RESULTS

STUDY POPULATION

From September 24, 2004, through March 13, 2008, patients were recruited from 127 clinical centers in 21 countries. Of 1088 patients who underwent randomization, 1086 (99.8%) were exposed to study medication (modified intention-to-

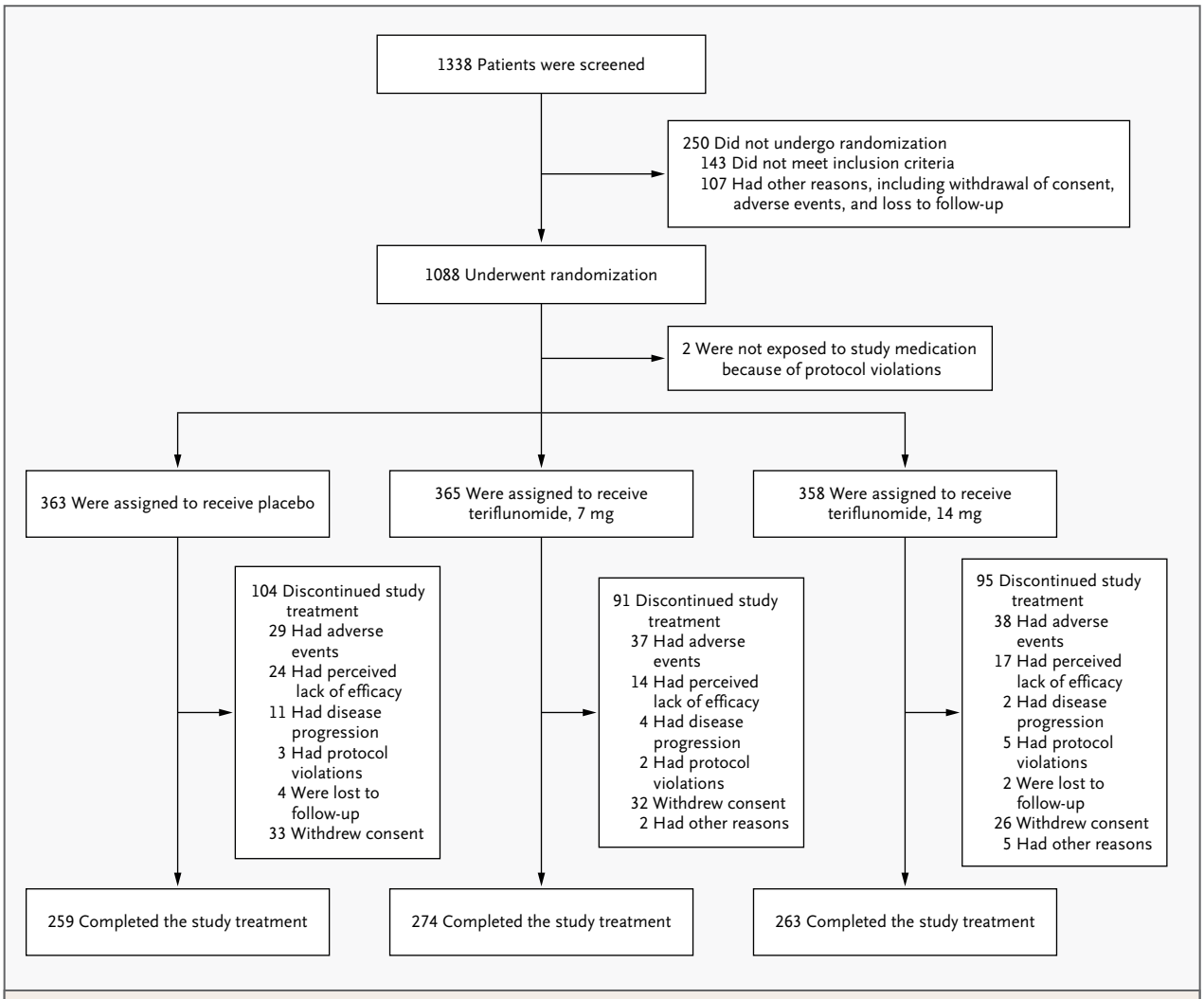

Figure 1. Numbers of Patients Who Were Screened, Underwent Randomization, and Completed the Study Treatment.

treat population). A total of 796 patients (73.2%) completed the study, including the use of study medication, with similar proportions of patients in the three study groups (71.3%, 74.9%, and 73.3% in the placebo, lower-dose teriflunomide, and higher-dose teriflunomide groups, respectively) (Fig. 1). Of the patients who discontinued the study medication prematurely, 31, 22, and 20 patients in the placebo, lower-dose teriflunomide, and higher-dose teriflunomide groups, respectively, completed the planned follow-up. The proportion of patients who discontinued the study medication because of disease progression was significantly smaller in the group receiving the 14-mg dose of teriflunomide than in the placebo group ($P=0.02$) (Fig. 1).

No significant differences were observed in baseline demographic and disease characteristics across the three groups (Table 1). Although the majority of patients had relapsing–remitting multiple sclerosis, a subgroup of patients had secondary progressive or progressive relapsing multiple sclerosis. The mean total lesion volume on MRI was approximately 19 ml, with 36.2% of patients having gadolinium-enhancing lesions at baseline. Seventy-three percent of patients had not received disease-modifying therapy during the 2 years before study entry. Very few MRI scans (<2%) were excluded from analysis, and no unbalanced pattern in the number of scans excluded was observed across the study groups (see the Supplementary Appendix).

Table 1. Baseline Demographic and Clinical Characteristics and MRI Assessments.*

Variable	Placebo (N=363)	Teriflunomide, 7 mg (N=366)	Teriflunomide, 14 mg (N=359)
Demographic characteristics			
Age — yr	38.4±9.0	37.4±9.0	37.8±8.2
Female sex — no. (%)	275 (75.8)	255 (69.7)	255 (71.0)
White race — no. (%)†	356 (98.3)	355 (97.3)	347 (96.9)
Region — no. (%)			
Western Europe	167 (46.0)	167 (45.6)	170 (47.4)
Eastern Europe	114 (31.4)	116 (31.7)	108 (30.1)
Americas	82 (22.6)	83 (22.7)	81 (22.6)
Clinical characteristics			
Time from first symptom of MS — yr	8.6±7.1	8.8±6.8	8.7±6.7
Relapses — no.			
In previous year	1.4±0.7	1.4±0.7	1.3±0.7
In previous 2 years	2.2±1.0	2.3±1.2	2.2±1.0
MS subtype — no. (%)			
Relapsing–remitting	329 (90.6)	333 (91.0)	333 (92.8)
Secondary progressive	22 (6.1)	17 (4.6)	12 (3.3)
Progressive relapsing	12 (3.3)	16 (4.4)	14 (3.9)
Use of disease-modifying therapy in previous 2 years — no. (%)	90 (24.8)	102 (27.9)	102 (28.4)
Interferon beta-1a	58 (16.0)	74 (20.2)	62 (17.3)
Interferon beta-1b	18 (5.0)	22 (6.0)	27 (7.5)
Glatiramer acetate	36 (9.9)	23 (6.3)	43 (12.0)
EDSS score‡	2.68±1.34	2.68±1.34	2.67±1.24
FIS score§	53.2±37.9	50.4±35.6	50.3±35.9
MRI assessments			
Total lesion volume — ml	19.34±18.94	20.37±20.59	18.08±17.49
Gadolinium-enhancing lesions¶			
No. of patients (%)	137 (38.2)	127 (35.3)	125 (35.2)
No. of lesions on T_1-weighted images	1.66±3.55	1.50±3.96	1.81±5.17
Volume of hypointense lesions on T_1-weighted images — ml	3.26±3.64	3.35±3.96	2.91±3.25
Brain parenchymal fraction‖	0.76±0.02	0.76±0.02	0.76±0.02

* Data are presented for the randomized population. Plus–minus values are means ±SD. All baseline characteristics were well matched among the three groups (P>0.05). MS denotes multiple sclerosis.
† Data on race were missing for one person in each study group. Race was self-reported.
‡ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating greater disability.
§ Scores on the Fatigue Impact Scale (FIS) range from 0 to 160, with higher scores indicating greater fatigue.
¶ Data on gadolinium-enhancing lesions were missing for four patients in the placebo group, six patients in the lower-dose teriflunomide group, and four patients in the higher-dose teriflunomide group.
‖ The brain parenchymal fraction was calculated as the inverse of the normalized cerebrospinal fluid volume segmented as described previously.[10]

EFFICACY

Relapses

Teriflunomide significantly reduced the annualized relapse rate (0.54 for placebo, vs. 0.37 for teriflunomide at either 7 or 14 mg; P<0.001 for both comparisons with placebo) (Table 2 and Fig. 2). In both teriflunomide groups, the time to a first relapse was longer, and more patients remained

Table 2. Clinical and MRI Results.*

Variable	Placebo (N=363)	Teriflunomide, 7 mg (N=365)	Teriflunomide, 14 mg (N=358)	P Value	
				Teriflunomide, 7 mg, vs. Placebo	Teriflunomide, 14 mg, vs. Placebo
Clinical outcomes					
Relapse rate					
Adjusted annualized rate (95% CI)†	0.54 (0.47–0.62)	0.37 (0.32–0.43)	0.37 (0.31–0.44)	<0.001	<0.001
Relative reduction vs. placebo — %		31.2	31.5		
Absence of relapse during 108 wk‡					
Percentage of patients (95% CI)	45.6 (40.2–51.0)	53.7 (48.3–59.1)	56.5 (51.0–62.0)	0.01	0.003
Hazard ratio vs. placebo (95% CI)§		0.76 (0.61–0.94)	0.72 (0.58–0.90)		
No. of relapses — no. of patients (%)					
0	179 (49.3)	211 (57.8)	217 (60.6)		
1	97 (26.7)	92 (25.2)	86 (24.0)		
2	48 (13.2)	49 (13.4)	33 (9.2)		
3	22 (6.1)	10 (2.7)	16 (4.5)		
≥4	17 (4.7)	3 (0.8)	6 (1.7)		
Sustained disability progression (≥12 wk)					
Percentage of patients (95% CI)‡	27.3 (22.3–32.3)	21.7 (17.1–26.3)	20.2 (15.6–24.7)	0.08	0.03
Hazard ratio vs. placebo (95% CI)§		0.76 (0.56–1.05)	0.70 (0.51–0.97)		
Hazard ratio reduction vs. placebo — %		23.7	29.8		
Change in FIS score from baseline¶‖	4.3±1.7	2.3±1.6	3.8±1.7	0.39	0.83
MRI outcomes					
Total lesion volume					
Change from baseline — ml	2.21±7.00	1.31±6.80	0.72±7.59	0.03	<0.001
Relative reduction vs. placebo — %**		39.4	67.4		

Volume of hypointense lesions on T_1-weighted images					
Change from baseline — ml	0.53±1.06	0.50±1.15	0.33±1.01	0.19	0.02
Relative reduction vs. placebo — %**		16.7	31.3		
Volume of hyperintense lesion components on T_2-weighted images††					
Change from baseline — ml	1.67±6.47	0.81±6.18	0.39±6.90	0.04	<0.001
Relative reduction vs. placebo — %**		44.0	76.7		
Gadolinium-enhancing lesions per T_1-weighted scan¶					
Estimated no. (95% CI)	1.33 (1.06–1.67)	0.57 (0.43–0.75)	0.26 (0.17–0.41)	<0.001	<0.001
Relative risk (95% CI)		0.43 (0.31–0.59)	0.20 (0.12–0.32)		
Absence of gadolinium-enhancing lesions on T_1-weighted images — no. of patients (%)‡‡	135 (39.0)	180 (51.4)	218 (64.1)	<0.001	<0.001
Unique active lesions per scan¶					
Estimated no. (95% CI)	2.46 (2.10–2.89)	1.29 (1.07–1.54)	0.75 (0.58–0.99)	<0.001	<0.001
Relative risk (95% CI)		0.52 (0.42–0.65)	0.31 (0.23–0.41)		
Brain parenchymal fraction§§					
Change from baseline‖	–0.004±0.001	–0.003±0.001	–0.003±0.001	0.19	0.35
Difference vs. placebo‖		0.001±0.001	0.001±0.001		
Relative reduction vs. placebo — %		25.0	25.0		

* Data are presented for the modified intention-to-treat population. The relative reductions versus placebo were calculated according to numbers before rounding. Plus–minus values are means ±SD, unless otherwise indicated. CI denotes confidence interval, and FIS Fatigue Impact Scale.

† The rate was derived from an analysis of the number of relapses with the use of a Poisson regression model adjusted for treatment and score on the Expanded Disability Status Scale (EDSS) at baseline and for geographic region, with the log of time during treatment serving as an offset variable.

‡ Values were derived from Kaplan–Meier estimates.

§ The hazard ratios and 95% CIs were calculated with the use of a Cox proportional-hazards model adjusted for treatment and EDSS score at baseline and for region. P values were calculated with the use of a log-rank test adjusted for treatment and EDSS score at baseline and for geographic region.

¶ Values were calculated with the use of a Poisson regression model adjusted for treatment, EDSS score, and number of lesions at baseline and for geographic region, with the log of the number of MRI scans serving as an offset variable.

‖ Plus–minus values are least-square means ±SE.

** Data are based on a mixed-effects model and repeated-measures analysis, with the use of a cube-root transformation of volume data.

†† This measure is the portion of the total lesion volume that appears hyperintense on T_2-weighted images (dual echo spin density and fluid-attenuation inversion recovery images) but does not appear hypointense on T_1-weighted images obtained after the administration of gadolinium.

‡‡ Data were missing for 17 patients in the placebo group, 15 patients in the lower-dose teriflunomide group, and 18 patients in the higher-dose teriflunomide group.

§§ Brain parenchymal fraction was calculated as the inverse of the normalized cerebrospinal fluid volume segmented as described previously[10] and assessed with the use of a mixed-effects model with repeated-measures analysis.

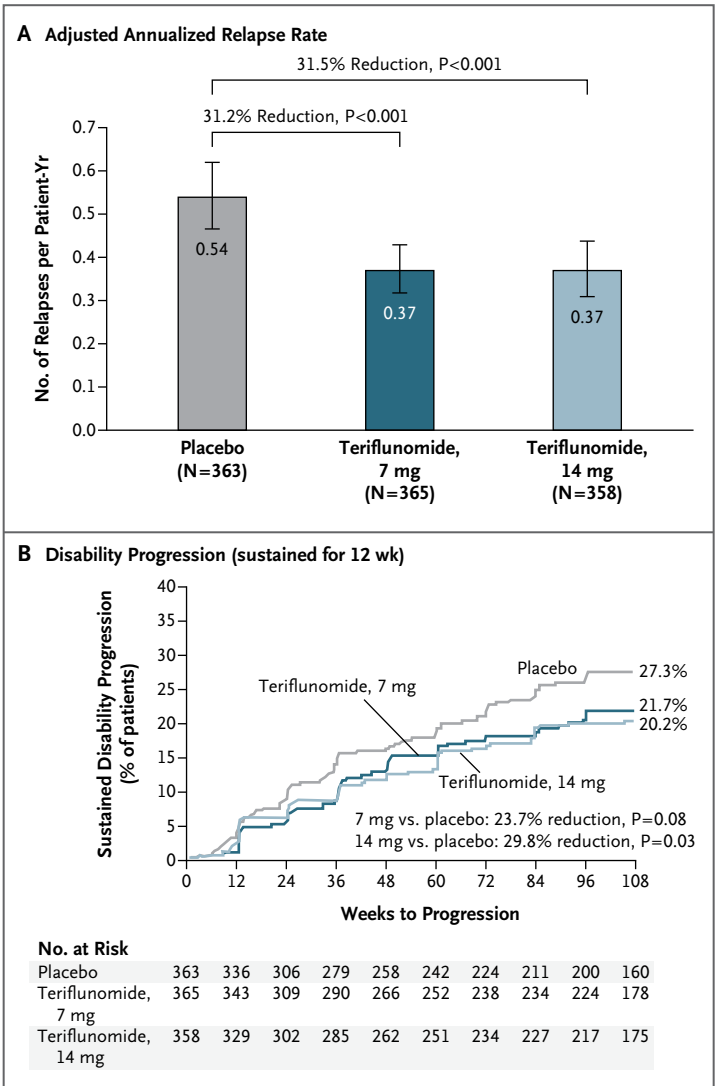

Figure 2. Annualized Relapse Rate and Sustained Disability Progression.
The adjusted annualized relapse rate (Panel A) was derived from an analysis of the number of relapses with the use of a Poisson regression model adjusted for treatment and score on the Expanded Disability Status Scale at baseline and geographic region, with the log of time during treatment serving as an offset variable. The relative reductions versus placebo were calculated according to numbers before rounding. I bars represent 95% confidence intervals. Panel B shows progression of disability that was sustained for at least 12 weeks.

free of relapse, as compared with the placebo group (Table 2, and see the Supplementary Appendix). Rates of relapse during the study were higher for patients who entered the trial early than for patients who entered late in the recruitment phase; the annualized relapse rate remained significantly lower in the teriflunomide groups than in the placebo group (see the Supplementary Appendix).

Disability

The estimated proportions of patients with confirmed progression of disability that was sustained for at least 12 weeks were 27.3%, 21.7%, and 20.2% with placebo, teriflunomide at 7 mg, and teriflunomide at 14 mg, respectively, representing relative risk reductions, as compared with placebo, of 23.7% for lower-dose teriflunomide (P=0.08) and 29.8% for higher-dose teriflunomide (P=0.03) (Table 2 and Fig. 2).

MRI Outcomes

Teriflunomide at both doses improved several MRI measures of disease activity, as compared with placebo (Table 2). The change in total lesion volume from baseline was significantly lower in the 7-mg and 14-mg groups than in the placebo group (P=0.03 and P<0.001, respectively). Patients in both teriflunomide groups had significantly fewer gadolinium-enhancing lesions per T_1-weighted scan than those in the placebo group (P<0.001 for both comparisons with placebo) (Table 2, and see the Supplementary Appendix). Fewer unique active lesions per scan were observed in both teriflunomide groups than in the placebo group (P<0.001 for both comparisons with placebo) (Table 2, and see the Supplementary Appendix). Changes from baseline in brain atrophy did not differ significantly among the three study groups (Table 2).

Effect on Fatigue

Patients reported only small changes from baseline in fatigue, as reflected by FIS scores, with no significant differences among the study groups (Table 2).

SAFETY AND ADVERSE-EVENT PROFILE

Common Adverse Events during Treatment

Similar proportions of patients in the placebo, lower-dose teriflunomide, and higher-dose teriflunomide groups had adverse events (87.5%, 89.1%, and 90.8%, respectively), serious adverse events (12.8%, 14.1%, and 15.9%), and adverse events leading to discontinuation of the study medication (8.1%, 9.8%, and 10.9%) (Table 3).

Among the most common adverse events (crude incidence, ≥10%) with an increased incidence in the teriflunomide groups (as compared with placebo) and with a dose effect were diarrhea, nau-

Table 3. Adverse Events.*

Adverse Event	Placebo (N=360)	Teriflunomide, 7mg (N=368)	Teriflunomide, 14 mg (N=358)
		number of patients (percent)	
All events			
At least one adverse event	315 (87.5)	328 (89.1)	325 (90.8)
Any adverse event leading to discontinuation of study medication	29 (8.1)	36 (9.8)	39 (10.9)
Any serious adverse event	46 (12.8)	52 (14.1)	57 (15.9)
Any event leading to death	0	0	0
Most common adverse events†			
Nasopharyngitis	98 (27.2)	94 (25.5)	93 (26.0)
Headache	64 (17.8)	81 (22.0)	67 (18.7)
Diarrhea	32 (8.9)	54 (14.7)	64 (17.9)
Fatigue	51 (14.2)	47 (12.8)	52 (14.5)
Elevated alanine aminotransferase level‡	24 (6.7)	44 (12.0)	51 (14.2)
Nausea	26 (7.2)	33 (9.0)	49 (13.7)
Hair thinning or decreased hair density	12 (3.3)	38 (10.3)	47 (13.1)
Influenza	36 (10.0)	34 (9.2)	43 (12.0)
Back pain	47 (13.1)	39 (10.6)	41 (11.5)
Urinary tract infection	35 (9.7)	27 (7.3)	37 (10.3)
Pain in arms or legs	47 (13.1)	26 (7.1)	33 (9.2)

* Data are presented for the safety population, defined as all patients who underwent randomization and were exposed to study medication, regardless of the amount of medication administered or the medication assigned at randomization. The safety analyses were conducted according to the treatment actually received.

† Adverse events listed are those with a crude incidence rate of at least 10% in any group. They are ranked by decreasing order of incidence in the higher-dose teriflunomide group.

‡ Elevated levels were reported as adverse events by the investigators; because these reports were based on investigators' judgment, the percentages reported here do not match those of the laboratory abnormalities presented in the text.

sea, hair thinning or decreased hair density, and elevated alanine aminotransferase levels. These events rarely led to discontinuation of the study medication (discontinuation rate for diarrhea, 0.0%, 0.3%, and 0.3% with placebo, teriflunomide at 7 mg, and teriflunomide at 14 mg, respectively; for nausea, 0.0%, 0.3%, and 0.0%; and for hair thinning or decreased hair density, 0.0%, 0.5%, and 1.4%). No deaths were reported.

Other Safety Findings

The incidence of elevated alanine aminotransferase levels (≥1 times the upper limit of the normal range) was higher with teriflunomide at 7 mg and 14 mg (54.0% and 57.3%, respectively) than with placebo (35.9%); the incidence of elevations that were at least 3 times the upper limit of the normal range was similar across study groups (6.3%, 6.7%, and 6.7%, respectively). Three patients (one in each group) had elevations in alanine aminotransferase that were at least 3 times the upper limit of the normal range and elevations in total bilirubin that were at least 2 times the upper limit of the normal range; of these three patients, one each had hepatitis C, incidental bile-duct stenosis, and cytomegalovirus infection.

Mean reductions in neutrophil and lymphocyte counts from baseline values were small in magnitude (≤1.0×10^9 per liter and ≤0.3×10^9 per liter, respectively) but were slightly more marked with teriflunomide at 14 mg than with the 7-mg dose or placebo. The reductions occurred during the first 3 months of treatment and stabilized over time. Moderate neutropenia (defined as a neutrophil count of <0.9×10^9 per liter) developed in three patients receiving teriflunomide; the neutropenia

resolved spontaneously with continued treatment in two of the patients, and in the third patient, it resolved after discontinuation of the study drug (see the Supplementary Appendix).

The incidence of serious infections was similar across groups (2.2%, 1.6%, and 2.5% with placebo, teriflunomide at 7 mg, and teriflunomide at 14 mg, respectively); no serious opportunistic infections were observed. One case of serious herpes zoster infection was observed in the placebo group. Three cases of serious pyelonephritis were reported in patients receiving teriflunomide at 14 mg; one case led to discontinuation of the study medication.

Because teriflunomide has not yet been approved for use in pregnancy, reporting of a pregnancy was handled as an adverse event. Eleven pregnancies occurred during the trial, including four spontaneous abortions (one in the placebo group and three in the higher-dose teriflunomide group) and six induced abortions (five in the lower-dose teriflunomide group and one in the higher-dose teriflunomide group). One patient in the higher-dose teriflunomide group (treated for 31 days of pregnancy) delivered a healthy baby, with no reported health concerns after 2 years. All patients discontinued the study medication and underwent an 11-day elimination period as soon as they became aware of being pregnant.

Malignant neoplasms were reported in four patients: three in the placebo group (one each with breast cancer, thyroid cancer, and cervical cancer) and one in the higher-dose teriflunomide group (with cervical carcinoma in situ, [stage 0], reported after 1.5 years of using the drug).

The proportion of patients with adverse events related to increased blood pressure was higher with teriflunomide at 7 mg and 14 mg (5.4% and 5.0%, respectively) than with placebo (3.1%). The mean (±SD) change from baseline to study end in supine systolic blood pressure was −0.99±14.32 mm Hg, 2.87±13.90 mm Hg, and 2.72±13.45 mm Hg with placebo, teriflunomide at 7 mg, and teriflunomide at 14 mg, respectively; the respective changes from baseline to study end in supine diastolic blood pressure were −0.87±9.79 mm Hg, 1.38±10.84 mm Hg, and 1.31±9.90 mm Hg. No patient discontinued the study medication because of increased blood pressure.

No increases in amylase and lipase levels (assessed on the basis of the mean change from baseline) were reported across the three study groups. One case of pancreatitis was reported in a patient receiving placebo.

The proportions of patients with hypersensitivity or skin disorders were generally higher with teriflunomide at 7 mg and 14 mg (10.3% and 11.2%, respectively) than with placebo (7.2%) (see the Supplementary Appendix). No instances of anaphylactic shock or serious hypersensitivity reactions were reported.

DISCUSSION

Once-daily oral treatment with teriflunomide provided sustained benefits for patients with relapsing multiple sclerosis during the 108-week study period. As compared with placebo, teriflunomide treatment resulted in significantly reduced rates of clinical relapse and (in the 14-mg group) a reduced risk of disability progression. Treatment with the drug also resulted in the suppression of active inflammatory lesions, as visualized on MRI. The magnitude of the benefits observed in patients receiving teriflunomide was modest but similar to those reported for the existing injectable disease-modifying therapies approved for use in patients with multiple sclerosis.[16-20] A possible dose effect was apparent, with less progression of disability and greater improvements in several MRI measures at the higher dose. As compared with the study populations in recent large trials of investigational oral disease-modifying therapies, the patients in our study had a slightly higher level of disease activity, in terms of the number of relapses before study entry, baseline EDSS scores, and MRI measures, a difference that may be related to temporal differences in trial recruitment (participants enrolled earlier in the recruitment period may be more affected than those enrolled later).[21-23] The rate of study discontinuation was similar to that observed in another recent large trial of oral disease-modifying therapies.[22]

The incidence of adverse events, serious adverse events, and adverse events leading to discontinuation of the study drug was similar across study groups. The incidence of elevated alanine aminotransferase levels (≥1 times the upper limit of the normal range) was higher with teriflunomide than with placebo; the incidence of elevations that were at least 3 times the upper limit of the normal range was similar across study groups, as was the incidence of serious infections. Although teriflunomide has a long elimination half-life, it can be rapidly eliminated from the body

during an elimination period in which cholestyramine is administered, should a patient choose to discontinue treatment or wish to become pregnant or in the case of a possible overdose or emerging toxicity.[14] An understanding of the long-term safety of teriflunomide in patients with relapsing multiple sclerosis, with regard to rare adverse events such as progressive multifocal leukoencephalopathy, must await future trials involving larger populations treated for longer periods.[24]

However, the safety experience with teriflunomide to date can be supplemented with long-term clinical experience with the prodrug, leflunomide, in patients with rheumatoid arthritis.[25] Data on more than 1.9 million patient-years of exposure have been collected since leflunomide was approved for the treatment of rheumatoid arthritis in 1998. During this long-term exposure period, two cases of progressive multifocal leukoencephalopathy have been reported in patients taking leflunomide.[2,26-28]

In conclusion, the findings from our phase 3 study suggest that teriflunomide is an effective new oral monotherapy for relapsing multiple sclerosis.

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