A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses

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Abstract—*Background:* Teriflunomide, a dihydro-orotate dehydrogenase inhibitor, has immunomodulatory effects, including the ability to suppress experimental allergic encephalomyelitis. In this randomized, double-blind, placebo-controlled Phase II study, the authors examined the safety and efficacy of oral teriflunomide in multiple sclerosis (MS) with relapses. *Methods:* Patients (n = 179) with relapsing–remitting MS (n = 157) or secondary progressive MS with relapses (n = 22) were randomized to receive placebo, teriflunomide 7 mg/day, or teriflunomide 14 mg/day for 36 weeks. MRI brain scans were performed every 6 weeks. The primary endpoint was the number of combined unique active lesions per MRI scan. Secondary endpoints included MRI-defined disease burden, relapse frequency, and disability increase. *Results:* The median number of combined unique active lesions per scan was 0.5, 0.2, and 0.3 in the placebo, teriflunomide 7 mg/day ($p < 0.03$ vs placebo), and teriflunomide 14 mg/day ($p < 0.01$ vs placebo) groups during the 36-week double-blind treatment phase. Teriflunomide-treated patients also had significantly fewer T1 enhancing lesions per scan, new or enlarging T2 lesions per scan, and new T2 lesions. Patients receiving teriflunomide 14 mg/day had significantly reduced T2 disease burden. Teriflunomide treatment resulted in trends toward a lower annualized relapse rate and fewer relapsing patients (14 mg/day only) vs placebo. Significantly fewer patients receiving teriflunomide 14 mg/day vs placebo demonstrated disability increase. Treatment was well tolerated; numbers of adverse events and serious adverse events were similar in all treatment groups. *Conclusion:* Oral teriflunomide was effective in reducing MRI lesions and was well tolerated in patients with relapsing multiple sclerosis.

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All disease-modifying therapies currently available for multiple sclerosis (MS) require administration by injection, highlighting the clear need for an effective and well-tolerated oral therapy. Teriflunomide, a metabolite of leflunomide, is an oral immunomodulator with anti-inflammatory activity.[1] Teriflunomide inhibits pyrimidine synthesis by binding to the enzyme dihydro-orotate dehydrogenase (DHO-DH)—the fourth enzyme in the de novo synthesis pathway of pyrimidines—in T cells and other rapidly dividing cell populations.[2,3] Teriflunomide has demonstrated prophylactic and therapeutic effects in animal models of autoimmune disease, such as the Lewis female rat model of experimental allergic encephalomyelitis.[1] In an experimental model of autoimmune neuritis, teriflunomide appears to act by a mechanism supplemental to its inhibition of DHO-DH by altering the tyrosine kinase activation of calcium mobilization.[4]

In this study, we examined the safety, efficacy, and optimal oral administration dose of teriflunomide in patients with MS with relapses, using an MRI metric as the primary study endpoint.

Methods. Patients eligible for randomization were required to be ages 18 to 65 and have clinically confirmed MS,[5,6] an Expanded Disability Status Scale (EDSS)[7] score of ≤6, two documented relapses in the previous 3 years, and one clinical relapse during the preceding year. Patients were excluded if they had prior treatment with interferon (IFN), γ-globulin, glatiramer acetate, or other noncorticosteroid immunomodulatory therapies in the 4 months prior to the trial. Men and women were required to practice effective contraception during the trial and for 24 months after drug discontinuation or to undergo a drug washout procedure.

All patients gave written informed consent for their participation. All patients were required to have an MRI scan at visit 1 (screening MRI scan) that showed abnormalities compatible with MS to be eligible for randomization.[5]

After a 4-week, treatment-free screening period, during which all baseline assessments were made, patients were randomized (1:1:1) to one of three treatment groups (placebo, teriflunomide 7 mg/day, or teriflunomide 14 mg/day). To reach steady-state concentrations more rapidly, each patient received twice the mainte-

*See the Appendix for a list of participating investigators.

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nance dose of teriflunomide or placebo (2 tablets/day) for the first week of treatment. Patients then received a maintenance dose (1 tablet/day) of placebo, teriflunomide 7 mg/day, or teriflunomide 14 mg/day for a further 35 weeks.

A 1:1:1 randomization to placebo, teriflunomide 7 mg, and teriflunomide 14 mg was stratified by baseline EDSS score to give two patient groups: those with EDSS scores ≤3.5 and those with scores >3.5. Teriflunomide and matching placebo tablets were supplied by sanofi-aventis (Frankfurt, Germany).

The study was approved by local institutional review boards and was conducted in compliance with the regulations of the Canadian Health Protection Branch and the French Health Products Safety Agency and all other applicable laws and regulations. The study complied with the ethical concepts described in the Declaration of Helsinki (Hong Kong amendment).

Efficacy assessments. MRI scans were performed at each center in accordance with a scanning protocol designed to standardize procedures and give reproducible positioning across all study centers.[8] MRI scans were performed at weeks −4 (visit 1) and 0 (baseline; visit 3), then every 6 weeks for 36 weeks (treatment phase; visits 4 to 10). Fifty contiguous, 3-mm-thick axial slices of the entire brain were acquired using unenhanced proton density/T2-weighted (PD/T2) and pre- and postgadolinium enhanced (0.1 mmol/kg, 5-minute delay) T1-weighted sequences (Gd-T1). All scans were then sent to the University of British Columbia (UBC) MS/MRI Research Group for central review and analysis. The UBC MS/MRI Analysis Group had no clinical knowledge of the history or treatment of any of the patients analyzed.

MRI lesion activity was determined from a sequential review of the patient's entire scan set by pairs of radiologists working together to reach consensus. When there was a disagreement, a third senior radiologist reviewed the films, and a final consensus was reached. Activity analysis was performed in three steps: 1) Gd-T1 scan analysis to identify newly enhancing and persistently enhancing T1 lesions; 2) PD/T2 scan analysis to identify new and enlarging T2 active lesions; 3) combined unique (CU) active lesion analysis (this final step was performed after the Gd-T1 and PD/T2 analyses to avoid double counting of simultaneous activity in single lesions). When an enhancing T1 lesion and an active T2 lesion were identified as being the same lesion, the Gd-T1 and PD/T2 numbers were linked in the database. Links could involve the current, previous, or subsequent scan in the series. Nonlinked Gd-T1 active and PD/T2 active lesions and linked Gd-T1 and PD/T2 active lesions were then combined to give counts of new CU active lesions and persistent CU active lesions.

The total area/volume of all MS lesions on the PD/T2 scans (burden of disease), initially marked by a radiologist, were determined using a semiautomated lesion segmentation algorithm supervised by a trained technician. The same technician analyzed all the scans for a patient from the same center. To minimize interobserver variability (mean interobserver coefficient of variation 10.5% compared with mean intraobserver coefficient of variation of 6.6%), the same technician analyzed all the scans for a patient from the same center; not more than two technicians were assigned to perform the analysis for each center. All completed analyses were then reviewed and accepted, or corrected if necessary, by a radiologist.

The primary efficacy variable was the number of CU active (new and persisting) lesions per MRI scan during the 36-week, double-blind treatment phase. Other MRI outcome measures included the number of T1 enhancing lesions, number of T2 active lesions, number of patients with CU active, T1 enhancing, and T2 active lesions, and percentage change from baseline to endpoint in the burden of disease (T2 lesion volume).

Clinical measures included the number of patients experiencing an MS relapse, annualized relapse rate, and number of relapsing patients requiring a course of steroids. A relapse was defined as the appearance of a new symptom or worsening of an old symptom due to MS lasting 48 hours in the absence of fever, preceded by period of stability of at least 30 days and accompanied by appropriate changes on neurologic examination.

Disability was assessed over time by measuring between-visit changes in EDSS score at visit 1 (screening) and visit 3 (baseline) and then every 12 weeks thereafter. Additional assessments included the number of patients in whom disability increased (defined as an increase in EDSS score of ≥1.0 in patients with a baseline EDSS score of ≤5.5 or an increase in EDSS score of ≥0.5 in patients with a baseline EDSS score of ≥5.5).

Both relapse and disability assessments were made by the treating (blinded) neurologist. Owing to the short duration of the study, confirmation of EDSS progression by follow-up assessment was not implemented. Safety was assessed by physical and neurologic examination, clinical laboratory analysis, and vital signs assessment. Spontaneously reported adverse events were recorded at clinic visits.

Compliance was determined by inspecting and counting all blister packs returned (used and unused) to the study center at every visit.

The primary analysis populations were the intent-to-treat (ITT) population (all randomized patients) and the safety-evaluable population (all randomized patients who received one or more doses of study medication). The secondary analysis population was the efficacy evaluable (all randomized patients for whom there was at least one on-treatment MRI assessment and including all data collected during the period from baseline to the last day of study medication + 14 days inclusively). Burden of disease, as measured by T2 lesion volume, was assessed in the completer population, which consisted of efficacy-evaluable patients who completed 231 days of treatment (i.e., the earliest day for visit 10 [36 weeks]) and who had an MRI scan at visit 10. Results in the efficacy-evaluable population were consistent with the ITT results reported herein.

For the primary efficacy variable (mean number of CU active lesions per MRI scan), active treatment groups were compared with placebo using rank analysis of covariance (ANCOVA) with treatment, stratum (EDSS at baseline ≤3.5 vs >3.5), and pooled center as fixed effects and the ranked mean prerandomization number of CU active lesions as the covariate. Other MRI and change from baseline variables (EDSS) were assessed by ANCOVA with treatment, stratum, and pooled center as fixed effects and baseline score as the covariate. Progression and relapse rates were tested with the Cochran–Mantel–Haenszel procedure. For the secondary variables, unadjusted probabilities were presented. Safety variables were analyzed using descriptive statistics. In addition, for the cumulative number of unique active lesions, a last-observation-carried-forward (LOCF) analysis was undertaken such that when a result for a scan was not available at a visit, the result from the previous visit could then be used.

Fifty-four evaluable patients per treatment group were considered sufficient to detect with 90% power an effect size of 0.32 using a two-sided Wilcoxon rank sum test and an α level of 0.05. This effect size for the Wilcoxon rank sum test corresponds to a parametric effect size (i.e., difference in means divided by the SD) of 0.67. Anticipating a 10% dropout rate, it was considered necessary to randomize 60 patients per treatment group for a total of 180 patients.

Data management and statistical analyses were conducted by sanofi-aventis and Accovion GmbH (Eschborn, Germany). An independent Data Safety Monitoring Board (see Appendix) was re-

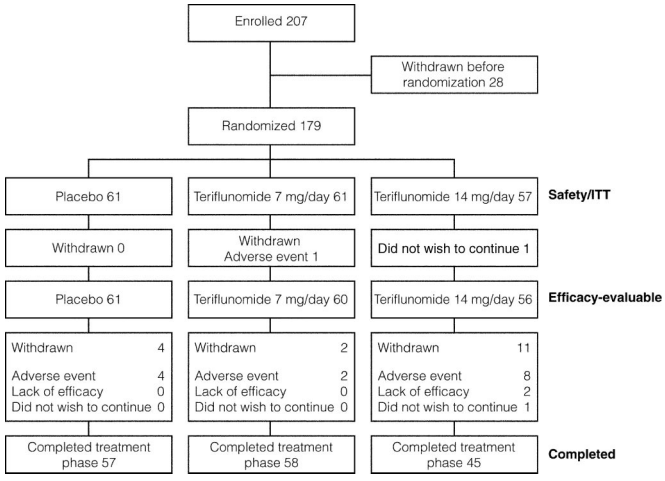

Figure 1. Patient flow for the intent-to-treat (ITT) population.

Table 1 *Patient demographics and baseline clinical and MRI variables (ITT population)*

Characteristic	Placebo, n = 61	Teriflunomide 7 mg/d, n = 61	Teriflunomide 14 mg/d, n = 57
Mean (SD) age, y	39.2 (8.7)	40.1 (9.3)	40.1 (9.1)
Male/female, no. of patients	20/41	15/46	12/45
Mean (SD) time since diagnosis, y	4.4 (5.7)	6.0 (5.6)	5.4 (6.2)
Mean (SD) disease duration, y	8.6 (7.9)	10.3 (8.1)	8.5 (7.1)
Type of MS, no. (%) of patients			
Relapsing–remitting	53 (86.9)	54 (88.5)	50 (87.7)
Secondary progressive	8 (13.1)	7 (11.5)	7 (12.3)
No. (%) of patients with T1 enhancing lesions	36 (59.0)	29 (47.5)	31 (54.4)
No. (%) of patients with combined unique active lesions	38 (62.3)	29 (47.5)	35 (61.4)
No. (%) of patients with new or enlarging T2 lesions	22 (36.1)	16 (26.2)	24 (42.1)
No. of combined unique active lesions/scan			
Mean ± SE	2.16 ± 0.63	1.30 ± 0.60	2.48 ± 0.62
Median	0.5	0.0	0.5
No. of T1 enhancing lesions/scan			
Mean ± SE	2.10 ± 0.62	1.23 ± 0.60	2.32 ± 0.61
Median	0.5	0.0	0.5
No. of new or enlarging T2 lesions/scan			
Mean ± SE	0.66 ± 0.27	0.77 ± 0.26	0.80 ± 0.26
Median	0.0	0.0	0.0
T2 lesion volume, mm^3			
Mean	9,119	10,338	8,475
Median	5,774	6,294	6,224
Median (range) baseline EDSS score	2.5 (0–6)	2.5 (0–6)	2.0 (0–6.5)
Median (range) no. of relapses			
In last 3 years	3 (1–9)	2 (2–5)	3 (2–6)
In last 12 months	1 (0–3)	1 (0–4)	1 (0–3)

T1 enhancing lesions comprisednewly enhancing or persistently enhancing T1 lesions at baseline; T2 active lesions comprised new, newly enlarging, or persistently enlarging T2 lesions from week −4 to baseline; combined unique active lesions comprised T1, and/or T2 active lesions. Slightly lower values were noted for most MRI variables reported in the low-dose teriflunomide group, although these differences were not significant.

ITT = intent to treat; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale.

sponsible for overseeing the data and the safety of patients participating in the study.

Results. This randomized, double-blind, placebo-controlled, parallel-group trial took place between April 2001 and March 2003 at 10 MS clinics in Canada and 6 in France. In total, 207 patients were screened. Of these, 179 patients (157 patients with relapsing–remitting MS and 22 patients with secondary progressive MS with relapses)—the ITT population—were randomized, and treated with placebo (n = 61), teriflunomide 7 mg/day (n = 61), or teriflunomide 14 mg/day (n = 57) for 36 weeks. Patient flow is shown in figure 1. Two patients were withdrawn from study medication before completing any efficacy assessments. Therefore, 177 patients were included in the efficacy-evaluable population (secondary analysis population). Baseline patient demographics and clinical and MRI variables were typical of a population with MS with relapses and were comparable between groups; however, slightly lower values were noted for most MRI variables reported in the low-dose teriflunomide group, although these differences were not significant (table 1). The distributions of previous medications for MS and concomitant medications given during the trial were also comparable across the groups.

Six patients (two in each treatment group) had fewer than two relapses in the previous 3 years or no clinical relapses in the preceding year, and one patient in the teriflunomide 14-mg/day group had an EDSS score of >6 at screening, thereby failing to meet inclusion criteria; these were not considered to warrant exclusion. However, protocol deviations occurred in 30 additional patients in the efficacy-evaluable population (placebo, n = 8; teriflunomide 7 mg/day, n = 9; and teriflunomide 14 mg/day, n = 13). Reasons for deviations were equally distributed across the three treatment groups. The most common protocol deviation was gadolinium not given within the specified time window; the protocol requirement was for scans to be obtained 5 minutes after the injection of contrast material,

***Table 2** MRI outcome measures (ITT population)*

Outcome measure	Treatment group			Mean difference (95% CI)	
	Placebo, n = 61	Teriflunomide 7 mg/d, n = 61	Teriflunomide 14 mg/d, n = 57	Teriflunomide 7 mg/d vs placebo	Teriflunomide 14 mg/d vs placebo
No. of CU active lesions/scan*					
Median	0.5	0.2	0.3	—	—
Mean (± SE)	2.68 ± 0.39	1.04 ± 0.37	1.06 ± 0.38	−1.64 (−2.69, −0.59)§	−1.62 (−2.68, −0.56)†
Relative reduction, %				−61.1	−61.3
No. of T1 enhancing lesions/scan*					
Median	0.50	0.17	0.17		
Mean ± SE	2.25 ± 0.32	0.87 ± 0.31	0.86 ± 0.32	−1.38 (−2.25, −0.51)‖	−1.39 (−2.27, −0.50)‡
No. of new or enlarging T2 lesions/scan*					
Median	0.3	0.17	0.17		
Mean ± SE	1.52 ± 0.24	0.41 ± 0.23	0.71 ± 0.24	−1.10 (−1.76, −0.45)‖	−0.81 (−1.47, −0.15)§
No. (%) of patients with CU active lesions	49 (80.3)	40 (65.6)	38 (66.7)		
No. (%) of patients with T1 enhancing lesions	45 (73.8)	37 (60.7)	35 (61.4)		
No. (%) of patients with new or enlarging T2 lesions	46 (75.4)	32 (53.3)	34 (59.7)		
Median change in BOD from baseline, %					
18 Weeks	1.1	−0.1	−3.8		
36 Weeks	5.2	2.9	−4.1‡		

BOD was determined in patients who completed the study from the total area/volume of all multiple sclerosis lesions on the proton density/T2-weighted scans. T1 enhancing lesions comprisednewly enhancing and persistently enhancing T1 lesions; T2 lesions comprised new, newly enlarging, and persistently enlarging T2 lesions; combined unique active lesions comprised T1 and T2 active lesions.

* Adjusted for baseline activity, Expanded Disability Status Scale strata, and study site.
† $p < 0.01$; ‡ $p < 0.02$; § $p < 0.03$; ‖ $p < 0.04$.

ITT = intent-to-treat; CU = combined unique; BOD = burden of disease.

but scans were acceptable for analysis if obtained within 30 minutes. Most of these delayed scans were for repeat scans to meet repositioning acceptance criteria. A second common protocol deviation was the use of corticosteroids for the treatment of relapses that could have interfered with interpretation of the MRI scans (placebo, n = 8; teriflunomide 7 mg/day, n = 7; teriflunomide 14 mg/day, n = 10).

Compliance was excellent overall. The median percentage of days on which patients took the prescribed dose of study medication was 99.2% for placebo, 99.2% for teriflunomide 7 mg/day, and 98.8% for teriflunomide 14 mg/day.

The effect of treatment on MRI outcomes is shown in table 2. Patients receiving teriflunomide 7 and 14 mg/day had significant reductions in the median number of CU active lesions per scan compared with placebo. There was no difference between the two treatment groups for the reduction of CU active lesions per scan. The cumulative mean number of CU lesions over the study period is shown in figure 2. CU lesions were decreased in teriflunomide-treated patients as early as 6 weeks, reaching significance by 12 weeks; this effect was maintained for the full duration of the 36-week, double-blind treatment period (teriflunomide 7 and 14 mg/day vs placebo; $p < 0.005$ for both groups, ANCOVA). Patients receiving teriflunomide 7 or 14 mg/day also had significant reductions in the median

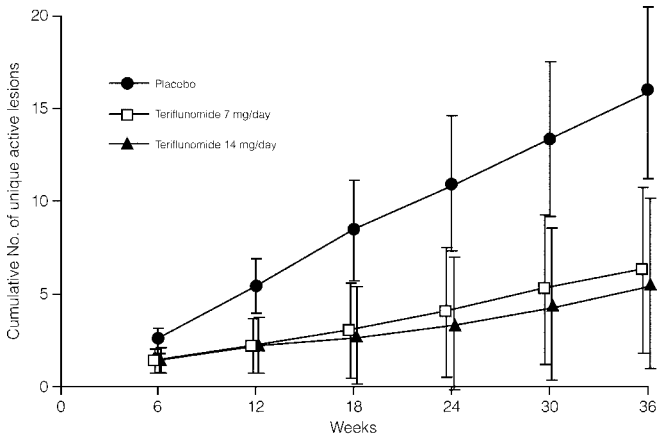

Figure 2. Cumulative mean number of combined unique active lesions adjusted for baseline.

Table 3 *Treatment-emergent adverse events occurring in ≥10% of patients (safety population)*

TEAE	No. (%) of patients		
	Placebo, n = 61	Teriflunomide 7 mg/d, n = 61	Teriflunomide 14 mg/d, n = 57
Headache	16 (26)	15 (25)	12 (21)
Nasopharyngitis	10 (16)	14 (23)	12 (21)
URTI	13 (21)	11 (18)	13 (23)
Alopecia	6 (10)	9 (15)	11 (19)
Sensory disturbance	9 (15)	10 (16)	8 (14)
Nausea	3 (5)	7 (11)	10 (18)
ALT increase	6 (10)	10 (16)	7 (12)
Paresthesia	3 (5)	7 (11)	8 (14)
Insomnia	8 (13)	9 (15)	5 (9)
Fatigue	10 (16)	6 (10)	7 (12)
Urinary tract infection	5 (8)	7 (11)	6 (11)
Back pain	4 (7)	5 (8)	8 (14)
Limb pain	2 (3)	7 (11)	6 (11)
Diarrhea	3 (5)	5 (8)	7 (12)
Arthralgia	2 (3)	8 (13)	4 (7)

TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; ALT = alanine aminotransferase.

number of T1 enhancing lesions per scan and the median number of new or enlarging T2 lesions per scan over the 36-week treatment period (table 2).

Fewer patients in the teriflunomide groups had T1 enhancing lesions, CU active lesions, and new or enlarging T2 lesions than in the placebo group. Burden of disease, as measured by T2 lesion volume, was also significantly lower in the completer population subjects who received teriflunomide 14 mg/day ($p = 0.0106$; table 2).

Patients receiving teriflunomide 7 or 14 mg/day had lower annualized relapse rates than placebo-treated patients (mean ± SD 0.58 ± 0.85 and 0.55 ± 1.12 vs 0.81 ± 1.22; NS). There was a trend toward a greater proportion of relapse-free patients in the teriflunomide 14 mg/day group compared with placebo (77 vs 62%; $p = 0.098$); fewer patients in the teriflunomide 14 mg/day group had relapses that required steroids compared with placebo (14 vs 23%; NS).

The proportion of patients showing disability increase (increased EDSS score at endpoint vs baseline) was lower in the teriflunomide 14 mg/day group compared with the placebo group (7.4 vs 21.3%; $p < 0.04$). This translates to a 69% relative reduction in the numbers of patients with EDSS increase at 36 weeks compared with placebo.

Treatment-emergent adverse events (TEAEs) were reported in all patients. Nasopharyngitis, alopecia, nausea, alanine aminotransferase increase, paresthesia, back pain, limb pain, diarrhea, and arthralgia were more commonly reported by patients in the teriflunomide treatment groups than in the placebo group; no significant between-group differences were observed. The majority of these were considered unrelated to study drug administration. TEAEs occurring in ≥10% of patients are presented in table 3. There were no deaths.

Serious TEAEs were reported in 19 patients (placebo, n = 7; teriflunomide 7 mg/day, n = 5; teriflunomide 14 mg/day, n = 7); these included elevated liver enzymes, hepatic dysfunction, neutropenia, rhabdomyolysis, and trigeminal neuralgia.

TEAEs resulting in withdrawal from the study occurred in 15 patients (placebo, n = 4; teriflunomide 7 mg/day, n = 3; teriflunomide 14 mg/day, n = 8). A total of six patients were withdrawn from the study because of abnormal alanine transaminase levels (placebo, n = 3; teriflunomide 7 mg/day, n = 1; teriflunomide 14 mg/day, n = 2). MS relapse led to withdrawal of one placebo patient; generalized rash and upper abdominal pain led to withdrawal of one patient each for a total of two patients in the teriflunomide 7-mg/day group; alopecia, erythema multiforme, urticaria, condyloma acuminatum, dyspepsia, and hypertension led to the withdrawal of one patient each for a total of six patients in the teriflunomide14-mg/day group. No permanent morbidity was observed for any patient.

Clinically noteworthy laboratory values were reported in 14 patients (placebo, n = 4; teriflunomide 7 mg/day, n = 8; teriflunomide 14 mg/day, n = 2). There were no relevant imbalances in the number of clinically relevant laboratory values across the treatment groups for any of the laboratory variables tested. Ten of the 14 patients had increases in liver function tests (alanine aminotransferase, aspartate aminotransferase, serum γ-glutamyl transferase, and total bilirubin) (placebo, n = 4; teriflunomide 7 mg/day, n = 4; teriflunomide 14 mg/day, n = 2). No clinically important differences in EKG, hematology, clinical chemistry, or urinalysis were observed between the treatment groups or over the 36-week study period.

Discussion. This Phase II "proof of concept" study is the first study to assess the efficacy and safety of oral teriflunomide in patients with relapsing MS. Treatment with either teriflunomide 7 or 14 mg/day resulted in the significant suppression of >61% of MRI activity relative to placebo, including: fewer CU active lesions, T1 gadolinium enhancing lesions, and new or enlarging T2 lesions on MRI. Patients receiving teriflunomide 14 mg/day had no increase in T2 lesion volume from baseline, reflecting a reduced accumulation of MRI burden of disease compared with placebo-treated patients. Treatment effects were detectable by MRI in the active treatment groups within 6 weeks of treatment initiation, as demonstrated by the mean number of unique active lesions over time. A more pronounced effect was noted by week 12, and this was sustained over the remainder of the study. Additionally, there was no evidence of opportunistic infection or impaired immune surveillance in any patient during this study.

Based on reproductive toxicity studies in animals receiving leflunomide (the parent compound of teriflunomide), female patients are advised not to become pregnant and males are cautioned not to father a child while on therapy (although animal data regarding male reproductive toxicity are unclear). There are few data in humans to support or refute the teratogenic potential of either leflunomide or teriflunomide. There is an ongoing study in pregnant

patients with rheumatoid arthritis (RA) to evaluate the safety of leflunomide when used early in pregnancy. Interim data show that pregnancy outcome was similar among leflunomide-exposed (n = 43), RA control (n = 78), and nondisease control (n = 47) patients.[9]

As the reproductive toxicity is not understood, strict contraceptive measures are recommended. Women who wish to become pregnant should undergo a washout procedure with either cholestyramine or activated charcoal after stopping treatment. A teriflunomide assay must be performed following completion of the washout procedure to confirm a plasma level of <0.02 mg/L (0.02 g/L), the level expected to present minimal teratogenic risk, based on available data. Without the washout procedure, it may take up to 2 years to reach plasma levels <0.02 mg/L owing to individual variation in drug clearance.

The MRI effects measured in our study are comparable with those reported for other approved disease-modifying therapies.[8,10] A 9-month subanalysis of the PRISMS Study demonstrated that the median number of CU active lesions was reduced by 80.7% and 87.5% for the 22- and 44-μg IFNβ-1a subcutaneous injection (Rebif) groups compared with placebo.[8]

Patients treated with a daily injection of glatiramer acetate 20 mg compared with placebo in a 9-month study of patients with relapsing–remitting MS had only a 30% suppression of gadolinium lesions. The rate of increase in T2 burden of disease was slower in patients treated with glatiramer acetate compared with placebo.[10] Similarly, results from the Multiple Sclerosis Collaborative Research Group (MSCRG) study of IM IFNβ-1a (Avonex) once weekly demonstrated a 35% ($p = 0.02$) decrease in gadolinium enhancing activity at year 1.[11] In this study, effects on T2 burden of disease did not reach significance.[12] Patients treated with 3 or 6 mg of IV natalizumab every 28 days for 6 months also showed reductions of up to 93 and 89% in the mean number of new enhancing lesions compared with placebo (0.7 and 1.1 vs 9.6 lesions per patient).[13]

Although effects on annualized relapse rate did not reach significance in our study, which was designed and powered based on the primary MRI endpoint, trends toward reducing relapses in favor of teriflunomide were noted. In addition, a lower proportion (NS) of teriflunomide patients experienced relapses or required steroids. The 32% observed difference in annualized relapse rates between the placebo and teriflunomide 14-mg/day groups is similar to that reported for IFNβ-1b, IFNβ-1a, and glatiramer acetate. The clinical trends observed in our study support the efficacy observed on the MRI surrogate.[14]

In a short-term small study such as this, it is unrealistic to expect a significant change in disability. However, there was a significant reduction (69%) in the number of patients in the teriflunomide 14-mg/day group who demonstrated disability worsening at study completion compared with placebo.

There was no dose effect on the primary endpoint of CU active lesions per scan or on its components of enhancing lesions and new or enlarging T2 lesions. However, evidence suggests that the higher dose of teriflunomide provided additional benefits, as the change over time in T2 lesion volume favored the higher dose (as did relapse rates and EDSS scores). Although this was a study primarily designed to examine MRI variables, beneficial trends in the clinical variables support the MRI findings. Additional scans are being performed on the subjects continuing teriflunomide treatment to evaluate the activity of teriflunomide on T2 lesion and brain volumes.

A total of 19 patients discontinued study medication prematurely during the 36-week treatment period, with more discontinuations in the teriflunomide 14-mg/day group than in the other groups. There was no difference in serious adverse events between treatment groups, nor was there any difference in the number of patients with significantly abnormal laboratory tests (e.g., transaminase levels over three times the upper limit of normal). Larger studies are needed to understand better both the efficacy and the safety profile of teriflunomide.

Appendix

The Data Safety Monitoring Board comprised the following: Timothy Vollmer, MD (Barrow Neurologic Institute, Phoenix, AZ), Fred D. Lublin, MD (Mount Sinai School of Medicine, NY), Gary Cutter (statistician, Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver), William E.M. Pryse-Phillips (Health Sciences Centre, St. John's, Newfoundland, Canada).

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References

1. Styren SD, Barbier AJ, Selk DE, et al. Beneficial effects of teriflunomide in experimental allergic encephalomyelitis. Program no. 344.5. Washington, DC: Society for Neuroscience, 2004. Available at www.sfn.scholarone.com/itin2004/ accessed. January 2005.
2. Bruneau JM, Yea CM, Spinella-Jaegle S, et al. Purification of human dihydro-orotate dehydrogenase and its inhibition by A77 1726, the active metabolite of leflunomide. Biochem J 1998;336:299–303.
3. Cherwinski HM, Cohn RG, Cheung P, et al. The immunosuppressant leflunomide inhibits lymphocyte proliferation by inhibiting pyrimidine biosynthesis. J Pharmacol Exp Ther 1995;275:1043–1049.
4. Korn T, Toyka K, Hartung HP, Jung S. Suppression of experimental autoimmune neuritis by leflunomide. Brain 2001;124:1791–1802.
5. Paty DW, Oger JJ, Kastrukoff LF, et al. MRI in the diagnosis of MS: a prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. Neurology 1988;38:180–185.
6. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13:227–231.
7. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444–1452.
8. Li DK, Paty DW, the UBC MS/MRI Analysis Research Group and the PRISMS Study Group. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta la in relapsing–remitting multiple sclerosis. Ann Neurol 1999;46:197–206.

9. Chambers CD, Johnson DL, Macaraeg GR, Jones KL. Pregnancy outcome following early gestational exposure to leflunomide: the Otis Rheumatoid Arthritis in Pregnancy Study (104). Pharmacoepidemiol Drug Saf 2004;13(suppl S1):S126–S127.
10. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. Ann Neurol 2001;49:290–297.
11. Jacobs LD, Cookfair DL, Rudick RA, et al. The Multiple Sclerosis Collaborative Research Group (MSCRG). Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996;39:385–394.
12. Simon JH, Jacobs LD, Campion M, et al. Magnetic resonance studies of intramuscular interferon β-1a for relapsing multiple sclerosis. Ann Neurol 1998;43:79–87.
13. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2003; 348:15–23.
14. Sormai MP, Bruzzi P, Comi G, Fillipi M. MRI metrics as surrogate markers for clinical relapse rate in relapsing–remitting MS patients. Neurology 2002;58:417–421.