ORIGINAL ARTICLE

Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis

Lawrence Steinman, M.D., Edward Fox, M.D., Ph.D., Hans-Peter Hartung, M.D., Enrique Alvarez, M.D., Ph.D., Peiqing Qian, M.D., Sibyl Wray, M.D., Derrick Robertson, M.D., DeRen Huang, M.D., Ph.D., Krzysztof Selmaj, M.D., Ph.D., Daniel Wynn, M.D., Gary Cutter, Ph.D., Koby Mok, Ph.D., Yanzhi Hsu, Ph.D., Yihuan Xu, Ph.D., Michael S. Weiss, J.D., Jenna A. Bosco, B.S., Sean A. Power, B.S., Lily Lee, Ph.D., Hari P. Miskin, M.Sc., and Bruce A.C. Cree, M.D., Ph.D., for the ULTIMATE I and ULTIMATE II Investigators*

ABSTRACT

BACKGROUND

The monoclonal antibody ublituximab enhances antibody-dependent cellular cytolysis and produces B-cell depletion. Ublituximab is being evaluated for the treatment of relapsing multiple sclerosis.

METHODS

In two identical, phase 3, double-blind, double-dummy trials (ULTIMATE I and II), participants with relapsing multiple sclerosis were randomly assigned in a 1:1 ratio to receive intravenous ublituximab (150 mg on day 1, followed by 450 mg on day 15 and at weeks 24, 48, and 72) and oral placebo or oral teriflunomide (14 mg once daily) and intravenous placebo. The primary end point was the annualized relapse rate. Secondary end points included the number of gadolinium-enhancing lesions on magnetic resonance imaging (MRI) by 96 weeks and worsening of disability.

RESULTS

A total of 549 participants were enrolled in the ULTIMATE I trial, and 545 were enrolled in the ULTIMATE II trial; the median follow-up was 95 weeks. In the ULTIMATE I trial, the annualized relapse rate was 0.08 with ublituximab and 0.19 with teriflunomide (rate ratio, 0.41; 95% confidence interval [CI], 0.27 to 0.62; P<0.001); in the ULTIMATE II trial, the annualized relapse rate was 0.09 and 0.18, respectively (rate ratio, 0.51; 95% CI, 0.33 to 0.78; P=0.002). The mean number of gadolinium-enhancing lesions was 0.02 in the ublituximab group and 0.49 in the teriflunomide group (rate ratio, 0.03; 95% CI, 0.02 to 0.06; P<0.001) in the ULTIMATE I trial and 0.01 and 0.25, respectively (rate ratio, 0.04; 95% CI, 0.02 to 0.06; P<0.001), in the ULTIMATE II trial. In the pooled analysis of the two trials, 5.2% of the participants in the ublituximab group and 5.9% in the teriflunomide group had worsening of disability at 12 weeks (hazard ratio, 0.84; 95% CI, 0.50 to 1.41; P=0.51). Infusion-related reactions occurred in 47.7% of the participants in the ublituximab group. Serious infections occurred in 5.0% in the ublituximab group and in 2.9% in the teriflunomide group.

CONCLUSIONS

Among participants with relapsing multiple sclerosis, ublituximab resulted in lower annualized relapse rates and fewer brain lesions on MRI than teriflunomide over a period of 96 weeks but did not result in a significantly lower risk of worsening of disability. Ublituximab was associated with infusion-related reactions. (Funded by TG Therapeutics; ULTIMATE I and II ClinicalTrials.gov numbers, NCT03277261 and NCT03277248.)

From the Beckman Center for Molecular Medicine, Stanford University, Stanford (L.S.), and the Weill Institute for Neurosciences, University of California, San Francisco, San Francisco (B.A.C.C.) — both in California; Central Texas Neurology Consultants, Round Rock (E.F.); Heinrich Heine University Medical School, Düsseldorf, Germany (H.-P.H.); the Brain and Mind Centre, University of Sydney, Sydney (H.-P.H.); Medical University of Vienna, Vienna (H.-P.H.); Palacký University Olomouc, Olomouc, Czech Republic (H.-P.H.); University of Colorado, Aurora (E.A.); Swedish Medical Center, Seattle (P.Q.); Hope Neurology, Knoxville, TN (S.W.); University of South Florida, Tampa (D.R.); Columbus Neuroscience, Westerville, OH (D.H.); the Department of Neurology, University of Warmia and Mazury, Olsztyn, and Center of Neurology, Lodz — both in Poland (K.S.); Consultants in Neurology, Northbrook, IL (D.W.); and TG Therapeutics, New York (G.C., K.M., Y.H., Y.X., M.S.W., J.A.B., S.A.P., L.L., H.P.M.). Dr. Steinman can be contacted at steinman@stanford.edu or at the Beckman Center for Molecular Medicine, Stanford University, 279 Campus Dr., Rm. B002, Stanford, CA 94305.

*A complete list of investigators in the ULTIMATE trials is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on August 25, 2022, at NEJM.org.

N Engl J Med 2022;387:704-14.
DOI: 10.1056/NEJMoa2201904
Copyright © 2022 Massachusetts Medical Society.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

The pathogenesis of multiple sclerosis includes the activity of B cells.[1] Monoclonal antibodies targeting the B-cell antigen CD20 (e.g., rituximab, ocrelizumab, and ofatumumab) have shown efficacy in patients with multiple sclerosis.[2-6] Ublituximab is a type I chimeric IgG1 monoclonal antibody that binds to an epitope on CD20 that is distinct from the epitopes targeted by other anti-CD20 antibodies.[7,8] Ublituximab is glycoengineered with a low fucose content in its fragment crystallizable region, which enhances its affinity for all variants of FcγRIIIa (or CD16A) and activates natural killer (NK)–cell function. In experimental studies, ublituximab showed NK cell–mediated antibody-dependent cellular cytolysis[7-9] while maintaining complement-mediated lysis.[10] In in vitro studies,[11] ublituximab had 25 to 30 times the antibody-dependent cellular cytolysis potential of other anti-CD20 antibodies. In a small phase 2, placebo-controlled trial involving participants with relapsing multiple sclerosis, ublituximab induced B-cell depletion within 24 hours.[8] Over a period of 48 weeks, participants who received ublituximab had an annualized relapse rate of 0.07 and displayed no gadolinium-enhancing lesions on T1-weighted magnetic resonance imaging (MRI).[8] We conducted two identically designed, phase 3, double-blind, randomized, active-controlled trials (ULTIMATE I and ULTIMATE II) in parallel to evaluate the efficacy and safety of ublituximab infusions as compared with oral teriflunomide, an inhibitor of pyrimidine synthesis, in patients with relapsing multiple sclerosis.

Methods

Trial Oversight

The trials were designed by the sponsor (TG Therapeutics), with guidance from an external steering committee. The sponsor analyzed the data, provided both of the trial drugs and the placebos, and paid for medical writing assistance. Confidentiality agreements were in place between the authors and the sponsor. The sponsor had the right to stop or delay the publication of the manuscript. An independent data and safety monitoring board regularly reviewed unblinded data and could advise the sponsor to stop the trial for efficacy, detrimental effects, or futility.

The protocols (available with the full text of this article at NEJM.org) were approved by the institutional review boards or independent ethics committees at each trial center (see the Supplementary Appendix, available at NEJM.org). The trials were conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

A Quick Take is available at NEJM.org

Participants

Key eligibility criteria were an age of 18 to 55 years; a diagnosis of relapsing multiple sclerosis (meeting 2010 revised McDonald criteria)[12]; at least two relapses in the previous 2 years, or one relapse or at least one gadolinium-enhancing lesion or both in the year before screening; brain MRI with abnormalities consistent with multiple sclerosis; a score on the Expanded Disability Status Scale (EDSS) of 0 to 5.5 at screening (scores range from 0 to 10.0, with higher scores indicating greater disability)[13]; and neurologic stability for at least 30 days before screening and the baseline assessment. Key exclusion criteria, including the use of previous disease-modifying treatments and the durations of washout periods, are provided in the Additional Methodology Details section in the Supplementary Appendix.

Trial Design

The ULTIMATE I and ULTIMATE II trials were identically designed, phase 3, multicenter, double-blind, double-dummy, randomized, active-controlled trials conducted in parallel at non-overlapping sites. Participants were randomly assigned in a 1:1 ratio by means of an interactive Web-response system to receive intravenous ublituximab (at a dose of 150 mg on day 1 for a duration of 4 hours, followed by 450 mg for a duration of 1 hour on day 15 and at weeks 24, 48, and 72) in addition to oral placebo or to receive oral teriflunomide (at a dose of 14 mg once daily starting on day 1 and continuing until the last day of week 95) in addition to intravenous placebo on the same schedule as that in the ublituximab group (Fig. S1 and Table S1 in the Supplementary Appendix). No stratification factors were used in the randomization process. An antihistamine (oral diphenhydramine at a dose of 50 mg or equivalent) and oral dexamethasone (at a dose of 10 to 20 mg) or equivalent glucocorticoid were administered 30 to 60 minutes before each dose of ublituximab or intravenous

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

placebo in all participants. Treatment of symptoms and reductions in infusion flow rates were permitted in order to manage infusion-related reactions. Acetaminophen premedication was allowed at the discretion of the site investigator for participants who had pyrexia after the week 1 dose. On cessation of trial medication (after early termination or at week 96), participants could enter a 20-week follow-up period for monitoring of safety and relapses and to undergo teriflunomide-accelerated elimination (additional information is provided in the protocol and the Supplementary Appendix).

END POINTS

The primary efficacy end point was the annualized relapse rate, defined as the number of confirmed relapses of multiple sclerosis per participant-year, according to prespecified criteria (see the Supplementary Appendix). Each suspected relapse was adjudicated by an independent panel to confirm a protocol-defined relapse. The trial sponsor team, site investigators, and the steering committee were unaware of treatment assignments throughout the trials.

There were six hierarchically ordered secondary end points: the total number of gadolinium-enhancing lesions per T1-weighted MRI scan by week 96; the total number of new or enlarging hyperintense lesions per T2-weighted MRI scan by week 96; worsening of disability confirmed at 12 weeks (pooled across the two trials); the number of participants with no evidence of disease activity from week 24 to week 96; the number of participants who had impaired status according to the Symbol Digit Modalities Test (a test for cognitive impairment that involves patients substituting a number for displayed geometric figures with the use of a key; impaired status was defined as a decrease from baseline of ≥4 points at any postbaseline assessment up to the week 96 visit)[14]; and the percentage change in brain volume from baseline to week 96 (Fig. S2). An MRI scan was obtained before administration of the trial drug and therefore was presumably not affected by glucocorticoids that were administered with infusions.

Prespecified tertiary end points, which were not included in the hierarchical analysis, were worsening of disability confirmed at 24 weeks (defined as an increase of ≥1.0 point from the baseline EDSS score if the baseline score was ≤5.5 or an increase of ≥0.5 points if the baseline score was >5.5, sustained for at least 24 weeks), pooled across trials; lessening of disability (defined as a reduction from the baseline EDSS score of ≥1.0 point, or ≥0.5 points if the baseline EDSS score was >5.5, sustained for at least 12 weeks or 24 weeks), pooled across the trials; and the change in the Multiple Sclerosis Functional Composite score (a three-part assessment of key clinical factors: leg function and ambulation, arm and hand function, and cognitive function; scores for each component are converted to standard scores [z scores], which are averaged to generate a single score). Participants reported adverse events at each visit; events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03. Clinical laboratory tests such as hematologic assessments, chemical analysis, pregnancy tests, 12-lead electrocardiography, and assessment of vital signs were conducted. Any suspected opportunistic infections in the central nervous system, including progressive multifocal leukoencephalopathy, were evaluated by experts who reviewed brain MRI scans and performed additional clinical and laboratory follow-up as needed. More information is provided in the protocol.

STATISTICAL ANALYSIS

On the basis of results from the OPERA trials,[7] and assuming that up to 10% of patients would withdraw from the trial and that there would be a 40% lower annualized relapse rate with ublituximab than with teriflunomide, we calculated that a sample size of 220 participants per group per trial and 1:1 randomization would provide a power of 80%, at a two-sided type I error rate of 0.05. A sample-size reassessment by an independent committee, the members of which were unaware of trial-group assignments, was prespecified and resulted in the target sample size being increased to 250 per group for each trial (see the Supplementary Appendix).

The efficacy analyses, with the exception of MRI-related analyses, were performed in the prespecified modified intention-to-treat populations, which included all participants who received at least one dose of a trial drug and had one baseline and at least one postbaseline efficacy assessment. The safety population included

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

all participants who received at least one dose of a trial drug. Safety data were collected during the treatment period and follow-up period until a participant's last visit. MRI end points were assessed in the subgroup of participants in the modified intention-to-treat population who had baseline and postbaseline MRI scans available. The annualized relapse rate was analyzed with the use of a negative binomial regression model for treatment differences between ublituximab and teriflunomide, with an offset for time in the trial, and with clinic region and EDSS score (baseline score of ≤3.5 or >3.5) as covariates. Details regarding the methods used for the analysis of secondary end points are provided in the statistical analysis plan (available with the protocol). Results of sensitivity analyses for efficacy end points as prespecified in the statistical analysis plan are provided in Tables S2 through S6.

If the results of the primary end point were significant, secondary end points were tested in a hierarchical manner in the order presented above. The results of end points at and after the first point of failure in the hierarchical analysis were considered to be not significantly different between the trial groups. All hypothesis tests were conducted at a two-sided significance level of 0.05. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute). Details are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

Between September 22, 2017, and October 4, 2018, participants from 104 sites across 10 countries (see the Supplementary Appendix) underwent randomization: 549 participants were included in the ULTIMATE I trial (274 participants in the ublituximab group and 275 in the teriflunomide group), and 545 participants were included in the ULTIMATE II trial (272 in the ublituximab group and 273 in the teriflunomide group). The median follow-up was 95 weeks. In the ULTIMATE I trial, 87.6% of the participants in the ublituximab group and 91.6% in the teriflunomide group completed the trial and had end-point data available; in the ULTIMATE II trial, 93.4% of the participants in the ublituximab group and 87.5% in the teriflunomide group completed the trial and had end-point data. Demographic and disease characteristics were similar in the two trials and in the treatment groups (Table 1). The representativeness of the trial population with respect to the demographic characteristics of persons with multiple sclerosis is shown in Table S7. As compared with the population of patients with multiple sclerosis in the United States, Black participants were underrepresented in both trials, owing to the majority of sites being in Eastern Europe.

EFFICACY

Primary End Point

In the ULTIMATE I trial, the adjusted annualized relapse rate over a period of 96 weeks was 0.08 in the ublituximab group and 0.19 in the teriflunomide group (rate ratio, 0.41; 95% confidence interval [CI], 0.27 to 0.62; P<0.001). The corresponding rates in the ULTIMATE II trial were 0.09 and 0.18 (rate ratio, 0.51; 95% CI, 0.33 to 0.78; P=0.002) (Table 2 and Fig. S4A).

MRI-Related End Points

In the ULTIMATE I trial, 265 participants in the ublituximab group and 270 participants in the teriflunomide group underwent imaging assessments; in the ULTIMATE II trial, 272 participants and 267 participants, respectively, underwent imaging assessments. In the ULTIMATE I trial, the mean total number of gadolinium-enhancing lesions per T1-weighted MRI scan was 0.02 in the ublituximab group and 0.49 in the teriflunomide group (rate ratio, 0.03; 95% CI, 0.02 to 0.06; P<0.001); in the ULTIMATE II trial, the corresponding numbers were 0.01 and 0.25 (rate ratio, 0.04; 95% CI, 0.02 to 0.06; P<0.001) (Table 2 and Fig. S4B). In the ULTIMATE I trial, the mean total number of new or enlarging hyperintense lesions per T2-weighted MRI scan was 0.21 in the ublituximab group and 2.79 in the teriflunomide group (rate ratio, 0.08; 95% CI, 0.06 to 0.10; P<0.001); in the ULTIMATE II trial, the corresponding numbers were 0.28 and 2.83 (rate ratio, 0.10; 95% CI, 0.07 to 0.14; P<0.001) (Table 2 and Fig. S4C). The percent change in brain volume was not considered to be significantly different between groups because of the failure of the preceding clinical end point in the hierarchical analysis (worsening of disability at 12 weeks), and because the 95% confidence

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

Table 1. Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristic	ULTIMATE I Trial		ULTIMATE II Trial	
	Ublituximab (N=271)	Teriflunomide (N=274)	Ublituximab (N=272)	Teriflunomide (N=272)
Age — yr	36.2±8.2	37.0±9.6	34.5±8.8	36.2±9.0
Female sex — no. (%)	166 (61.3)	179 (65.3)	178 (65.4)	176 (64.7)
Race — no. (%)†				
White	264 (97.4)	266 (97.1)	269 (98.9)	268 (98.5)
Black	6 (2.2)	6 (2.2)	2 (0.7)	3 (1.1)
Other	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.4)
Type of multiple sclerosis — no. (%)				
Relapsing–remitting	264 (97.4)	270 (98.5)	268 (98.5)	267 (98.2)
Secondary progressive	7 (2.6)	4 (1.5)	4 (1.5)	5 (1.8)
Time since symptom onset — yr	7.5±6.5	6.8±5.9	7.3±6.5	7.4±6.3
Time since diagnosis — yr	4.9±5.2	4.5±5.0	5.0±5.6	5.0±5.2
No previous disease-modifying therapy — no. (%)‡	162 (59.8)	162 (59.1)	138 (50.7)	155 (57.0)
Previous disease-modifying therapy — no. (%)				
Interferon§	52 (19.2)	49 (17.9)	71 (26.1)	58 (21.3)
Glatiramer acetate	45 (16.6)	36 (13.1)	40 (14.7)	34 (12.5)
Laquinimod	19 (7.0)	22 (8.0)	29 (10.7)	30 (11.0)
Dimethyl fumarate	8 (3.0)	7 (2.6)	4 (1.5)	1 (0.4)
Fingolimod	5 (1.8)	2 (0.7)	2 (0.7)	3 (1.1)
Other	7 (2.6)	17 (6.2)	17 (6.2)	18 (6.6)
No. of relapses in previous 12 mo	1.3±0.6	1.4±0.7	1.3±0.6	1.2±0.6
No. of relapses in previous 24 mo	1.8±1.0	2.0±1.1	1.8±0.9	1.8±0.9
EDSS score at screening¶	3.0±1.2	2.9±1.2	2.8±1.3	3.0±1.2
Volume of lesions on T2-weighted MRI — cm^3‖	15.9±16.0	14.9±15.8	14.7±13.5	15.7±17.5
No. of T2 lesions‖	64.1±38.6	60.4±37.0	65.3±41.2	64.0±41.2
Absence of gadolinium-enhancing lesions on T1-weighted MRI scan — no./total no. (%)‖	153/270 (56.7)	156/272 (57.4)	131/272 (48.2)	135/270 (50.0)
No. of gadolinium-enhancing lesions at baseline‖	2.3±5.5	1.6±3.7	2.6±5.8	2.5±5.5

* Plus–minus values are means ±SD. The modified intention-to-treat population included all participants who received at least one dose of a trial drug and had one baseline and at least one postbaseline efficacy assessment. MRI denotes magnetic resonance imaging.
† Race was reported by the participants.
‡ No previous disease-modifying therapy was defined as no disease-modifying therapy in the 5 years before trial entry.
§ Interferon therapies include interferon beta, interferon beta-1a, and interferon beta-1b.
¶ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10.0, with higher scores indicating greater disability.
‖ Data were missing for 1 participant in the ublituximab group and 2 participants in the teriflunomide group in the ULTIMATE I trial and for 2 participants in the teriflunomide group in the ULTIMATE II trial.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

intervals for the between-group differences included zero in the ULTIMATE II trial (but not in the ULTIMATE I trial).

Disability-Related End Points

In the prespecified pooled analysis, 5.2% of the participants in the ublituximab group had worsening of disability confirmed at 12 weeks, as compared with 5.9% of the participants in the teriflunomide group (hazard ratio, 0.84; 95% CI, 0.50 to 1.41; P=0.51) (Table 2 and Fig. 1A); 3.3% of the participants in the ublituximab group had worsening of disability confirmed at 24 weeks, as compared with 4.8% of the participants in the teriflunomide group (hazard ratio, 0.66; 95% CI, 0.36 to 1.21) (Fig. 1A and Table S8). These and all subsequent results were not considered to be significantly different between trial groups because of the failure of the hierarchical analysis. In the ULTIMATE I trial, no evidence of disease activity was observed in 44.6% of the participants in the ublituximab group and in 15.0% of the participants in the teriflunomide group. Similar results were observed in the ULTIMATE II trial, with 43.0% and 11.4%, respectively, having no evidence of disease activity (Table 2 and Fig. S5). The percentage of participants with impairment according to the Symbol Digit Modalities Test was similar in the two groups in both trials (in the ULTIMATE I trial, 29.2% in the ublituximab group and 31.8% in the teriflunomide group; in the ULTIMATE II trial, 29.0% and 31.6%, respectively) (Table 2).

In the prespecified pooled tertiary analysis that was not included in the hierarchical analysis and from which no conclusions can be drawn, 12.0% of the participants who received ublituximab had lessening of disability confirmed at 12 weeks, as compared with 6.0% of the participants who received teriflunomide (hazard ratio, 2.16; 95% CI, 1.41 to 3.31); 9.6% of the participants who received ublituximab had lessening of disability confirmed at 24 weeks, as compared with 5.1% of the participants who received teriflunomide (hazard ratio, 2.03; 95% CI, 1.27 to 3.25) (Fig. 1B). With respect to the tertiary end point of change from baseline in the Multiple Sclerosis Functional Composite score, in the ULTIMATE I trial, the change to week 96 was 0.47 points in the ublituximab group and 0.27 points in the teriflunomide group. In the ULTIMATE II trial, the corresponding values were 0.52 points and 0.28 points, respectively (Fig. S6).

CD19+ B-Cell Counts

Participants who received ublituximab had a 96% decrease in the median number of CD19+ B cells 24 hours after the first dose, and participants who received teriflunomide had a 53% increase. Through the end of the double-blind period, counts were reduced by 97% with ublituximab and by 18% with teriflunomide (Fig. S7).

SAFETY

Adverse Events and Deaths

In a pooled analysis of the two trials, 486 of 545 participants (89.2%) who received ublituximab and 501 of 548 participants (91.4%) who received teriflunomide had at least one adverse event. Grade 3 or higher adverse events occurred in 116 participants (21.3%) who received ublituximab and in 77 (14.1%) who received teriflunomide. The most common adverse events that occurred in at least 10% of ublituximab recipients were infusion-related reactions (47.7%), headache (34.3%), nasopharyngitis (18.3%), pyrexia (13.9%), and nausea (10.6%). Adverse events that occurred in at least 10% of teriflunomide recipients included headache (26.6%), nasopharyngitis (17.9%), alopecia (15.3%), infusion-related reactions (12.2%), and diarrhea (10.6%) (Table S9).

Serious adverse events occurred in 59 ublituximab recipients (10.8%) and in 40 teriflunomide recipients (7.3%) (Table 3). Three deaths occurred among ublituximab recipients — one each as a result of pneumonia, encephalitis after measles, and salpingitis after an ectopic pregnancy.

Infections

Infections occurred in 304 participants (55.8%) who received ublituximab and in 298 participants (54.4%) who received teriflunomide. Most infections were respiratory tract–related and were grade 1 or 2 in severity. Nasopharyngitis occurred in 18.3% of ublituximab recipients and in 17.9% of teriflunomide recipients; respiratory

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

Table 2. End Points (Modified Intention-to-Treat Population) and Prespecified Pooled Analysis.*

End Points	ULTIMATE I Trial			ULTIMATE II Trial			Pooled Trials		
	Ublituximab (N=271)	Teriflunomide (N=274)	P Value	Ublituximab (N=272)	Teriflunomide (N=272)	P Value	Ublituximab (N=543)	Teriflunomide (N=546)	P Value
Primary end point									
Adjusted annualized relapse rate (95% CI)	0.08 (0.04 to 0.14)	0.19 (0.12 to 0.28)		0.09 (0.05 to 0.17)	0.18 (0.11 to 0.29)				
Rate ratio (95% CI)	0.41 (0.27 to 0.62)		<0.001	0.51 (0.33 to 0.78)		0.002			
Secondary MRI-related end points†									
Gadolinium-enhancing lesions per T1-weighted MRI scan by wk 96, per scan per participant‡									
Mean (95% CI)	0.02 (0.01 to 0.03)	0.49 (0.35 to 0.68)		0.01 (0.00 to 0.02)	0.25 (0.16 to 0.39)				
Rate ratio (95% CI)	0.03 (0.02 to 0.06)		<0.001	0.04 (0.02 to 0.06)		<0.001			
New or enlarging hyperintense lesions per T2-weighted MRI scan by wk 96§									
Mean (95% CI)	0.21 (0.14 to 0.32)	2.79 (2.14 to 3.64)		0.28 (0.20 to 0.40)	2.83 (2.13 to 3.77)				
Rate ratio (95% CI)	0.08 (0.06 to 0.10)		<0.001	0.10 (0.07 to 0.14)		<0.001			
Percent change in brain volume from baseline to wk 96¶									
Least-squares mean (95% CI)	−0.20 (−0.23 to −0.17)	−0.13 (−0.16 to −0.10)		−0.19 (−0.23 to −0.16)	−0.18 (−0.21 to −0.15)				
Difference	−0.07 (−0.11 to −0.04)		—	−0.02 (−0.05 to 0.02)		—			
Secondary disability-related end points									
Worsening of disability confirmed at 12 wk‖									
No. of participants (%)							28 (5.2)	32 (5.9)	
Hazard ratio (95% CI)							0.84 (0.50 to 1.41)		0.51
No evidence of disease activity, wk 24 to wk 96**									
No. of participants (%)	121 (44.6)	41 (15.0)		117 (43.0)	31 (11.4)				
Odds ratio (95% CI)	5.44 (3.54 to 8.38)		—	7.95 (4.92 to 12.84)		—			

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

Worsening on Symbol Digit Modalities Test from baseline to wk 96						
No. of participants (%)	79 (29.2)	87 (31.8)		79 (29.0)	86 (31.6)	
Odds ratio (95% CI)	0.87 (0.60 to 1.26)		—	0.86 (0.60 to 1.25)		—

* All rate ratios, hazard ratios, odds ratios, and difference values are for the ublituximab group as compared with the teriflunomide group. The order of the secondary end points according to the hierarchical analysis plan is provided in the Statistical Analysis section in the Supplementary Appendix. The hierarchy failed at the third secondary end point (worsening of disability confirmed at 12 weeks). Dashes indicate P values that are not provided because of the failure of hierarchical testing results.

† Secondary MRI-related end points were assessed in 265 participants in the ublituximab group and 270 participants in the teriflunomide group in the ULTIMATE I trial and in 272 participants in the ublituximab group and 267 participants in the teriflunomide group in the ULTIMATE II trial.

‡ The total number of gadolinium-enhancing T1-lesions was calculated as the sum of the individual number of lesions at weeks 12, 24, 48, and 96, divided by the total number of MRI scans of the brain.

§ The total number of new or enlarging lesions was calculated as the sum of the individual number of lesions at weeks 24, 48, and 96, divided by the total number of MRI scans of the brain.

¶ The change in brain volume was assessed with the use of a mixed model for repeated measures of the percent changes from baseline in the cube root–transformed volume.

‖ Worsening of disability that was confirmed at 12 weeks was defined as an increase of 1.0 or more points in the EDSS score if the baseline score was 5.5 or lower, or an increase of 0.5 or more points if the baseline score was greater than 5.5, sustained for at least 12 weeks.

** No evidence of disease activity was defined as no confirmed relapses, no MRI activity, and no worsening of disability at 12 weeks from week 24 to week 96, including week 24.

tract infections occurred in 7.7% and 6.9%, respectively; pharyngitis occurred in 5.9% and 2.2%, respectively; and urinary tract infections occurred in 4.0% and 5.3%, respectively. Serious infections occurred in 5.0% of ublituximab recipients and in 2.9% of teriflunomide recipients. Seven participants (1.3%) who received ublituximab and 1 participant (0.2%) who received teriflunomide discontinued one of the trials because of an infection. No opportunistic infections were reported. Changes in immunoglobulin levels are shown in Figure S8.

Herpes virus–associated infections occurred in 5.7% of ublituximab recipients and in 4.6% of teriflunomide recipients. All were grade 1 or 2 in severity and resolved. There were no cases of progressive multifocal leukoencephalopathy in either group over a period of 96 weeks.

Infusion-Related Reactions

Infusion-related reactions occurred in 47.7% of the participants who received ublituximab. Pyrexia, headache, chills, and influenza-like illness were the most frequently reported events. Most were mild to moderate in severity (as graded by the investigator), were reported at the time of the first infusion (43.3%), and decreased in frequency with subsequent doses (Fig. S9). Grade 3 or higher infusion-related reactions were observed in 2.8% of the participants who received ublituximab. Two participants had a grade 4 infusion-related reaction. One participant had anaphylaxis during the second infusion; the participant recovered, and no further doses of ublituximab were administered. The other participant had a decrease in lymphocytes at the first infusion; treatment was not needed, and the dosage was not changed. Six participants (1.1%) discontinued ublituximab because of an infusion-related reaction, including three participants during the first infusion and three after the first infusion (Table S10).

DISCUSSION

In the ULTIMATE I and II trials, which involved participants with relapsing multiple sclerosis, treatment with ublituximab resulted in a lower annualized relapse rate and fewer brain lesions on MRI than teriflunomide. The percentage of participants with worsening of disability was similar in the two treatment groups. In both trials,

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

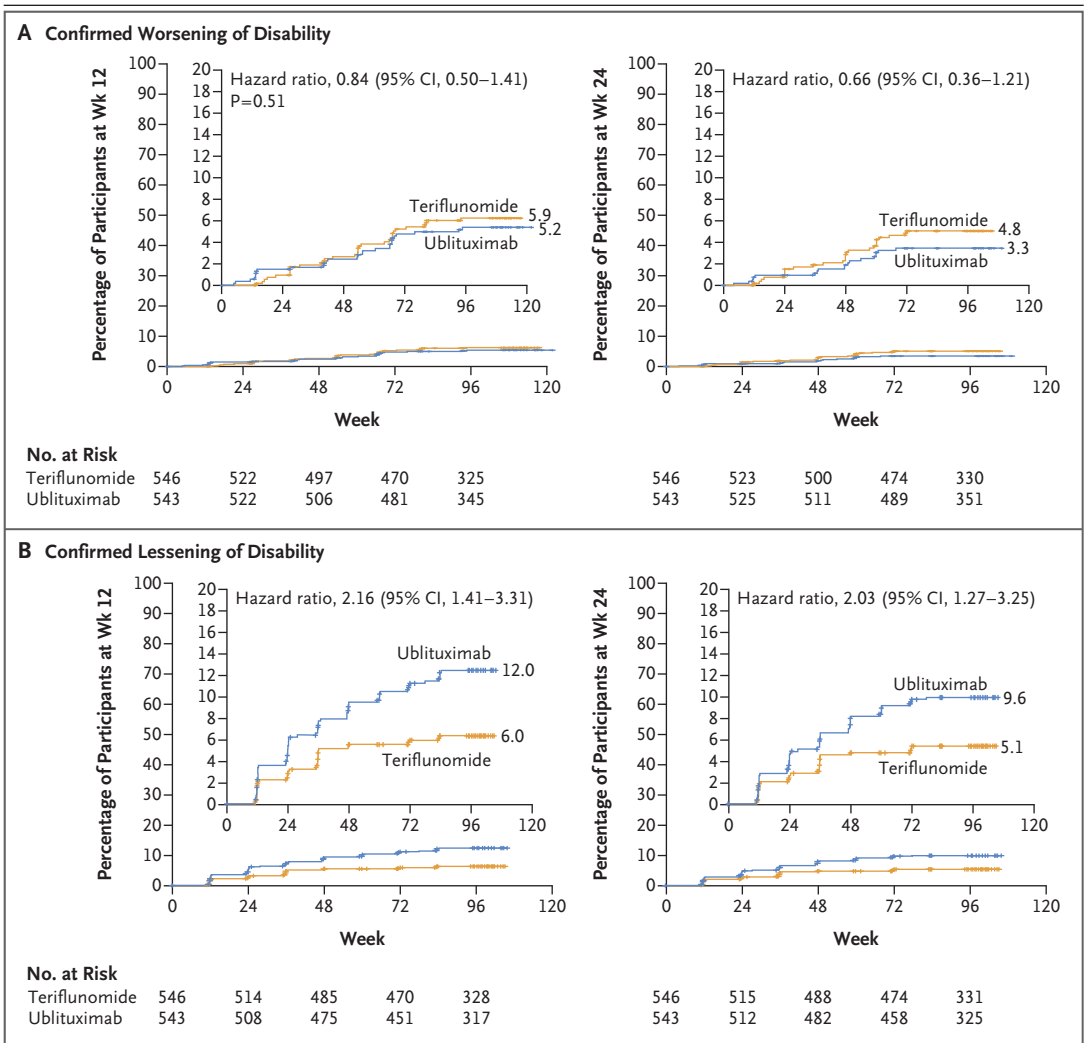

Figure 1. Confirmed Worsening of Disability and Lessening of Disability.

Shown are Kaplan–Meier estimates of the percentages of participants in the modified intention-to-treat population with worsening of disability confirmed at 12 weeks and at 24 weeks (Panel A) and of participants with lessening of disability confirmed at 12 weeks and at 24 weeks (Panel B) pooled across both trials. The modified intention-to-treat population included all participants who received at least one dose of a trial drug and had one baseline and at least one postbaseline efficacy assessment. Because of the failure in the hierarchical testing of the end point of worsening of disability confirmed at 12 weeks, between-group differences in worsening of disability at 24 weeks and lessening of disability were not considered to be significant. Participants were at risk until week 84; worsening of disability or lessening of disability that first occurred at week 96 could not be confirmed. Hazard ratios were estimated with the use of a Cox regression model with treatment group as a covariate. The tick marks indicate censored data. The inset in each panel shows the same data on an enlarged y axis.

teriflunomide was associated with a numerically lower rate of worsening of disability than that reported in previous studies with this drug, but no conclusions can be drawn from these comparisons.[4,15] The low annualized relapse rate in both groups in each of the current trials may have led to a lower rate of worsening of disability associated with relapse.

After 6 months, similar slight reductions in brain volume were observed in the two groups in each trial (Fig. S11). The percent change in brain volume from baseline to week 96 may have been

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

Table 3. Adverse Events (Safety Population).*

Event	ULTIMATE I Trial		ULTIMATE II Trial	
	Ublituximab (N=273)	Teriflunomide (N=275)	Ublituximab (N=272)	Teriflunomide (N=273)
	number of participants (percent)			
Any adverse event	235 (86.1)	245 (89.1)	251 (92.3)	256 (93.8)
Adverse event leading to treatment discontinuation	18 (6.6)	2 (0.7)	5 (1.8)	2 (0.7)
Infection	135 (49.5)	133 (48.4)	169 (62.1)	165 (60.4)
Infusion-related reaction	120 (44.0)	19 (6.9)	140 (51.5)	48 (17.6)
Neoplasm†	0	0	2 (0.7)	1 (0.4)
Serious adverse event	31 (11.4)	19 (6.9)	28 (10.3)	21 (7.7)
Serious infection‡	15 (5.5)	6 (2.2)	12 (4.4)	10 (3.7)
Death§	2 (0.7)	0	1 (0.4)	0

* The safety population included all participants who received at least one dose of a trial drug. Shown are the data collected during the double-blind, controlled treatment period.
† In both trials, neoplasms that occurred in the ublituximab group were endometrial (time to onset, 558 days) and uterine (time to onset, 210 days). A tongue neoplasm (time to onset, 494 days) occurred in the teriflunomide group.
‡ In both trials, the most frequently reported serious infections were pneumonia in the ublituximab group and urinary tract infections in the teriflunomide group.
§ The deaths that occurred in the ublituximab group were due to pneumonia (deemed to be possibly related to treatment), encephalitis (after measles), and salpingitis (after ectopic pregnancy).

obscured by an early increase in brain volume in the teriflunomide group, an observation that has been reported previously.[15,16]

Infusion-related reactions were common with ublituximab and occurred in almost half the participants; the reactions may have been related to cytokine release from immune cells (B and NK cells) on interaction of the Fc antibody domain with Fcγ receptors on effector cells.[17] Infusion-related reactions associated with ublituximab were mostly mild to moderate in severity and decreased in frequency with subsequent doses, despite increases in infusion flow rates after the first infusion. Six participants discontinued ublituximab because of infusion-related reactions, including five grade 2 infusion-related reactions and one grade 4 event of anaphylaxis. Although no opportunistic infections occurred in either group in either of the trials, a higher frequency of infections, including serious infections, was observed with ublituximab than with teriflunomide. Long-term assessment of ublituximab is required to determine whether progressive multifocal leukoencephalopathy would occur with continued treatment.

A limitation of these trials is that they do not allow inferences to be made regarding the efficacy of ublituximab as compared with other multiple sclerosis therapies that are more potent than teriflunomide. The baseline characteristics of the participants were generally consistent with previous anti-CD20 trials in relapsing multiple sclerosis, with the exception that participants from Eastern Europe were overrepresented.

In these two 96-week trials involving participants with multiple sclerosis, annualized relapse rates were lower with intravenous ublituximab than with oral teriflunomide. Ublituximab was associated with infusion-related reactions. Larger and longer trials are required to determine the efficacy and safety of ublituximab in patients with relapsing multiple sclerosis, including comparison with other disease-modifying treatments such as existing anti-CD20 monoclonal antibodies.

Supported by TG Therapeutics.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.
A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.
We thank the participants and their families for their participation and commitment to these trials; the clinical trial team for the conduct of the trials; and Marina P. Gehring and Rachel Speer of Luminology Scientific Communications for medical writing assistance with an earlier version of the manuscript.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.

REFERENCES

1. Comi G, Bar-Or A, Lassmann H, et al. Role of B cells in multiple sclerosis and related disorders. Ann Neurol 2021;89:13-23.

2. Graf J, Mares J, Barnett M, et al. Targeting B cells to modify MS, NMOSD, and MOGAD: part 1. Neurol Neuroimmunol Neuroinflamm 2020;8(1):e918.

3. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376:221-34.

4. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. N Engl J Med 2020;383:546-57.

5. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017;376:209-20.

6. Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. Neurology 2016;87:2074-81.

7. Le Garff-Tavernier M, Decocq J, de Romeuf C, et al. Analysis of CD16+CD56dim NK cells from CLL patients: evidence supporting a therapeutic strategy with optimized anti-CD20 monoclonal antibodies. Leukemia 2011;25:101-9.

8. Fox E, Lovett-Racke AE, Gormley M, et al. A phase 2 multicenter study of ublituximab, a novel glycoengineered anti-CD20 monoclonal antibody, in patients with relapsing forms of multiple sclerosis. Mult Scler 2021;27:420-9.

9. Le Garff-Tavernier M, Herbi L, de Romeuf C, et al. Antibody-dependent cellular cytotoxicity of the optimized anti-CD20 monoclonal antibody ublituximab on chronic lymphocytic leukemia cells with the 17p deletion. Leukemia 2014;28:230-3.

10. de Romeuf C, Dutertre C-A, Le Garff-Tavernier M, et al. Chronic lymphocytic leukaemia cells are efficiently killed by an anti-CD20 monoclonal antibody selected for improved engagement of FcgammaRIIIA/CD16. Br J Haematol 2008;140:635-43.

11. Alvarez E, Steinman L, Fox EJ, Hartung H-P, Qian P, Wray S, et al. Reduced disease progression with ublituximab vs teriflunomide in the phase 3 ULTIMATE I and II studies in relapsing multiple sclerosis. In: Abstracts from the 36th Annual Meeting of the Consortium of Multiple Sclerosis Centers, June 1–4, 2022. National Harbor, MD: Consortium of Multiple Sclerosis Centers. abstract.

12. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.

13. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-52.

14. Benedict RH, DeLuca J, Phillips G, et al. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult Scler 2017;23:721-33.

15. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365:1293-303.

16. Wolinsky JS, Narayana PA, Nelson F, et al. Magnetic resonance imaging outcomes from a phase III trial of teriflunomide. Mult Scler 2013;19:1310-9.

17. Paul F, Cartron G. Infusion-related reactions to rituximab: frequency, mechanisms and predictors. Expert Rev Clin Immunol 2019;15:383-9.

Copyright © 2022 Massachusetts Medical Society.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org by TOM HSIUNG on February 27, 2025. For personal use only.
No other uses without permission. Copyright © 2022 Massachusetts Medical Society. All rights reserved.