ORIGINAL ARTICLE

Ofatumumab versus Teriflunomide in Multiple Sclerosis

S.L. Hauser, A. Bar-Or, J.A. Cohen, G. Comi, J. Correale, P.K. Coyle, A.H. Cross, J. de Seze, D. Leppert, X. Montalban, K. Selmaj, H. Wiendl, C. Kerloeguen, R. Willi, B. Li, A. Kakarieka, D. Tomic, A. Goodyear, R. Pingili, D.A. Häring, K. Ramanathan, M. Merschhemke, and L. Kappos, for the ASCLEPIOS I and ASCLEPIOS II Trial Groups*

ABSTRACT

BACKGROUND

Ofatumumab, a subcutaneous anti-CD20 monoclonal antibody, selectively depletes B cells. Teriflunomide, an oral inhibitor of pyrimidine synthesis, reduces T-cell and B-cell activation. The relative effects of these two drugs in patients with multiple sclerosis are not known.

METHODS

In two double-blind, double-dummy, phase 3 trials, we randomly assigned patients with relapsing multiple sclerosis to receive subcutaneous ofatumumab (20 mg every 4 weeks after 20-mg loading doses at days 1, 7, and 14) or oral teriflunomide (14 mg daily) for up to 30 months. The primary end point was the annualized relapse rate. Secondary end points included disability worsening confirmed at 3 months or 6 months, disability improvement confirmed at 6 months, the number of gadolinium-enhancing lesions per T1-weighted magnetic resonance imaging (MRI) scan, the annualized rate of new or enlarging lesions on T2-weighted MRI, serum neurofilament light chain levels at month 3, and change in brain volume.

RESULTS

Overall, 946 patients were assigned to receive ofatumumab and 936 to receive teriflunomide; the median follow-up was 1.6 years. The annualized relapse rates in the ofatumumab and teriflunomide groups were 0.11 and 0.22, respectively, in trial 1 (difference, −0.11; 95% confidence interval [CI], −0.16 to −0.06; P<0.001) and 0.10 and 0.25 in trial 2 (difference, −0.15; 95% CI, −0.20 to −0.09; P<0.001). In the pooled trials, the percentage of patients with disability worsening confirmed at 3 months was 10.9% with ofatumumab and 15.0% with teriflunomide (hazard ratio, 0.66; P=0.002); the percentage with disability worsening confirmed at 6 months was 8.1% and 12.0%, respectively (hazard ratio, 0.68; P=0.01); and the percentage with disability improvement confirmed at 6 months was 11.0% and 8.1% (hazard ratio, 1.35; P=0.09). The number of gadolinium-enhancing lesions per T1-weighted MRI scan, the annualized rate of lesions on T2-weighted MRI, and serum neurofilament light chain levels, but not the change in brain volume, were in the same direction as the primary end point. Injection-related reactions occurred in 20.2% in the ofatumumab group and in 15.0% in the teriflunomide group (placebo injections). Serious infections occurred in 2.5% and 1.8% of the patients in the respective groups.

CONCLUSIONS

Among patients with multiple sclerosis, ofatumumab was associated with lower annualized relapse rates than teriflunomide. (Funded by Novartis; ASCLEPIOS I and II ClinicalTrials.gov numbers, NCT02792218 and NCT02792231.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Hauser at the UCSF Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, 675 Nelson Rising Ln., San Francisco, CA 94158, or at stephen.hauser@ucsf.edu; or to Dr. Kappos at the Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine, and Biomedical Engineering, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland, or at kapposl-pa@usb.ch.

*A complete list of investigators in the ASCLEPIOS I and ASCLEPIOS II Trial Groups is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Hauser and Kappos contributed equally to this article.

N Engl J Med 2020;383:546-57.
DOI: 10.1056/NEJMoa1917246

The pathophysiology of multiple sclerosis involves B cells. Anti-CD20 monoclonal antibodies that induce B-cell depletion, such as rituximab and ocrelizumab, are effective disease-modifying therapies for multiple sclerosis.[1-4] Ofatumumab, a fully human antibody that is used to treat chronic leukemia, binds to a region distinct from that of other anti-CD20 antibodies, including the smaller and the larger loop of CD20 receptors.[5] In experimental models, a high binding affinity and slow off-rate (slow dissociation of the binding between ofatumumab and the CD20 receptor in B cells) result in efficient B-cell lysis, mediated through complement-dependent and, to a lesser extent, antibody-dependent cytotoxicity.[5-7] In patients with multiple sclerosis, ofatumumab can be given at lower doses[8,9] than those studied in chronic lymphocytic leukemia and rheumatoid arthritis,[10-12] and ofatumumab can be administered subcutaneously by the patient after initial doses are given under medical supervision.[8] Experimental models have shown that there may be more direct access to lymph nodes through the lymphatic system with subcutaneous administration than with intravenous infusion,[13,14] but this has not been tested under clinical conditions. On treatment cessation, B-cell repletion and reconstitution of humoral immunity have been reported to occur faster with ofatumumab than with other intravenously administered B-cell–targeted therapies.[15-17]

Teriflunomide, an oral disease-modifying therapy for relapsing multiple sclerosis, inhibits pyrimidine synthesis, reducing T-cell and B-cell activation.[18,19] According to the results of one comparative prospective trial[4] and a network meta-analysis,[20] the efficacy of teriflunomide to reduce annualized relapse rates is similar to that of interferons and glatiramer acetate, but according to observational studies[21,22] it is probably inferior to other oral and monoclonal antibody treatments for multiple sclerosis. We report the results of two phase 3, randomized, double-blind, double-dummy, active-controlled clinical trials of identical design, which assessed the efficacy and safety of subcutaneous ofatumumab as compared with oral teriflunomide.

METHODS

TRIAL OVERSIGHT

The ASCLEPIOS I and II trials were designed by the sponsor (Novartis Pharma) in consultation with the steering committee. The investigators collected data, which were analyzed by the sponsor. The investigators, the sponsor, and the steering committee were unaware of treatment assignments throughout the trials. An independent data monitoring committee reviewed the safety of treatment using regular analyses performed by independent statisticians, who were not involved in the conduct of the trials. The manuscript was drafted with medical writing assistance funded by the sponsor. All the authors, including those employed by Novartis, had full access to the data and were involved in the critical review of all drafts of the manuscript. All the authors vouch for the accuracy and completeness of the data, the accurate reporting of adverse events, and the fidelity of the trials to the protocols (available with the full text of this article at NEJM.org). There were confidentiality agreements in place between the authors and the sponsor. Novartis supplied the trial drugs and placebo. The trials were conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice[23] and the principles of the Declaration of Helsinki.[24] The protocol was approved by an institutional review board or ethics committee at each trial site. All the patients or their legal representatives provided written informed consent before commencing trial-related procedures.

PATIENTS

Eligibility criteria at screening included an age of 18 to 55 years; a diagnosis of multiple sclerosis (according to the 2010 revised McDonald criteria[25]) with a relapsing–remitting course or a secondary progressive course with disease activity (according to the criteria of Lublin et al.[26]); an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 (scores range from 0 to 10.0, with higher scores indicating greater disability[27]); at least one relapse in the year before screening, at least two relapses in the 2 years before screening, or at least one lesion detected with the use of gadolinium enhancement (gadolinium-enhancing lesion) on magnetic resonance imaging (MRI) in the year before randomization; and a neurologically stable condition for at least 1 month before randomization. Key exclusion criteria, including the use of previous disease-modifying treatments and the durations of washout periods, are listed in the Additional Methodology Details section and Table S1 in the Supplementary Appendix, available at NEJM.org.

TRIAL DESIGN

ASCLEPIOS I and II were randomized, double-blind, double-dummy, active-controlled, multicenter trials of identical design that were conducted concurrently. Patients, centers, and investigators could participate in only one of the trials. The trials featured a blinded sample-size reestimation to adjust the sample size and trial duration on the basis of a predefined overall minimum event rate. Each trial was powered for the primary end point (annualized relapse rate); the combined trials provided the required sample size and power for the preplanned meta-analysis of disability worsening confirmed at 3 months or 6 months. Eligible patients were randomly assigned in a 1:1 ratio through interactive response technology to receive ofatumumab at a dose of 20 mg subcutaneously every 4 weeks after 20-mg loading doses at days 1, 7, and 14 or oral teriflunomide at a dose of 14 mg once daily, for up to 30 months. Patients in the ofatumumab group also received oral placebo and patients in the teriflunomide group also received subcutaneous placebo corresponding to the active drug in the other group. Patients received their first subcutaneous injection at the trial site, which was administered by a health care provider (investigator, trial nurse, or trial coordinator). On days 7 and 14 and at month 1, patients returned to the site to administer the injection themselves under the supervision of trial staff, who provided training on the correct method. The patient's ability to administer the injection had to be demonstrated and documented before administration at home after month 1 was permitted. Randomization was stratified according to geographic region and subtype of multiple sclerosis. (For more on trial design, see the Additional Methodology Details section in the Supplementary Appendix.)

END POINTS

The primary end point was the annualized relapse rate up to the end of the trial. The annualized relapse rate was defined as the number of confirmed relapses of multiple sclerosis per year, according to prespecified criteria. Secondary clinical end points were disability worsening confirmed at 3 months, disability worsening confirmed at 6 months, and disability improvement (i.e., lessening of disability) confirmed at 6 months; a prespecified meta-analysis of these end points used the combined data from both trials. Secondary MRI end points included the number of gadolinium-enhancing lesions per T1-weighted MRI scan, the number of new or enlarging lesions on T2-weighted MRI per year, and the annual rate of brain-volume loss (see the protocols of the trials). A secondary biomarker end point was the serum neurofilament light chain concentration at month 3 and beyond, analyzed centrally by Navigate BioPharma using single-molecule-array immunoassay technology. Exploratory secondary end points included the relationship between neurofilament light chain concentration at baseline and the formation of new or enlarging lesions on T2-weighted MRI or brain-volume loss. Adverse events were recorded at all visits and graded according to the Common Terminology Criteria for Adverse Events (CTCAE).[28] (For more on trial end points, see the Additional Methodology Details section and Safety section in the Supplementary Appendix.)

STATISTICAL ANALYSIS

We calculated that a sample size of 900 patients per trial would provide greater than 90% power in each trial to detect a 40% lower annualized relapse rate with ofatumumab than with teriflunomide. In the combined data from both trials, a sample of 900 patients per trial (i.e. a total of 1800 patients) would provide 90% power and 80% power to detect a 38.6% lower risk of disability worsening confirmed at 3 months and at 6 months, respectively, with ofatumumab than with teriflunomide. Sample size could be increased to a maximum of 1250 patients per trial, and the end of the trials was declared on the basis of a statistical projection when sufficient events had accumulated to power the analysis for the primary end point and the two end points of disability worsening. (For details, see the statistical analysis plan, available with the protocols at NEJM .org, and the Statistical Analyses section in the Supplementary Appendix.)

Efficacy analyses were carried out according to the intention-to-treat principle. Data on the annualized relapse rate were analyzed with the use of a negative binomial-regression model, with an offset for time spent in the trial in years to adjust for varying treatment durations among patients. The type I error was controlled by a statistical testing procedure, with seven prespecified secondary end points tested; disability worsening confirmed at 3 months or 6 months and disabil-

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Full Analysis Set).*

Characteristic	ASCLEPIOS I Trial		ASCLEPIOS II Trial	
	Ofatumumab (N=465)	Teriflunomide (N=462)	Ofatumumab (N=481)	Teriflunomide (N=474)
Age — yr†	38.9±8.8	37.8±9.0	38.0±9.3	38.2±9.5
Female sex — no. (%)	318 (68.4)	317 (68.6)	319 (66.3)	319 (67.3)
Type of multiple sclerosis — no. (%)				
Relapsing–remitting	438 (94.2)	434 (93.9)	452 (94.0)	450 (94.9)
Secondary progressive	27 (5.8)	28 (6.1)	29 (6.0)	24 (5.1)
Time since symptom onset — yr	8.36±6.84	8.18±7.21	8.20±7.40	8.19±7.38
Time since diagnosis — yr	5.77±6.05	5.64±6.20	5.59±6.38	5.48±6.00
No previous disease-modifying therapy — no. (%)	191 (41.1)	182 (39.4)	195 (40.5)	181 (38.2)
Previous disease-modifying therapy — no. (%)‡				
Any interferon beta	189 (40.6)	193 (41.8)	197 (41.0)	193 (40.7)
Glatiramer acetate	124 (26.7)	106 (22.9)	118 (24.5)	149 (31.4)
Dimethyl fumarate	36 (7.7)	37 (8.0)	36 (7.5)	44 (9.3)
Teriflunomide	8 (1.7)	6 (1.3)	13 (2.7)	9 (1.9)
Daclizumab	5 (1.1)	12 (2.6)	8 (1.7)	7 (1.5)
Fingolimod	10 (2.2)	15 (3.2)	13 (2.7)	10 (2.1)
Natalizumab	31 (6.7)	36 (7.8)	26 (5.4)	20 (4.2)
Any B-cell therapy§	2 (0.4)	3 (0.6)	0	0
Laquinimod	5 (1.1)	4 (0.9)	2 (0.4)	7 (1.5)
Other disease-modifying therapy¶	52 (11.2)	65 (14.1)	68 (14.1)	81 (17.1)
No. of relapses in previous 12 mo	1.2±0.6	1.3±0.7	1.3±0.7	1.3±0.7
No. of relapses in previous >12–24 mo	0.9±0.9	0.9±1.2	0.7±0.9	0.8±1.0
EDSS score‖	2.97±1.36	2.94±1.36	2.90±1.34	2.86±1.37
No. of gadolinium-enhancing lesions per T1-weighted MRI scan	1.7±4.9	1.2±2.6	1.6±4.1	1.5±4.1
Absence of gadolinium-enhancing lesions on T1-weighted MRI — no. (%)	291 (62.6)	293 (63.4)	270 (56.1)	291 (61.4)
Volume of lesions on T2-weighted MRI — cm^3	13.2±13.3	13.1±14.6	14.3±14.2	12.0±13.0
Neurofilament light chain concentration — pg/ml	13.3±13.2	11.7±9.3	14.7±18.2	13.4±14.0
Normalized brain volume — cm^3	1439±81	1442±79	1441±77	1446±77

* Plus–minus values are means ±SD. Data on time since symptom onset were missing for 1 patient in the teriflunomide group in the ASCLEPIOS II trial. Data on the number of relapses in the previous more than 12 to 24 months were missing for 1 patient in each group in the ASCLEPIOS II trial. Data on the Expanded Disability Status Scale (EDSS) score were missing for 1 patient in the teriflunomide group in each trial. Data on the number of gadolinium-enhancing lesions per T1-weighted magnetic resonance imaging (MRI) scan were missing for 11 patients in the ofatumumab group and for 10 in the teriflunomide group in the ASCLEPIOS I trial and for 12 in the ofatumumab group and 4 in the teriflunomide group in the ASCLEPIOS II trial. Data on the volume of lesions on T2-weighted MRI were missing for 4 patients in the ofatumumab group and for 5 in the teriflunomide group in the ASCLEPIOS I trial and for 8 in the ofatumumab group and 1 in the teriflunomide group in the ASCLEPIOS II trial. Data on neurofilament light chain concentration were missing for 18 patients in the ofatumumab group and for 41 in the teriflunomide group in the ASCLEPIOS I trial and for 35 in the ofatumumab group and 42 in the teriflunomide group in the ASCLEPIOS II trial. Data on normalized brain volume were missing for 5 patients in the ofatumumab group and for 8 in the teriflunomide group in the ASCLEPIOS I trial and for 12 in the ofatumumab group and 1 in the teriflunomide group in the ASCLEPIOS II trial.

† Age at baseline was calculated from the date of the first administration of trial drug and the birth year (no exact birth date was captured for reasons of data privacy). Eligibility for trial entry was assessed at the screening visit.

‡ A patient could be counted in multiple categories.

§ In the ASCLEPIOS I trial, rituximab had been received by 1 patient in the teriflunomide group, and ocrelizumab had been received by 2 patients in the ofatumumab group and by 2 in the teriflunomide group.

¶ This category includes all medications that were recorded by the investigator as a disease-modifying therapy but were not included in the listed medications.

‖ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10.0, with higher scores indicating worse disability. The score at baseline was defined as the score at the last assessment before the first dose administration of trial drug. Eligibility was assessed at the screening visit.

Table 2. Clinical, MRI, and Biomarker End Points (Full Analysis Set).*

End Point	ASCLEPIOS I Trial			ASCLEPIOS II Trial			Pooled Trials		
	Ofatumumab (N=465)	Teriflunomide (N=462)	P Value	Ofatumumab (N=481)	Teriflunomide (N=474)	P Value	Ofatumumab (N=946)	Teriflunomide (N=936)	P Value
Primary end point									
Total no. of relapses	90	177		95	198				
No. of patients evaluated	454	452		469	469				
Adjusted annualized relapse rate (95% CI)	0.11 (0.09 to 0.14)	0.22 (0.18 to 0.26)		0.10 (0.08 to 0.13)	0.25 (0.21 to 0.30)				
Difference (95% CI)	−0.11 (−0.16 to −0.06)		<0.001	−0.15 (−0.20 to −0.09)		<0.001			
Rate ratio (95% CI)	0.49 (0.37 to 0.65)		<0.001	0.42 (0.31 to 0.56)		<0.001			
Disability-related end points									
Disability worsening confirmed at 3 mo									
No. of events during the trial/no. of patients	45/465	63/459		43/479	62/472		88/944	125/931	
Kaplan–Meier estimate at 24 mo — %	11.3	15.4		10.5	14.6		10.9	15.0	
Hazard ratio (95% CI)	0.65 (0.45 to 0.96)			0.66 (0.45 to 0.97)			0.66 (0.50 to 0.86)		0.002
Disability worsening confirmed at 6 mo									
No. of events during the trial/no. of patients	35/465	53/459		36/479	46/472		71/944	99/931	
Kaplan–Meier estimate at 24 mo — %	8.2	13.0		8.0	10.9		8.1	12.0	
Hazard ratio (95% CI)	0.61 (0.40 to 0.93)			0.76 (0.49 to 1.17)			0.68 (0.50 to 0.92)		0.01
Disability improvement confirmed at 6 mo									
No. of events during the trial/no. of patients	33/375	26/363		41/374	27/360		74/749	53/723	
Kaplan–Meier estimate at 24 mo — %	9.7	8.2		12.3	8.1		11.0	8.1	
Hazard ratio (95% CI)	1.19 (0.71 to 1.98)			1.52 (0.93 to 2.47)			1.35 (0.95 to 1.92)		0.09
MRI-related end points									
Gd+ lesions on T1-weighted MRI									
No. of patients evaluated	432	422		439	434				
Mean no. of lesions per scan (95% CI)	0.01 (0.01 to 0.02)	0.45 (0.36 to 0.58)		0.03 (0.02 to 0.05)	0.51 (0.40 to 0.66)				
Rate ratio (95% CI)	0.03 (0.01 to 0.05)		<0.001	0.06 (0.04 to 0.10)		<0.001			
New or enlarging lesions on T2-weighted MRI by end of trial									
No. of patients evaluated	440	431		448	443				
Mean no. of lesions per yr (95% CI)	0.72 (0.61 to 0.85)	4.00 (3.47 to 4.61)		0.64 (0.55 to 0.75)	4.15 (3.64 to 4.74)				
Rate ratio (95% CI)	0.18 (0.15 to 0.22)		<0.001	0.15 (0.13 to 0.19)		<0.001			

Brain-volume change						
No. of patients evaluated	418	409		437	434	
Annual rate of change (95% CI) — %†	−0.28 (−0.34 to −0.22)	−0.35 (−0.41 to −0.29)		−0.29 (−0.35 to −0.23)	−0.35 (−0.42 to −0.29)	
Difference (95% CI) — percentage points	0.07 (−0.02 to 0.15)		0.12	0.07 (−0.02 to 0.15)		0.13
Serum NfL concentration						
At 3 mo						
No. of patients evaluated	430	404		425	423	
Geometric mean (95% CI) — pg/ml	8.8 (8.5 to 9.1)	9.4 (9.1 to 9.8)	0.01	8.9 (8.6 to 9.2)	10.0 (9.7 to 10.4)	<0.001
At 12 mo						
No. of patients evaluated	414	399		406	406	
Geometric mean (95% CI) — pg/ml	7.0 (6.7 to 7.3)	9.6 (9.2 to 10.1)	<0.001	7.1 (6.8 to 7.4)	9.5 (9.1 to 10.0)	<0.001
At 24 mo						
No. of patients evaluated	371	350		345	349	
Geometric mean (95% CI) — pg/ml	6.9 (6.6 to 7.2)	9.0 (8.6 to 9.5)	<0.001	6.8 (6.5 to 7.1)	9.0 (8.6 to 9.4)	<0.001

* All difference values, rate ratios, and hazard ratios are for ofatumumab compared with teriflunomide. Gd+ denotes gadolinium enhancing, and NfL neurofilament light chain.
† The annual rate of brain-volume change was estimated according to the slope from a random-coefficient model, on the basis of assessment of the percentage change from baseline in brain volume performed at month 12, month 24, and at the end of the trial.

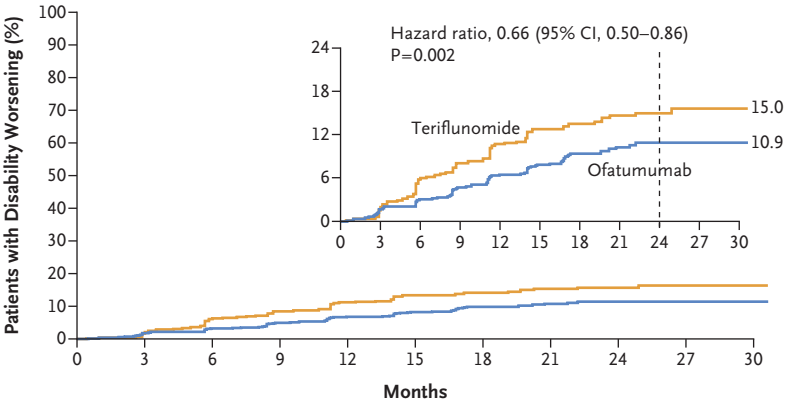
ity improvement confirmed at 6 months were tested in preplanned meta-analyses of the combined trials only if the primary null hypothesis for the annualized relapse rate was rejected in both trials independently. Other secondary end points were tested in hierarchical sequential order in each trial (number of gadolinium-enhancing lesions per T1-weighted MRI scan, annualized rate of new or enlarging lesions on T2-weighted MRI, serum neurofilament light chain concentration, and annual rate of brain-volume loss) as long as all preceding null hypotheses could be rejected (Fig. S1).

Data from disability-related end points were analyzed with the use of a Cox proportional-hazards model, stratified according to trial. Numbers of gadolinium-enhancing lesions on T1-weighted MRI and new or enlarging lesions on T2-weighted MRI were assessed with the use of negative binomial-regression models; for analysis of data on gadolinium-enhancing lesions on T1-weighted MRI, the number of available MRI scans was used as an offset; for lesions on T2-weighted MRI, the time between the last available scan and baseline scan was used as an offset.

Data on serum neurofilament light chain concentration were analyzed with the use of a repeated-measures model after log transformation of the data; the treatment effect is reported as a percentage reduction in neurofilament light chain concentration on the basis of the ratio of geometric means (relative reduction in geometric means with ofatumumab vs. teriflunomide). The annual rate of brain-volume loss was estimated as the marginal slope estimate from a random-coefficient model with random intercept and slope on the basis of assessments of the percentage change from baseline in brain volume performed at month 12, month 24, and at the end of the trial. The primary end point and key secondary end points used analysis methods that handle missing data under missing-at-random assumptions. Empirical evidence for data missing at random is presented in Table S2 and Figures S2 and S3, together with sensitivity analyses under missing-not-at-random assumptions for the primary and key secondary disability-related end points (Tables S3 and S4).

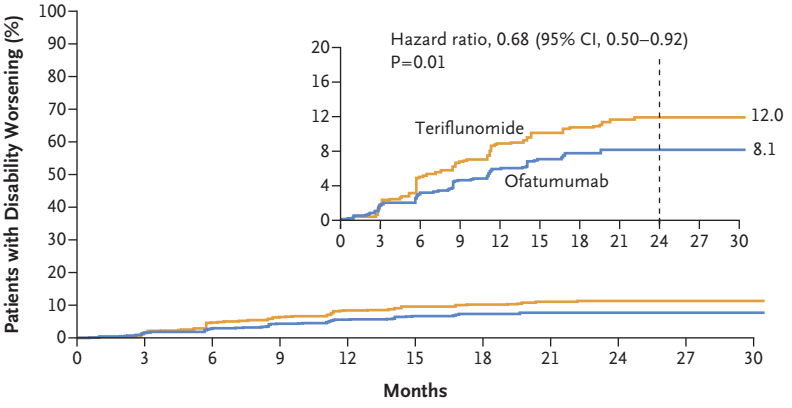
The safety population included all the patients who received trial drugs. Safety data were collected during the treatment period (screening to end of trial) and the safety follow-up period until

A Disability Worsening Confirmed at 3 Mo



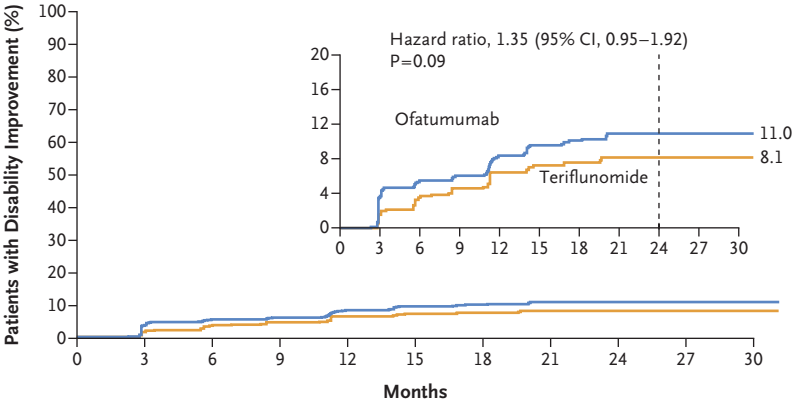
No. at Risk											
Ofatumumab	944	908	878	844	810	784	534	319	176	49	1
Teriflunomide	932	901	841	804	756	718	478	298	146	41	1

B Disability Worsening Confirmed at 6 Mo



No. at Risk											
Ofatumumab	944	908	878	845	815	791	544	324	180	50	1
Teriflunomide	932	902	849	812	769	734	487	305	151	43	1

C Disability Improvement Confirmed at 6 Mo



No. at Risk											
Ofatumumab	749	705	676	657	625	598	396	239	135	33	1
Teriflunomide	724	704	665	642	606	575	374	244	124	29	2

Figure 1 (facing page). Confirmed Disability Worsening and Improvement.

Shown are Kaplan–Meier estimates of the percentages of patients with disability worsening confirmed at 3 months (Panel A) and at 6 months (Panel B) and of patients with disability improvement (i.e., lessening of disability) confirmed at 6 months (Panel C) in time-to-event analyses in the combined trial populations. Disability worsening confirmed at 3 months or 6 months was defined as an increase from baseline in the Expanded Disability Status Scale (EDSS) score (on a scale from 0 to 10.0, with higher scores indicating worse disability) that was sustained for at least 3 or 6 months. For patients with a baseline EDSS score of 0, an increase in the EDSS score of at least 1.5 points was required; for patients with a baseline EDSS score of 1.0 to 5.0, the criterion was an increase of at least 1.0 point; and for patients with a baseline EDSS score of at least 5.5 points, the criterion was an increase of at least 0.5 points. Disability improvement confirmed at 6 months was defined as a decrease from baseline in the EDSS score that was sustained for at least 6 months. For patients with baseline EDSS scores of 2.0 to 6.0 points, a decrease of at least 1.0 point was required; for patients with baseline EDSS scores of 6.5 to 9.0 points, a decrease of at least 0.5 points was required. The numbers shown on the curves represent Kaplan–Meier estimates of the risk of the event at 24 months (marked by the vertical dashed line). The insets show the same data on an expanded y axis.

a patient's last visit. After the last dose of trial drug, patients were followed for at least 9 months. Adverse events that occurred during the treatment period were reported from the first dose and up to 100 days (approximately 5 times the half-life of ofatumumab) after permanent trial-drug discontinuation, and all serious adverse events that were reported up to the last visit by the last patient were analyzed. Safety end points are reported for the individual and combined trials.

RESULTS

PATIENTS

From October 2016 through March 2018, a total of 1882 patients were enrolled at 385 sites in 37 countries: 927 in ASCLEPIOS I (465 assigned to ofatumumab and 462 to teriflunomide) and 955 in ASCLEPIOS II (481 assigned to ofatumumab and 474 to teriflunomide). The median time in trial was 1.6 years (1.5 years in ASCLEPIOS I and 1.6 years in ASCLEPIOS II). More than 30% of the patients had a time in trial longer than 2 years (Table S2). Individual times in trial and times to trial-drug discontinuation and trial discontinuation are presented in Figures S2 and S3. The demographic and disease characteristics of the patients at baseline were similar in the two trials and in the treatment groups (Table 1). In ASCLEPIOS I, the trial was completed by 89.5% of the patients in the ofatumumab group and by 81.4% of those in the teriflunomide group. In ASCLEPIOS II, the corresponding percentages were 82.5% and 82.1%. Screening, randomization, and follow-up are summarized in Figure S4.

EFFICACY

Primary End Point

In ASCLEPIOS I, the adjusted annualized relapse rate was 0.11 with ofatumumab and 0.22 with teriflunomide (difference, −0.11; 95% confidence interval [CI], −0.16 to −0.06; P<0.001). The corresponding rates in ASCLEPIOS II were 0.10 and 0.25 (difference, −0.15; 95% CI, −0.20 to −0.09; P<0.001) (Table 2).

Disability-Related End Points

In the meta-analysis of both trials, the percentage of patients (Kaplan–Meier estimate at month 24) with disability worsening confirmed at 3 months was 10.9% with ofatumumab and 15.0% with teriflunomide (hazard ratio, 0.66; 95% CI, 0.50 to 0.86; P=0.002) (Fig. 1A and Table 2). The percentage of patients with disability worsening confirmed at 6 months was 8.1% with ofatumumab and 12.0% with teriflunomide (hazard ratio, 0.68; 95% CI, 0.50 to 0.92; P=0.01) (Fig. 1B and Table 2). Corresponding percentages of patients with disability improvement confirmed at 6 months from both trials were 11.0% with ofatumumab and 8.1% with teriflunomide (hazard ratio, 1.35; 95% CI, 0.95 to 1.92; P=0.09) (Fig. 1C and Table 2). The effect of ofatumumab on confirmed disability worsening was consistent across the two trials, as was the absence of a significant between-group difference in confirmed disability improvement (Table 2).

MRI-Related End Points

In ASCLEPIOS I, the mean number of gadolinium-enhancing lesions per T1-weighted MRI scan was 0.01 with ofatumumab and 0.45 with teriflunomide (97% lower number of lesions with ofatumumab, P<0.001); in ASCLEPIOS II, the corresponding numbers were 0.03 and 0.51, respectively (94% lower with ofatumumab, P<0.001) (Table 2). In ASCLEPIOS I, the mean number of

new or enlarging lesions per year on T2-weighted MRI was 0.72 with ofatumumab and 4.00 with teriflunomide (82% lower number of lesions with ofatumumab, P<0.001); corresponding values in ASCLEPIOS II were 0.64 and 4.15, respectively (85% lower with ofatumumab, P<0.001) (Table 2 and Table S5). The annual rate of brain-volume loss did not differ significantly between the ofatumumab group and the teriflunomide group (−0.28% with ofatumumab and −0.35% with teriflunomide in ASCLEPIOS I and −0.29% with ofatumumab and −0.35% with teriflunomide in ASCLEPIOS II) (Table 2 and Fig. S5).

Serum Neurofilament Light Chain Concentration

In ASCLEPIOS I, the serum neurofilament light chain concentration was lower in the ofatumumab group than in the teriflunomide group by 7% at month 3 (P=0.01), by 27% at month 12, and by 23% at month 24. Corresponding differences in ASCLEPIOS II were 11% (P<0.001), 26%, and 24% (Table 2 and Fig. S6). Adjusted annualized mean rates of new or enlarging lesions on T2-weighted MRI according to quartiles of neurofilament light chain concentration at baseline are presented in Table S6 and Figure S7.

SAFETY

Adverse Events

Adverse events up to 100 days after the last administration of a trial drug, serious adverse events up to the last visit by the last patient, adverse events leading to treatment discontinuation, and deaths are summarized in Table 3. In the combined analyses, 791 of 946 patients (83.6%) in the ofatumumab group reported an adverse event, as compared with 788 of 936 patients (84.2%) in the teriflunomide group. Adverse events that occurred in at least 10% of the patients treated with ofatumumab were injection-related reactions, nasopharyngitis, headache, injection-site reaction, upper respiratory tract infection, and urinary tract infection; events that occurred in at least 10% of those treated with teriflunomide were nasopharyngitis, injection-related reactions, alopecia, upper respiratory tract infection, headache, and diarrhea (Table S7). Serious adverse events were reported in 9.1% of the patients treated with ofatumumab and 7.9% of those treated with teriflunomide. One death occurred in the teriflunomide group (aortic dissection) during the post-treatment follow-up period.

Infections

Infections and infestations were reported in 488 patients (51.6%) who received ofatumumab and 493 (52.7%) who received teriflunomide. Infections reported in 10% or more of the patients in either group across both trials were nasopharyngitis (18.0% with ofatumumab and 16.7% with teriflunomide), upper respiratory tract infection (10.3% and 12.8%, respectively), and urinary tract infection (10.3% and 8.3%, respectively). The percentage of patients who reported a serious infection was 2.5% with ofatumumab and 1.8% with teriflunomide. The percentage of patients who reported a herpesvirus-associated infection was 4.9% in the ofatumumab group and 4.2% in the teriflunomide group. All herpesvirus-associated infections were mild (CTCAE grade 1) or moderate (grade 2), resolved while patients continued therapy, and did not lead to treatment discontinuation. Bronchitis was reported in 2.5% of the patients treated with ofatumumab and in 3.5% of those treated with teriflunomide; corresponding percentages for pneumonia were 0.3% and 0.7%, respectively. Appendicitis was reported in 8 patients who received ofatumumab and in 2 who received teriflunomide. No opportunistic infections were reported (Table S7).

Injection-Related Reactions

At least one injection-related systemic reaction, defined as systemic reactions occurring within 24 hours after injection (see the list of symptoms in the Safety section in the Supplementary Appendix), was reported in 20.2% of the patients who received ofatumumab and in 15.0% of those given placebo injections in the teriflunomide group (for details on injection-related premedication, see Tables S8 and S9). Injection-site reactions occurred in 10.9% and 5.6% of patients who received ofatumumab or placebo injections, respectively. Most injection-related systemic reactions (e.g., headache, flushing, and "other") occurred at the first injection (14.4% and 7.5% among the patients who received ofatumumab or placebo-dummy injections, respectively) (Fig. S8), were mild or moderate (grades 1 or 2), and were managed without treatment. Two severe (grade 3) injection-related systemic reactions were reported in the ofatumumab group (0.2%), one of which led to drug discontinuation after the first injection (0.1%). No life-threatening or anaphylactoid injection-related reactions (grade 4) were reported.

After the fourth injection, 74.4% of patients administered ofatumumab at home.

Other Safety Findings

Five neoplasms (0.5%) occurred in the ofatumumab group (two cases of basal-cell carcinoma and one case each of malignant melanoma in situ, recurrent non-Hodgkin's lymphoma, and invasive breast carcinoma) and four (0.4%) in the teriflunomide group (two cases of basal-cell carcinoma and one case each of cervix carcinoma and fibrosarcoma) (Table 3). Findings regarding B-cell depletion and antidrug-binding antibodies are reported in Figures S9 through S11.

DISCUSSION

In these two simultaneously conducted active-controlled trials involving patients with relapsing multiple sclerosis, both ofatumumab and teriflunomide were associated with low relapse rates. The relapse rate was significantly lower with ofatumumab than with teriflunomide in each of the two trials. In a prespecified meta-analysis of both trials, the percentages of patients with disability worsening confirmed at 3 months or 6 months were lower with ofatumumab than with teriflunomide, but the groups did not differ significantly with respect to confirmed disabili-

Table 3. Adverse Events (Safety Population).*

Variable	ASCLEPIOS I Trial		ASCLEPIOS II Trial	
	Ofatumumab (N=465)	Teriflunomide (N=462)	Ofatumumab (N=481)	Teriflunomide (N=474)
	number of patients (percent)			
Any adverse event	382 (82.2)	380 (82.3)	409 (85.0)	408 (86.1)
Adverse event leading to treatment discontinuation	27 (5.8)	24 (5.2)	27 (5.6)	25 (5.3)
Infection	229 (49.2)	238 (51.5)	259 (53.8)	255 (53.8)
Injection-related systemic reaction†	75 (16.1)	76 (16.5)	116 (24.1)	64 (13.5)
Serious adverse event	48 (10.3)	38 (8.2)	38 (7.9)	36 (7.6)
Serious infection‡	12 (2.6)	7 (1.5)	12 (2.5)	10 (2.1)
Serious injection-related reaction	2 (0.4)	0	0	0
Neoplasm§	3 (0.6)	3 (0.6)	2 (0.4)	1 (0.2)
Death	0	0	0	1 (0.2)¶

* Shown is the number of patients with at least one event and the percentage of all patients in each group. Adverse events were coded according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 20.0. Relapses of multiple sclerosis that were reported as adverse events were excluded.

† Only reactions or symptoms that occurred within 24 hours after injection are included (i.e., time to onset of reaction, ≤24 hours).

‡ Serious infections and infestations that were reported in the ofatumumab group were appendicitis (in 8 patients), gastroenteritis (in 3), urinary tract infection (in 3), influenza (in 2), and cystitis, escherichia urinary tract infection, kidney infection, lower respiratory tract infection, neutropenic sepsis, osteomyelitis, pneumonia, upper respiratory tract infection, urosepsis, and viral respiratory tract infection (in 1 patient each). Serious infections and infestations that were reported in the teriflunomide group were appendicitis (in 2 patients), urinary tract infection (in 2), and abscess of the sweat glands, campylobacter infection, cystitis, influenza pneumonia, osteomyelitis, paronychia, peritonitis, pneumonia, postoperative abscess, salpingo-oophoritis, sepsis, tickborne viral encephalitis, and viral infection (in 1 patient each).

§ Neoplasms that were reported in patients receiving ofatumumab were one case of malignant melanoma in situ (time to onset, 39 days), one case of invasive breast carcinoma (time to onset, 149 days), one case of recurrent non-Hodgkin's lymphoma (time to onset, 31 days), and two cases of basal-cell carcinoma (time to onset, 120 and 258 days). Neoplasms that were reported in patients receiving teriflunomide were one case of fibrosarcoma (time to onset, 652 days), one case of cervix carcinoma (time to onset, 341 days), and two cases of basal-cell carcinoma (time to onset, 8 and 401 days). None of the malignant events were considered by the investigator to be related to trial treatment, and no cluster of neoplasms was identified.

¶ The cause of death was aortic dissection.

ty improvement. The results of these trials do not permit any inferences to be made about the efficacy of ofatumumab as compared with other drugs for multiple sclerosis that are considered to be more potent than teriflunomide.

Ofatumumab was also superior to teriflunomide in suppressing lesion activity on MRI. Lesion counts on MRI in the teriflunomide groups were higher than those previously reported in one phase 3 trial of teriflunomide as compared with placebo,[19] which suggests a population with more disease activity overall in the ASCLEPIOS trials, differences in the assessment methods used at the MRI analysis centers,[29] or both. Ofatumumab lowered serum concentrations of neurofilament light chain, a marker of neuroaxonal damage.[30] However, despite greater reductions in neurofilament light chain concentrations with ofatumumab than with teriflunomide, change in brain volume did not differ significantly between the two treatments. This discrepancy between two markers of tissue damage needs further analysis. Ofatumumab lowered B-cell numbers during the 4-week loading regimen, and the initial B-cell depletion was maintained by monthly injections.

Injection-related reactions were more frequent with ofatumumab than with placebo injections in the teriflunomide group, particularly with the first injection. Premedication was used for the first injection by less than 70% of the patients, with decreasing usage thereafter. The reason for the observed imbalance in appendicitis as an adverse event with ofatumumab is unknown, and no signal for appendicitis has been observed with ofatumumab treatment in phase 2 studies in multiple sclerosis and other autoimmune indications[8-12] or with other anti-CD20 therapies in multiple sclerosis.[1-3]

Ofatumumab was associated with lower annualized relapse rates than teriflunomide and showed benefit with respect to most secondary clinical and MRI end points but not confirmed disability improvement. Ofatumumab was associated with a higher frequency of injection-related systemic reactions, predominantly with the first injection, than was placebo injection. Larger and longer trials are required to determine the long-term effect and risks of ofatumumab as compared with other disease-modifying treatments, including other anti-CD20 monoclonal antibodies.

Supported by Novartis Pharma.

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 patients for their participation in and commitment to these trials; Willi Maurer, Xi Dong, Heinz Schmidli, Ekkehard Glimm, and Mouna Akacha for their innovative statistical work on the flexible-duration trial design, which reduced the time and burden for the patients enrolled; Marina Savelieva, Joseph Kahn, Gordon Graham, and Huixin Yu for the dose-finding work for subcutaneous ofatumumab in multiple sclerosis; Erik Wallstroem, Amit Khanna, Goeril Karlsson, and Nikos Sfikas for their involvement in compound selection and trial design; the clinical trial team for the conduct of the ASCLEPIOS trials; and Angela Pozo Ramajo and Liz Hambly of Oxford PharmaGenesis for medical writing assistance and copyediting assistance, respectively, with an earlier version of the manuscript.

APPENDIX

The authors' full names and academic degrees are as follows: Stephen L. Hauser, M.D., Amit Bar-Or, M.D., Jeffrey A. Cohen, M.D., Giancarlo Comi, M.D., Jorge Correale, M.D., Patricia K. Coyle, M.D., Anne H. Cross, M.D., Jerome de Seze, M.D., David Leppert, M.D., Xavier Montalban, M.D., Krzysztof Selmaj, M.D., Heinz Wiendl, M.D., Cecile Kerloeguen, M.Sc., Roman Willi, Ph.D., Bingbing Li, Ph.D., Algirdas Kakarieka, M.D., Davorka Tomic, D.V.M., Alexandra Goodyear, M.D., Ratnakar Pingili, M.B., B.S., Dieter A. Häring, Ph.D., Krishnan Ramanathan, Ph.D., Martin Merschhemke, M.D., and Ludwig Kappos, M.D.

The authors' affiliations are as follows: the UCSF Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, San Francisco (S.L.H.); the Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia (A.B.-O.); the Department of Neurology, Mellen Center for Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland (J.A.C.); the Institute of Experimental Neurology and Multiple Sclerosis Center IRCCS, San Raffaele Hospital, Milan (G.C.); the Department of Neurology, Fleni, Buenos Aires (J.C.); the Department of Neurology, Stony Brook University, Stony Brook, NY (P.K.C.); Washington University School of Medicine, St. Louis (A.H.C.); the University Hospital of Strasburg and Clinical Investigation Center INSERM 1434, Strasburg, France (J.S.); University Hospital Basel (D.L.), Novartis Pharma (C.K., R.W., A.K., D.T., D.A.H., K.R., M.M.), and the Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine, and Biomedical Engineering, University Hospital and University of Basel (L.K.) — all in Basel, Switzerland; the Department of Neurology–Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitari Vall d'Hebron, Barcelona (X.M.); the University of Warmia and Mazury, Olsztyn, and the Center of Neurology, Lodz — both in Poland (K.S.); the Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany (H.W.); and Novartis Pharmaceuticals, East Hanover, NJ (B.L., A.G., R.P.).

REFERENCES

1. 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.
2. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008;358:676-88.
3. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017;376:209-20.
4. Vermersch P, Czlonkowska A, Grimaldi LM, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler 2014;20:705-16.
5. Lin TS. Ofatumumab: a novel monoclonal anti-CD20 antibody. Pharmgenomics Pers Med 2010;3:51-9.
6. Engelberts PJ, Voorhorst M, Schuurman J, et al. Type I CD20 antibodies recruit the B cell receptor for complement-dependent lysis of malignant B cells. J Immunol 2016;197:4829-37.
7. Semple KM, Gonzaléz CM, Zarr M, Austin JR, Patel V, Howard KE. Evaluation of the ability of immune humanized mice to demonstrate CD20-specific cytotoxicity induced by ofatumumab. Clin Transl Sci 2019;12:283-90.
8. Bar-Or A, Grove RA, Austin DJ, et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis: the MIRROR study. Neurology 2018;90(20):e1805-e1814.
9. Sorensen PS, Lisby S, Grove R, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology 2014;82:573-81.
10. Novartis Pharmaceuticals. Arzerra (ofatumumab) prescribing information. 2016 (https://www.novartis.us/sites/www.novartis.us/files/arzerra.pdf).
11. Kurrasch R, Brown JC, Chu M, et al. Subcutaneously administered ofatumumab in rheumatoid arthritis: a phase I/II study of safety, tolerability, pharmacokinetics, and pharmacodynamics. J Rheumatol 2013;40:1089-96.
12. Quattrocchi E, Østergaard M, Taylor PC, et al. Safety of repeated open-label treatment courses of intravenous ofatumumab, a human anti-CD20 monoclonal antibody, in rheumatoid arthritis: results from three clinical trials. PLoS One 2016;11(6):e0157961.
13. Kähäri L, Fair-Mäkelä R, Auvinen K, et al. Transcytosis route mediates rapid delivery of intact antibodies to draining lymph nodes. J Clin Invest 2019;129:3086-102.
14. Theil D, Smith P, Huck C, et al. Imaging mass cytometry and single-cell genomics reveal differential depletion and repletion of B-cell populations following ofatumumab treatment in cynomolgus monkeys. Front Immunol 2019;10:1340.
15. Genentech. Ocrevus (ocrelizumab) prescribing information. 2020 (https://www.gene.com/download/pdf/ocrevus_prescribing.pdf).
16. Leppert D. Comparison of the B-cell recovery time following discontinuation of anti-CD20 therapies. ECTRIMS Online Library. October 25, 2017 (https://onlinelibrary.ectrims-congress.eu/ectrims/2017/ACTRIMS-ECTRIMS2017/199644/david.leppert.comparison.of.the.b-cell.recovery.time.following.discontinuation.html).
17. Roll P, Palanichamy A, Kneitz C, Dorner T, Tony H-P. Regeneration of B cell subsets after transient B cell depletion using anti-CD20 antibodies in rheumatoid arthritis. Arthritis Rheum 2006;54:2377-86.
18. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:247-56.
19. 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.
20. Fogarty E, Schmitz S, Tubridy N, Walsh C, Barry M. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: systematic review and network meta-analysis. Mult Scler Relat Disord 2016;9:23-30.
21. Buron MD, Chalmer TA, Sellebjerg F, et al. Comparative effectiveness of teriflunomide and dimethyl fumarate: a nationwide cohort study. Neurology 2019;92(16):e1811-e1820.
22. Kalincik T, Kubala Havrdova E, Horakova D, et al. Comparison of fingolimod, dimethyl fumarate and teriflunomide for multiple sclerosis. J Neurol Neurosurg Psychiatry 2019;90:458-68.
23. International Conference on Harmonisation. ICH harmonized tripartite guideline: Guideline for Good Clinical Practice. J Postgrad Med 2001;47:45-50.
24. World Medical Association. WMA Declaration of Helsinki: ethical principles for medical research involving human subjects. 2006 (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/).
25. 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.
26. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83:278-86.
27. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-52.
28. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). 2017 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).
29. Schach S, Scholz M, Wolinsky JS, Kappos L. Pooled historical MRI data as a basis for research in multiple sclerosis — a statistical evaluation. Mult Scler 2007;13:509-16.
30. Disanto G, Barro C, Benkert P, et al. Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis. Ann Neurol 2017;81:857-70.