Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis

S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.-P. Hartung, B. Hemmer,
F. Lublin, X. Montalban, K.W. Rammohan, K. Selmaj, A. Traboulsee,
J.S. Wolinsky, D.L. Arnold, G. Klingelschmitt, D. Masterman, P. Fontoura,
S. Belachew, P. Chin, N. Mairon, H. Garren, and L. Kappos,
for the OPERA I and OPERA II Clinical Investigators*

ABSTRACT

BACKGROUND

B cells influence the pathogenesis of multiple sclerosis. Ocrelizumab is a humanized monoclonal antibody that selectively depletes CD20+ B cells.

METHODS

In two identical phase 3 trials, we randomly assigned 821 and 835 patients with relapsing multiple sclerosis to receive intravenous ocrelizumab at a dose of 600 mg every 24 weeks or subcutaneous interferon beta-1a at a dose of 44 μg three times weekly for 96 weeks. The primary end point was the annualized relapse rate.

RESULTS

The annualized relapse rate was lower with ocrelizumab than with interferon beta-1a in trial 1 (0.16 vs. 0.29; 46% lower rate with ocrelizumab; P<0.001) and in trial 2 (0.16 vs. 0.29; 47% lower rate; P<0.001). In prespecified pooled analyses, the percentage of patients with disability progression confirmed at 12 weeks was significantly lower with ocrelizumab than with interferon beta-1a (9.1% vs. 13.6%; hazard ratio, 0.60; 95% confidence interval [CI], 0.45 to 0.81; P<0.001), as was the percentage of patients with disability progression confirmed at 24 weeks (6.9% vs. 10.5%; hazard ratio, 0.60; 95% CI, 0.43 to 0.84; P=0.003). The mean number of gadolinium-enhancing lesions per T_1-weighted magnetic resonance scan was 0.02 with ocrelizumab versus 0.29 with interferon beta-1a in trial 1 (94% lower number of lesions with ocrelizumab, P<0.001) and 0.02 versus 0.42 in trial 2 (95% lower number of lesions, P<0.001). The change in the Multiple Sclerosis Functional Composite score (a composite measure of walking speed, upper-limb movements, and cognition; for this z score, negative values indicate worsening and positive values indicate improvement) significantly favored ocrelizumab over interferon beta-1a in trial 2 (0.28 vs. 0.17, P=0.004) but not in trial 1 (0.21 vs. 0.17, P=0.33). Infusion-related reactions occurred in 34.3% of the patients treated with ocrelizumab. Serious infection occurred in 1.3% of the patients treated with ocrelizumab and in 2.9% of those treated with interferon beta-1a. Neoplasms occurred in 0.5% of the patients treated with ocrelizumab and in 0.2% of those treated with interferon beta-1a.

CONCLUSIONS

Among patients with relapsing multiple sclerosis, ocrelizumab was associated with lower rates of disease activity and progression than interferon beta-1a over a period of 96 weeks. Larger and longer studies of the safety of ocrelizumab are required. (Funded by F. Hoffmann–La Roche; OPERA I and II ClinicalTrials.gov numbers, NCT01247324 and NCT01412333, respectively.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Hauser at the 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 University Hospital Basel, University of Basel, Petersgraben 4, CH-4301 Basel, Switzerland, or at ludwig.kappos@usb.ch.

DESPITE THE AVAILABILITY OF SEVERAL disease-modifying treatments for relapsing forms of multiple sclerosis, patients often continue to have clinical and subclinical disease activity, and neurologic disability continues to accrue. Thus, there is a need for more effective treatments with acceptable safety profiles.[1-3]

B cells are thought to influence the underlying pathogenesis of multiple sclerosis by means of antigen presentation,[4] autoantibody production,[5,6] cytokine regulation,[4] and the formation of ectopic lymphoid aggregates in the meninges, which possibly contribute to cortical demyelination and neurodegeneration.[7,8] Ocrelizumab is a humanized monoclonal antibody that selectively targets CD20, a cell-surface antigen that is expressed on pre-B cells, mature B cells, and memory B cells but not on lymphoid stem cells and plasma cells.[9] Humanized anti-CD20 antibody was designed to reduce immunogenicity, which was shown in a phase 2 study.[10] Ocrelizumab binds to the large extracellular loop of CD20 with high affinity, selectively depleting CD20-expressing B cells[11,12] while preserving the capacity for B-cell reconstitution and preexisting humoral immunity.[13,14] B-cell depletion is achieved by means of several mechanisms, including antibody-dependent cell-mediated phagocytosis, antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis.[15]

On the basis of results from previous phase 2 studies of the chimeric anti-CD20 antibody rituximab[16] and ocrelizumab,[10] we undertook two phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group trials (OPERA I and OPERA II) to investigate the efficacy and safety of ocrelizumab, as compared with subcutaneous interferon beta-1a, in patients with relapsing multiple sclerosis. The two trials used identical protocols but were conducted independently at nonoverlapping trial sites (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

METHODS

TRIAL OVERSIGHT

The sponsor, F. Hoffmann–La Roche, designed the trials in consultation with members of the OPERA I and OPERA II steering committee. Data were collected by the site investigators, queries were responded to by site personnel, and the data were analyzed by the sponsor; the aggregated and individual results of the participants were reviewed by the sponsor and steering committee. An independent data and safety monitoring committee reviewed ongoing safety data and provided guidance on trial continuation, modification, or termination (see the Study Oversight section in the Supplementary Appendix).

All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. A subgroup of authors, which included academic authors and authors who are employees of the sponsor, drafted the manuscript, and all the authors approved the final version and made the decision to submit the manuscript for publication. Medical-writing assistance was funded by the sponsor. The trial was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice[17] and the Declaration of Helsinki.[18]

PATIENTS

Key eligibility criteria included an age of 18 to 55 years; a diagnosis of multiple sclerosis (according to the 2010 revised McDonald criteria[19]); an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 at screening (scores range from 0 to 10.0, with higher scores indicating a greater degree of disability[20]); at least two documented clinical relapses within the previous 2 years or one clinical relapse within the year before screening; magnetic resonance imaging (MRI) of the brain showing abnormalities consistent with multiple sclerosis; and no neurologic worsening for at least 30 days before both screening and baseline (day 1 trial visit). The key exclusion criteria were a diagnosis of primary progressive multiple sclerosis, previous treatment with any B-cell–targeted therapy or other immunosuppressive medication as defined in the protocol (available at NEJM.org; also see the Additional Methodology Details section in the Supplementary Appendix), and a disease duration of more than 10 years in combination with an EDSS score of 2.0 or less at screening. All the patients provided written informed consent.

TRIAL DESIGN

In the OPERA I trial, patients from 141 trial sites across 32 countries underwent randomization between August 31, 2011, and February 14, 2013. In the OPERA II trial, patients from 166 trial sites

across 24 countries underwent randomization between September 20, 2011, and March 28, 2013. Patients were randomly assigned, in a 1:1 ratio, to receive ocrelizumab at a dose of 600 mg by means of intravenous infusion every 24 weeks, administered as two 300-mg infusions on days 1 and 15 for the first dose and as a single 600-mg infusion thereafter, or interferon beta-1a at a dose of 44 μg (Rebif, EMD Serono), administered subcutaneously three times weekly throughout the 96-week treatment period (Fig. S1 in the Supplementary Appendix). Patients in each group received a matching subcutaneous or intravenous placebo, as appropriate. All the patients received one 100-mg dose of intravenous methylprednisolone before each infusion. Prophylaxis with analgesic or antipyretic agents and an antihistamine was recommended, but the decision to use these medications was left up to the infusion center. Adjustment of the infusion rate and treatment of symptoms during infusion were permitted in order to manage infusion-related reactions.

Randomization was performed centrally with the use of an independent interactive Web-response system. Each trial center had separate treating and examining investigators, all of whom were unaware of the treatment assignments throughout the trial. The examining investigator conducted the neurologic assessments, including the Multiple Sclerosis Functional Composite (a composite quantitative measure, expressed as a z score, of walking speed, upper-limb coordinated movements, and cognition; for this z score, negative values indicate worsening and positive values indicate improvement)[21] and the EDSS. The EDSS assessment and data collection were captured with the use of a real-time, electronic data-entry system in conjunction with an algorithm and central consistency check and feedback on the basis of expert review. MRI scans were analyzed centrally at an MRI reading center by personnel who were unaware of the treatment assignments. Details are provided in the protocol, including the statistical analysis plan, and in Table S9 in the Supplementary Appendix.

TRIAL PROCEDURES AND END POINTS

The primary end point was the annualized relapse rate by 96 weeks, which reflects the number of relapses meeting the prespecified criteria that were observed per person-year of follow-up (see the Supplementary Appendix). There were 10 hierarchically ordered secondary end points: the proportion of patients with disability progression confirmed at 12 weeks in a pooled time-to-event analysis of both trials through week 96, in which disability progression was defined as an increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 weeks; the total (cumulative) mean number of gadolinium-enhancing lesions identified on T_1-weighted MRI of the brain at weeks 24, 48, and 96; the total number of new or newly enlarged hyperintense lesions on T_2-weighted MRI of the brain at weeks 24, 48, and 96; a pooled analysis of the proportion of patients with disability improvement confirmed at 12 weeks through week 96, which was defined as a reduction from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 weeks in patients with a baseline EDSS score of at least 2.0; a pooled time-to-event analysis of the rate of disability progression confirmed at 24 weeks through week 96; the total number of new hypointense lesions on T_1-weighted MRI of the brain at weeks 24, 48, and 96; the change in the Multiple Sclerosis Functional Composite score from baseline to week 96; the percentage change in brain volume from week 24 to week 96; the change in the physical-component summary score of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36, on which scores range from 0 to 100, and higher scores indicate better physical health–related quality of life) from baseline to week 96; and the proportion of patients with a baseline EDSS score of at least 2.0 who had no evidence of disease activity (defined as no relapse, no disability progression confirmed at 12 weeks or at 24 weeks, no new or newly enlarged lesions on T_2-weighted MRI, and no gadolinium-enhancing lesions on T_1-weighted MRI) by week 96. The analysis of percentage change in brain volume was performed with the use of SIENA/X software.[22] Additional secondary end points were the pharmacokinetics, pharmacodynamics, and immunogenicity of ocrelizumab; and the safety profile of ocrelizumab.

STATISTICAL ANALYSIS

We performed efficacy analyses in the intention-to-treat population (all the patients who underwent randomization) or, for the end point of no evidence of disease activity, in a modified inten-

tion-to-treat population that excluded patients who were withdrawn from the trial for reasons other than efficacy failure or death and who had no evidence of clinical disease activity at the time of treatment discontinuation in the trial. The annualized relapse rate was analyzed with the use of a negative binomial model testing for treatment differences between ocrelizumab and interferon beta-1a, with adjustment according to geographic region and baseline EDSS score. A significant result at a two-sided alpha of 0.05 would show the superiority of ocrelizumab with regard to a lower annualized relapse rate than that observed with interferon beta-1a.

The sample size for each trial was based on an estimated annualized relapse rate of 0.165 in the ocrelizumab group and 0.33 in the interferon beta-1a group. Using a two-sided t-test, we calculated that a sample of 400 patients per group would provide the trials with 84% statistical power to maintain a type I error rate of 0.05 and to detect a 50% lower rate with ocrelizumab than with interferon beta-1a (assuming a withdrawal rate of approximately 20%).

According to the statistical analysis plans of the individual trials, 10 secondary efficacy end points were prespecified to be tested in a hierarchical order at a two-sided alpha of 0.05 (see the Supplementary Appendix). Seven end points of this hierarchy were to be tested in each individual trial, and three end points (disability progression confirmed at 12 weeks and at 24 weeks and disability improvement confirmed at 12 weeks) were to be assessed in the pooled data set. From the first P value that was above 0.05, all subsequent P values in the predetermined hierarchy were considered to be nonconfirmatory (i.e., descriptive only). (See the Statistical Analysis section in the Supplementary Appendix.)

All patients who received any study treatment were included in the safety population. All data collected during the double-blind, double-dummy treatment period and the safety follow-up were included in the main safety analyses. Data from patients who entered the safety follow-up earlier than week 96 were included in this analysis from the time that they entered the safety follow-up until week 96. Safety outcomes are reported for the individual trials with the exception of herpesvirus infections and neoplasms, for which pooled data are presented because of low incidences.

RESULTS

PATIENTS

Overall, 1656 patients underwent randomization (intention-to-treat population), with 821 patients in the OPERA I trial and 835 in the OPERA II trial. The demographic and disease characteristics at baseline were similar in the assigned groups in the two trials (Table 1). In the OPERA I trial, 366 of 410 patients (89.3%) in the ocrelizumab group and 340 of 411 (82.7%) in the interferon beta-1a group completed the 96-week treatment; in the OPERA II trial, 360 of 417 (86.3%) and 320 of 418 (76.6%), respectively, completed the 96-week treatment (Fig. S2 in the Supplementary Appendix). There was no interaction between treatment group and trial, which allowed the pooling of data for the prespecified planned hierarchical analysis (Table S9 in the Supplementary Appendix). In the pooled analysis, which included 827 patients treated with ocrelizumab and 829 treated with interferon beta-1a, all the primary and secondary end points significantly favored the ocrelizumab group over the interferon beta-1a group.

EFFICACY

Relapses

Clinical, MRI, and patient-reported outcomes are summarized in Table 2. The primary end point, the annualized relapse rate at 96 weeks, in the OPERA I trial was 0.16 in the ocrelizumab group, as compared with 0.29 in the interferon beta-1a group (difference, 0.14 annualized relapses [differences are based on unrounded data]). In the OPERA II trial, the annualized relapse rate was 0.16 in the ocrelizumab group, as compared with 0.29 in the interferon beta-1a group (difference, 0.14 annualized relapses) (Table 2). These findings indicate a 46% lower annualized relapse rate with ocrelizumab in the OPERA I trial and a 47% lower rate with ocrelizumab in the OPERA II trial (P<0.001 for both comparisons).

Disability

In the prespecified pooled analysis, the percentage of patients with disability progression confirmed at 12 weeks was 9.1% in the ocrelizumab group, as compared with 13.6% in the interferon beta-1a group (40% lower risk with ocrelizumab; hazard ratio, 0.60; 95% confidence interval [CI], 0.45 to 0.81; P<0.001) (Fig. 1A). Over the 96-week

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	OPERA I Trial		OPERA II Trial	
	Ocrelizumab (N=410)	Interferon Beta-1a (N=411)	Ocrelizumab (N=417)	Interferon Beta-1a (N=418)
Age — yr	37.1±9.3	36.9±9.3	37.2±9.1	37.4±9.0
Female sex — no. (%)	270 (65.9)	272 (66.2)	271 (65.0)	280 (67.0)
Geographic region — no. (%)				
United States	105 (25.6)	105 (25.5)	112 (26.9)	114 (27.3)
Rest of the world	305 (74.4)	306 (74.5)	305 (73.1)	304 (72.7)
Time since symptom onset — yr	6.74±6.37	6.25±5.98	6.72±6.10	6.68±6.13
Time since diagnosis — yr	3.82±4.80	3.71±4.63	4.15±4.95	4.13±5.07
No. of relapses in previous 12 mo	1.31±0.65	1.33±0.64	1.32±0.69	1.34±0.73
No previous disease-modifying therapy — no./total no. (%)†	301/408 (73.8)	292/409 (71.4)	304/417 (72.9)	314/417 (75.3)
Previous disease-modifying therapy — no./total no. (%)‡	107/408 (26.2)	117/409 (28.6)	113/417 (27.1)	103/417 (24.7)
Interferon	81/408 (19.9)	86/409 (21.0)	80/417 (19.2)	75/417 (18.0)
Glatiramer acetate	38/408 (9.3)	37/409 (9.0)	39/417 (9.4)	44/417 (10.6)
Natalizumab	0/408	1/409 (0.2)	1/417 (0.2)	0/417
Fingolimod	1/408 (0.2)	0/409	4/417 (1.0)	0/417
Dimethyl fumarate	1/408 (0.2)	0/409	0/417	0/417
Other	2/408 (0.5)	3/409 (0.7)	1/417 (0.2)	1/417 (0.2)
Mean EDSS score§	2.86±1.24	2.75±1.29	2.78±1.30	2.84±1.38
No. of gadolinium-enhancing lesions on T_1-weighted MRI — no./total no. (%)				
0	233/405 (57.5)	252/407 (61.9)	252/413 (61.0)	243/415 (58.6)
1	64/405 (15.8)	52/407 (12.8)	58/413 (14.0)	62/415 (14.9)
2	30/405 (7.4)	30/407 (7.4)	33/413 (8.0)	38/415 (9.2)
3	20/405 (4.9)	16/407 (3.9)	15/413 (3.6)	14/415 (3.4)
≥4	58/405 (14.3)	57/407 (14.0)	55/413 (13.3)	58/415 (14.0)
No. of lesions on T_2-weighted MRI	51.04±39.00	51.06±39.90	49.26±38.59	51.01±35.69
Volume of lesions on T_2-weighted MRI — cm^3	10.84±13.90	9.74±11.28	10.73±14.28	10.61±12.30
Normalized brain volume — cm^3	1500.93±84.10	1499.18±87.68	1503.90±92.63	1501.12±90.98

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who underwent randomization. There were no significant differences in the baseline characteristics between groups in each trial and between the two trials. A full listing of countries involved in the trials is provided in the Supplementary Appendix. Data on the number of relapses within the previous 12 months were missing for 1 patient in the interferon beta-1a group in the OPERA I trial and for 1 patient in each group in the OPERA II trial. Data on the number and volume of lesions on T_2-weighted MRI were missing for 2 patients in the ocrelizumab group and for 3 in the interferon beta-1a group in the OPERA I trial and for 3 in the ocrelizumab group and 2 in the interferon beta-1a group in the OPERA II trial. Data on the normalized brain volume were missing for 4 patients in the ocrelizumab group and for 7 in the interferon beta-1a group in the OPERA I trial and for 3 in the ocrelizumab group and 4 in the interferon beta-1a group in the OPERA II trial.
† Data include patients who were untreated with any disease-modifying therapy in the 2 years before screening. The inclusion criteria did not select for untreated patients.
‡ Data on previous treatment were collected only for the 2 years before screening. Patients could be counted in several categories. Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, or methotrexate within 2 years before screening was an exclusion criterion. Patients treated with natalizumab were eligible for the trial only if the duration of treatment with natalizumab was less than 1 year. Other medications were intravenous immune globulin, mycophenolate mofetil, and azathioprine (protocol deviation if ≤24 months before screening).
§ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10.0, with higher scores indicating worse disability.[20] Data were missing for one patient in the interferon beta-1a group in the OPERA I trial.

Table 2. Clinical and MRI End Points during the 96-Week Trials.*

End Point	OPERA I Trial			OPERA II Trial			Pooled Trials		
	Ocrelizumab (N=410)	Interferon Beta-1a (N=411)	P Value	Ocrelizumab (N=417)	Interferon Beta-1a (N=418)	P Value	Ocrelizumab (N=827)	Interferon Beta-1a (N=829)	P Value
Primary end point									
Annualized relapse rate at 96 wk (95% CI)	0.16 (0.12 to 0.20)	0.29 (0.24 to 0.36)		0.16 (0.12 to 0.20)	0.29 (0.23 to 0.36)				
Rate ratio (95% CI)	0.54 (0.40 to 0.72)		<0.001	0.53 (0.40 to 0.71)		<0.001			
Secondary clinical end points									
Disability progression confirmed at 12 wk†‡									
Patients with event — %	7.6	12.2		10.6	15.1		9.1	13.6	
Hazard ratio (95% CI)	0.57 (0.37 to 0.90)		0.01	0.63 (0.42 to 0.92)		0.02	0.60 (0.45 to 0.81)		<0.001
Disability improvement confirmed at 12 wk†‡									
No. of patients evaluated	310	306		318	308		628	614	
Patients with event — %	20.0	12.4		21.4	18.8		20.7	15.6	
Difference — %	61		0.01	14		0.40	33		0.02
Disability progression confirmed at 24 wk†‡									
Patients with event — %	5.9	9.5		7.9	11.5		6.9	10.5	
Hazard ratio (95% CI)	0.57 (0.34 to 0.95)		0.03	0.63 (0.40 to 0.98)		0.04	0.60 (0.43 to 0.84)		0.003
MSFC score§									
Adjusted mean score at wk 96 (95% CI)	0.21 (0.15 to 0.27)	0.17 (0.11 to 0.24)		0.28 (0.22 to 0.33)	0.17 (0.11 to 0.23)				
Difference (95% CI)	0.04 (−0.04 to 0.12)		0.33	0.11 (0.03 to 0.18)		0.004			
Patient-reported outcome									
Change in SF-36 physical-component summary score from baseline to wk 96¶									
Adjusted mean score (95% CI)	0.04 (−0.86 to 0.93)	−0.66 (−1.59 to 0.28)		0.33 (−0.55 to 1.20)	−0.83 (−1.76 to 0.09)				
Difference (95% CI)	0.69 (−0.41 to 1.80)		0.22‖	1.16 (0.05 to 2.27)		0.04‖			
Exploratory end point									
No evidence of disease activity by wk 96‡**									
No. of patients evaluated	382	384		379	375				
Patients with no evidence of disease activity — %	47.9	29.2		47.5	25.1				
Difference — % (95% CI)	64 (36 to 98)		<0.001‖	89 (54 to 132)		<0.001‖			

Secondary MRI end points

	Ocrelizumab	Interferon beta-1a	Ocrelizumab	Interferon beta-1a
Cumulative no. of gadolinium-enhancing lesions on T_1-weighted MRI by wk 96*††				
Any lesion — % of patients	8.3	30.2	9.8	36.1
Mean no. of lesions per scan (95% CI)	0.02 (0.01 to 0.03)	0.29 (0.20 to 0.41)	0.02 (0.01 to 0.04)	0.42 (0.31 to 0.56)
Rate ratio (95% CI)	0.06 (0.03 to 0.10)	<0.001	0.05 (0.03 to 0.09)	<0.001
Total no. of new or newly enlarged hyperintense lesions on T_2-weighted MRI by wk 96*††				
Any lesion — % of patients	38.3	61.3	39.1	62.0
Mean no. of lesions per scan (95% CI)	0.32 (0.26 to 0.41)	1.41 (1.12 to 1.78)	0.33 (0.26 to 0.41)	1.90 (1.54 to 2.36)
Rate ratio (95% CI)	0.23 (0.17 to 0.30)	<0.001	0.17 (0.13 to 0.23)	<0.001
New hypointense lesions on T_1-weighted MRI by wk 96*††				
Mean no. of lesions per scan (95% CI)	0.42 (0.34 to 0.52)	0.98 (0.78 to 1.24)	0.45 (0.36 to 0.56)	1.26 (1.00 to 1.57)
Rate ratio (95% CI)	0.43 (0.33 to 0.56)	<0.001	0.36 (0.27 to 0.47)	<0.001
Brain-volume change from wk 24 to 96				
Mean percentage change (95% CI)	−0.57 (−0.66 to −0.49)	−0.74 (−0.83 to −0.65)	−0.64 (−0.73 to −0.54)	−0.75 (−0.85 to −0.65)
Difference in rate of brain-volume loss — %	22.8	0.004‖	14.9	0.09‖

* All rate ratios, hazard ratios, and difference values are for the ocrelizumab group versus the interferon beta-1a 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.

† Only the pooled analysis was prespecified. The individual-trial results are presented for additional context and transparency. Disability progression that was confirmed at 12 or 24 weeks was defined as an increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 or 24 weeks. Disability improvement that was confirmed at 12 weeks was defined as a reduction from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 weeks in patients with a baseline EDSS score of at least 2.0

‡ For these end points, individual-trial-level P values were not part of the hierarchical statistical analysis testing procedure.
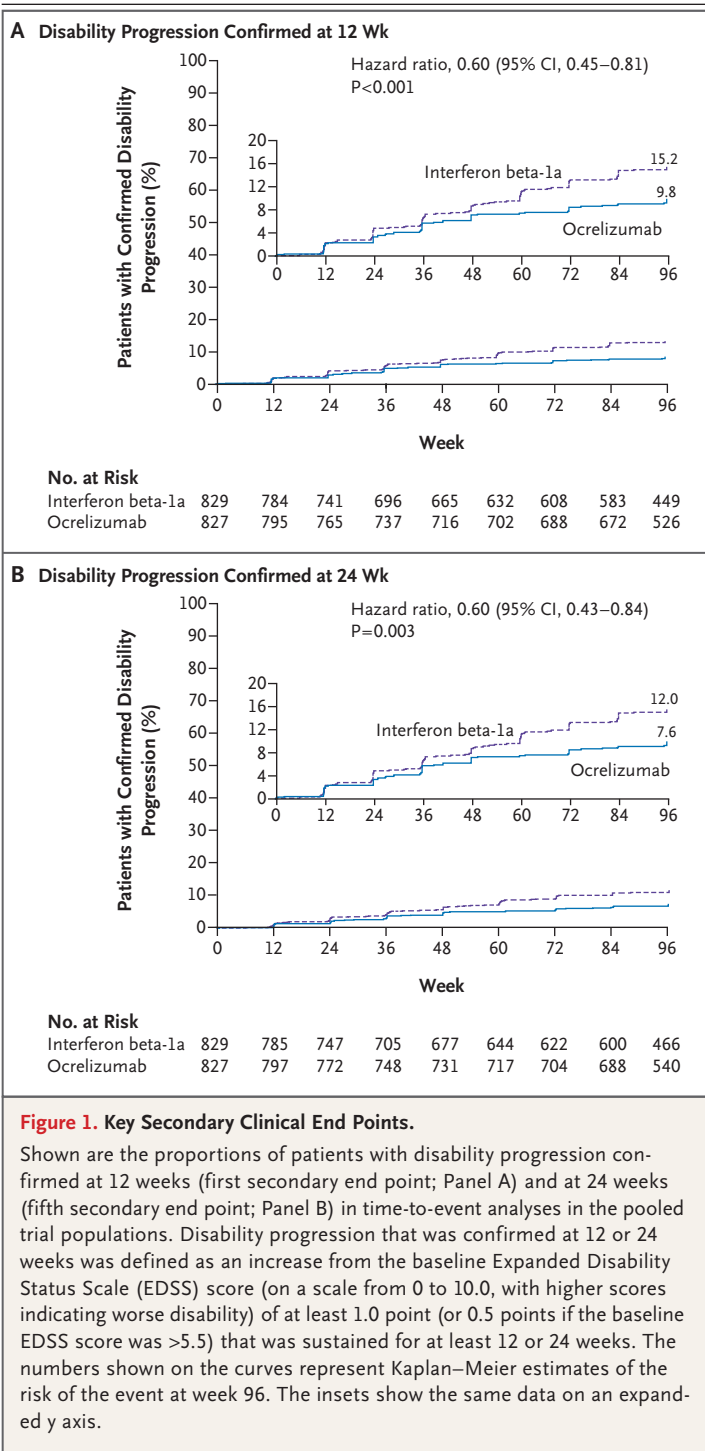
§ The Multiple Sclerosis Functional Composite (MSFC) consists of a composite quantitative measure of walking speed, upper-limb coordinated movements, and cognition; for this z score (numerical value reflects the number of standard deviations from a reference population), negative values indicate worsening and positive values indicate improvement in function.[21] MSFC scores were adjusted according to baseline MSFC score, interaction between baseline MSFC score and visit, geographic region (United States vs. the rest of the world), and baseline EDSS score (<4.0 vs. ≥4.0).[23]

¶ The physical-component summary score of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) ranges from 0 to 100, with higher scores indicating better physical health–related quality of life.

‖ Nominal P values are reported but are nonconfirmatory (i.e., descriptive only) as a consequence of the failure in the statistical hierarchical testing procedure.

** No evidence of disease activity was defined as no protocol-defined relapse, no events of disability progression confirmed at 12 weeks, no new or newly enlarged lesions on T_2-weighted MRI, and no gadolinium-enhancing lesions. As prespecified, the end point of no evidence of disease activity was assessed in a modified intention-to-treat population that excluded patients who were withdrawn for reasons other than efficacy failure or death and who did not have clinical disease activity at the time of treatment discontinuation in the trial.

†† The total number of 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.

A Disability Progression Confirmed at 12 Wk

Hazard ratio, 0.60 (95% CI, 0.45–0.81)
P<0.001

Interferon beta-1a — 15.2
Ocrelizumab — 9.8

No. at Risk

Interferon beta-1a	829	784	741	696	665	632	608	583	449
Ocrelizumab	827	795	765	737	716	702	688	672	526

B Disability Progression Confirmed at 24 Wk

Hazard ratio, 0.60 (95% CI, 0.43–0.84)
P=0.003

Interferon beta-1a — 12.0
Ocrelizumab — 7.6

No. at Risk

Interferon beta-1a	829	785	747	705	677	644	622	600	466
Ocrelizumab	827	797	772	748	731	717	704	688	540

Figure 1. Key Secondary Clinical End Points.

Shown are the proportions of patients with disability progression confirmed at 12 weeks (first secondary end point; Panel A) and at 24 weeks (fifth secondary end point; Panel B) in time-to-event analyses in the pooled trial populations. Disability progression that was confirmed at 12 or 24 weeks was defined as an increase from the baseline Expanded Disability Status Scale (EDSS) score (on a scale from 0 to 10.0, with higher scores indicating worse disability) of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 or 24 weeks. The numbers shown on the curves represent Kaplan–Meier estimates of the risk of the event at week 96. The insets show the same data on an expanded y axis.

(Fig. 1B). The effect of ocrelizumab on the risk of confirmed disability progression in each of the two trials was consistent with the prespecified pooled analysis (Table 2).

In a pooled analysis, the percentage of patients with disability improvement confirmed at 12 weeks was 20.7% in the ocrelizumab group, as compared with 15.6% in the interferon beta-1a group (33% higher rate of improvement with ocrelizumab, P=0.02) (Fig. S5 in the Supplementary Appendix). The effect of ocrelizumab on the rate of confirmed disability improvement was significant in the OPERA I trial but nonsignificant in the OPERA II trial (Table 2).

The difference in the adjusted mean change in the Multiple Sclerosis Functional Composite score from baseline to week 96 between the ocrelizumab group and the interferon beta-1a group was 0.04 in the OPERA I trial (P=0.33, which was the first nonsignificant P value in the hierarchical testing) and 0.11 in the OPERA II trial (P=0.004) (Table 2, and Fig. S6 in the Supplementary Appendix). As a result of the failure in the statistical hierarchical testing, all the P values for the subsequent secondary efficacy end points, including the change in the SF-36 quality-of-life physical-component summary and the measure of no evidence of disease activity, were considered to be nonconfirmatory.

In the intention-to-treat population in the OPERA I trial, 47.9% of the patients in the ocrelizumab group had no evidence of disease activity by 96 weeks (exploratory end point), as compared with 29.2% of those in the interferon beta-1a group. In the OPERA II trial, 47.5% of the patients in the ocrelizumab group had no evidence of disease activity by 96 weeks, as compared with 25.1% of those in the interferon beta-1a group. These findings were considered to be nonconfirmatory as a result of failure of the hierarchical analysis (Table 2, and Table S6 in the Supplementary Appendix).

MRI-Related Secondary End Points

The total mean number of gadolinium-enhancing lesions per T_1-weighted MRI scan in the OPERA I trial was 0.02 with ocrelizumab versus 0.29 with interferon beta-1a (94% lower number of lesions with ocrelizumab, P<0.001). The values in the OPERA II trial were 0.02 with ocrelizumab versus 0.42 with interferon beta-1a (95% lower number of lesions with ocrelizumab, P<0.001) (Table 2

trial period, the rate of disability progression confirmed at 24 weeks was 6.9% in the ocrelizumab group, as compared with 10.5% in the interferon beta-1a group (40% lower risk with ocrelizumab; hazard ratio, 0.60; 95% CI, 0.43 to 0.84; P=0.003)

and Fig. 2, and Fig. S7 in the Supplementary Appendix).

The total mean numbers of new or newly enlarged hyperintense lesions per T_2-weighted MRI scan in the OPERA I trial was 0.32 with ocrelizumab versus 1.41 with interferon beta-1a (77% lower number of lesions with ocrelizumab, P<0.001). The values in the OPERA II trial were 0.33 with ocrelizumab versus 1.90 with interferon beta-1a (83% lower number of lesions with ocrelizumab, P<0.001) (Table 2, and Figs. S8 and S13 in the Supplementary Appendix). Most of the new or newly enlarged lesion activity on T_2-weighted MRI in the ocrelizumab groups occurred between baseline and week 24 (Fig. S8 in the Supplementary Appendix). From week 24 to week 48, the number of lesions was 94% lower in the ocrelizumab group than in the interferon beta-1a group in the OPERA I trial and 96% lower in the ocrelizumab group than in the interferon beta-1a group in the OPERA II trial. From week 48 to week 96 the number of lesions was 98% lower and 97% lower in the ocrelizumab group than in the interferon beta-1a group in the OPERA I trial and the OPERA II trial, respectively.

The total mean number of new hypointense lesions on T_1-weighted MRI in the OPERA I trial was 0.42 with ocrelizumab versus 0.98 with interferon beta-1a (57% lower number of lesions with ocrelizumab, P<0.001). The values in the OPERA II trial were 0.45 with ocrelizumab versus 1.26 with interferon beta-1a (64% lower number of lesions with ocrelizumab, P<0.001) (Table 2, and Fig. S9 in the Supplementary Appendix). As a result of the failure in the statistical hierarchical testing, the differences in the percentage of brain-volume loss from week 24 to week 96 between the ocrelizumab group and the interferon beta-1a group were nonconfirmatory in the OPERA I trial (nominal P=0.004) and nonsignificant in the OPERA II trial (nominal P=0.09) (Table 2, and Fig. S10 in the Supplementary Appendix).

SAFETY
Adverse Events
A total of 327 of 408 patients (80.1%) in the ocrelizumab group reported an adverse event in the OPERA I trial, as compared with 331 of 409 (80.9%) in the interferon beta-1a group; the corresponding values in the OPERA II trial were 360 of 417 patients (86.3%) and 357 of 417 (85.6%) (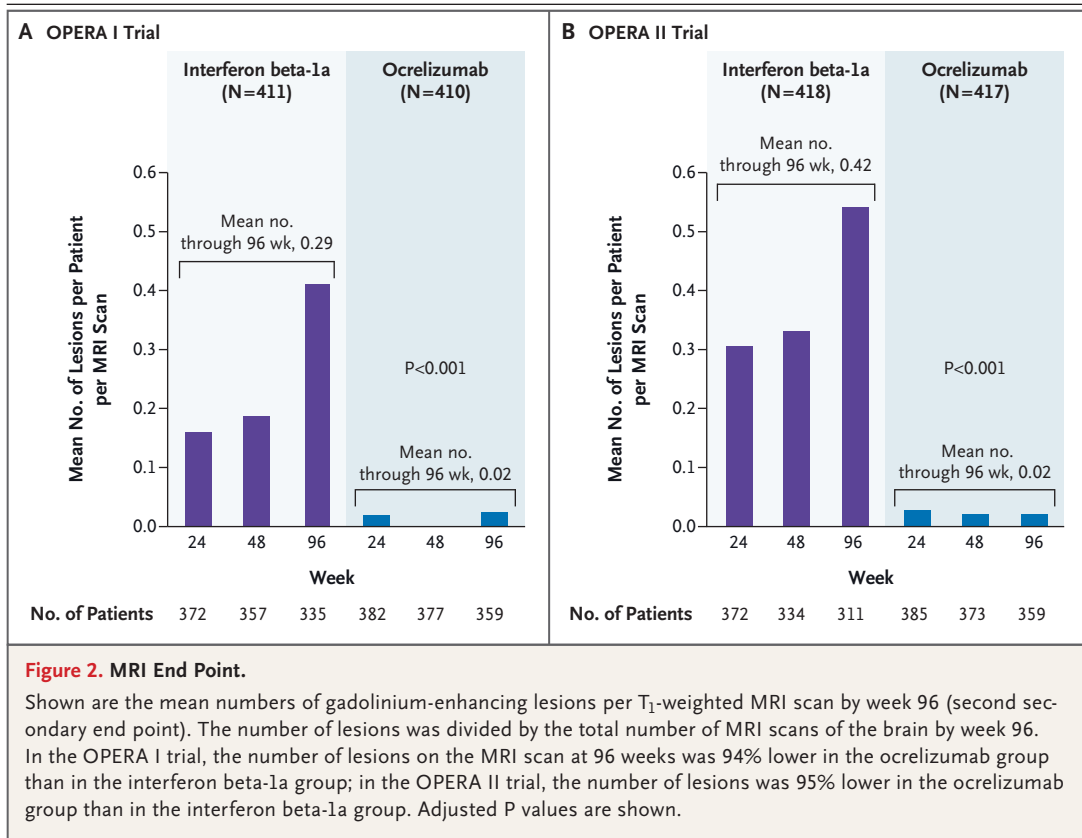Table 3). The most common adverse events were infusion-related reaction, nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection in patients treated with ocrelizumab and influenza-like illness, injection-site erythema, headache, urinary tract infection, and upper respiratory tract infection in patients treated with interferon beta-1a.

Serious adverse events were reported in 6.9% of the patients treated with ocrelizumab and in 7.8% of those treated with interferon beta-1a in the OPERA I trial and in 7.0% of the patients treated with ocrelizumab and in 9.6% of those treated with interferon beta-1a in the OPERA II trial (Table 3). Three deaths occurred, including one death in the ocrelizumab group (suicide in the OPERA II trial) and two in the interferon beta-1a group (one suicide in the OPERA I trial, and one death due to mechanical ileus in the OPERA II trial).

Infections
Infection was reported in 232 patients (56.9%) in the ocrelizumab group and in 222 (54.3%) in the interferon beta-1a group in the OPERA I trial; the corresponding values in the OPERA II trial were 251 (60.2%) and 219 (52.5%) (Table 3). The most common infections (reported in ≥10% of the patients in either group across both trials) were upper respiratory tract infection, nasopharyngitis, and urinary tract infection. There were more reports in the ocrelizumab group than in the interferon beta-1a group of upper respiratory tract infection (15.2% vs. 10.5%) and nasopharyngitis (14.8% vs. 10.2%), whereas urinary tract infection was more frequent in the interferon beta-1a group (11.6% vs. 12.1%). The overall percentage of patients reporting a serious infection was 1.3% in the ocrelizumab group and 2.9% in the interferon beta-1a group (Table S5 in the Supplementary Appendix). The same pattern was seen when we used a broader definition of serious infection, including nonserious infection treated with an intravenous antiinfective treatment (1.8% in the ocrelizumab group vs. 3.8% in the interferon beta-1a group). No opportunistic infections were reported in any group over the duration of either trial.

Across the two trials, the percentage of patients reporting herpesvirus-associated infection was 5.9% in the ocrelizumab group and 3.4% in the interferon beta-1a group (Tables S3 and S4 in the Supplementary Appendix). All these events

Figure 2. MRI End Point.

Shown are the mean numbers of gadolinium-enhancing lesions per T₁-weighted MRI scan by week 96 (second secondary end point). The number of lesions was divided by the total number of MRI scans of the brain by week 96. In the OPERA I trial, the number of lesions on the MRI scan at 96 weeks was 94% lower in the ocrelizumab group than in the interferon beta-1a group; in the OPERA II trial, the number of lesions was 95% lower in the ocrelizumab group than in the interferon beta-1a group. Adjusted P values are shown.

were mild or moderate (Common Terminology Criteria for Adverse Events grade 1 or 2, as defined in Supplementary Appendix), with one exception: in the OPERA I trial, a patient treated with ocrelizumab for 1.6 years was hospitalized for a severe genital herpes simplex infection, which resolved with treatment.

Infusion-Related Reactions

More patients in the ocrelizumab group (34.3%) than in the interferon beta-1a group (9.7%) had at least one infusion-related reaction. Patients in the interferon beta-1a group received placebo infusions. In the OPERA I trial, at least one infusion-related reaction occurred in 30.9% of the patients in the ocrelizumab group and in 7.3% of those in the interferon beta-1a group; the corresponding values in the OPERA II trial were 37.6% and 12.0%. Most infusion-related reactions were mild to moderate, were reported at the first infusion of dose 1 (Fig. S11 in the Supplementary Appendix), and were managed with infusion adjustments and treatment of symptoms. One patient in the ocrelizumab group in the OPERA I trial had a life-threatening episode of bronchospasm during the

first infusion of dose 1; the patient declined hospitalization, recovered with treatment, and was withdrawn from the trial according to the protocol. The most frequent symptoms of infusion-related reaction with ocrelizumab included pruritus, rash, throat irritation, and flushing.

Laboratory Assessments

CD19+ cells represent a measure of B-cell counts in anti-CD20–treated patients. The level of CD19+ cells decreased to negligible levels with ocrelizumab treatment by week 2. (See the Additional Methodology Details section and Fig. S12 in the Supplementary Appendix.)

Antidrug-binding antibodies developed in 3 of 825 patients (0.4%) who received ocrelizumab across the two trials, with neutralizing antibodies developing in 1 patient in the OPERA II trial. Across the two trials, neutralizing anti–interferon beta-1a antibodies were detected in 21.3% of the patients.

Neoplasms

Across these two 96-week trials, four neoplasms (in 0.5% of patients) occurred in the ocrelizu-

Table 3. Adverse Events (Safety Population).*

Variable	OPERA I Trial		OPERA II Trial	
	Ocrelizumab (N=408)	Interferon Beta-1a (N=409)	Ocrelizumab (N=417)	Interferon Beta-1a (N=417)
	no. of patients (%)			
Any adverse event	327 (80.1)	331 (80.9)	360 (86.3)	357 (85.6)
Adverse event leading to treatment discontinuation	13 (3.2)	26 (6.4)	16 (3.8)	25 (6.0)
At least 1 infusion-related reaction	126 (30.9)	30 (7.3)	157 (37.6)	50 (12.0)
Infection†	232 (56.9)	222 (54.3)	251 (60.2)	219 (52.5)
System organ class infection or infestation	231 (56.6)	216 (52.8)	251 (60.2)	217 (52.0)
Herpes infection				
Herpes zoster	9 (2.2)	4 (1.0)	8 (1.9)	4 (1.0)
Oral herpes	9 (2.2)	8 (2.0)	15 (3.6)	9 (2.2)
Neoplasm‡	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)
Death§	0	1 (0.2)	1 (0.2)	1 (0.2)
Any serious adverse event	28 (6.9)	32 (7.8)	29 (7.0)	40 (9.6)
Serious infection or infestation¶	5 (1.2)	12 (2.9)	6 (1.4)	12 (2.9)

* Shown are data collected during the double-blind, controlled treatment period. Table S5 in the Supplementary Appendix provides an up-to-date list of adverse events (including serious adverse events) for the pooled trials, including data that were based on information available as of January 20, 2016. The safety population included all the patients who received any study drug. Data for patients who underwent randomization and received a therapy that was different from that intended are summarized according to the therapy actually received. Patients who did not undergo randomization but who received a study drug were included in the safety population, and their data are summarized according to the therapy actually received.
† Infections were identified either as adverse events as defined in the *Medical Dictionary for Regulatory Activities* infections system organ class "infections and infestations" or as an adverse event with pathogen information provided.
‡ The neoplasms reported in the OPERA I trial were ductal breast carcinoma (in two patients) and renal cancer (in one) in the ocrelizumab group and mantle-cell lymphoma (in one) in the interferon beta-1a group. The neoplasms reported in the OPERA II trial were malignant melanoma (in one patient) in the ocrelizumab group and squamous-cell carcinoma (in one) in the interferon beta-1a group. For an up-to-date list of all additional neoplasms recorded in the latest extended safety follow-up analysis of all exposure until June 30, 2016, (including open-label extension data) across the OPERA I, OPERA II, ORATORIO, and phase 2 trials of ocrelizumab in patients with multiple sclerosis, see the Supplementary Appendix of Montalban et al.[24]
§ Deaths occurring during the trials were due to suicide (one in the ocrelizumab group in the OPERA II trial and one in the interferon beta-1a group in the OPERA I trial) and mechanical ileus (one in the interferon beta-1a group in the OPERA II trial).
¶ Serious infections and infestations reported in the ocrelizumab group were appendicitis (in three patients), cellulitis (in two), pyelonephritis (in two), and biliary sepsis, device-related infection, herpes simplex infection, pneumonia, and upper respiratory tract infection (in one patient each). Serious infections and infestations reported in the interferon beta-1a group were appendicitis (in three patients), limb abscess (in two), injection-site cellulitis (in two), pneumonia (in two), urinary tract infection (in two), and acute tonsillitis, anal abscess, infective cholecystitis, cystitis, infectious enterocolitis, viral gastritis, gastroenteritis, perirectal abscess, staphylococcal septic arthritis, staphylococcal sepsis, tooth infection, viral infection, and viral pericarditis (in one patient each).

mab group (two cases of invasive ductal breast carcinoma, one case of renal-cell carcinoma, and one case of malignant melanoma), and two occurred (in 0.2%) in the interferon beta-1a group (one case of mantle-cell lymphoma and one case of squamous-cell carcinoma in the chest) (Table 3). Between the clinical cutoff dates of the two trials (April 2, 2015, in the OPERA I trial and May 12, 2015, in the OPERA II trial) and June 30, 2016, five additional cases of neoplasm (two cases of breast cancer, two cases of basal-cell skin carcinoma, and one case of malignant melanoma) were detected during the open-label extension study, during which all the patients received ocrelizumab. As of June 30, 2016, the overall incidence rate of first neoplasm among patients treated with ocrelizumab across all studies involving patients with multiple sclerosis was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure), as compared with 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving interferon beta-1a or placebo). (See Table S6 in the Supplementary

Appendix for the ORATORIO trial, the results of which are now published in the *Journal*.[24])

DISCUSSION

In the OPERA I and OPERA II trials, ocrelizumab was associated with significantly lower annualized relapse rates (the primary end point) than the active comparator, interferon beta-1a, during the 96-week treatment period. In addition, patients receiving ocrelizumab had better outcomes, as assessed in the first 6 of 10 secondary end points in the hierarchical testing. Ocrelizumab was associated with a lower rate of disability progression confirmed at 12 weeks and at 24 weeks than interferon beta-1a, both in the prespecified pooled analysis and in each of the two phase 3 trials separately. Ocrelizumab also was associated with a higher rate of disability improvement confirmed at 12 weeks (a secondary end point) than interferon beta-1a in the pooled analysis.

These findings were supported by a significantly greater suppression of development of new areas of inflammation (as assessed by means of MRI of the brain with the use of gadolinium enhancement) and new or newly enlarged plaque formation (as measured by lesions on T_2-weighted MRI) (Figs. S7 and S8 in Supplementary Appendix). However, the change in Multiple Sclerosis Functional Composite score, whole brain-volume loss, and the change in the SF-36 physical-component summary score were significantly better with ocrelizumab than with interferon beta-1a in one trial but not in the other. Although the findings were nonconfirmatory as a result of failure of the hierarchical analysis, the percentages of patients who had no evidence of disease activity were higher with ocrelizumab than with interferon beta-1a in the two trials.

Infusion-related reactions were more common in patients treated with ocrelizumab than in those treated with interferon beta-1a and included one life-threatening (grade 4) bronchospasm. The most likely mechanism for an infusion-related reaction is a type 2 hypersensitivity reaction, in which cytokines are released from an effector cell after the ligation of low-affinity Fc receptors by ocrelizumab-opsonized B cells.[25] The incidence and severity of infusion-related reactions decreased over the administration of subsequent doses; however, such reactions could occur at any infusion. The limited immunogenicity of ocrelizumab was shown by the low incidence of antidrug antibodies among patients treated with ocrelizumab; the incidence of neutralizing antibodies with interferon beta-1a was consistent with historical data.[26,27]

The traditional view of the pathophysiology of multiple sclerosis is that it is predominantly a T-cell–mediated disease. The findings in our two trials are consistent with evidence that B cells play a role in the pathogenesis of multiple sclerosis.[28,29] The mechanism of action of ocrelizumab involves immunomodulation by means of the reduction in the number and function of CD20+ B cells.[30,31] The trafficking of activated oligoclonal populations of B cells between the central nervous system and peripheral circulation has been observed in persons with relapsing multiple sclerosis,[32,33] and the disruption of this network may explain the effects of ocrelizumab in our trials. Lymphoid stem cells and plasma cells lack CD20, and thus B-cell reconstitution and preexisting humoral immunity should be relatively preserved with ocrelizumab treatment.[26,27,34]

The numerical imbalance in the neoplasms observed in the OPERA I trial and in the ORATORIO trial,[24] which involved patients with primary progressive multiple sclerosis, warrants ongoing evaluation in the context of the epidemiology of neoplasm in the population of patients with multiple sclerosis and long-term experience with ocrelizumab and other anti-CD20 treatments.[35-37] No cases of progressive multifocal leukoencephalopathy (PML) have been reported so far with ocrelizumab across all clinical studies (F. Hoffman–La Roche data on file). Further long-term assessment of the safety profile of ocrelizumab is required in order to fully characterize the risk of uncommon adverse events, including PML.

Inflammation and neurodegeneration are understood to be two distinct but overlapping mechanisms of the pathogenesis of multiple sclerosis,[38,39] with inflammation dominating the early stages of disease.[40] The use of current therapies in patients with relapsing multiple sclerosis has been associated with an improved overall prognosis, as compared with the pretreatment era. However, most treated patients still have worsening neurologic disability over time in this lifelong disease.[3,41-43] Additional and extended studies will be required in order to determine whether the outcomes observed in these 96-week trials, including a near-complete cessation of new plaque

formation as assessed by MRI of the brain, translate into enhanced protection against accrual of disability over the long term.

APPENDIX

The authors' full names and academic degrees are as follows: Stephen L. Hauser, M.D., Amit Bar-Or, M.D., Giancarlo Comi, M.D., Gavin Giovannoni, M.D., Hans-Peter Hartung, M.D., Bernhard Hemmer, M.D., Fred Lublin, M.D., Xavier Montalban, M.D., Kottil W. Rammohan, M.D., Krzysztof Selmaj, M.D., Anthony Traboulsee, M.D., Jerry S. Wolinsky, M.D., Douglas L. Arnold, M.D., Gaelle Klingelschmitt, Ph.D., Donna Masterman, M.D., Paulo Fontoura, M.D., Ph.D., Shibeshih Belachew, M.D., Ph.D., Peter Chin, M.D., Nicole Mairon, M.D., Hideki Garren, M.D., Ph.D., and Ludwig Kappos, M.D.

The authors' affiliations are as follows: the University of California, San Francisco (S.L.H.), and Genentech, South San Francisco (D.M., P.C., H.G.) — both in California; McGill University (A.B.-O., D.L.A.) and NeuroRx Research (D.L.A.), Montreal, and University of British Columbia, Vancouver, BC (A.T.) — both in Canada; University Vita-Salute San Raffaele, Milan (G.C.); Barts and the London School of Medicine and Dentistry, London (G.G.); Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf (H.-P.H.), and the Technical University of Munich and Munich Cluster for Systems Neurology, Munich (B.H.) — both in Germany; Icahn School of Medicine at Mount Sinai, New York (F.L.); Hospital Vall d'Hebron University, Barcelona (X.M.); University of Miami, Miami (K.W.R.); Medical University of Lodz and Center for Neurology, Lodz, Poland (K.S.); McGovern Medical School, University of Texas Health Science Center at Houston, Houston (J.S.W.); and F. Hoffmann–La Roche (G.K., P.F., S.B., N.M.) and University Hospital Basel, University of Basel (L.K.), Basel, Switzerland.

REFERENCES

1. Winkelmann A, Loebermann M, Reisinger EC, Hartung HP, Zettl UK. Disease-modifying therapies and infectious risks in multiple sclerosis. Nat Rev Neurol 2016;12:217-33.
2. Kappos L, Bates D, Edan G, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol 2011;10:745-58.
3. Cree BA, Gourraud PA, Oksenberg JR, et al. Long-term evolution of multiple sclerosis disability in the treatment era. Ann Neurol 2016;80:499-510.
4. Li R, Rezk A, Miyazaki Y, et al. Proinflammatory GM-CSF-producing B cells in multiple sclerosis and B cell depletion therapy. Sci Transl Med 2015;7:310ra166.
5. Genain CP, Cannella B, Hauser SL, Raine CS. Identification of autoantibodies associated with myelin damage in multiple sclerosis. Nat Med 1999;5:170-5.
6. Storch MK, Piddlesden S, Haltia M, Iivanainen M, Morgan P, Lassmann H. Multiple sclerosis: in situ evidence for antibody- and complement-mediated demyelination. Ann Neurol 1998;43:465-71.
7. Serafini B, Rosicarelli B, Magliozzi R, Stigliano E, Aloisi F. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. Brain Pathol 2004;14:164-74.
8. Howell OW, Reeves CA, Nicholas R, et al. Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. Brain 2011;134:2755-71.
9. Sorensen PS, Blinkenberg M. The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects. Ther Adv Neurol Disord 2016;9:44-52.
10. Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011;378:1779-87.
11. Klein C, Lammens A, Schäfer W, et al. Response to: monoclonal antibodies targeting CD20. MAbs 2013;5:337-8.
12. Genovese MC, Kaine JL, Lowenstein MB, et al. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I/II randomized, blinded, placebo-controlled, dose-ranging study. Arthritis Rheum 2008;58:2652-61.
13. Martin F, Chan AC. B cell immunobiology in disease: evolving concepts from the clinic. Annu Rev Immunol 2006;24:467-96.
14. DiLillo DJ, Hamaguchi Y, Ueda Y, et al. Maintenance of long-lived plasma cells and serological memory despite mature and memory B cell depletion during CD20 immunotherapy in mice. J Immunol 2008;180:361-71.
15. Klein C, Lammens A, Schäfer W, et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. MAbs 2013;5:22-33.
16. 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.
17. International Conference on Harmonisation. ICH harmonized tripartite guideline: Guideline for Good Clinical Practice. J Postgrad Med 2001;47:45-50.
18. WMA Declaration of Helsinki — ethical principles for medical research involving human subjects. Ferney-Voltaire, France: World Medical Association, 2013 (http://www.wma.net/en/30publications/10policies/b3/).
19. 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.
20. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444-52.
21. Fischer JS, Jak AJ, Kniker JE, Rudick RA, Cutter G. Multiple Sclerosis Functional Composite (MSFC): administration and scoring manual (revised). National Multiple Sclerosis Society, 2001 (http://main.nationalmssociety.org/docs/HOM/MSFC_Manual_and_Forms.pdf).
22. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17:479-89.
23. Cohen JA, Cutter GR, Fischer JS, et al. Use of the multiple sclerosis functional composite as an outcome measure in a phase 3 clinical trial. Arch Neurol 2001;58:961-7.
24. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med. DOI: 10.1056/NEJMoa1606468.
25. Caon C, Namey M, Meyer C, et al. Prevention and management of infusion-

associated reactions in the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) Program. Int J MS Care 2015;17:191-8.

26. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012;380:1829-39.

27. Al-SabbaghA. Neutralizing antibodies in MS therapy: reviewing the Rebif experience. Mult Scler 2007;13:8-13.

28. Hauser SL. The Charcot Lecture — beating MS: a story of B cells, with twists and turns. Mult Scler 2015;21:8-21.

29. von Büdingen HC, Kuo TC, Sirota M, et al. B cell exchange across the blood-brain barrier in multiple sclerosis. J Clin Invest 2012;122:4533-43.

30. Stern JN, Yaari G, Vander Heiden JA, et al. B cells populating the multiple sclerosis brain mature in the draining cervical lymph nodes. Sci Transl Med 2014;6:248ra107.

31. Lehmann-Horn K, Kronsbein HC, Weber MS. Targeting B cells in the treatment of multiple sclerosis: recent advances and remaining challenges. Ther Adv Neurol Disord 2013;6:161-73.

32. Palanichamy A, Apeltsin L, Kuo TC, et al. Immunoglobulin class-switched B cells form an active immune axis between CNS and periphery in multiple sclerosis. Sci Transl Med 2014;6:248ra106.

33. Kamburova EG, Koenen HJ, Borgman KJ, ten Berge IJ, Joosten I, Hilbrands LB. A single dose of rituximab does not deplete B cells in secondary lymphoid organs but alters phenotype and function. Am J Transplant 2013;13:1503-11.

34. Rebif: European summary of product characteristics. London: European Medicines Agency (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000136/WC500048681.pdf).

35. Nielsen NM, Rostgaard K, Rasmussen S, et al. Cancer risk among patients with multiple sclerosis: a population-based register study. Int J Cancer 2006;118:979-84.

36. Kingwell E, Bajdik C, Phillips N, et al. Cancer risk in multiple sclerosis: findings from British Columbia, Canada. Brain 2012;135:2973-9.

37. Rituxan (rituximab): injection for intravenous use prescribing information. Silver Spring, MD: Food and Drug Administration, 2010 (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf).

38. Brück W. The pathology of multiple sclerosis is the result of focal inflammatory demyelination with axonal damage. J Neurol 2005;252:Suppl 5:v3-v9.

39. Hauser SL, Chan JR, Oksenberg JR. Multiple sclerosis: prospects and promise. Ann Neurol 2013;74:317-27.

40. Bar-Or A. The immunology of multiple sclerosis. Semin Neurol 2008;28:29-45.

41. Goodin DS, Traboulsee A, Knappertz V, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon β-1b trial in multiple sclerosis. J Neurol Neurosurg Psychiatry 2012;83:282-7.

42. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. JAMA Neurol 2015;72:152-8.

43. Trojano M, Pellegrini F, Fuiani A, et al. New natural history of interferon-beta-treated relapsing multiple sclerosis. Ann Neurol 2007;61:300-6.

Copyright © 2016 Massachusetts Medical Society.

TRACK THIS ARTICLE'S IMPACT AND REACH

Visit the article page at NEJM.org and click on the Metrics tab for a dashboard that logs views, citations, media references, and commentary, with easy linking. Learn more at www.nejm.org/page/article-metrics-faq.