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Long-Term Treatment With Ocrelizumab in Patients With Early-Stage Relapsing MS

Nine-Year Data From the OPERA Studies Open-Label Extension

João J. Cerqueira,[1] Achim Berthele,[2] Bruce A.C. Cree,[3] Massimo Filippi,[4,5] Gabriel Pardo,[6] Owen R. Pearson,[7] Anthony Traboulsee,[8] Tjalf Ziemssen,[9] Timothy Vollmer,[10] Corrado Bernasconi,[11] Corey R. Mandel,[12] Inessa Kulyk,[11] Cathy Chognot,[11] Catarina Raposo,[11] Hans-Martin Schneble,[13] Gian-Andrea Thanei,[13] Elodie Incera,[14] and Eva K. Havrdová[15]

Correspondence
Prof. Cerqueira
jcerqueira@med.uminho.pt

Neurology® 2025;104:e210142. doi:10.1212/WNL.0000000000210142

Abstract

Background and Objectives

Patients with multiple sclerosis (MS) may demonstrate better disease control when treatment is initiated on high-efficacy disease-modifying therapies (DMTs) from onset. This subgroup analysis assessed the long-term efficacy and safety profile of the high-efficacy DMT ocrelizumab (OCR) as first-line therapy for early-stage relapsing MS (RMS).

Methods

Post hoc exploratory analyses of efficacy and safety were performed in a subgroup of treatment-naive patients with RMS who received ≥1 dose of OCR in the multicenter OPERA I/II (NCT01247324/NCT01412333) studies. Patients were randomized to OCR or interferon β-1a for 96 weeks (double-blind controlled treatment period [DBP]), before switching to OCR in the open-label extension (OLE). Efficacy assessments included no evidence of disease activity (NEDA-3), 24-week confirmed disability progression (CDP), MRI lesion activity, change in whole-brain volume; with safety outcomes assessed over a 9-year treatment period.

Results

Overall, 757 patients were included (interferon-treated n = 382, mean age 36.3 years, 65.7% female; OCR-treated n = 375, mean age 35.5 years, 64.0% female); 505 of 757 (66.7%) completed 9 years of follow-up. The difference in NEDA status between OCR-treated and interferon-treated patients achieved during the DBP (72.5% and 43.8%, respectively, odds ratio 3.48, 95% CI 2.52–4.81) was maintained throughout the 7-year OLE (48.2% vs 25.7%; odds ratio 2.72, 95% CI 1.94–3.82). No 24-week CDP was observed in 78.7% of OCR-treated patients over 9 years. Brain volume loss over the entire study period remained numerically higher among patients starting OCR later (p = 0.09 at OLE at week 336). During the DBP, safety profiles in both groups were similar; no new safety signals were observed during the OLE. Over >9 years of continuous OCR treatment, the rate of infections remained low and stable over time.

Discussion

A higher proportion of OCR-treated patients achieved NEDA status compared with interferon-treated patients during the DBP, which was maintained throughout the OLE. After switching to OCR, disability accrual and brain volume loss among interferon-treated patients became similar

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[1]Life and Health Sciences Research Institute, School of Medicine, University of Minho, Braga, Portugal; [2]Department of Neurology, School of Medicine, Technical University of Munich, Germany; [3]Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco; [4]Neurology Unit, Neurophysiology Service, Neurorehabilitation Unit, Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy; [5]Vita-Salute San Raffaele University, Milan, Italy; [6]Multiple Sclerosis Center of Excellence, Oklahoma Medical Research Foundation, Oklahoma City; [7]Department of Neurology, Morriston Hospital, Swansea, United Kingdom; [8]Division of Neurology, University of British Columbia, Vancouver, Canada; [9]Center of Clinical Neuroscience, Department of Neurology, University Clinic Carl Gustav Carus, Dresden University of Technology, Germany; [10]Department of Neurology, Rocky Mountain Multiple Sclerosis Center at Anschutz Medical Campus, University of Colorado Denver; [11]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [12]Genentech Inc., San Francisco, CA; [13]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [14]IQVIA Inc., Paris, France; and [15]Department of Neurology and Center of Clinical Neuroscience, First Medical Faculty, General University Hospital and Charles University, Prague, Czech Republic.

The Article Processing Charge was funded by Roche.

Glossary

AE = adverse event; **ARR** = annualized relapse rate; **cCDP** = composite CDP; **CDP** = confirmed disability progression; **COVID-19** = coronavirus disease 2019; **CTCAE** = Common Terminology Criteria for AEs; **DBP** = double-blind controlled treatment period; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **Gd** = gadolinium; **HR** = hazard ratio; **IFN** = interferon; **IgG** = immunoglobulin G; **LLN** = lower limit of normal; **MMRM** = mixed-effects model of repeated measures; **MS** = multiple sclerosis; **NEDA** = no evidence of disease activity; **NfL** = neurofilament light chain; **OCR** = ocrelizumab; **OLE** = open-label extension; **PY** = patient-years; **RMS** = relapsing MS; **SAE** = serious AE; **SI** = serious infection.

to the OCR–OCR group, but disability and brain volume loss accrued during interferon treatment were not recovered. Possible study limitations include assessment bias due to unmaintained blinding during the OLE. These data support OCR as first-line therapy for these patients.

Classification of Evidence

This study provides Class II evidence that OCR delays disease progression in treatment-naïve patients with early-stage RMS.

Introduction

Multiple sclerosis (MS) is a chronic and progressive disease from onset; although initially its progression might be subtle, it becomes more apparent over time.[1] Patients who receive early treatment show long-term benefits to disease progression,[2] delaying worsening of quality of life, and reducing the socioeconomic burden on patients and health care systems.[3] Although patients are still often started on lower-efficacy disease-modifying therapies (DMTs), followed by therapy escalation in response to disease activity or progression,[4] evidence suggests that earlier treatment with high-efficacy DMTs is more beneficial for preventing disability accrual.[2,5] Nevertheless, the question whether treating patients with an escalating approach or first-line treatment with high-efficacy therapies remains in dispute.[6]

Inflammation associated with B cells plays an important role in the induction of tissue injury early in the MS disease course.[7] Ocrelizumab (OCR; Ocrevus, Genentech Inc., South San Francisco, CA) is a humanized monoclonal antibody that selectively targets $CD20^+$ B cells and is approved for relapsing MS (RMS) and early primary progressive MS.[8,9] OCR treatment preserves preexisting humoral immunity, and B cells can reconstitute once dosing is discontinued.[10] In the OPERA I/II trials, OCR demonstrated superior efficacy for preventing relapses and confirmed disability progression (CDP) for RMS, with a favorable and manageable safety profile, as well as a higher rate of disability improvement, compared with subcutaneous interferon (IFN) β-1a given 3 times weekly.[11] Significant benefits of OCR on MRI outcomes, compared with patients receiving IFN, were also reported.[11] Although it has been demonstrated that starting OCR earlier reduces the risk of irreversible disability accumulation compared with starting with a low-efficacy treatment such as IFN,[11] or on placebo,[12] there are limited data, requiring additional evidence as to whether this would also apply to patients who are treatment naïve and relatively early in their disease course.

This subgroup analysis was conducted to assess over >9 years the long-term efficacy and safety of OCR in patients with early RMS in the double-blind and open-label extension (OLE) periods of the OPERA studies. The primary research question in this analysis is do the long-term efficacy and safety data support the use of the high-efficacy DMT OCR as first-line therapy for patients with early-stage RMS?

Methods

Trial Design and Patients

OPERA I (NCT01247324) and OPERA II (NCT01412333) were phase III, multicenter, randomized, double-blind, double-dummy, IFN-controlled trials assessing the efficacy and safety of OCR treatment in patients with RMS. Detailed study methodology was reported previously[11] and is summarized here.

Patients were randomly assigned, in a 1:1 ratio, to receive either 600 mg OCR by 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 IFN β-1a at a dose of 44 μg (Rebif; EMD Serono Inc., Boston, MA), administered subcutaneously 3 times weekly throughout the 96-week treatment period. Patients entered the OLE as per the previously described protocol.[13] At the start of the OLE phase, patients who received OCR in the double-blind controlled treatment period (DBP) continued OCR (OCR–OCR group) and patients from the IFN β-1a group were switched to OCR (IFN–OCR group), given every 24 weeks. The first patient completing the DBP entered the OLE phase in August 2013. The clinical cutoff date for inclusion of data in this analysis was November 26, 2021, with ≥9 years of follow-up in the study (year defined as a double cycle, 48 weeks).

Patients from the main OPERA I/II studies were selected for this early RMS subgroup analysis based on the 2 following criteria: both a confirmed diagnosis of RMS (per 2010

McDonald criteria)[14] ≤2 years before inclusion in the study and no previous DMT treatment.

Standard Protocol Approvals, Registrations, and Patient Consents

The trial protocols (NCT01247324 and NCT01412333) were approved by the relevant institutional review boards/ethics committees. Written informed consent was provided by all patients.

Efficacy Assessments

The following endpoints are reported for the DBP and OLE phases, using the pooled OPERA trial population.

No Evidence of Disease Activity

No evidence of disease activity (NEDA-3) status was defined as the combined absence of protocol-defined relapses, 24-week CDP, new or enlarging T2 lesions, or T1 gadolinium (Gd)–enhancing lesions over the reported period. Participants who withdrew from the study because of lack of efficacy or death are included in the analysis with NEDA-3 status. NEDA estimates are calculated at the end of the DBP (week 96) and at OLE week 336 over the entire reported period of the study.

24-Week CDP and Composite CDP

24-week CDP was defined as an increase in the Expanded Disability Status Scale (EDSS) score from baseline EDSS by at least 1.0 point (increase of ≥0.5 points if baseline EDSS score >5.5), with confirmation of the change over a period of at least 24 weeks after the initial assessment. 24-week composite CDP (cCDP), based on data only available for the 96-week DBP period, was defined as meeting at least one of the following 3 criteria: (1) an increase in 24-week CDP, (2) an increase from baseline of at least 20% in the time taken to complete the Nine-Hole Peg Test (applied to the average of both hands), or (3) an increase from baseline of at least 20% in the time taken to complete the Timed 25-Foot Walk Test, sustained for a period of at least 24 weeks. Time to onset of cCDP is defined as the first occurrence of a confirmed progression event according to at least one of these criteria. Time to 24-week CDP (DBP and OLE) and time to 24-week cCDP (DBP only) were assessed and plotted in cumulative incidence curves.

Annualized Relapse Rate

The annualized relapse rate (ARR) was calculated as the total number of protocol-defined relapses from DBP baseline, divided by the total patient-years (PY) of exposure to that treatment. Protocol-defined relapses were defined as the occurrence of new or worsening neurologic symptoms attributable to MS with an increase of at least half a step on the EDSS, 2 points on one of the appropriate Functional Systems Scores scale, or 1 point on 2 or more of the appropriate FSS for all patients in the treatment group.

Brain MRI Outcomes

MRI lesion activity was measured in both treatment groups using the total number of new or newly enlarged T2 lesions and total number of T1 Gd-enhancing lesions on brain MRI, assessed at baseline, study weeks 24, 48, and 96, as well as every 48 weeks in the OLE phase. To assess full efficacy, unconfounded by MRI lesion activity carried over during the first 4–8 weeks from treatment initiation, a rebaselining approach for MS lesions as per recent recommendations.[15] As such, MRI data were rebaselined at week 24 in this study. Percentage change in whole-brain volume from baseline was assessed using SIENA/SIENAX software.[16] Percentage change in cortical gray matter volume and white matter volume from baseline was assessed using paired Jacobian integration.[17]

Neurofilament Light Chain Levels

Age-adjusted serum neurofilament light chain (NfL) levels were assessed, and distributions within the DBP population were assessed. Serum NfL levels over the course of the DBP and OLE were monitored. NfL levels were compared with those obtained from a healthy donor cohort,[18] in which serum and plasma samples were collected from 118 healthy individuals of age range 24–66 years. Serum samples were assessed for NfL using the SIMOA assay (Quanterix NfL Advantage Kit). Serum-based measurements were assessed at each clinic visit (every 6 months).

Safety Reporting

Safety assessments consisted of monitoring and recording adverse events (AEs) and serious AEs (SAEs) from the first randomized dose onward until the clinical cutoff date. The 2019 novel coronavirus disease (COVID-19) was declared a global pandemic by the World Health Organization in 2020, when the RMS patient population under study was in its seventh year of OCR therapy. To enable a consistent assessment over time, COVID-19–specific AEs were excluded from this analysis because extensive analyses of COVID-19 infections in patients treated with OCR have been previously published.[19-22] Safety outcomes including AEs, SAEs, and AEs leading to treatment discontinuation were monitored and coded as per Medical Dictionary for Regulatory Activities (versions 18.0 to 24.1). AE severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE). The safety population included all randomized patients who received at least 1 dose of OCR treatment. The single-drop method was used to examine the risk of serious infections (SIs) during the period of immunoglobulin G (IgG) below the lower limit of normal (LLN) compared with the risk of SIs during the period of IgG ≥LLN (eFigure 1). The duration of exposure of single-drop IgG <LLN was defined as the duration from the day the first laboratory value <LLN until the day the laboratory value normalized to ≥LLN; the SIs with onset dates in between were counted.

Statistical Methods

This was a post hoc exploratory analysis of the OPERA I and II study. Statistical approaches, including the analyses of primary and secondary endpoints, were described previously.[11] The analysis data set consisted of the early RMS subset

(see "Trial Design and Patients" above for the definition) of the intention-to-treat population of the OPERA study; missing data were not imputed. ARR was analyzed with the use of a negative binomial generalized linear model. Time to 24-week CDP and cCDP (the latter only being derivable in the DBP) were evaluated based on the time from baseline to the first assessment meeting the endpoint definition, using Kaplan–Meier plots and Cox regression analysis. The change in whole-brain volume over time was analyzed using a mixed-effects model of repeated measures (MMRM) with an unstructured covariance to account for within-patient variance between visits. NfL data at baseline were compared using an age-adjustment methodology described previously[18] to ensure that cohorts were not confounded by their age differences and to derive age-adjusted healthy donor NfL levels. Change from baseline in NfL was modeled using an MMRM. Patients who discontinued treatment early for reasons other than lack of efficacy or death and had NEDA before early discontinuation were excluded. Safety outcomes are reported as incidence rates (events per 100 PY of exposure) with Poisson distribution-based CIs. Multiple occurrences of the same AE in 1 patient were counted multiple times. All statistical hypotheses were tested at the 5% significance level against 2-sided alternatives.

Data Availability

Qualified researchers may request access to individual patient-level data through the clinical study data request platform.[23] Further details on Roche criteria for eligible studies are available online.[24] Further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents are available online.[25]

Results

Efficacy Analyses

Patient Disposition and Analysis Population

As previously reported,[13] >90% of patients in both groups from the total OPERA study who completed the DBP (where no treatment crossover was allowed) entered the OLE phase. Of the patients enrolled in the OPERA studies, 757 met the criteria for analysis as part of the early RMS, treatment-naive subgroup (constituting the ITT population), comprising 382 patients in the IFN–OCR group and 375 patients in the OCR–OCR group. The approximate balance of these 2 groups is compatible with very limited selection bias. Baseline demographics and patient characteristics were similar between the groups (Table 1).

On completing the DBP, 19 (5%) patients from the IFN–OCR group and 12 (3%) patients from the OCR–OCR group did not enter the OLE phase. In this early RMS treatment-naive subgroup, 505 of 757 (67%) patients remained on OCR treatment at 9-year follow-up. The overall percentage of patients who discontinued OCR treatment due to AEs was 9.9% and 8.3% in the IFN–OCR and OCR–OCR groups, respectively (see Figure 1 for withdrawal from study reasons).

Table 1 Baseline Demographics and Disease Characteristics of Treatment-Naive Patients With Early RMS Who Entered the OLE Phase From the IFN β-1a and OCR Double-Blind Controlled Treatment Period Groups

	IFN β-1a (N = 382)	OCR (N = 375)
Age, y		
Mean (SD)	36.3 (9.3)	35.5 (9.3)
Median	36.0	37.0
Sex, n (%)		
Female	251 (65.7)	240 (64.0)
Male	131 (34.3)	135 (36.0)
Duration since diagnosis, y, mean (SD)	0.6 (0.5)	0.6 (0.4)
Duration since MS symptom onset, y, mean (SD)	3.4 (4.1)	3.1 (4.0)
EDSS, mean (SD)	2.4 (1.2)	2.4 (1.1)
T1 Gd+, n (%)		
0	219 (58.1)	209 (56.5)
≥1	158 (41.9)	161 (43.5)
No. of T2 lesions, mean (SD)	44.8 (36.3)	44.8 (38.8)

Abbreviations: EDSS = Expanded Disability Status Scale; IFN = interferon β-1a; MS = multiple sclerosis; OCR = ocrelizumab; OLE = open-label extension; RMS = relapsing multiple sclerosis; T1 Gd+ = T1-weighted contrast-enhancing lesion.

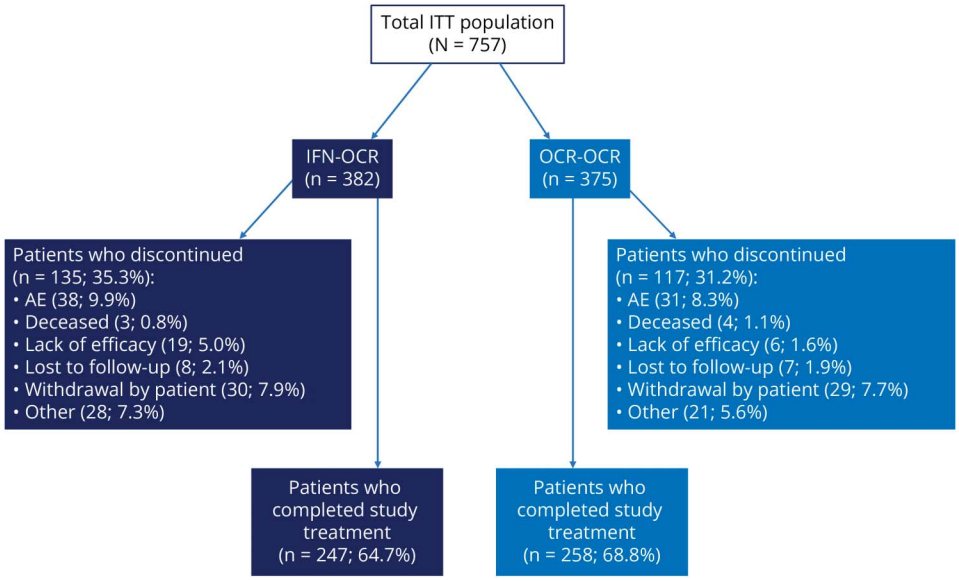
NEDA-3 With MRI Rebaseline at Week 24

At week 96 (2 years) in the DBP, 72.5% of OCR-treated patients achieved NEDA status compared with 43.8% of IFN-treated patients (odds ratio 3.48, 95% CI 2.52–4.81; $p < 0.0001$) and significantly fewer OCR-treated patients had T1 enhancing lesions, new/enlarging T2 lesions, or protocol-defined relapses (Table 2). At OLE week 336 (9 years), 48.2% of patients in the OCR–OCR group maintained NEDA status vs approximately 25.7% in the IFN–OCR group (Table 2). After patients in the IFN–OCR arm switched to OCR in the OLE period, the ARR, MRI activity, and the rate of disability accumulation became similar to OCR–OCR group; however, the differences that developed between the groups during the DBP continued to influence the differences in NEDA at OLE week 336.

Time to 24-Week Composite CDP and CDP

Time to 24-week cCDP during the DBP showed a statistically significant difference between the IFN–OCR and OCR–OCR groups (hazard ratio [HR] 0.70, 95% CI 0.50–0.98, $p = 0.039$), indicating that there was a 30% lower risk of reaching 24-week cCDP in the OCR–OCR group compared with the IFN–OCR group during the DBP (Figure 2A). Numerical

Figure 1 Summary of Treatment Disposition at OLE Week 336 (Year 9)[a] of Follow-up



The total ITT population referred to here includes those patients completing the double-blind treatment phase and meeting the criteria for analysis as part of the early RMS, treatment-naive subgroup. Of the 382 and 375 patients included in the IFN–OCR and OCR–OCR cohorts, respectively, the number of participants who discontinued due to study withdrawal, being lost to follow-up, lack of efficacy, died, or had AEs was calculated; percentages in parentheses. [a] 96 weeks (2 years) in the double-blind period plus 267 weeks (7 years) in the OLE. AE = adverse event; IFN = interferon; ITT = intention-to-treat; OCR = ocrelizumab; OLE = open-label extension.

benefits (HR 0.66, 95% CI 0.39–1.11) were observed for the 24-week CDP outcomes during the DBP for the OCR–OCR group compared with the IFN–OCR group. Although the rates of progression between treatment groups became similar following the switch to OCR for the IFN–OCR group (eFigure 2), the benefits observed to 24-week CDP for the OCR–OCR group were maintained throughout the 9-year period (OLE week 336) (Figure 2B).

Annualized Relapse Rate

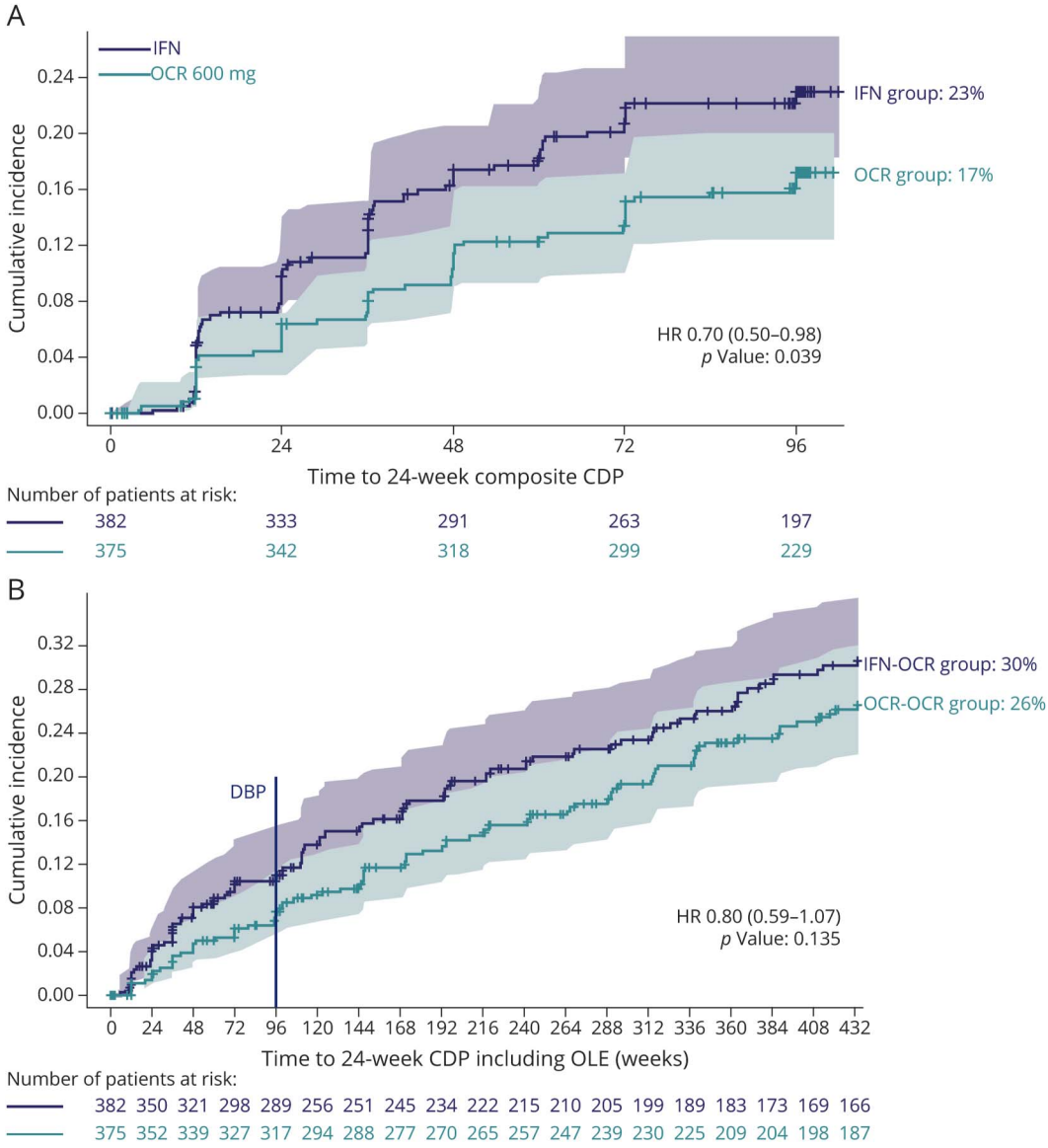
The OCR–OCR group showed an overall ARR of 0.05 (up to OLE week 336), compared with an ARR of 0.09 in the

Table 2 Rates of NEDA and Components at Week 96 (2 Years) in the Double-Blind Controlled Treatment Period and at OLE Week 336 (9 Years)

	IFN–OCR (N = 382), n (%)	OCR–OCR (N = 375), n (%)	Odds ratio (95% CI)	*p* Value
DBP week 96 (2 y)[a]	347	345		
NEDA[a,b]	152 (43.8)	250 (72.5)	3.48 (2.52–4.81)	<0.0001
No 24-wk CDP	338 (88.5)	346 (92.3)	1.60 (0.97–2.62)	0.0623
No PDRs	277 (72.5)	310 (82.7)	1.77 (1.24–2.52)	0.0013
No Gd-enhancing T1 lesions[b]	309 (80.9)	368 (98.1)	12.16 (5.49–26.92)	<0.0001
No new or enlarging T2 lesions[b]	239 (62.6)	356 (94.9)	10.75 (6.50–17.78)	<0.0001
DBP + OLE week 336 (9 y)[a]	327	303		
NEDA[a]	84 (25.7)	146 (48.2)	2.72 (1.94–3.82)	<0.0001
No 24-wk CDP	286 (74.9)	295 (78.7)	1.25 (0.89–1.75)	0.2024
No PDRs	251 (65.7)	285 (76.0)	1.62 (1.18–2.23)	0.0029
No Gd-enhancing T1 lesions[b]	300 (78.5)	367 (97.9)	12.11 (5.76–25.46)	<0.0001
No new or enlarging T2 lesions[b]	210 (55.0)	336 (89.6)	7.04 (4.76–10.41)	<0.0001

Abbreviations: CDP = confirmed disability progression; DBP = double-blind controlled treatment period; Gd = gadolinium; IFN = interferon; NEDA = no evidence of disease activity; OCR = ocrelizumab; PDR = protocol-defined relapse.
Patients who were withdrawn prematurely from their treatment were considered as having an event if they withdrew due to efficacy, failure, or death, or if they had an event before withdrawal.
[a] NEDA-3 was calculated for all patients with readings on all components.
[b] MRI data from week 24 of the DBP were used as a baseline, with Gd+ T1 or new or enlarging T2 lesions detected onward being used for the derivation of the endpoint data.

Figure 2 (A) Time to Onset of cCDP for at Least 24 Weeks During the DBP and (B) Time to Onset of CDP for at Least 24 Weeks During the DBP and OLE



Curves show Kaplan–Meier estimates of the proportion of patients with (A) cCDP and (B) CDP events throughout the DBP and OLE treatment period (OLE week 336; 9 years). cCDP = composite CDP; CDP = confirmed disability progression; DBP = double-blind controlled treatment period; HR = hazard ratio; IFN = interferon; OCR = ocrelizumab; OLE = open-label extension; W = week.

IFN–OCR group (p = 0.0036; adjusted rate ratio of 0.627), due to a higher rate of relapses during the DBP.

Brain Volume Change

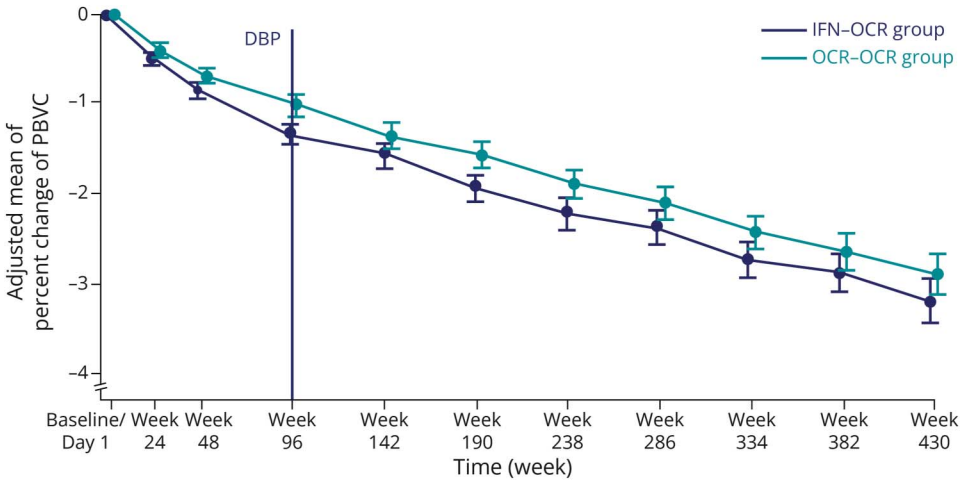
During the DBP, patients receiving IFN incurred greater brain volume loss than patients receiving OCR ($p < 0.001$ at week 96). Although the brain volume loss slowed after IFN–OCR patients were switched to OCR, the brain volume loss occurred in these patients during the DBP persisted in OLE and the brain volume loss rates over the entire study period remained numerically higher among patients starting OCR treatment later (p = 0.09 at OLE week 336) (Figure 3).

NfL Levels

Age-adjusted NfL levels from the subgroup were similar between both treatment arms at baseline and were elevated compared with the healthy donor cohort (eFigure 3). Treatment with OCR led to a significant reduction in NfL levels, observed by week 12, with a greater reduction observed at week 96 of the DBP (change from baseline at week 96: −50.3% [−53.1% to −47.4%], $p < 0.001$), where levels of NfL reached healthy donor ranges[18] (eFigure 3).

At week 96 of the DBP, patients treated with OCR had lower levels of NfL than patients treated with IFN (−38.0% [−41.6% to −34.2%], $p < 0.001$). On switching from IFN to OCR

Figure 3 Percentage Change in Total Brain Volume From Baseline in the DBP and OLE



Adjusted mean and 95% CI estimates of percentage change from baseline in total normalized brain volume were from a mixed-effects model of repeated measures using unstructured covariance matrix with the following explanatory variables: treatment (IFN vs OCR), baseline normalized brain volume, geographic region (the United States vs ROW), baseline EDSS category (<2, ≥2), treatment duration, as well as the interactions of study week with treatment (IFN vs OCR) and with baseline normalized brain volume. DBP = double-blind controlled treatment period; EDSS = Expanded Disability Status Scale; IFN = interferon; OCR = ocrelizumab; OLE = open-label extension; PBVC = percentage brain volume change; ROW = rest of world.

during the OLE, NfL levels in the IFN–OCR group reached the same levels as those in the OCR–OCR group (eFigure 3). NfL levels remained within the healthy donor range throughout the OLE period (up to week 334; 9 years).

Safety Analyses

The overall safety profile was similar between the 2 groups during the DBP. The cumulative incidence rates of AEs and SAEs in all patients who received OCR over the DBP + OLE period were consistent with those observed during the DBP, as well as with those in the OCR all-exposure group (Table 3). With COVID-19–related AEs excluded, the rate of AEs per 100 PY was 196.06 (95% CI 192.07–200.11). The most frequently reported AEs were infections at a rate of 65.94 (63.64–68.31). Over >9 years of continuous OCR treatment, the rate of infections remained low and stable over time. Similar infection rates were observed in the DBP + OLE period as those seen in the IFN arm during the DBP, 65.09 (59.87–72.39), and in the all-exposure OCR population, 67.37 (66.36–68.39).

The question of whether long-term treatment with OCR may increase the risk of infections has been previously discussed.[26]

Table 3 AE Rates for the Treatment-Naive, Early RMS Subgroup During the DBP, DBP + OLE, and the Ocrelizumab All-Exposure Population, Excluding COVID-19

	Early RMS, treatment-naive, OPERA OLE			
	DBP		DBP + OLE	
AE Rate per 100 PY (95% CI)	IFN β-1a (N = 382; 661.5 PY)	OCR (N = 374, 663.7 PY)	OCR (N = 668; 4,695.0 PY)	OCR all-exposure[a] OCR (N = 5,848; 25,153.1 PY)
Any AEs	327.57 (313.92–341.66)	311.15 (297.88–324.87)	196.06 (192.07–200.11)	230.12 (228.25–232.01)
AEs leading to discontinuation	4.69 (3.18–6.65)	2.11 (1.15–3.54)	1.19 (0.90–1.55)	0.93 (0.81–1.06)
Serious AEs	4.69 (3.18–6.65)	4.22 (2.80–6.10)	5.84 (5.17–6.57)	6.90 (6.58–7.23)
Fatal outcomes	0.15 (0.00–0.84)	0.00 (0.00–0.56)	0.04 (0.01–0.15)	0.16 (0.12–0.22)
Malignancies[b]	0.15 (0.00–0.84)	0.45 (0.09–1.32)	0.53 (0.34–0.79)	0.47 (0.39–0.57)
Infections	65.09 (59.87–72.39)	83.33 (76.53–90.57)	65.94 (63.64–68.31)	67.37 (66.36–68.39)
Serious infections	2.42 (1.38–3.93)	0.90 (0.33–1.97)	1.28 (0.98–1.64)	2.04 (1.87–2.22)
IRR	5.90 (4.19–8.06)	34.20 (29.90–38.96)	11.69 (10.74–12.71)	22.96 (22.37–23.56)

Abbreviations: AE = adverse event; DBP = double-blind controlled treatment period; IFN = interferon; IRR = infusion-related reaction; OCR = ocrelizumab; OLE = open-label extension; PY = patient-years; RMS = relapsing multiple sclerosis.
Multiple occurrences of the same AE in 1 patient were counted multiple times. 95% CI was calculated using an exact method based on the Poisson distribution.
[a] The OCR all-exposure population refers to all OCR-treated patients with RMS and PMS across the OCR trials as of November 2021. ClinicalTrials.gov identifier numbers: NCT00676715 (phase II), NCT01247324 (OPERA I), NCT01412333 (OPERA II), NCT01194570 (ORATORIO), NCT02545868 (VELOCE), NCT02637856 (CHORDS), NCT02861014 (CASTING), NCT02688985 (OBOE), NCT03085810 (ENSEMBLE), NCT03523858 (CONSONANCE), and NCT03599245 (LIBERTO).
[b] The reported malignant events were basal cell carcinoma (9; 2 patients had multiple events), invasive ductal breast carcinoma (4), breast cancer (2), malignant melanoma (2), intraductal proliferative breast lesion, metastatic malignant melanoma, adenocarcinoma of the colon, colon cancer, prostate cancer, chondrosarcoma, dermatofibrosarcoma protuberans, and papillary thyroid cancer (1 each).

When accounting for the COVID-19 pandemic, the rate of SIs was 1.28 (0.98–1.65) and has remained stable overtime with no new or particular pattern of SI identified by year. Pneumonia (0.28 per 100 PY, 95% CI 0.15–0.47) and urinary tract infections (0.04 per 100 PY, 95% CI 0.01–0.15) were among the most frequently reported SIs per 100 PY; the majority of patients affected by SIs experienced CTCAE grade 3 intensity SIs (74%), with the majority resolving (95%). The rate of SIs leading to treatment discontinuation was low (0.13 per 100 PY, 95% CI 0.05–0.28). The rate of fatalities with COVID-19 terms excluded, at 0.04 (0.01–0.15), was consistent with DBP and lower than that observed in the OCR all-exposure group.

Although an increased rate of SIs was observed during periods of IgG <LLN (6.46 per 100 PY, 95% CI 3.34–11.29) compared with normal levels (1.94 per 100 PY, 1.56–2.39), the type, severity, latency (treatment year from commencement of OCR therapy), duration, and outcome of SIs observed during episodes of IgG below LLN were consistent with the overall SIs observed in patients treated with OCR. Twelve SI events were reported in 10 patients of the early RMS subgroup, when IgG <LLN; most of which (8/12) were of CTCAE grade 3 intensity, fully recovered (8/12), and were not treatment limiting (11/12). When excluding COVID-19–related infections, in patients with IgG <LLN, no SIs with a fatal outcome were reported.

Classification of Evidence

This study provides Class II evidence that OCR delays disease progression in treatment-naive patients with early-stage RMS.

Discussion

The current analysis addresses the question of whether OCR offers greater benefit compared with IFN β-1a when used as a first-line, long-term therapy in treatment-naive RMS patients with disease diagnosis ≤2 years before inclusion in the study. In comparison with IFN β-1a, treatment with OCR more effectively decreased the overall disease activity, including the risk of disability progression, relapse activity, and brain volume loss. It is important to note that the higher disability accrual and average brain volume loss observed during the 2 years on IFN treatment were not recovered, even after switching to OCR, indicating that initiating treatment with OCR earlier in the disease course is beneficial to patients with RMS.

These results are consistent with existing evidence that starting higher-efficacy treatment early in the MS disease course is of greater therapeutic benefit than therapeutic escalation. The efficacy data obtained in this subpopulation are similar to the results observed in the overall OPERA I/II cohorts.[11] Benefits to 24-week CDP and cCDP were observed for patients treated with OCR during the DBP phase compared with those treated with IFN β-1a. During the OLE phase, when all patients were treated with OCR, the difference in 24-week CDP between the IFN–OCR and OCR–OCR groups remained, indicating that although in OLE, the 24-week CDP rate became similar to that of the OCR–OCR group, the disability accrued during the treatment with IFN in DBP remained and did not recover after switching to OCR. The difference in NEDA rates observed between the IFN β-1a and OCR groups during the DBP similarly remained during the OLE period, indicating that the probability of controlling disease activity over the 9 years of follow-up was significantly better when OCR was commenced earlier. Relapse rates were very low in the OCR–OCR group, translating to a group level rate of 1 relapse every 20 years. This rate is important because in the RMS population, higher rates of relapses are typically observed.[27] Similar to NEDA and 24-week CDP, numerical benefits to total brain volume loss observed for patients on OCR during the DBP were maintained during the OLE, also indicating that neuronal tissue damage accrued during treatment with IFN β-1a is not restored after switching to OCR.

NfL levels, a marker of neuroaxonal injury, have been shown to correlate with acute inflammatory disease (e.g., T1 Gd+ lesions and relapses) and associated with disease worsening.[28,29] Findings from the overall OPERA I/II cohorts showed that baseline NfL strongly associated with MRI worsening (including whole-brain volume loss and thalamic volume loss). Beyond its association with acute disease activity, persistently elevated NfL levels during effective suppression of disease activity were associated with future progression (CDP-24 weeks on EDSS).[30]

In the DBP, OCR was able to more effectively decrease serum NfL levels than IFN β-1a, with NfL being reduced to healthy donor ranges by week 96. Switching to OCR led to a reduction of NfL in the IFN–OCR arm, with both groups reaching similar average levels of this marker.

The results of this study also show no new safety signals with OCR long-term treatment in this early RMS population, with a safety profile that is similar to that observed for the total population in the OPERA I/II studies. The retention rate observed in the early RMS subgroup at 9 years was 67%, and safety was not a major reason for withdrawal from the study. AE rates observed in this subgroup were similar to those observed in the total OPERA cohorts,[13] indicating that there is no increased risk of AEs with initiating OCR treatment earlier. Across the total population in this substudy, infections were the most frequently reported AEs; however, infection rates were similar to those observed in the IFN arm during the DBP, as well as the OCR all-exposure clinical study population, suggesting that there is no increased risk of infections in patients with early RMS who started treatment with OCR first line. SIs reported in this subgroup were also similar to those observed in the all-exposure group, with no patterns between starting OCR and SI occurrence. It is important to note that SIs rarely led to withdrawals and largely resolved. Although SI rates were observed to increase during periods of reduced IgG levels in the univariate analysis, these SIs were

not treatment limiting and were consistent with the overall SI profile observed in the all-exposure population. In addition, the multivariate analysis performed on the all-exposure RMS population in OPERA studies demonstrated that only the presence of ≥2 comorbidities was associated with an increased risk of SIs, but notably, not the time on OCR treatment or IgG levels.[31,32]

In our analysis, the incidence ratio (IR) of malignancies remained within the epidemiology reference range. During the DBP, the IR of all malignancies was 0.45 (95% CI 0.09–1.32) and across the DBP and OLE, the IR was 0.53 (95% CI 0.34–0.79); these data are comparable with those reported in a Danish population-based register study (IR 0.67 [95% CI 0.22–2.07]).[33]

These results are supported by data from the recent ENSEMBLE phase IIIb study, which demonstrated a favorable safety profile in patients with early diagnosed relapsing-remitting MS treated with first-line OCR over 4 years,[34] indicating that OCR is beneficial for long-term use in patients across the RMS spectrum, including as a first-line treatment in patients with early RMS.

Possible limitations to this study include assessment bias, which could have been introduced due to the lack of maintenance of blinding during the OLE. Finally, although the proportion of patients completing the 9 years of follow-up was relatively high (67%), attrition bias still remains a risk within the cohort; even if the discontinuation rates in the IFN arm were higher than those in the OCR arm.

These data support the use of the high-efficacy therapy OCR as a first-line therapy in patients diagnosed with early-stage RMS, for improved long-term clinical outcomes with a favorable safety profile, similar to what was observed in the overall OCR-treated population. This further reinforces the use of an initial high-efficacy therapy, which can provide beneficial short-term and long-term effects on disease progression as compared with an escalation approach for patients with MS.[35]

Acknowledgment

The authors thank all patients, their families, and the participating sites and investigators who participated in this trial (including the OPERA I/II Steering Committee, which provided study oversight). The authors also thank the independent data monitoring committee for performing data analysis and safety monitoring. The authors would like to thank Kalpesh Prajapati for his support with input into the statistical analyses. The trial data were collected by the Steering Committee and study investigators and analyzed by the study sponsor. Submission of the manuscript for publication was agreed upon by the authors and the Steering Committee.

Author Contributions

J.J. Cerqueira: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. A. Berthele: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. B.A.C. Cree: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. M. Filippi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. G. Pardo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. O.R. Pearson: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. A. Traboulsee: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. T. Ziemssen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. T. Vollmer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. C. Bernasconi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C.R. Mandel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. I. Kulyk: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. C. Chognot: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. C. Raposo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. H.-M. Schneble: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. G.-A. Thanei: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. E. Incera: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. E.K. Havrdová: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design.

Study Funding

This research was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. The sponsor was responsible for the overall study management (monitoring), drug supply, data management, statistical analysis, PK, MRI image analysis, drug safety process, and medical writing of clinical study reports. Editorial support (including assistance with revisions to the manuscript for non-intellectual content, figure redraws, and copy-editing) was

provided by Simon Foale, PhD, of Nucleus Global, United Kingdom; and funded by F. Hoffmann-La Roche Ltd. The authors had full editorial control of the manuscript and provided their final approval of all content.

Disclosure

J.J. Cerqueira has received consultancy fees from Biogen, F. Hoffmann-La Roche Ltd, Novartis, Almirall, Janssen, Bristol Myers Squibb, Merck, and Zambon; and research grants from Biogen, F. Hoffmann-La Roche Ltd, Merck, and Novartis; as well as the Portuguese Foundation for Science and Technology and Clinical Academic Centre Braga. A. Berthele has received consultancy and/or speaker fees from Alexion, Bayer HealthCare, Biogen, Celgene, and F. Hoffmann-La Roche Ltd. His institution has received compensation for clinical trials from Alexion, Biogen, Merck, Novartis, F. Hoffmann-La Roche Ltd, and Sanofi. B.A.C. Cree in the past 36 months has received personal compensation for consulting from Alexion, Atara, Autobahn, Avotres, Biogen, EMD Serono, Horizon, Neuron23, Novartis, Sanofi, TG Therapeutics, and Therini; and received research support from Genentech Inc. M. Filippi is Editor-in-Chief of the *Journal of Neurology*, is an associate editor of the journals *Human Brain Mapping*, *Radiology*, and *Neurological Sciences*; received compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, Roche, and Sanofi; for speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and Teva; for participation in advisory boards for Alexion, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, and Takeda; and for scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol Myers Squibb, Eli Lilly, Novartis, and Sanofi-Genzyme; and receives research support from Biogen Idec., Merck-Serono, Novartis, Roche, the Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA). G. Pardo has served on advisory boards and/or speakers bureau(s) for Biogen Idec., Celgene/Bristol Myers Squibb, EMD Serono, Greenwich Biosciences, Janssen, Novartis, F. Hoffmann-La Roche Ltd/Genentech, Sanofi-Genzyme, TG Therapeutics, Viela Bio/Horizon Therapeutics, Alexion Pharmaceuticals, and PRIME Education; and is a member of the Scientific Advisory Board of Progentec Diagnostics Inc. O.R. Pearson has received honoraria and travel expenses from Biogen, Bayer, Genzyme, Merck, Novartis, F. Hoffmann-La Roche Ltd, and Teva; and served on advisory boards/acted as a speaker for Biogen, Celegene-BMS, Janssen, Novartis, Sanofi-Genzyme, Merck, and F. Hoffmann-La Roche Ltd. A. Traboulsee has received research support from Sanofi-Genzyme and F. Hoffmann-La Roche Ltd; has received consultancy fees from Sanofi-Genzyme and F. Hoffmann-La Roche Ltd; and has received honoraria for his involvement in speakers' bureau activities for Sanofi-Genzyme and F. Hoffmann-La Roche Ltd. T. Ziemssen has received consultancy and/or speaking fees from Almirall, Bayer, Biogen, Merck, Novartis, F. Hoffmann-La Roche Ltd, Sanofi, and Teva; and has received grant/research support from Biogen, Novartis, Sanofi, and Teva. T. Vollmer has received compensation for activities such as advisory boards, lectures, and consultancy from the following companies and organizations: Biogen, Genentech/F. Hoffmann-La Roche Ltd, and Novartis; and has received research support from Rocky Mountain Multiple Sclerosis Center, Celgene, Biogen, Anokion, Genentech, F. Hoffmann-La Roche Ltd, GW Pharma, and TG Therapeutics Inc. C. Bernasconi received consultancy fees as a contractor for F. Hoffmann-La Roche Ltd during the execution of this work; he is now owner of Limites Medical Research Ltd, Vacallo, Switzerland. C.R. Mandel has received personal compensation for serving as an employee of Genentech and has received stock or an ownership interest from Genentech Inc. I. Kulyk is an employee of F. Hoffmann-La Roche Ltd. C. Chognot is an employee of and a shareholder in F. Hoffmann-La Roche Ltd. C. Raposo is an employee of and a shareholder in F. Hoffmann-La Roche Ltd. H.-M. Schneble is an employee of and a shareholder in F. Hoffmann-La Roche Ltd. G.-A. Thanei is an employee of and a shareholder in F. Hoffmann-La Roche Ltd. E. Incera has received consultancy fees from F. Hoffmann-La Roche Ltd for statistical assistance; and is an employee of IQVIA Solutions, Inc. E.K. Havrdová has received honoraria/research support from Biogen, F. Hoffmann-La Roche Ltd, Janssen, Bristol Myers Squibb, Merck-Serono, Novartis, Sanofi-Genzyme, and Teva; has served on advisory boards for Actelion, Biogen, Celgene, Merck-Serono, Novartis, and Sanofi-Genzyme; and has been supported by the Czech Ministry of Education project Cooperatio LF1, research area Neuroscience, and the project National Institute for Neurological Research (Programme EXCELES, ID project no. LX22NPO5107)—funded by the European Union-Next Generation EU. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* February 23, 2024. Accepted in final form October 7, 2024. Submitted and externally peer reviewed. The handling editor was Deputy Editor Olga Ciccarelli, MD, PhD, FRCP.

References

1. De Stefano N, Giorgio A, Battaglini M, et al. Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes. *Neurology*. 2010;74(23):1868-1876. doi:10.1212/WNL.0b013e3181e24136
2. Wiendl H, Gold R, Berger T, et al. Multiple Sclerosis Therapy Consensus Group (MSTCG): position statement on disease-modifying therapies for multiple sclerosis (white paper). *Ther Adv Neurol Disord*. 2021;14:17562864211039648. doi:10.1177/17562864211039648
3. Dillon P, Heer Y, Karamasioti E, et al. The socioeconomic impact of disability progression in multiple sclerosis: a retrospective cohort study of the German NeuroTransData (NTD) registry. *Mult Scler J Exp Transl Clin*. 2023;9(3):20552173231187810. doi:10.1177/20552173231187810
4. Fernández O, Delvecchio M, Edan G, et al. Survey of diagnostic and treatment practices for multiple sclerosis in Europe. *Eur J Neurol*. 2017;24(3):516-522. doi:10.1111/ene.13236
5. Fisher KS, Cuascut FX, Rivera VM, Hutton GJ. Current advances in pediatric onset multiple sclerosis. *Biomedicines*. 2020;8(4):71. doi:10.3390/biomedicines8040071
6. Ontaneda D, Tallantyre E, Kalincik T, Planchon SM, Evangelou N. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. *Lancet Neurol*. 2019;18(10):973-980. doi:10.1016/S1474-4422(19)30151-6
7. Machado-Santos J, Saji E, Tröscher AR, et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells. *Brain*. 2018;141(7):2066-2082. doi:10.1093/brain/awy151

8. Genentech. *Ocrevus (Ocrelizumab) [Full Prescribing Information]*. 2020. Accessed January 20, 2020. gene.com/download/pdf/ocrevus_prescribing.pdf.
9. European Medicines Agency. *Ocrevus [Summary of Product Characteristics]*. 2021. Accessed January 18, 2021. ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf.
10. 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(1):361-371. doi:10.4049/jimmunol.180.1.361
11. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376(3):221-234. doi:10.1056/NEJMoa1601277
12. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209-220. doi:10.1056/NEJMoa1606468
13. Hauser S, Kappos L, Arnold D, et al. Five-years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. *Neurology*. 2020;95(13):e1854-e1867. doi:10.1212/WNL.0000000000010376
14. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292-302. doi:10.1002/ana.22366
15. Wattjes MP, Ciccarelli O, Reich DS, et al. 2021 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. *Lancet Neurol*. 2021;20(8):653-670. doi:10.1016/S1474-4422(21)00095-8
16. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *NeuroImage*. 2002;17(1):479-489. doi:10.1006/nimg.2002.1040
17. Nakamura K, Guizard N, Fonov VS, Narayanan S, Collins DL, Arnold DL. Jacobian integration method increases the statistical power to measure gray matter atrophy in multiple sclerosis. *Neuroimage Clin*. 2014;4:10-17. doi:10.1016/j.nicl.2013.10.015
18. Harp C, Thanei GA, Jia X, et al. Development of an age-adjusted model for blood neurofilament light chain. *Ann Clin Transl Neurol*. 2022;9(4):444-453. doi:10.1002/acn3.51524
19. Pedotti R, Muros-Le Rouzic E, Raposo C, Schippling S, Jessop N. Understanding the impacts of COVID-19 pandemic in people with multiple sclerosis treated with ocrelizumab. *Mult Scler Relat Disord*. 2021;55:103203. doi:10.1016/j.msard.2021.103203
20. Hauser SL, Kappos K, Chognot C, et al. Safety of ocrelizumab in multiple sclerosis: updated analysis in patients with relapsing and primary progressive multiple sclerosis. Poster presented at ECTRIMS 2022. P326.
21. Hughes R, Pedotti R, Koendgen H. COVID-19 in persons with multiple sclerosis treated with ocrelizumab: a pharmacovigilance case series. *Mult Scler Relat Disord*. 2020;42:102192. doi:10.1016/j.msard.2020.102192
22. Hughes R, Whitley L, Fitovski K, et al. COVID-19 in ocrelizumab-treated people with multiple sclerosis. *Mult Scler Relat Disord*. 2021;49:102725. doi:10.1016/j.msard.2020.102725
23. Vivli Inc. A Global Clinical Research Data Sharing Platform. 2024. Accessed September 17, 2024. vivli.org/.
24. Vivli Inc. Our Members: Roche. 2024. Accessed September 17, 2024. https://vivli.org/ourmember/roche/.
25. F. Hoffmann-La Roche Ltd. Our Commitment to Transparency of Clinical Study Information. 2024. Accessed September 17, 2024. https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.
26. Hauser SL, Kappos L, Montalban X, et al. Safety of ocrelizumab in patients with relapsing and primary progressive multiple sclerosis. *Neurology*. 2021;97(16):e1546-e1559. doi:10.1212/WNL.0000000000012700
27. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain*. 2010;133(pt 7):1914-1929. doi:10.1093/brain/awq118
28. Kuhle J, Kropshofer H, Haering DA, et al. Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. *Neurology*. 2019;92(10):e1007-e1015. doi:10.1212/WNL.0000000000007032
29. Barro C, Benkert P, Disanto G, et al. Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. *Brain*. 2018;141(8):2382-2391. doi:10.1093/brain/awy154
30. Bar-Or A, Thanei GA, Harp C, et al. Blood neurofilament light levels predict non-relapsing progression following anti-CD20 therapy in relapsing and primary progressive multiple sclerosis: findings from the ocrelizumab randomised, double-blind phase 3 clinical trials. *EBioMedicine*. 2023;93:104662. doi:10.1016/j.ebiom.2023.104662
31. Derfuss T, Bermel R, Lin CJ, et al. Risk factors for serious infections in patients with MS receiving long-term ocrelizumab treatment: multivariate analyses. Poster presented at EAN 2022. EPO-403.
32. Hauser SL, Kappos L, Montalban X, et al. Safety of ocrelizumab in multiple sclerosis: updated analysis in patients with relapsing and progressive multiple sclerosis. Poster presented at ECTRIMS 2023. P304.
33. 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(4):979-984. doi:10.1002/ijc.21437
34. Hartung H, Brochet B, Freedman M, et al. Treatment-naive patients with early-stage relapsing-remitting multiple sclerosis showed low disease activity after 2-year ocrelizumab therapy, with no new safety signals: the Phase IIIb ENSEMBLE study. Paper presented at: Multiple Sclerosis Journal 2022.
35. He A, Merkel B, Brown JWL, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol*. 2020;19(4):307-316. doi:10.1016/S1474-4422(20)30067-3