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Ocrelizumab treatment for relapsing-remitting multiple sclerosis after a suboptimal response to previous disease-modifying therapy: A nonrandomized controlled trial

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Abstract

Background: Many patients with multiple sclerosis (MS) experience suboptimal disease control despite the use of disease-modifying therapy (DMT).

Objective: To assess the efficacy and safety of ocrelizumab (OCR) in patients with relapsing-remitting MS (RRMS) and suboptimal response to prior DMTs.

Methods: Patients with RRMS and suboptimal responses (one clinically reported relapse and/or lesion activity) after ⩾6 months on another DMT were enrolled. OCR 600 mg was given intravenously every 24 weeks. The primary outcome was no evidence of disease activity (NEDA), defined as the absence of protocol-defined relapse, confirmed disability progression (CDP), T1 Gd-enhancing lesions, and new/enlarging T2 lesions.

Results: The intention-to-treat (ITT) population included 608 patients; NEDA was analyzed in a modified ITT (mITT) population ($n = 576$ (94.7%)). Over 96 weeks, 48.1% of mITT patients achieved NEDA, and most were free from protocol-defined relapse (89.6%), CDP (89.6%), and T1 Gd-enhancing lesions (95.5%); 59.5% had no new/enlarging T2 lesions. Safety observations were consistent with findings in the pivotal trials.

Conclusion: Consistent efficacy of OCR on clinical and magnetic resonance imaging (MRI) disease activity measures and progression was shown in patients with RRMS and a suboptimal response to prior DMTs; no new safety signals were observed.

Keywords: Multiple sclerosis, switch, ocrelizumab, safety, MRI, disease progression

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Introduction

Multiple sclerosis (MS) is a chronic, progressive, and unpredictable disease of the central nervous system that may result in substantial long-term physical disability, cognitive impairment, and other effects that affect multiple aspects of everyday life.[1] Despite significant developments in the treatment landscape for MS over the past 15 years, including the approval of numerous high-efficacy therapies, a large proportion of patients continue to experience clinical and subclinical disease activity,[2] which may ultimately lead to accumulation of permanent neurological deficits.[3] Underlying reasons for suboptimal response to disease-modifying therapy (DMT) may vary across patients, owing to the highly heterogeneous nature of the disease; aside from physiological drivers, these reasons may be linked to more practical aspects of the treatment, such as adherence or patient preference. Whatever the reason, switching patients who experience a suboptimal treatment response on one DMT to a more effective option, before significant neurological damage has occurred, is critical to minimize disease progression and ensure optimal long-term outcomes.[4]

Strategies for terminating one DMT and initiating a new one have been suggested.[5–7] These recommendations are based on factors such as the individual patient's disease history, previous treatment regimen,

definition of failure to respond, and benefit–risk assessment. However, a standard protocol for switching treatments has yet to be established. Evidence describing the transition from one drug to another is crucial to help support these decisions.[8]

Ocrelizumab (OCR) is a humanized monoclonal antibody that selectively targets CD20, an antigen expressed on the surface of pre-, mature, and memory B cells, which plays a critical role in the pathogenesis of MS.[9] In the pivotal Phase III clinical trials in patients with relapsing MS (OPERA I and OPERA II),[10] treatment with OCR was associated with significantly lower rates of disease activity and progression than treatment with interferon (IFN) β-1a. Given the success of these studies, it is of interest to see whether switching to OCR might be effective in patients who had a suboptimal response on another DMT. Evidence from the OPERA trials is limited in this regard, because only 27% of participants received a DMT in the 2 years prior to study entry.[10] Furthermore, the reasons for stopping their previous DMT may or may not have been due to a suboptimal response, and finally, not all currently available DMTs were approved for treatment of MS at the time the OPERA studies were initiated.

The specific benefits of OCR in patients with a suboptimal response to other DMTs are being investigated in two Phase IIIb studies in patients with relapsing-remitting MS (RRMS), including one trial in North America (CHORDS, NCT02637856) and another based in the European Union (CASTING, NCT02861014). Here, we present the efficacy and safety findings from CHORDS.

Patients and methods

Patients and study design

CHORDS (NCT02637856) was a prospective, multicenter, open-label, single-arm study that enrolled patients aged 18–55 years with a diagnosis of RRMS (2010 revised McDonald criteria),[11] a time from first symptom of $\leqslant$ 12 years and a screening Expanded Disability Status Scale (EDSS) score of 0.0–5.5. EDSS raters were experienced, and the same rater was used for each patient when possible. Prior to screening, patients received $\leqslant$ 3 other DMTs and were required to have completed an adequate course (i.e. $\geqslant$ 6 months) on $\geqslant$ 1 DMT. Importantly, patients discontinued the most recent adequately used DMT because of a suboptimal response, defined as having one of the following qualifying events: $\geqslant$ 1 clinically reported relapse, $\geqslant$ 1 T1 gadolinium (Gd)-enhancing lesion on brain magnetic resonance imaging (MRI), or $\geqslant$ 2 new and/or enlarging T2 lesions on brain MRI despite being on a stable dose of the same DMT for $\geqslant$ 6 months. In patients who were on a stable dose of a DMT for $>$ 1 year, the qualifying event must have occurred within the last 12 months of treatment before screening.

Study enrollment began on 11 February, 2016, and lasted until the required sample size was achieved (approximately 18 months). An estimated sample size of 600 was required to achieve 80% probability that the half-width of the 95% confidence interval (CI) was at most 4%, assuming that 45% of patients would be event free over 96 weeks. The proportion of 45% was based on pooled data from OPERA I and OPERA II, including all patients who had a baseline EDSS of $\geqslant$ 2.0.[10] Institutional Review Board approval was obtained at each study site, and all participants provided written informed consent.

All participants received OCR, which was administered as an initial dose of two 300 mg infusions (600 mg total) separated by 14 days (i.e. Days 1 and 15) followed by single 600 mg infusions every 24 weeks thereafter. Infusions were administered according to US prescribing information.[12] Assessments of effectiveness and safety were conducted every 24 weeks (Figure 1(a)). Patients who discontinued for reasons of lack of efficacy or death were considered to have had a protocol-defined event. After patients received their fourth dose, they had the option to continue to receive commercially available OCR. Those who chose not to enter a safety follow-up period for 24 weeks from the date of their last infusion.

Outcomes

The primary efficacy outcome was no evidence of disease activity (NEDA), defined as the proportion of patients who were free of any protocol-defined events during the 96-week study period, including protocol-defined relapse, $\geqslant$ 24-week confirmed disability progression (CDP) on the EDSS, T1 Gd-enhancing lesions on brain MRI, and new and/or enlarging T2 lesions on brain MRI. The primary outcome was also examined in several patient subgroups, including those who received 1 versus $>$ 1 previous DMT and those who were eligible for the study based on MRI activity alone. Secondary endpoints included the proportion of patients free from any protocol-defined event for 24 and 48 weeks, time-to-event analyses (i.e. first protocol-defined event, relapse, T1 Gd-enhancing lesion, new and/or enlarging T2 lesion, or 24-week CDP event), annualized relapse rate

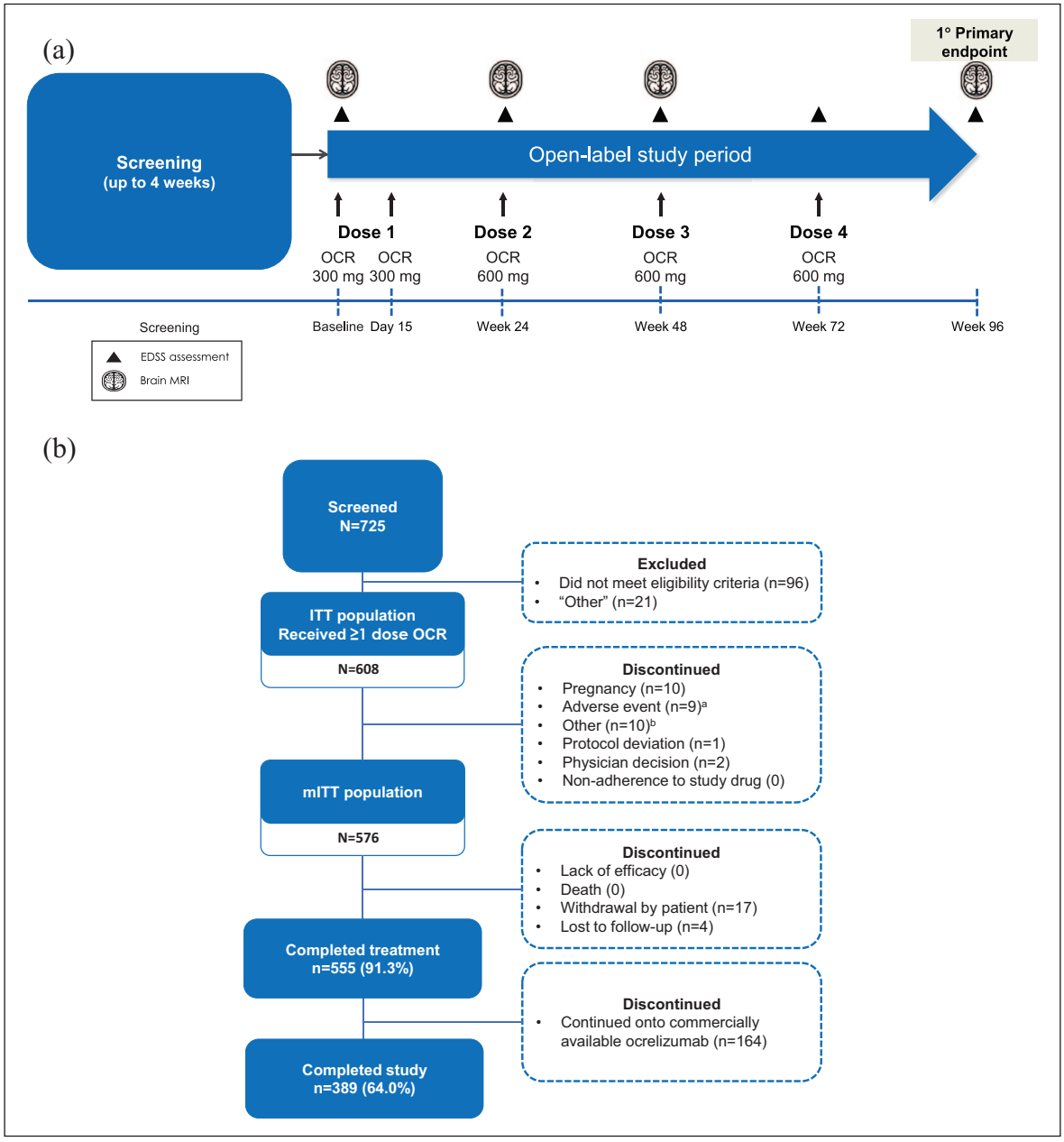

Figure 1. (a) CHORDS study design and (b) CONSORT diagram. DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; ITT: intention-to-treat; mITT: modified ITT; OCR: ocrelizumab.
[a]Adverse events leading to study treatment discontinuation were rash ($n=1$), coccidioidomycosis ($n=1$), Crohn's disease ($n=1$), subdural hematoma ($n=1$), mental disorder ($n=1$), latent tuberculosis ($n=1$), interstitial granulomatous dermatitis ($n=1$), diarrhea ($n=1$), and multiple sclerosis relapse ($n=1$).
[b]Other reasons for discontinuation were site closure without the patient wanting to transfer to another site ($n=6$), desire to become pregnant ($n=2$), incarceration ($n=1$), and drug abuse ($n=1$), which was exclusionary per protocol.

(ARR) at Week 96 and MRI endpoints (i.e. total number of T1 Gd-enhancing lesions, total number of new and/or enlarging T2 lesions, and change in total T2 lesion volume from baseline) at Weeks 24, 48, and 96. This study also included several exploratory outcomes, including change from baseline in EDSS, brain volume, and patient-reported outcomes (PROs; Multiple Sclerosis Impact Scale (MSIS)-29, Treatment Satisfaction with Medicines Questionnaire (SATMED-Q), Treatment Satisfaction Questionnaire for Medication (TSQM)) at Weeks 24, 48, and 96.

Two interim analyses were performed during the study, according to patient enrollment and availability

of data of interest. Interim analyses were used for hypothesis generation, abstraction/publication for major scientific conferences, or other purposes, as applicable.

Statistical analysis

The primary endpoint and its components were evaluated using a modified ITT (mITT) population (Figure 1(b)), which excluded patients who discontinued OCR treatment early without any protocol-defined events and for reasons other than lack of efficacy or death. This approach is consistent with the pivotal trials[10] and helped to ensure that patients who left the study for reasons completely unrelated to disease activity (e.g. pregnancy, study site closure, or change in eligibility status) were not imputed as having an event. Data from any unscheduled visit within each respective 24-week interval were included. Results are presented along with two-sided 95% CI calculated using the Clopper–Pearson exact method.

All other efficacy and safety endpoints were evaluated in the complete ITT/safety population, defined as all patients who received ⩾1 dose of OCR. Time-to-onset data were calculated using the Kaplan–Meier method. The ARR was estimated using a negative binomial model adjusted for the number of previous DMTs (1 or >1) and baseline EDSS (<2.5 vs ⩾2.5) and including the log-transformed years of OCR exposure time as an offset variable. The proportion of patients with T1 Gd-enhancing lesions and those with new and/or enlarging T2 lesions on brain MRI were calculated at Weeks 24, 48, and 96. Change from baseline in total T2 lesion volume was analyzed through a longitudinal mixed-effects model for repeated measures (MMRMs) adjusted for baseline T2 lesion volume, number of previous DMTs (1 or >1), baseline T2 lesion volume by visit interaction, and baseline EDSS score (<2.5 vs ⩾2.5).

Exploratory clinical outcomes, including change from baseline on EDSS and PROs, were estimated using a longitudinal MMRM adjusted for visit, baseline score, number of previous DMTs (1 or >1), and baseline score by visit interaction; for PROs, the model was also adjusted for baseline EDSS score (<2.5 vs ⩾2.5).

Results

Patient demographics and baseline characteristics

A total of 608 patients enrolled across 90 study sites in the United States and Canada. All patients received treatment with OCR and were included in the ITT population. The mITT population included 576 patients (94.7%). Most patients ($n=555$ (91.3%)) completed treatment. The most common reasons for treatment discontinuation included withdrawal by patient (17 (2.8%)), pregnancy and other (each 10 (1.6%)), and adverse events (AEs; 9 (1.5%); Figure 1(b)). After completion of study treatment, 164 patients (36.0%) continued to receive commercially available OCR. The remaining 389 patients (64.0%) entered the 24-week safety follow-up period and completed the study.

At baseline, patients had a mean (*SD*) age of 37.2 (8.6) years, time since diagnosis of 4.20 (3.03) years, and duration since first MS symptom of 5.39 (3.25) years (Table 1). The most common qualifying event for enrollment on study was MS relapse only (269 patients (44.2%)) followed by ⩾1 T1 Gd-enhancing lesion on brain MRI only (87 patients (14.3%)) and ⩾1 new and/or enlarging T2 lesion on brain MRI only (84 patients (13.8%)); some patients had multiple qualifying events.

Prior to study enrollment, most patients received one (335 (55.1%)) or two (220 (36.2%)) unique DMTs, with a mean (*SD*) duration of last DMT use of 26.38 (23.6) months and time from end of last DMT to initiation of OCR of 1.5 (1.9) months (Table 1). The most frequently used DMTs prior to initiation of OCR were glatiramer acetate (300 patients (49.3%)), dimethyl fumarate (215 patients (35.4%)), and fingolimod (122 patients (20.1%); Table 1).

Efficacy of OCR

After 96 weeks, 48.1% of patients in the mITT population had NEDA (Table 2). The majority of patients were also free from individual components of the primary endpoint, including protocol-defined relapse (89.6%), ⩾24-week CDP (89.6%), and T1 Gd-enhancing lesions (95.5%), while 59.5% were free from new and/or enlarging T2 lesions. Examination of these outcomes for the 24- and 48-week periods showed consistent results, with 59.0% and 51.2% of patients having NEDA, respectively. The majority of patients were also free from protocol-defined relapses (94.1% and 92.3%), ⩾24-week CDP (90.8%; 48-week period only), and T1 Gd-enhancing lesions (96.4% and 95.9%), while 62.3% and 60.6% were free from new and/or enlarging T2 lesions.

Comparable findings were observed in patient subgroups. Of those who enrolled in the study based on

Table 1. Baseline demographics and disease characteristics among patients with RRMS.

Characteristic	ITT population ($N = 608$)
Demographics	
Age, years	
Mean (*SD*)	37.2 (8.6)
Median (range)	37.0 (18–55)
Female, *n* (%)	438 (72.0)
White, *n* (%)	495 (81.4)
Weight, mean, kg	81.47
BMI, mean, kg/m^2	28.58
Medical history	
Duration since MS diagnosis, years	
Mean (*SD*)	4.20 (3.03)
Median (range)	3.43 (0.2–26.9)
Duration since first MS symptom, years	
Mean (*SD*)	5.39 (3.25)
Median (range)	4.88 (0.5–28.1)
Duration of last DMT, months	
Mean (SD)	26.38 (23.6)
Median (range)	18.84 (1.1–240.5)
Duration between end of last DMT to initiation of OCR, months	
Mean (*SD*)	1.4 (1.9)
Median (Q1, Q3)	0.95 (0.46, 1.84)
Prior DMT use	
No. of prior unique DMTs used, *n* (%)	
1	335 (55.1)
2	220 (36.2)
⩾3	53 (8.8)
Last DMT used prior to OCR initiation, *n* (%)	
Glatiramer acetate	187 (30.8)
Dimethyl fumarate	175 (28.8)
Fingolimod	92 (15.1)
Teriflunomide	55 (9.0)
IFN β-1a SC	46 (7.6)
IFN β-1a IM	25 (4.1)
IFN β-1a PEG	17 (2.8)
IFN β-1b	8 (1.3)
Natalizumab[a]	3 (0.5)
Qualifying events for enrollment, *n* (%)	
MS relapse only	269 (44.2)
⩾1 T1 Gd-enhancing lesion only	87 (14.3)
New and/or enlarging T2 lesion only	84 (13.8)
MS relapse + ⩾1 T1 Gd-enhancing lesion	50 (8.2)
MS relapse + new and/or enlarging T2 lesion only	47 (7.7)
MS relapse + ⩾1 T1 Gd-enhancing lesion + new and/or enlarging T2 lesion	24 (3.9)
⩾1 T1 Gd-enhancing lesion + new and/or enlarging T2 lesion	47 (7.7)

BMI: body mass index; DMT: disease-modifying treatment; Gd: gadolinium; IFN: interferon; IM: intramuscular; ITT: intention-to-treat; MS: multiple sclerosis; OCR: ocrelizumab; PEG: polyethylene glycol; RRMS: relapsing-remitting MS; SC: subcutaneous.

[a]Patients were eligible for the study if the duration of treatment with natalizumab was < 1 year and natalizumab was not used within 12 months prior to screening, unless failure was due to confirmed, persistent antidrug antibodies.

Table 2. Proportion of patients with NEDA (primary efficacy outcome) and free from individual protocol-defined events (secondary outcomes).

Proportion of patients, n/*N* (%) 95% CI[a]	Weeks 0–96	Weeks 0–48	Weeks 0–24
NEDA	277/576 (48.1)[b] 43.9–52.3	295/576 (51.2) 47.0–55.4	340/576 (59.0) 54.9–63.1
No relapse	502/560 (89.6) 86.8–92.0	517/560 (92.3) 89.8–94.4	527/560 (94.1) 91.8–95.9
No ⩾24-week CDP	498/556 (89.6) 86.7–92.0	505/556 (90.8) 88.1–93.1	–
No T1 Gd-enhancing lesions	532/557 (95.5) 93.4–97.1	534/557 (95.9) 93.9–97.4	537/557 (96.4) 94.5–97.8
No new/enlarging T2 lesions	341/573 (59.5) 55.4–63.6	347/573 (60.6) 56.4–64.6	357/573 (62.3) 58.2–66.3

CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; Gd: gadolinium; NEDA: no evidence of disease activity (i.e. absence of protocol-defined relapse, ⩾24-week CDP, T1 Gd-enhancing lesions, and new/enlarging T2 lesions).
[a]95% CI of proportion was constructed using the Clopper–Pearson exact method.
[b]Primary endpoint.

MRI criteria alone, 51.7%, 46.4%, and 45.4% had NEDA after 24, 48, and 96 weeks, respectively (Supplementary Table S1a). Findings in patients grouped by previous DMT use (1 DMT vs > 1 DMT) demonstrated no significant differences in the proportion who had NEDA (50.9% vs 44.5%) or freedom from the individual protocol-defined events (relapse, 90.0% vs 89.2%; ⩾24-week CDP, 90.9% vs 87.9%; T1 Gd-enhancing lesions, 95.8% vs 95.1%; and new/enlarging T2 lesions, 61.4% vs 57.1%) over 96 weeks (Supplementary Table S1b).

A total of 71 protocol-defined relapses were reported over 1413 patient-years followed, corresponding to an unadjusted ARR of 0.050 and an adjusted ARR of 0.046 (Supplementary Table S2). Most relapse activity was observed during the first 48 weeks of OCR treatment, with the highest number of relapses occurring in the first 24 weeks and decreasing during subsequent epochs (Supplementary Table S2). MRI activity was also reduced over time, including the proportion of patients with T1 Gd-enhancing lesions (Week 24, 3.3%; Week 48, 1.4%; and Week 96, 1.1%), those with new and/or enlarging T2 lesions (Week 24, 36.0%; Week 48, 4.5%; and Week 96, 2.7%), and overall T2 lesion volume (mean (*SE*) change from baseline: Week 24, −0.48 (0.12) cm^3; Week 48, −0.55 (0.12) cm^3; Week 96, −0.56 (0.13) cm^3; Supplementary Table S2). Exploratory measures of disability and brain volume also showed improvement with OCR. Over the 96-week period, small changes in EDSS scores from baseline were observed, with the largest decrease observed at Week 24 (adjusted mean (*SE*) change, −0.130 (0.035)), minor reductions were maintained at subsequent time points (Supplementary Table S2). The rate of brain volume change slowed over time, with an overall percentage change from baseline of −0.28% at Week 24, −0.50% at Week 48, and −0.72% at Week 96 (Supplementary Table S2).

PROs also improved with OCR treatment. Noticeable reductions in physical and psychological disability, as measured by the MSIS-29, were observed at Week 24, which were sustained through the end of the study (Supplementary Table S3). Findings from the TSQM II questionnaire demonstrated marked improvements in patient satisfaction with OCR treatment over the study period, with increases in scores for effectiveness, convenience, side effects, and global satisfaction; analogous results were observed on the SATMED-Q (Supplementary Table S3).

Safety of OCR

Overall, 525 patients (86.3%) reported a total of 2858 events (Table 3). The most common AEs included infusion-related reactions (IRRs; 43.3%), urinary tract infections (14.8%), and nasopharyngitis (10.5%); most events were mild to moderate in severity. Severe (Grade 3) or life-threatening (Grade 4) AEs were reported by 69 (11.3%) and 11 (1.8%) patients, respectively, and most commonly included infections and infestations (2.8%); injury, poisoning, and procedural complications (2.3%); and nervous system disorders (2.1%). Treatment interruptions or other modifications (e.g. reduction in infusion rate, delaying the date of the next infusion) related to AEs occurred in 108 patients (17.8%). Six patients (< 1.0%) withdrew from treatment because of nonserious AEs, including one patient each for diarrhea,

Table 3. Safety outcomes.

	OCR (N=608)
Patients with ⩾1 AE, *n*	525
Number of events	2858
AEs occurring in ⩾5% of patients by SOC and PT, *n* (%)	
Eye disorders	39 (6.4)
Gastrointestinal disorders	120 (19.7)
Nausea	32 (5.3)
General disorders and administration site conditions	127 (20.9)
Fatigue	58 (9.5)
Infections and infestations	307 (50.5)
Urinary tract	90 (14.8)
Nasopharyngitis	64 (10.5)
Upper respiratory tract	57 (9.4)
Sinusitis	37 (6.1)
Injury, poisoning, and procedural complications	303 (49.8)
IRR	263 (43.3)
Investigations	56 (9.2)
Musculoskeletal and connective tissue disorders	148 (24.3)
Pain in extremity	36 (5.9)
Nervous system disorders	187 (30.8)
Headache	56 (9.2)
Renal and urinary disorders	43 (7.1)
Reproductive system and breast disorders	35 (5.8)
Psychiatric disorders	88 (14.5)
Respiratory, thoracic, and mediastinal disorders	66 (10.9)
Skin and subcutaneous tissue disorders	89 (14.6)
Patients with ⩾1 SAE, *n*	47
Number of events	59
SAEs occurring in ⩾2 of patients by SOC and PT, *n* (%)	77 (12.7)
Blood and lymphatic system disorders	2 (0.3)
Cardiac disorders	2 (0.3)
Gastrointestinal disorders	4 (0.7)
General disorders and administration site conditions	2 (0.3)
Hepatobiliary disorders	3 (0.5)
Cholecystitis acute	2 (0.3)
Immune system disorders	2 (0.3)
Infections and infestations	9 (1.5)
Appendicitis	3 (0.5)
Pyelonephritis	2 (0.3)
Urinary tract infection	2 (0.3)
Injury, poisoning, and procedural complications	6 (1.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	4 (0.7)
Nervous system disorders	10 (1.6)
MS relapse	3 (0.5)
Encephalopathy	2 (0.3)
Seizure	2 (0.3)
Syncope	2 (0.3)
Psychiatric disorders	5 (0.8)
Suicidal ideation	3 (0.5)

AE: adverse event; IRR: infusion-related reaction; MS: multiple sclerosis; OCR: ocrelizumab; PT: preferred term; SAE: serious AE; SOC: system organ class.

interstitial granulomatous dermatitis, latent tuberculosis, mental disorder, and rash; additionally, one patient discontinued treatment due to nonserious coccidioidomycosis, a fungal infection with a high risk of dissemination in immunocompromised patients.

Consistent with findings in the pivotal OPERA I and OPERA II trials, IRRs were the most frequently reported AE with OCR, with 519 events occurring in 263 patients (43.3%); the majority experienced Grade 1 (134 (22.0%)) or Grade 2 (124 (20.4%)) events. Grade 3 (severe) events were rare, occurring in five patients (0.8%), and no Grade 4 (life-threatening) or Grade 5 (death) IRRs were observed. The incidence of IRRs was highest with the first infusion of Dose 1 (33.9%) and decreased with subsequent infusions (Dose 1, Day 15, 10.5%; Dose 2, 16.8%; Dose 3, 11.9%; and Dose 4, 9.5%). In patients experiencing severe IRRs, the infusion was immediately interrupted, additional symptomatic therapy was initiated, and the infusion could be restarted at a reduced rate after the event resolved. No patients discontinued because of IRRs.

Serious AEs (SAEs) were reported by 47 patients (7.7%; Table 3), leading to a treatment modification or interruption in two patients (0.3%) and to treatment withdrawal in two patients (new Crohn's disease, subdural hematoma). SAEs reported in >2 patients included appendicitis, MS relapse, and suicidal ideation ($n=3$ patients each), and acute cholecystitis, encephalopathy, pyelonephritis, seizure, syncope, and urinary tract infections ($n=2$ patients each). Serious infections were reported in nine patients (1.5%; Table 3). Overall, no AEs of special interest (included cases of potential drug-induced liver injury and suspected transmission of an infectious agent) were identified in this study.

Discussion

In this study of patients with RRMS and a recent history of suboptimal response to previous DMT, initiation of OCR treatment showed reductions in both clinical and MRI measures of disease activity, with 48.1% of patients experiencing NEDA during the 96-week study period. These findings further support the benefits of OCR observed in post hoc analyses of the pooled OPERA I and OPERA II studies, which demonstrated NEDA rates of 47.7%, 49.5%, and 42.8% in the overall population and in patients with and without prior DMT, respectively.[13] The first postbaseline MRI was performed at the Week 24 visit and captured all lesion activity that occurred in the intervening period, driving the percentage of patients with lesions, particularly T2 lesions, and affecting the percentage of patients achieving the primary endpoint. This likely reflects the time necessary for OCR to exert its pharmacological effects, which is supported by epoch analyses showing a considerable decrease in both relapse and T2 lesion activity after 24 weeks.

Patients in this study were relatively early in their disease course, and, despite previous DMT use, had active disease, supporting the need for a shift in the MS treatment paradigm toward earlier initiation of high-efficacy DMTs.[14] The benefits of earlier OCR initiation were previously demonstrated in the open-label extension of the two OPERA trials. Patients who initiated OCR during the double-blind period had significantly less disease progression compared with those who switched to OCR in the extension after 96 weeks on IFN β-1a.[15] Findings from the current study are consistent with those of other reports, demonstrating the benefits of switching therapy after a suboptimal response on IFN therapy.[16,17]

An important aspect of CHORDS was the inclusion of patients with a suboptimal response defined only by MRI activity. The findings in this group demonstrated that OCR treatment was effective, even in patients without clinically apparent disease, and may suggest the importance of switching patients to a new treatment with subclinical disease activity, not just clinical events.[18,19]

PROs are an important aspect of treatment assessment in MS, because they reflect aspects of the disease that are meaningful to patients but that may not be captured with more traditional measures, such as relapse or EDSS. Furthermore, PROs may have a substantial impact on treatment adherence, which is an essential factor in the effectiveness of any drug.[20–22] In this study, OCR treatment was associated with improvements from baseline in the physical and psychological components of the MSIS-29 and with increased treatment satisfaction, as measured by the TSQM II and SATMED-Q.

There are several considerations when interpreting the data, including the open-label design of the study, lack of a comparator arm, and lack of MRI rebaselining, as all events in the first 24 weeks were considered. Baseline PRO scores may have been influenced not only by patients' awareness that they were receiving OCR but also by their impressions of their previous DMT.[23] In addition, one-third of patients in this trial continued to receive commercially available OCR and were not included in the safety follow-up period; however, AEs occurring in these patients were expected to be reported with standard pharmacovigilance.

Findings from the similar European CASTING study will improve our understanding of OCR use in patients who respond poorly to other treatments. Preliminary results presented at EAN 2020 showed that the proportion of patients with NEDA at the end of 96 weeks in CASTING (52.0%) was similar to that in CHORDS (48.1%); a higher percentage of NEDA was observed after rebaselining MRI activity at Week 8 in CASTING (74.8%).[24]

Conclusion

This study provides evidence of the benefits of OCR treatment in patients with early RRMS who had a suboptimal treatment response to previous DMT. Consistent efficacy was observed across clinical and MRI activity measures of inflammation and disease progression over 96 weeks, including in patients who only had evidence of subclinical disease activity. Safety in this study population reflected that previously observed in pivotal studies and in the real world.

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Declaration of Conflicting Interests

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Data Sharing Statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm

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Supplemental material

Supplemental material for this article is available online.

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