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RESEARCH ARTICLE

Real-world experience of ocrelizumab in multiple sclerosis in a Spanish population

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Abstract

Objective: Pivotal trial have shown that patients with multiple sclerosis (MS) receiving ocrelizumab had better outcomes. However, data on ocrelizumab in clinical practice are limited. The aim of this study was to evaluate the preliminary safety profile and effectiveness of ocrelizumab treatment for multiple sclerosis (MS) in a real-world clinical setting. **Methods**: We conducted a retrospective study including consecutive patients from nine public hospitals in south-eastern Spain who received ocrelizumab after it was approved. **Results**: A total of 228 MS patients were included (144 with relapsing–remitting MS [RRMS], 25 secondary progressive MS [SPMS], and 59 primary progressive MS [PPMS]). Median follow-up period was 12 months (range, 1-32). No evidence of disease activity (NEDA) status at year 1 was achieved in 91.2% of the relapsing MS (RMS) population, while disability progression was detected in 37.5% of the PPMS patients (median follow-up period, 19 months). The most common adverse events reported were infusion-related reactions and infections, with the most common infections being urinary tract infections followed by upper respiratory infections and COVID-19. **Interpretation**: The preliminary results in our real-world setting show that ocrelizumab presented excellent results in suppressing disease activity with a favorable and consistent safety profile.

Introduction

The humanized anti-CD20 B-cell-depleting antibody ocrelizumab was approved in Europe for treating adults with relapsing forms of multiple sclerosis (RMS) with active disease or early primary progressive multiple sclerosis (PPMS) with imaging features characteristic of inflammatory activity.[1] In the 96-week OPERA I and II trials in patients with RMS, ocrelizumab significantly reduced annualized relapse rates versus interferon β-1a by 46% and the number of gadolinium-enhancing lesions (GELs) by 94%.[2] Likewise, in the ORATORIO trial in patients

with PPMS, ocrelizumab significantly reduced the risk of confirmed disability progression in comparison with placebo.[3] However, the pool of PPMS patients who are candidates for this drug in a clinical setting of European countries differs from the population studied in the pivotal phase 3 randomized clinical trials (RCTs) with respect to the requirement of evidence of inflammatory activity from magnetic resonance imaging (MRI) (T1 GELs and/or new or enlarging T2 lesions), which was not one of the RCT inclusion criteria.[3] In these studies, ocrelizumab was generally well-tolerated, with mild-to-moderate infusion-related reactions (IRRs) and infections being the most common adverse events (AEs).[4]

Although RCTs are essential to establish the efficacy of a new drug, they have limited external validity, since enrollment of patients with different comorbidities or previous treatments may be limited by the inclusion criteria. Therefore, real-world studies provide more useful information on the treatment tolerability, effectiveness, and safety of the drug.[5] Real-world data on ocrelizumab are limited since only a few such studies have been published in Europe.[6-8] This study aimed to describe the tolerability, effectiveness, and safety of ocrelizumab for PPMS and RMS in clinical practice in a multicenter study in south-eastern Spain.

Methods

Patients and study design

This multicenter, retrospective, observational study was conducted in nine general hospitals belonging to the public healthcare network in south-eastern Spain. All patients enrolled in this study had received at least one infusion of ocrelizumab, as part of standard MS care until June 30, 2020. Patients involved in any ocrelizumab trial were excluded. MS was diagnosed according to the 2017 McDonald criteria.[9] We included both RMS forms: relapsing–remitting multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis (SPMS)[10] and PPMS and retrospectively analyzed demographic and clinical data.

Baseline data for the following aspects were collected from medical records: (a) demographic characteristics, (b) MS subtype, (c) disease-modifying therapy (DMT) before starting ocrelizumab treatment, (d) Expanded Disability Status Scale (EDSS) score, (e) number of relapses in the previous year, (f) time since MS diagnosis, (g) number of GELs on T1-weighted sequences of baseline MR sequences, and (h) reason for switching to ocrelizumab.

The standard patient follow-up protocol after ocrelizumab initiation included visits at 3, 6, and 12 months and every 6 months thereafter. During the COVID-19 pandemic, some follow-up visits were conducted by phone. Variables and outcomes assessed during follow-up were as follows: (a) duration of follow-up, (b) number of relapses, (c) EDSS score at the last in-person visit, (d) number of ocrelizumab cycles, (e) AEs, (f) number of GELs on the first MRI scan after ocrelizumab initiation (4–6 months), (g) number of new or enlarging T2-lesions and T1 GELs in the annual MRI scans, and (h) discontinuation of ocrelizumab and its reason.

Patients underwent brain MRI (using 1.5 T or 3 T scanners) before ocrelizumab initiation (baseline) and every year thereafter, including scans with a gadolinium (Gd) contrast at baseline and year 1. In some cases, control MRI at 4 to 6 months (re-baseline MRI) or spinal cord MRI was performed on an individual basis. MRI scans were assessed by experienced radiologists and by the attending neurologist.

Clinical and MRI outcomes

A relapse was defined as new or recurrent symptoms and objective typical findings of MS with a duration of at least 24 h, in the absence of fever or infection.[9] Disability progression was defined as a sustained ($\geq$ 3 months) EDSS score increase of 1.5 points if the baseline EDSS score was 0; 1 point if the baseline score was 1 to 5.5; and 0.5 points if the baseline EDSS score was 6.0 or more. Disability improvement was defined as a sustained ($\geq$ 3 months) EDSS score reduction of 0.5 points if the baseline EDSS score was 6.5 or more or 1 point if the baseline score was 6.0 or less,[11] and was only assessed in patients with baseline EDSS score $\geq$ 2. Disability progression was only analyzed in patients with a follow-up period longer than 1 year. MRI activity was defined as the presence of T1 GELs or new/enlarging T2 lesions on the year 1 MRI scan.

No evidence of disease activity (NEDA) outcome was assessed in RMS patients who were followed up for at least 1 year. NEDA status was defined as the combined absence of clinical (relapses and disability progression) and MRI activity.[12]

Treatment protocol

Ocrelizumab was administered according to the standard schedule recommended in its summary of product characteristics.[1] Before ocrelizumab administration, all patients were evaluated by their attending neurologist for symptoms suggestive of COVID-19 or other infections.

Two different premedication protocols to minimize IRRs were applied at the discretion of the prescribing

physician: standard premedication which included 100 mg intravenous methylprednisolone, H1-antihistamine, and/or paracetamol, while extended premedication also included H2-antihistamine and increased hydration. Patients remained at the hospital during the ocrelizumab infusion and 1 h after for monitoring IRRs, which included all symptoms and events occurring during or within 24 h of the infusion and were graded as mild, moderate, severe, or life-threatening according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[13]

Statistical analysis

Quantitative variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR or range) and compared using the Student t test or Mann–Whitney U test depending on the normality of the distribution as assessed by the Kolmogorov-Smirnov test. Qualitative variables were presented as absolute and relative frequencies and were compared with the chi-squared test. The annualized relapse rate (ARR) was calculated as number of relapses divided by the total patient-years of exposure to ocrelizumab. We compared the number of patients showing T1 GELs on MRI and relapses at baseline and follow-up assessments using McNemar's test. We also performed a bivariate analysis followed by a binary logistic regression to identify characteristics that were independent predictors of disability progression, NEDA status, IRR, or infections. All calculations were performed with a statistical significance of 5% and for every relevant parameter, we calculated a confidence interval (CI) of 95%. The statistical package used was the IBM SPSS Statistics version 25.

Ethics

The institutional ethics committee of the Hospital General Universitario de Alicante approved the study (reference number: PI-2019-116) and all research was completed in accordance with the Declaration of Helsinki guidelines for research practice. Informed consent was obtained from all patients.

Results

Baseline characteristics

A total of 228 patients (124 women and 104 men), who had received at least the first infusion of ocrelizumab were included. Their demographic and clinical characteristics and a comparison with the pivotal clinical trials are summarized in Table 1.

Eighty-three patients (36.4%) were treatment naïve. Before starting ocrelizumab, patients' most recent treatments included fingolimod ($n = 34$), beta-interferon ($n = 26$), natalizumab ($n = 21$), rituximab ($n = 18$), dimethyl fumarate (DMF) ($n = 17$), teriflunomide ($n = 9$), glatiramer acetate ($n = 9$), alemtuzumab ($n = 6$), cladribine ($n = 2$), and azathioprine ($n = 2$). The main reason for switching to ocrelizumab was treatment failure due to clinical activity, MRI activity, or both (114/145, 78.6%). Safety concerns due to progressive multifocal leukoencephalopathy (PML) risk in patients treated with natalizumab were the second-most common reason for switching to ocrelizumab (15/145, 10.3%). Twelve patients (8.3%) switched to ocrelizumab due to AEs of previous therapy (fingolimod, 5; rituximab, 3; natalizumab, 2; alemtuzumab, 1; and interferon, 1), including one patient who switched to ocrelizumab due to serum sickness with rituximab. The other reasons (2.8%) were conformance with the center´s protocol following commercialization of ocrelizumab (2 patients), lack of compliance with the monitoring protocol for natalizumab (1 patient), and unknown reasons (1 patient).

Relevant comorbidities according to the treating neurologist (Table 2) were present in 47 patients (20.6%), with cardiovascular risk factors being the most common ($n = 14$, 6.1%), followed by autoimmune diseases ($n = 10$, 4.4%), psychiatric disorders ($n = 5$, 2.2%), and cardiac diseases ($n = 5$, 2.2%).

Clinical and MRI outcomes after ocrelizumab initiation

The clinical course and radiological evolution (Table 3) were assessed with a global median follow-up of 12 months (range, 1–32 months). The median number of ocrelizumab infusions was 3 (range, 1 to 6). The follow-up period was longer in PPMS patients than in those with RMS (median, 19 vs. 10 months, $P < 0.001$).

After starting treatment with ocrelizumab, 13 (7.7%) RMS patients had a relapse. All relapses were evaluated by a neurologist within 2 weeks. The mean annualized relapse rate in the RMS population fell from 1.11 (95% CI: 0.95–1.23) before ocrelizumab initiation to 0.09 (95% CI: 0.05–0.16) after the treatment initiation ($P < 0.001$). Seven patients (7/102, 6.9%) had MRI activity at 12 months after ocrelizumab: three (3.0%) had Gd-enhancing lesions and five (4.9%) had new T2 lesions (none of them had a re-baseline MRI for comparison). The median time of follow-up in patients with and without disease activity was not statistically different.

Among the 48 patients with PPMS with a follow-up longer than 1 year, 18 (37.5%) experienced disability progression (Fig. 1), which was significantly higher

Table 1. Baseline characteristics of our OCRE-SE cohort in comparison with the OPERA I/II and ORATORIO clinical trials.

	OCRE-SE						
	Full cohort (n = 228)	RRMS (n = 144)	SPMS (n = 25)	PPMS (n = 59)	OPERA I[4] (n = 410)	OPERA II[4] (n = 417)	ORATORIO[5] (n = 488)
Age (years), mean ± SD	42.7 ± 11.2	39.5 9.	48.2 ± 9.4	48.4 ± 9.3	37.1 ± 9.3	37.2 ± 9.1	44.7 ± 7.9
Female sex, n (%)	124 (54.4)	89 (61.8)	10 (40.0)	25 (42.4)	270 (65.9)	271 (65.0)	237 (48.6)
MS duration (years), mean ± SD	6.98 ± 6.66	7.28 ± 6.63	11.88 ± 7.25	4.18 ± 4.94	6.74 ± 6.37	6.72 ± 6.10	2.9 ± 3.2
Previous DMT[1], n/total (%)	145/228 (63.6)	108/144 (75.0)	24/25 (96.0)	13/59 (22.0)	107/408 (26.2)	113/417 (27.1)	55/488 (11.3)
Interferon-beta	26/228 (11.4)	19/144 (13.2)	4/25 (16.0)	3/59 (6.2)	81/408 (19.8)	80/417 (19.2)	–
Glatiramer acetate	9/228 (3.9)	6/144 (4.2)	2/25 (8.0)	1/59 (1.5)	38/408 (9.3)	39/417 (9.4)	–
DMF	17/228 (7.4)	16/144 (11.1)	1/25 (4.0)	1/59 (1.5)	1/408 (0.2)	–	–
Teriflunomide	9/228 (4.0)	8/144 (5.6)	–	1/59 (1.5)	–	–	–
Fingolimod	34/228 (14.9)	25/144 (17.4)	6/25 (24.0)	3/59 (4.6)	1/408 (0.2)	4/417 (1.0)	–
Cladribine	2/228 (0.9)	2/144 (1.4)	–	–	–	–	–
Natalizumab	21/228 (9.2)	17/144 (11.8)	3/25 (12.0)	1/59 (4.6)	–	1/417 (0.2)	–
Alemtuzumab	6/228 (2.6)	4/144 (2.8)	2/25 (8.0)	-	–	–	–
Rituximab	18/228 (7.9)	11/144 (7.6)	5/25 (20.0)	2/59 (3.1)	–	–	–
Others	3/228 (1.3)	–	1[2]/25 (4.0)	2[3]/59 (3.1)	2/408 (0.4)	1/417 (0.2)	–
Reason for change							
Treatment failure, n (%)	114/145 (78.6)	85/108 (78.7)	16/24 (69.5)	13/13 (100.0)	NA	NA	–
Side effects, n (%)	12/145 (8.3)	9/108 (8.3)	4/24 (13.0)	–	NA	NA	–
PML risk (JCV+), n (%)	15/145 (10.3)	12 (11.1)	3/24 (13.0)	–	NA	NA	–
Others, n (%)	4/145 (2.8)	2 (1.9)	1/24 (4.3)	–	NA	NA	–
Baseline EDSS, mean ± SD	3.58 ± 1.83	2.80 ± 1.60	5.32 ± 1.16	4.75 ± 1.43	2.86 ± 1.24	2.78 ± 1.30	4.7 ± 1.2
Median (IQR)	3.5 (2.5-5.5)	2.5 (2-3.5)	6 (4-6)	4.5 (2-7.5)			4.5 (2.5-7.0)
Relapses in the previous year							
≥1, n/total (%)	131/165 (79.4)	112/142 (78.8)	19/23 (82.6)		NA	NA	
mean ± SD	1.11 ± 0.81	1.12 ± 0.77	1.09 ± 0.99		1.31 ± 0.65	1.32 ± 0.69	
Baseline Gd-enhancing lesions							
≥1, n/total (%)	88/217 (40.6)	65/137 (47.4)	6/24 (25.0)	17/56 (30.4)	172/405 (42.4)	161/413 (39.0)	133/484 (27.5)
mean ± SD	1.27 ± 3.19	1.64 ± 3.82	0.38 ± 0.88	0.75 ± 1.63	NA	NA	–

RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; MS, multiple sclerosis; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; PML, progressive multifocal leukoencephalopathy

[1]Last DMT before OCR in OCRE-SE.

[2]Azathioprine.

[3]Azathioprine and Laquinimod (clinical trial).

[4]OPERA I and II data adapted from Hauser, SL et al, NEJM, 2017.

[5]ORATORIO adapted from Montalban X et al, NEJM, 2017.

($P < 0.001$) than the disability progression rate in the RMS groups (3.3% and 17.6% in the RRMS and SPMS groups, respectively). Only four PPMS patients showed disability improvement (8.3%) compared to the 12 (20%) in the RRMS group. None of the SPMS patients experienced disability improvement during the follow-up period. Disability progression was associated with male gender, higher baseline EDSS score, PPMS phenotype, absence of Gd-enhancement in the baseline MRI, and longer follow-up period. In the binary logistic regression analysis, only male gender (OR 5; 95% CI, 1.31-9.4) and a longer follow-up period (OR 1.13; 95% CI: 1–1.3) remained independent predictors for disability progression in our study.

Finally, NEDA status was achieved in 91.2% of the RMS patients with more than 1 year of follow-up (n = 57). None of the baseline characteristics (age, disease duration, EDSS score, prior DMT, prior relapses, baseline MRI activity, or comorbidities) were statistically associated with the achievement of NEDA status.

Safety, tolerance, and persistence

The most frequent AEs were IRRs and infections (Table 4). None of the baseline characteristics (age, type of MS, disease duration, EDSS score, or comorbidities) were related to the occurrence of these AEs. IRRs (n = 53, 23.2%) were mostly mild to moderate (Fig. 2)

Table 2. Comorbidities in our patients treated with ocrelizumab (n = 47/228, 20.6%)

Type of comorbidity	Diagnosis	n
Cardiovascular risk factors (n = 14, 6.1%)	Current smokers	5
	Diabetes mellitus	4
	Morbid obesity	2
	High blood pressure	1
	Dyslipidemia	1
	Obstructive sleep apnea	1
Autoimmune (n = 10, 4.4%)	Autoimmune *thyroid* diseases	2
	Idiopathic thrombocytopenic purpura	2
	Psoriasis	1
	Uveitis	1
	Inflammatory bowel disease	1
	Sjogren's syndrome and antiphospholipid syndrome	1
	Vitiligo	1
	Celiac disease	1
Psychiatric disorders (n = 5, 2.2%)	Bipolar disorder	3
	Depression	2
Cardiac diseases (n = 5, 2.2%)	Ischemic cardiomyopathy	3
	Dilated cardiomyopathy	1
	Arrhythmia	1
Neoplasm (n = 4, 1.7%)	Pituitary adenoma	2
	Cervical lymph node carcinoma metastasis from unknown primary site	1
	Spinal schwannoma	1
Infections (n = 2, 0.8%)	Chronic inactive hepatitis B (carrier)	1
	Persistent *human papillomavirus type 16* infection	1
Others (n = 9, 3.9%)	Lumbar disc hernia	2
	Arthrosis	2
	Cerebral palsy	1
	Microcephaly and intellectual disability	1
	Avascular necrosis of the hip	1
	Thrombocythemia	1
	Chronic obstructive pulmonary disease	1

Table 3. Clinical and MRI outcomes at Year 1.

	OCRE-SE		
	RRMS (n = 144)	SPMS (n = 25)	PPMS (n = 59)
Follow-up (months), median (IQR/range)	10 (6–13)	13 (8.5–14)	19 (13–25)
mean ± SD	9.6 ± 4.7	12.1 ± 5.6	18.5 ± 7.9
Ocrelizumab infusions, median (IQR/range)	2 (1–3)	3 (2–3)	4 (3-5)
Relapse free[1], n/total (%)	124/136 (91.2)	24/25 (96.0)	
ARR post-OCR (95% CI)	0.10 (0.05-0.18)	0.04 (0.001-0.22)	
EDSS[1], n/total (%)			
Improvement[2]	12/60 (20.0)	0/17 (0.0)	4/48 (8.3)
Progression[3]	2/60 (3.3)	3/17 (17.6)	18/48 (37.5)
MRI activity, n/total (%)	3/44 (6.8)	0/13 (0)	4/45 (8.9)
Gd-enhancing lesions ≥ 1	1/44	0/13	2/45 (4.4)
New T2 lesions	3/44	0/13	2/42 (4.8)
NEDA-3[1], n/total (%)	40/44 (91)	12/13 (92)	

RRMS, relapsing–remitting multiple sclerosis; aSPMS, active secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; NEDA, no evidence of disease activity

[1]OCRE-SE: only includes data from patients with at least 1 year of follow-up.

[2]Confirmed disability improvement for ≥ 12 weeks

[3]Confirmed disability progression for ≥ 12 weeks

and responded well to management (reduction in infusion rate and administration of symptomatic therapy if needed). Only one patient was admitted to the hospital for 24 h after developing fever and a generalized rash following the first infusion; he recovered with symptomatic therapy. The rate of IRRs decreased from the first infusion (22.3%) to the second (11.7%) and thereafter (7.3%). The patient with a history of rituximab-induced serum sickness tolerated the infusions well without showing disease recurrence after the first cycle (two infusions) of ocrelizumab. The standard and extended premedication protocols were used in 129 (56.6%) and 99 (43.4%) patients, respectively. The IRR rates associated with the two premedication protocols showed no significant differences. No patient discontinued treatment due to IRRs.

Twenty-five patients (11%) developed infections. Urinary tract infections were the most common, followed by upper respiratory infections and COVID-19. Three patients (1.3%) in our cohort contracted COVID-19. They were all men (two PPMS and one RRMS), aged 32 to 49 years, and had EDSS scores of 0, 6, and 7.5. Only the oldest and the more disabled patient required hospitalization and supplementary oxygen. Fortunately, all of them recovered to their previous neurological and physical condition. Three herpes virus infections were observed (two herpes zoster and one herpes simplex infections). No opportunistic infections were reported and, except for the patient with COVID-19, no patient required hospitalization for infection.

Within the observation period, two other patients developed serious AEs. The first was a 51-year-old woman with a history of heavy smoking and chronic obstructive pulmonary disease. She had SPMS with baseline EDSS score of 6.5. She was diagnosed with metastatic small cell lung carcinoma after 6 months on ocrelizumab (two cycles of treatment), received palliative care, and died

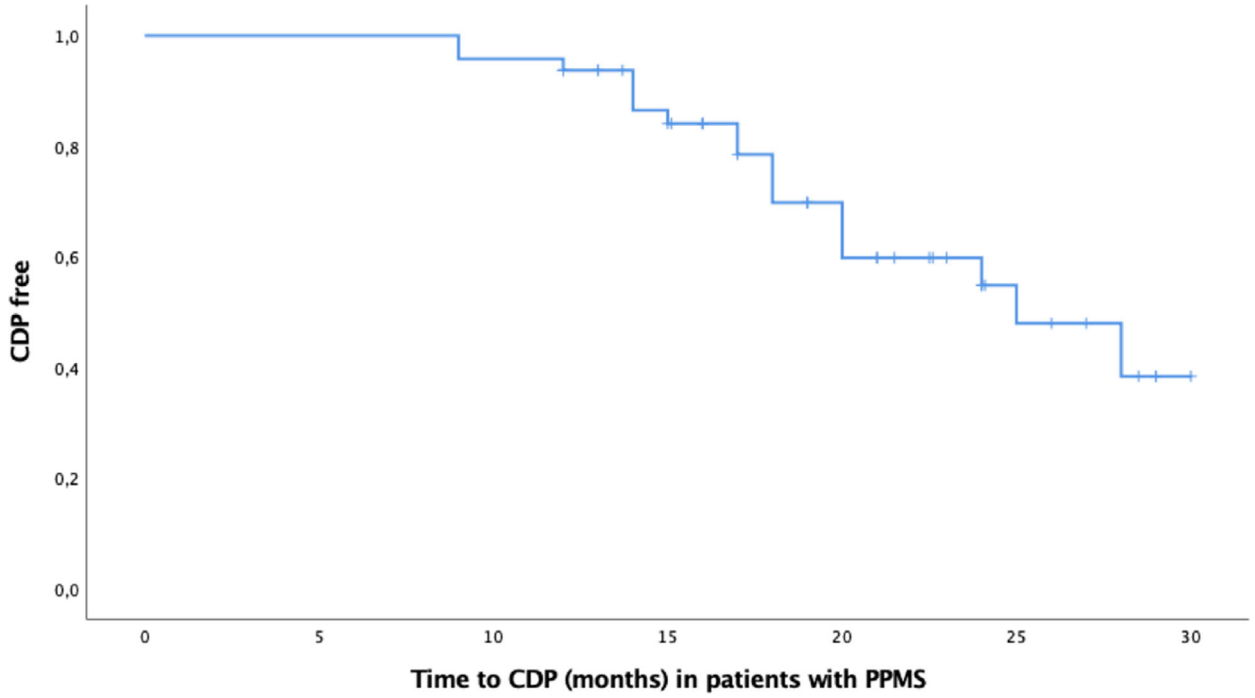

Figure 1. Kaplan–Meier survival curve of confirmed disability progression (CDP) after ocrelizumab. PPMS: primary progressive multiple sclerosis

3 months later. None of the four patients with a prior history of neoplasms showed recurrence. The second patient was a 49-year-old PPMS patient with a pulmonary bilateral thromboembolism. This event was not considered to be related to ocrelizumab, so the patient continued taking the drug after hospitalization.

Five patients (2.2%) discontinued ocrelizumab: the reasons were death, pregnancy, patient's choice, and ineffectiveness. The patient who discontinued treatment due to pregnancy became pregnant 1 month after receiving the second cycle of ocrelizumab; she did not experience any relapse or medical complications during pregnancy, and she delivered a term-healthy new-born (birth weight, 2800 g) by natural vaginal birth.

Discussion

Ocrelizumab has been approved in Europe for the treatment of patients with MS, but data on its real-world use are limited.[6-8] We present the largest and longest European real-world study to date, including MRI data not available in other studies.

Compared with the cohort of the OPERA trial, our RMS cohort was slightly older and had a longer duration of disease. Despite these differences, NEDA status at year 1 was achieved in 91% of the patients. The disability progression rate in the PPMS group was higher than that in the ORATORIO trial (37.5% vs. 32.9%), which is especially notable considering the shorter follow-up of our cohort (19 vs. 35 months). The higher progression rate in our cohort might be explained by the older age of our PPMS patients. However, we cannot exclude the deleterious effects of the current SARS-CoV-2 pandemic, which have resulted in reduction in physical activity due to preventive home isolation and discontinuation of physical therapy. Similar to Daniel et al.,[8] we also found some PPMS patients (8.3%) showing an early improvement in their EDSS score, which was not observed in any SPMS patients and has not been described in the pivotal trials; this could be related to control of disease activity.

One of the major strengths of real-world studies is that they provide information about patients with different comorbidities and prior treatments, who are not always included in clinical trials. In our study, the most common comorbidities were cardiovascular risk factors, autoimmunity, and mood disorders, with a similar profile as described in previous studies[6,14] but with a lower frequency of both cardiovascular risk factors and mood disorders since we only considered relevant conditions if they were under pharmacological treatment, caused complications, or influenced the patient's disability or quality of life. In practice, anti-CD20 therapy is frequently selected for patients with MS and other autoimmune diseases, so this category could have been overestimated in

Table 4. Safety data in OCRE-SE and pooled OPERA I/II and ORATORIO populations.

Adverse event	OCRE-SE (n = 228)	OPERA I/II[3] (n = 825)	ORATORIO[4] (n = 488)
Total patient-years (PY)	231	1448	1606
Adverse events leading to discontinuation (rate per 100 PY)	0.43	2.35	1.25
Serious adverse events (SAE) (rate per 100 PY)	1.73	5.4	10.2
Infections (rate per 100 PY)	10.82	84.5	70.8
Urinary tract infection, n/total (%)	10/228 (4.4)	96/825 (11.6)	195/488 (40.1)
Upper respiratory tract infection, n/total (%)	4/228 (1.8)	125/825 (15.2)	59/488 (12.1)
		-	-
COVID-19, n/total (%)	3/228 (1.3)	-	-
Cellulitis, n/total (%)	2/228 (0.9)	17/825 (2.1)	-
Herpes zoster, n/total (%)	2/228 (0.9)	-	-
Gastroenteritis, n/total (%)	2/228 (0.9)	-	-
Others[1], n/total (%)	5/228 (2.2)		
Serious infections (rate per 100 PY)	0.43	0.83	2.74
Infusion-related reactions (rate per 100 PY)	22.94	34.9	31.0
Malignancies (rate per 100 PY)	0.43	0.28	0.93
Others[2] (rate per 100 PY)	1.73		
Deaths (rate per 100 PY)	0.43	0.07	0.25

[1]Other infections: 1 herpes simplex labialis, 1 pneumonia, 1 dental abscess, 1 oral candidiasis, 1 otitis.
[2]Others: 1 bilateral pulmonary thromboembolism, 1 recurrent skin rash, 1 biliary colic, 1 alopecia areata.
[3]Pooled data from OPERA I and II. Hauser SL et al. Neurology. 2020.
[4]ORATORIO adapted from Montalban X et al, NEJM, 2017

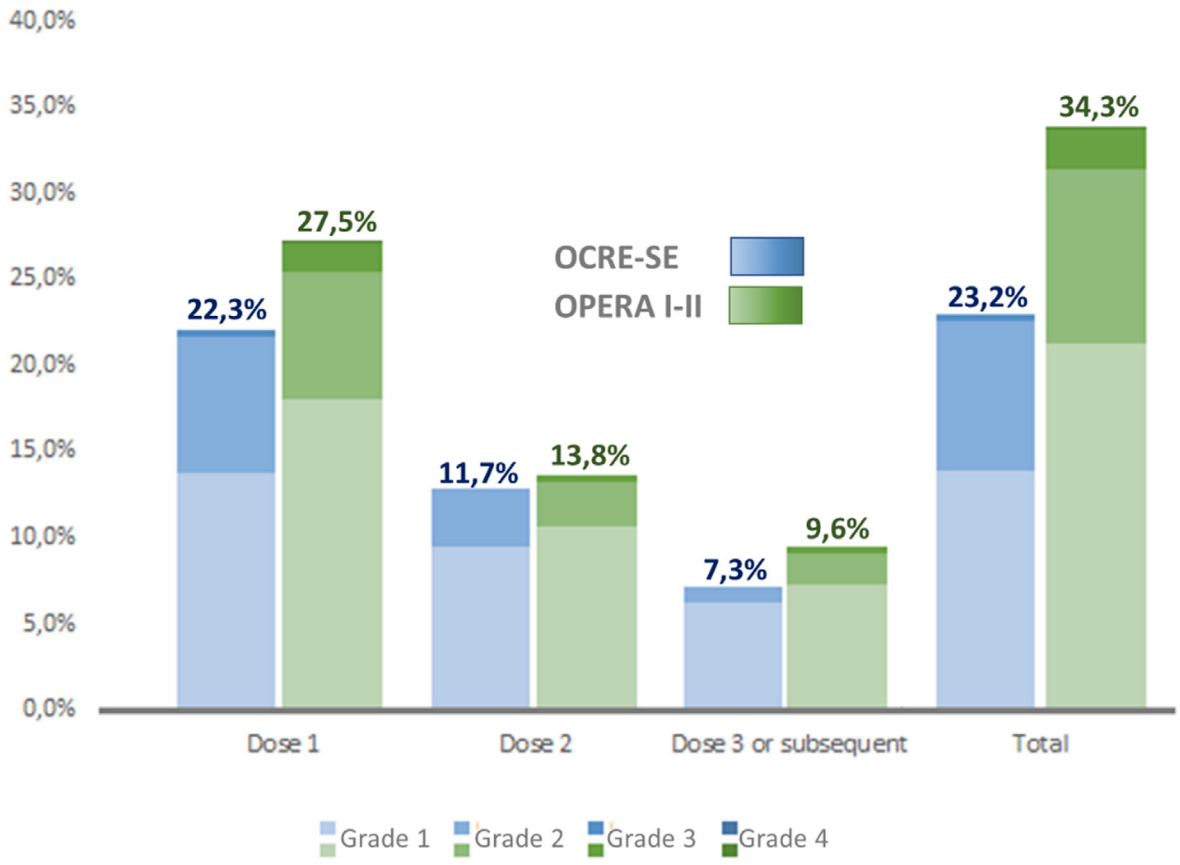

Figure 2. Percentage of infusion-related reactions in each cycle of ocrelizumab. Comparison between OCRE-SE and OPERA I-II pooled data

our study. Comorbidities are linked to faster neurological deterioration.[14] However, in our study, comorbidities did not influence the possibility of achieving NEDA status, disability progression, or AEs.

About three quarters of the RMS patients included in the OPERA trial were treatment naïve, and the most common previous therapies were interferon and glatiramer acetate.[2] Nonetheless, prior treatment per se did not influence the magnitude of the beneficial effect of ocrelizumab.[15] In contrast, in our cohort and other observational studies, most RMS patients have been previously treated, with most patients receiving highly effective DMTs.[6,7] Nevertheless, ocrelizumab still exhibited high effectiveness not only after switching from first-line injectable treatments but also after switching from highly effective agents such as alemtuzumab, natalizumab, fingolimod, and cladribine, although the number of participants is still low.

As observed in phase 3 trials and the other real-world studies, mild-to-moderate IRRs and mild infections were the most common AEs. The percentage of IRRs in our study (23%) was lower than those in the pivotal clinical trials (ORATORIO: 39.9%, OPERA: 34.3%).[2,3] However, we did not observe a lower rate of IRR with the modified premedication protocol, unlike Conte et al.[16] The change from rituximab to ocrelizumab was well-tolerated even in patients who switched due to serum sickness disease or considerable IRRs.

Anti-CD20 B-cell-depleting drugs such as rituximab may increase the risk of infections over time.[17] The most common infections observed in the clinical trials of ocrelizumab were upper respiratory tract and urinary tract infections. Minor infections were reported in 8% and 5% of patients in two recent observational studies.[6,7] In our cohort, this proportion was slightly higher (11%), which may be explained by the longer follow-up interval with ocrelizumab in our series. Besides, upper respiratory tract infections were likely underreported since most patients do not consult their physicians for symptoms of nasopharyngitis. Furthermore, in our case, the measures to prevent COVID-19 implemented in the recent months may have helped avoid other respiratory infections, as seen with influenza in Australia.[18] However, the rate of serious infections requiring hospitalization, which is rarely affected by reporting bias, was actually lower in our cohort than in the pivotal clinical trials. While most reported infections for ocrelizumab to date have been minor, a few isolated cases of severe viral infections, such as fulminant hepatitis associated with echovirus 25 and HSV-2 encephalitis, have been reported.[19,20] Considering the ongoing coronavirus pandemic, there are concerns regarding the increased risk of severe COVID-19 in MS patients receiving immunosuppressive DMT.[21] A registry-based cohort study of 347 patients with MS from France found that age, EDSS score, and obesity were independent risk factors for severe COVID-19, and that there was no association between DMT exposure and COVID-19 severity.[22] The COVID-19 rate in patients on ocrelizumab in our cohort was 1.3%, which is lower than the population-based seroprevalence in Spain (4.6%),[23] and, reassuringly, the evolution of our three affected patients was favorable, consistent with other studies.[24-29] The low rate of COVID-19 infection in our cohort may be explained by the early preventive measures that were adopted by our patients in the pandemic.[30]

Our study is subject to the limitations of a retrospective design and a short follow-up period. Moreover, regression to the mean should be taken into account to assess the annualized relapse rate after the start of ocrelizumab.[31] On the other hand, this study provided MRI and NEDA data that are not available from other real-world studies. Besides, the study was conducted in a general hospital setting with universal healthcare access, eliminating the bias of a tertiary referral center or unequal access to healthcare or DMTs.

In conclusion, our real-world experience confirms the short-term effectiveness, tolerability, and safety of ocrelizumab. Further studies are needed to assess patient outcomes with longer follow-up periods.

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Conflicts of Interest

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