Multiple Sclerosis and Related Disorders 86 (2024) 105570

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Efficacy and safety of ocrelizumab in patients with relapsing multiple sclerosis: Real-world experience of two Swiss multiple sclerosis centers

L Diem [a,b,*], A Ovchinnikov [c], C Friedli [a,d], H Hammer [a], N Kamber [a], A Chan [a], A Salmen [a], O Findling [c,1], R Hoepner [a,1]

[a] Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Freiburgstrasse, Bern, Switzerland
[b] Neurocenter, Lucerne Cantonal Hospital, Lucerne, 6000, Switzerland
[c] Department of Neurology, Cantonal Hospital Aarau (Kantonsspital Aarau), Tellstrasse, Aarau, Switzerland
[d] Department of Neurology, Waikato Hospital, Hamilton, New Zealand

ARTICLE INFO

Key Words:
Ocrelizumab
Multiple sclerosis
Relapsing multiple sclerosis
Immunotherapy

ABSTRACT

Background: Ocrelizumab (OCR) is a humanized monoclonal antibody directed against CD-20 positive lymphocytes, mainly B-lymphocytes. OCR is approved for treatment of primary progressive (PPMS) and relapsing multiple sclerosis (RMS). This study aims to provide real-world safety and efficacy data of people with RMS treated with OCR in two Swiss Multiple Sclerosis (MS) centers.

Methods: We have conducted a retrospective data analysis using the patient cohorts from the Cantonal Hospital Aarau and Bern University Hospital (RMS: $n = 235$). Statistical analyses were performed with Mann–Whitney U-Test, Chi-squared test and Spearman-Rho-Correlation. Adjustment for multiple testing was performed by Bonferroni procedure.

Results: After initiation of OCR, there was a decrease in disease activity in RMS patients. In our study, 152/190 (80.0 %) RMS patients fulfilled the criteria for NEDA-3 12 months and 88/104 (84.6 %) showed NEDA-3 24 months after OCR initiation. The most frequent adverse events (AEs) in our study were infections, taking place in 78/235 (33.2 %) RMS patients. COVID-19 was the most common infection, followed by urinary infections and other respiratory infections and infectious adverse events occurred significantly more frequent in patients with reduced IgG serum concentration.

Conclusions: Our real-world study showed OCR being associated with low rates of any type of MS disease activity as indicated by NEDA-3. The adverse event profile is comparable to the known events especially infections and an association between infections and reduced IgG serum concentration was found.

1. Introduction

B-lymphocytes, which express CD-20 antigen on the cell surface, are supposed to be actively involved in the chronic inflammation present during multiple sclerosis (MS) disease (Gelfand et al., 2017). Immunotherapy with Ocrelizumab (OCR), which is a humanized anti-CD-20 monoclonal antibody, was approved by the US Food and Drug Administration (FDA) (Pharmacology, A.C.o.C. 2017) and by the Swissmedic in 2017 (Swissmedic 2018) and in 2018 by European Medicines Agency (EMA) ((EMA) 2018) for treatment of patients with relapsing (RMS) and primary progressive forms of multiple sclerosis (PPMS) (Hauser et al., 2017; Montalban et al., 2017).

In the OPERA I and II trials in patients with RRMS, OCR significantly reduced ARR vs. interferon β−1a by 46 % and the number of gadolinium-enhancing lesions by 94 %. (Hauser et al., 2017) In these studies, the most common adverse events of OCR were mild to moderate infusion-related reactions and infections (Hauser et al., 2017; Hauser et al., 2020).

Randomized controlled trials (RCTs) are essential for demonstrating efficacy and safety prior market approval. However, their power is limited partly because the results may not be broadly generalizable, as the inclusion of patients with different comorbidities, previous treatments, or elderly patients may be restricted. Studies under real-world conditions may therefore complement RCTs. In the last three years,

* Corresponding author.
E-mail address: diem.lara@gmail.com (L. Diem).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.msard.2024.105570
Received 14 January 2024; Received in revised form 7 March 2024; Accepted 21 March 2024
Available online 30 March 2024

the number of real-world data studies on OCR has increased (currently about 8 studies, supplementary Table 1) but is still limited (Prockl et al., 2020; Coban et al., 2021; Daniels et al., 2020; Fernandez-Diaz et al., 2021; Ellwardt et al., 2020; Pontieri et al., 2022; Buttmann, 2020; Cellerino et al., 2021; Sempere et al., 2020; Braune, 2020; al., S.K.e. 2019)

The aim of our real-world study is to provide information about treatment efficiency for RMS patients, considering their previous treatment and comorbidities in two Swiss MS centers.

2. Methods

2.1. Patients and study design

We have conducted a retrospective study in two Swiss MS centers (Cantonal Hospital Aarau and University Hospital in Bern), collecting the information of in total 235 RMS patients (Fig. 1). Eligible patients were identified using the following search terms "MS and Ocrelizumab or Ocrevus" in the centers Aarau and Bern to search local clinical information systems within the following time frames: January 2016 till January 2022. In these 2 centers, the patients were seen 6 and 12 months after the start of ocrelizumab, subsequently every 6 months. During the consultation, relapses were evaluated and EDSS and laboratory chemical tests were performed. Patients underwent brain MRI (using 1.5 T or 3 T scanners) every year after start of ocrelizumab. In some cases, control MRI at 4 to 6 months (re-baseline MRI) was performed on an individual basis. MRI before ocrelizumab start was performed on an individual basis. Baseline follow-up information's were collected from medical records: age, sex, first manifestation and time point of MS diagnosis, type of multiple sclerosis, disease modifying therapy (DMT) before starting with OCR (supplementary Table 2), Expanded Disability Status Scale (EDSS) score at OCR initiation and 24, 12 months (+/- 8 weeks) before and after start of OCR treatment, information about relapses before (12 and 24 months) and under OCR therapy, magnetic resonance imaging (MRI) findings at 24, 12 (+/- 8 weeks) months before and after the beginning of the OCR treatment, lymphocyte and neutrophil count, liver parameters, serum immunoglobulin G (IgG) under the therapy, adverse events including infusion related reactions (IRR).

2.2. Clinical and mri outcomes

MS diagnosis was in accordance with the currently valid 2017 McDonald criteria (A.J. Thompson et al., 2018). As a clinical MS relapse, we have considered a new onset of the neurological symptoms with a minimal duration of at least 24 h, considering the absence of infection/fever, Uhthoff-phenomenon (A.J. Thompson et al., 2018).

Disease progression was defined as an increase of the EDSS Score by 1 point if the baseline EDSS was 0 to 5.5 and by 0.5 points if the baseline EDSS score was $\geq$ 6.0 compared to the last clinical assessment (Kalincik et al., 2015). EDSS improvement was defined as a decrease of the EDSS Score by 1 point if the baseline EDSS was 0 to 5.5 and by 0.5 points if the baseline EDSS score was $\geq$ 6.0 compared to the last clinical assessment.

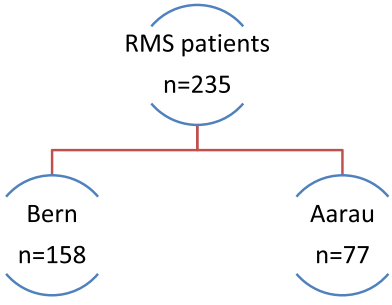

Fig. 1. Total number of patients in our cohort.
Abbreviations: RMS: relapsing MS

Annualized relapse rate (ARR) was defined as the number of relapses with onset occurring during a specific period, adjusted to a one-year period. Radiological activity in MRI scans was classified by the presence of T1 -Gadolinium enhancing lesions (GELs), new or enlarging T2 lesions compared to the last scan. No evidence of disease activity (NEDA-3) was considered as the main criteria for clinical efficacy assessment and consisted of the following information: presence of MS relapses, and/or radiological evidence of disease activity (and/or disability progression (Pandit, 2019). Hypogammaglobulinemia for IgG was defined as a serum IgG concentration below < 6.0 g/l (17). The overall IgG decrease was calculated as follows: (IgG value just before OCR therapy initiation - last IgG value under OCR therapy)/time in years. Agranulocytosis was defined as absolute neutrophil count below < 500 cells per microliter (µl) (MSD Manual: Normal Laboratory Values) and transaminase increase as Aspartate transaminase and/or Alanine transaminase > 35 U/l (MSD Manual: Normal Laboratory Values). Adverse events classified using the Common Terminology Criteria for Adverse Events (CTCAE) (Common Terminology Criteria for Adverse Events (CTCAE)).

2.3. Statistics

Quantitative variables are described using the mean and 95 % confidence interval (95 %CI) or median and interquartile range (IQR) and compared with Wilcoxon Test. Qualitative variables are presented as absolute and relative frequencies and were compared with Mc-Nemar-Test. Adjustment for multiple testing was performed by Bonferroni procedure regarding each domain independently. The statistical package used was the IBM SPSS Statistics version 28.

2.4. Ethics

The ethics committee of North-West and Central Switzerland approved the study (Project-ID: AG 2016–02,233 amendment 01 03.05.2021; BE 2017–01,369).

3. Results

3.1. Baseline characteristics

We conducted a retrospective observational study between April 2016 and January 2022, including 235 RMS patients in the two Swiss MS centers (Fig. 1). The majority of patients were female (157/235 (66.8)) and the mean age was 40.6 years (95 % confidence interval (95 %CI) (38.8–41.9); n = 235). Median EDSS before OCR treatment was 2.0 (interquartile range (IQR) ±1.5) n = 235). Mean disease duration was 9.3 years (95 %CI (8.4–10.2); n = 235).

The number of naïve, defined as without any prior immunotherapy, RMS patients was 75/235 (31.9 %). RMS patients switched mainly from (highly) active therapies (95/235), while from mild/moderate therapies were by (65/235). In our cohort there were 7 patients on rituximab. In these patients, side effects were the reason for switching to ocrelizumab. Prior to initiation of therapy with OCR, 49/75 of naïve patients and 66/160 of pretreated patients had relapses 12 months before start with OCR, respectively. Median EDSS in both groups was 2.0 (naïve median (±IQR) 2.0 (±1.5), n = 75; pretreated mean (±IQR) 2.0 (±1.6), n = 160). MRI data were available in 65 of the naïve patients and of these 41/65 showed radiological activity. Of the 148 pretreated patients in whom MRI data were available, 56/148 showed MRI activity.

3.2. Treatment efficacy

Data on relapses, EDSS progression, and MRI activity 12 month after OCR start were available in 190 patients. After initiation of OCR, there was a decrease in disease activity in RMS patients after 12 months. The number of patients with relapse (before OCR: 60/190 (31.6 %) vs. after

OCR: 5/190 (2.6 %), p-value <0.001) and the ARR (before OCR: 0.4 (0.3–0.4), $n = 190$ vs. after OCR 0.03 (0.003–0.05), $n = 190$, p-value <0.001) dropped significantly by 92.5 % after initiation of OCR. Relapses under ocrelizumab occurred on a mean of 1.1 years (95 %CI 0.20–3.08, $n = 11$) after the start of therapy. In addition, there was a significant decrease in MRI disease activity (new T2 lesions and/or Gd-enhancement lesions before OCR: 88/190 (46.3 %) vs. after OCR: 22/190 (11.6 %); p-value <0.001). The median EDSS remained stable in the majority of patients (stable EDSS: 165/190 (86.8 %); EDSS improvement: 9/19 (4.7 %), EDSS decline: 16/190 (8.4 %), table 3). In our study, 152/190 (80.0 %) RMS patients fulfilled the criteria for NEDA-3 12 months after beginning of OCR, while 38/190 (20.0 %) showed evidence of disease activity (EDA): mainly presenting with MRI activity alone (19/38 radiological activity without relapse or EDSS progression; 11/38 only progression; 2/38 radiological activity with progression; 4/38 only relapse; 1/38 relapse with progression and 1/38 with all 3 activity criteria, Table 1). Considering the new term "Progression Independent of Relapse Activity "(PIRA) 13/38 of the patients with disease activity met the criteria for PIRA after 12 months. NEDA-3 status at 12 months was not associated with disease duration ($p = 0.115$) or pre-treatment status ($p = 0.172$)

There were complete data sets on clinical and paraclinical course of 104/190 patients even after 24 months. In this cohort with a 24 months follow up the disease course was stable with low radiological activity (4/104, 3.8 %) and low ARR (mean (95 %CI) 0.04 (0.001–0.08), $n = 104$). At 24 months, 88/104 (84.6 %) of the RMS patients fulfilled the criteria for NEDA-3 with EDSS progression being the main reason for EDA in 9/104 patients (table 1). This is reflected in a small but significant EDSS increase in the whole cohort (before OCR 2.0 (±2.0), $n = 104$ vs. after OCR 2.5 (±1.5), $n = 104$, $p = 0.003$, table 3). In number EDSS progression was present in 9/104 patients whereas a stable EDSS was seen in 89/104 and EDSS improvement only in 6/104. After 24 months, 9/16 patients with disease activity met the criteria of PIRA. NEDA-3 status at 24 months was not associated with disease duration ($p = 0.119$) or pre-treatment status ($p = 0.353$)

3.3. Adverse events (AEs)

No fatal AE occurred. Severe AEs were COVID-19 with hospitalization (9/235, 3.8 %), agranulocytosis (2/235, 0.9 %) and cytokine release syndrome CTCAE grade III (1/235, 0.4 %) for which the patient was also hospitalized (1/235, 0.4 %).

Internationally recognized premedication protocols were used prior OCR infusions (1 g Paracetamol p.o., 5 mg Levocetirizin p.o. and 100 – 125 mg Methylprednisolone i.v.) (Ovchinnikov and Findling, 2022). One patient had a cytokine release syndrome Grade III with fever, exanthema, nausea and hypotension and need hospitalization with steroids, nonsteroidal anti-inflammatory drug and volume substitution.

The most frequently documented AEs in our study were infections (86/235, 36.6 %), namely COVID-19 (including COVID-19 with hospitalization 60/235, 25.5 %) urinary (10/235, 4.3 %) and non SARS-CoV-2 respiratory tract (9/235, 3.8 %) infections. Thirty RMS patients with bacterial infection or COVID-19 needed to be treated with antibiotics or sotrovimab and 9/235 (3.8 %) patients with COVID-19 need hospitalization (table 1).

Two patients developed agranulocytosis (Late-onset neutropenia, defined by low absolute neutrophil count < 500 cells per microliter (µl)), occurring approximately 3–4 weeks after the DMT application (Wolach et al., 2010)). The cause of neutropenia was defined as AEs in the frame of OCR therapy because other etiology, such as bone marrow pathology, infection or autoimmune component, were excluded. None of these two patients experienced fatale outcomes. MS disease remains also stable. After the management of neutropenia, both patients voluntarily discontinued OCR therapy.

In our data, none of the patients presented severe (grade III or IV) lymphocytopenia. The mean lymphocyte count during the OCR therapy was 1.9 (95 %CI (1.7–2.6), n = 228).

Before starting treatment with ocrelizumab, 4/208 (0.02 %) of the patients had hypogammaglobulimia. All patients had primary hypogammaglobulinemia. Serologically examined IgG level 24 months after OCR initiation was in mean 8.2 (95 %CI (7.8–8.5), n = 208). In total 36 patients of our study presented with hypogammaglobulinemia defined by IgG < 6.0 g/l (17). Severe infections (with hospitalization and/or treatment) occurred in nearly have of the patients with IgG < 6.0 g/l, which was significantly more frequent compared to those without reduced IgG serum concentration (17/36 (47.2 %) vs. 13/172 (7.6 %), $p < 0.001$). In 189 patients, we had IgG levels at baseline and during therapy with OCR. Throughout the OCR treatment, 79.4 % (150/189) of the RMS patients showed an IgG decrease. In all patients with IgG-follow up, mean IgG-change was −0.40 g/l per years (95 %CI, −0.47- −0.34, range −1.9 - 1.0, $n = 189$).

Six patients became pregnant during treatment with OCR. Mean time between last infusion and positive pregnancy test was 4.7 months (95 % CI (1.6–7.8), $n = 6$). In two pregnancies, this time span was shorter than 3 months. All pregnancies were free of complications, 2 children were delivered by caesarian section (1 elective caesarian section, 1 caesarian section for breech presentation and fetal macrosmia) and no child had other complications.

4. Discussion

In 2018, OCR was introduced for patients with RMS. However, real-world data on the post-marketing use of OCR are still limited. Our study provides real-world data of two Swiss MS centers. The main findings are: 1) In line with the results of RCT and previously published real-world data, it showed efficacy in patients with RMS. 2) Tolerability of OCR was in general good, however infections, IgG decline and the association between both seen in our cohort highlight the need for pharmacovigilance and management strategies for MS patients treated with OCR.

The population characteristics of real-world data often differ from RCTs. Indeed our RMS cohort has a higher disease duration and percentage of pretreated patients compared to the OPERA population (Hauser et al., 2017).

Compared with most Real World Data studies (RWDS), our RMS cohort was comparable in terms of age (mean our study: 40.6 vs. range (mean age in years) RWDS 36.3–43.9), disease duration (mean our study: 9.3 vs. range (mean disease duration in years) RWDS 7.7–10.8), and EDSS (mean 2.3 vs. range (mean EDSS) RWDS 2.5–2.9) (Prockl et al., 2020; Fernandez-Diaz et al., 2021; Ellwardt et al., 2020; Pontieri et al., 2022; Buttmann, 2020; Sempere et al., 2020; Braune, 2020). However, the proportion of pretreated RRMS patients was higher in our study than in most RWDS (mean 68.1% vs. range RWDS 7.8–20 %) (Prockl et al., 2020; Ellwardt et al., 2020; Pontieri et al., 2022; Buttmann, 2020; Sempere et al., 2020; Braune, 2020).

In line with the pivotal study and other RWDS, our study confirmed the efficacy of OCR in patients with RMS. The OPERA trials were mainly associated with a low rate of disability progression at 12 and 24 weeks of the follow-up. The percentage of patients who met NEDA-3 status was comparable to other RWDS (Fernandez-Diaz et al., 2021; Cellerino et al., 2021; Sempere et al., 2020), although few RWDS have reported using NEDA-3 status.

About three-quarters of RMS patients in the OPERA trial were treatment-naïve, and the most common previous therapies were interferon and glatiramer acetate (Hauser et al., 2017). In contrast, in our cohort and other observational studies (Fernandez-Diaz et al., 2021; Cellerino et al., 2021), most RMS patients were previously treated, with most patients receiving highly active DMTs, and disease activity was the reason for switching in about one quarter of patients.

The most frequent AEs in our study were infections, taking place in 86/235 (36.6 %) RMS patients (table 1). COVID-19 was the most common one, followed by urinary infections and other respiratory infections (table 1). All of our patients recovered from the infections, thirty RMS

Table 1
Characteristics of RMS patients under OCR.

Patients characteristics	RMS (n = 235)
Age years, mean (95 %CI), n	40.6 (38.8–41.9), 235
Female sex, n (%)	157/235 (66.8)
Time since diagnosis, years, mean (95 %CI), n	9.3 (8.40–10.2), 235
EDSS at the beginning of OCR-therapy median (±IQR), n	2.0 (±1.5), 235
Duration of the OCR-therapy, years, mean (95 %CI), n	2.9 (2.8–3.1), 235
DMT	
No previous DMT, n (%)	75/235 (31.9)
Previously treated with any DMT, n (%)	160/235 (68.1)
mild/ moderate therapies, n (%)	65/235 (27.7)
Interferon beta-1b, n (%)	5/65 (7.7)
Interferon beta-1a, n (%)	8/65 (12.3)
Glatirameracetat, n (%)	12/65 (18.4)
Teriflunomid, n (%)	7/65 (10.7)
Dimethyl Fumarate, n (%)	33/65 (50.7)
(highly-) active therapies, n (%)	95/235 (40.4)
Fingolimod, n (%)	49/95 (51.7)
Natalizumab, n (%)	35/95 (36.8)
Rituximab, n (%)	7/95 (7.3)
Other*, n (%)	4/95 (4.2)
Reason for stopping the previous immunotherapy	
JCV AI positivity in natalizumab treated patients, n (%)	22/160 (13.7)
AEs, n (%)	61/160 (38.1)
Disease activity, n (%)	70/160 (43.8)
Pregnancy, n (%)	5/160 (3.1)
Unknown, n (%)	2/160 (1.3)
Disease activity 12 months before OCR start in all patients	
EDSS	
EDSS, median (±IQR), n	2.0 (±2.0), 235
Relapse	
Patient with relapse, n (%)	113/235 (48.1)
Radiological activity	
Patients with MRI activity, n (%)	97/213 (45.5)
New cerebral T1 GELs and/or new cerebral T2 lesions, n (%)	85/97 (87.6)
New spinal T1 GELs and/or new spinal T2 lesions, n (%)	12/97 (12.4)
Disease activity 12 months before OCR start in naïve patients	
EDSS	
EDSS, median (±IQR), n	2.0 (±1.5), 75
Relapse	
Patient with relapse, n (%)	47/75 (62.7)
Radiological activity	
Patients with MRI activity, n (%)	41/65 (63.1)
New cerebral T1 GELs and/or new cerebral T2 lesions, n (%)	40/41 (97.6)
New spinal T1 GELs and/or new spinal T2 lesions, n (%)	1/41 (2.4)
Disease activity 12 months before OCR start in patients receiving any previous immunotherapy	
EDSS	
EDSS, median (±IQR), n	2.0 (±1.6), 160
Relapse	
Patient with relapse, n (%)	66/160 (41.3)
Radiological activity	
Patients with MRI activity, n (%)	56/148 (37.8)
New cerebral T1 GELs and/or new cerebral T2 lesions, n (%)	46/56 (82.1)
New spinal T1 GELs and/or new spinal T2 lesions, n (%)	10/56 (17.9)
Disease activity during OCR treatment	
NEDA-3 at 12 months	
NEDA-3, n (%)	152/190 (80.0)
EDA, n (%)	38/190 (20.0)
Only radiological activity, n (%)	19/38 (50.0)
Only relapse, n (%)	4/38 (10.5)
Only EDSS progression*, n (%)	11/38 (28.9)

(*continued on next page*)

Table 1 (*continued*)

Disease activity during OCR treatment	
NEDA-3 at 12 months	
Radiological activity & relapse, n (%)	0/38 (0.0)
Radiological activity & EDSS progression**, n (%)	2/38 (5.3)
Relapse & EDSS progression**, n (%)	1/38 (2.6)
All three criteria (radiological activity, relapse & EDSS progression), n (%)	1/38 (2.6)
NEDA-3 at 24 months	
NEDA-3, n (%)	88/104 (84.6)
EDA, n (%)	16/104 (15.4)
Only radiological activity, n (%)	3/16 (18.8)
Only relapse, n (%)	1/16 (6.3)
Only EDSS progression**, n (%)	9/16 (56.3)
Radiological activity & relapse, n (%)	3/16 (18.8)
Radiological activity & EDSS progression**, n (%)	0/16 (0.0)
Relapse & EDSS progression**, n (%)	0/16 (0.0)
All three criteria (radiological activity, relapse and EDSS progression), n (%)	0/16 (0.0)
Safety	
Infections, n (%)	86/235 (36.6)
Urinary tract infections, n (%)	10/78 (12.8)
Respiratory tract infections, n (%)	9/78 (11.5)
Gastrointestinal tract infections, n (%)	1/78 /1.3)
COVID-19 without hospitalization, n (%)	51/78 (65.4)
COVID-19 with hospitalization, n (%)	9/78 (11.5)
Other infections, n (%)	6/78 (7.7)
Treatment of any infections with antibiotics or Sotrovimab, n (%)	30/235 (13.2)
Severe infections (infection with hospitalization and/or treatment, n (%)	31/235 (13.2)
Increased transaminases***, n (%)	4/235 (1.7)
Lymphopenia**** CTCAE grade II, n (%)	2/235 (0.4)
Agranulocytosis*****, n (%)	2/235 (0.8)
Hypogammaglobulinemia******, n (%)	36/208 (17.3)
Cytokine release syndrome during OCR infusion (CTCAE Grad III, n (%)	1/235 (0.4)
Lymphocyte (G/l) value during OCR, mean (95Cl%), n	1.9 (1.7–2.6), 228
IgG value (g/l) during OCR, mean (95Cl%), n	8.2 (7.8–8.5), 208
IgG decrease compared to baseline, n (%)	161/184 (87.5)
Annualized IgG change (g/l), mean (95Cl%), n	−0.40 (0.47-(−0.34), 189
Annualized IgG change (g/l) in patients ≤ 55 years, mean (95Cl%), n	−0.35 (−0.41- (−0.28)), 156
Annualized IgG change (g/l) in patients > 55 years, mean (95Cl%), n	−0.65 (−0.84- (−0.36)),32
Severe infections in patients with IgG < 6 g/l, n (%)	17/36 (42.7)
Severe infections in patients with IgG > 6 g/l, n (%)	13/172 (7.6)
Pregnancy during OCR therapy, n (%)	6/234 (2.6)
Time between last OCR infusion and positive pregnancy test, months, mean (95 %CI), n	4.7 (1.6–7.8), 6
Pregnancy/Delivery complication, n (%)	0/6 (0.0)

Abbreviations: AE: adverse events; cMRI: cerebral Magnetic Resonance Tomography; CTCAE: Common Terminology Criteria for Adverse Events; DMT: Disease-modifying therapy; EDA: evidence of disease activity; EDSS: The Expanded Disability Status Scale; GELs: Gadolinium-enhanced Lesions; IQR: Interquartile range; JCV AI: John Cunningham Virus Antibody Index; n: number of observations; NEDA-3: no evidence of disease activity-3; OCR: Ocrelizumab; RMS: relapsing MS; 95 %CI: 95 % Confidence interval.

Other*: mitoxantrone, daclizumab.

EDSS progression**: elevation of the EDSS Score of 1 point from the baseline EDSS was 0 to 5.5 and 0.5 points if the baseline EDSS score was 6.0 or more compared to the last clinical assessment.

Increased transaminases***: Aspartate transaminase > 35 U/l and/or Alanine transaminase > 45 U/l.

Lymphopenia****: CTCAE Grade 0/ normal: ≧1/G/l, Grade I: 0.80–0.99 G/l, Grade II: 0.50 – 0.79 G/l, Grade III: 0.20–0.49 G/l, Grade IV: <0.20 G/l.

Agranulocytosis*****: Neutrophils < 500 cells per microliter (μl) corresponding to CTCAE Grade IV.

Hypogammaglobulinemia******: IgG serum level < 6.0 g/l with or without infection (Infections CTCAE: CTCAE grade 2 requiring oral antibiotic intervention; CTCAE grade 3 and grade 4 requiring hospitalization, and/or intravenous antibiotics).

patients (12.8 %) received antibiotic therapy. Regarding different real-world data and RCTs, the same predominance of urinary and respiratory infections was observed (Fernandez-Diaz et al., 2021; Ellwardt et al., 2020; Pontieri et al., 2022; Buttmann, 2020; Sempere et al., 2020; al., S.K.e. 2019).

Decreasing serum immunoglobulin levels with an elevated risk for infections due to therapeutic CD 20 B-cell depletion were demonstrated previously for OCR (Hauser et al., 2021) and rituximab (Barmettler et al., 2018) but not for ofatumumab (Hauser et al., 2022). In our study, we also detected hypogammaglobulinemia (defined by IgG < 6.0 g/l, 36/208 (17.3 %)) and severe infections (with hospitalization and/or treatment) were more frequent in the patients with IgG < 6.0 g/l compared to those with IgG serum levels ≥ 6.0 g/l.

Within the OPERA studies, an IgG decrease during OCR treatment was noticed (Hauser et al., 2021). The annualized IgG decrease in our cohort was slightly higher than the one identified in the RCTs (−0.40 g/L vs −0.32 g/L), which could be explained by differences in age as well as pretreatment (Table 2). (Gelfand et al., 2017). Especially immunosenescence in the elderly should be investigated in the future, because focusing on those patients with an age > 55 years, not included in the pivotal trials, an even 1.5-fold increased decreased annualized IgG serum concentration was present (−0.65 g/L (95 %CI −0.84-(−0.46)), range −1.9–0.17 $n = 32$)). Pharmacovigilance strategies focusing on infections as well as IgG serum concentration are especially important as we have demonstrated clinical relevance of this laboratory finding predisposing for infectious adverse events in our cohort.

However, the effect of hypogammaglobulinemia might not be limited to that. A recent retrospective study by our group showed a possible association between hypogammaglobulinemia and fatigue (Diem et al., 2022). In this regard, an ongoing prospective observational

Table 2
Comparison of baseline characteristics of Diem et al. and the OPERA I. trial (Hauser et al., 2017).

Baseline characteristics	Diem et al. (n = 235)	OPERA OCR arm (n = 410)	OPERA Interferon arm (n = 411)
Age (years), mean, SD	40.4 (12.1)	37.1 (9.3)	36.9 (9.3)
Female, n (%)	157 (67)	270 (66)	272 (66)
Duration of the disease, y, mean, SD	9.3 ± 9.0	3.8 ± 4.8	3.7 ± 4.6
EDSS before OCR, median, SD	2.3 ± 1.6	2.9 ± 1.2	2.8 ± 1.3
Naïve, n (%)	75 (32)	301 (74)	292 (71)
Previously treated patients, n (%)	160 (68)	107 (26)	117 (29)

Abbreviations: EDSS: Expanded Disability Status Scale; OCR: Ocrelizumab; RMS: relapsing MS; n: number of observations; SD: standard deviation; y: years.

Table 3
Comparison disease activity before and 12/24 months after OCR start in RMS patients.

	Before start OCR-therapy	12 months after OCR-therapy start	p-value
Median EDSS (±IQR), n	2.0 (±2.0), 190	2.0 (±2.0), 190	0.043
Patients with relapse, n (%)	60/190 (31.6)	5/190 (2.6)	**<0.001**
Mean ARR, (95Cl%), n	0.4 (0.3–0.4), 190	0.03 (0.003–0.05), 190	**<0.001**
Radiological activity, n (%)	88/190 (46.3)	22/190 (11.6)	**<0.001**
	Before start OCR-therapy	24 months after OCR-therapy start	p-value
Median EDSS (±IQR), n	2.0 (±2.0), 104	2.5 (±1.5), 104	**0.003**
Patients with relapse, n (%)	42/104 (40.4)	4/104 (3.8)	**<0.001**
Mean ARR, (95Cl%), n	0.2 (0.2–0.4), 104	0.04 (0.001–0.08), 104	**<0.001**
Radiological activity, n (%)	38/104 (36.5)	5/104 (4.8)	**<0.001**

Abbreviations: ARR: Annualized relapse rate; EDSS: Expanded Disability Status Scale; IQR: Interquartile range; OCR: Ocrelizumab; 95 %CI: 95 % Confidence interval.
Statistics: Quantitative variables are described using the mean and 95 % confidence interval (95 %CI) and compared with Wilcoxon Test. Qualitative variables are presented as absolute and relative frequencies and were compared with McNemar-Test. Adjustment for multiple testing was performed by Bonferroni procedure in regard to each domain independently: p-value= 0.0125.

trial (NCT05357781) to investigate whether or not the association between IgG serum level and fatigue is mediated via infections irrespectively of MS immunotherapy is on the way.

When interpreting our data, the limitations of a retrospective study with heterogeneous and different follow-up times resulting from different time points of treatment switch must be considered. Here especially the heterogeneity of real world data in comparison to homogenous data from randomized controlled trials has to be taken into account.

Concluding our study confirms the efficacy and safety profile of OCR and highlights the need for monitoring and pharmacovigilance strategies to tailor a safe treatment with OCR to the individual risk profile of each MS patient.

CRediT authorship contribution statement

L Diem: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **A Ovchinnikov:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **C Friedli:** Writing – review & editing, Data curation. **H Hammer:** Writing – review & editing. **N Kamber:** Writing – review & editing. **A Chan:** Writing – review & editing. **A Salmen:** Writing – review & editing, Data curation. **O Findling:** Writing – review & editing, Data curation. **R Hoepner:** Writing – review & editing, Formal analysis, Data curation.

Declaration of competing interest

There are no conflicts of interest regarding this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.105570.

References

al., S.K.e., 2019. Utilization, safety, and Tolerability of ocrelizumab: Year 2 Data from the Providence Ocrelizumab Registry.
Barmettler, S., 2018. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. JAMa Netw. Open. 1 (7), e184169.
Braune, S., 2020. Real-world experience with ocrelizumab in the German neurotransdata registry. Mult. Scler. J.
Buttmann, M., 2020. Assessing the real-world effectiveness of ocrelizumab in patients with multiple sclerosis-confidence one-year interim analysis [abstract]. Mult. Scler. J.
Cellerino, M., 2021. Predictors of Ocrelizumab Effectiveness in Patients with Multiple Sclerosis. Neurotherapeutics. 18 (4), 2579–2588.
Coban, H., 2021. Real-world experience of ocrelizumab initiation in a diverse multiple sclerosis population. Mult. Scler. Relat. Disord. 53, 103021.
Common Terminology Criteria for Adverse Events (CTCAE). Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.
Daniels, K., 2020. Real-World Results of Ocrelizumab Treatment for Primary Progressive Multiple Sclerosis. Mult. Scler. Int. 2020, 5463451.
Diem, L., 2022. Hypogammaglobulinemia: a contributing factor to multiple sclerosis fatigue? Mult. Scler. Relat. Disord. 68, 104148.
Ellwardt, E., 2020. *Ocrelizumab initiation in patients with MS:* a *multicenter observational study*. Neurol. Neuroimmunol. Neuroinflamm. 7 (4).
(EMA), 2018. Ocrelizumab. E.M.A.
Fernandez-Diaz, E., 2021. Real-world experience of ocrelizumab in multiple sclerosis in a Spanish population. Ann. Clin. Transl. Neurol. 8 (2), 385–394.
Gelfand, J.M., Cree, B.A.C., Hauser, S.L., 2017. Ocrelizumab and Other CD20(+) B-Cell-Depleting Therapies in Multiple Sclerosis. Neurotherapeutics. 14 (4), 835–841.
Hauser, S.L., 2017. *Ocrelizumab* versus *Interferon Beta-1a in Relapsing Multiple Sclerosis*. N. Engl. J. Med. 376 (3), 221–234.
Hauser, S.L., 2020. Five years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. Neurology. 95 (13), e1854–e1867.
Hauser, S.L., 2021. Safety of ocrelizumab in patients with relapsing and primary progressive multiple sclerosis. Neurology. 97 (16), e1546–e1559.
Hauser, S.L., 2022. Safety experience with continued exposure to ofatumumab in patients with relapsing forms of multiple sclerosis for up to 3.5 years. Mult. Scler. 28 (10), 1576–1590.
Kalincik, T., 2015. Defining reliable disability outcomes in multiple sclerosis. Brain 138 (Pt 11), 3287–3298.
Montalban, X., 2017. *Ocrelizumab* versus *Placebo in Primary Progressive Multiple Sclerosis*. N. Engl. J. Med. 376 (3), 209–220.
MSD Manual: Normal Laboratory Values. Available from: https://www.msdmanuals.com/professional/resources/normal-laboratory-values/normal-laboratory-values.
Ovchinnikov, A., Findling, O., 2022. An overview of pivotal trials and real-world evidence for CD20-depleting therapy in multiple sclerosis: immunotherapy with rituximab, ocrelizumab, and ofatumumab. Wien. Med. Wochenschr. 172 (15–16), 359–364.
Pandit, L., 2019. No evidence of disease activity (NEDA) in multiple sclerosis - shifting the goal posts. Ann. Indian Acad. Neurol. 22 (3), 261–263.
Pharmacology, A.C.o.C., 2017. FDA Approves OCREVUS (Ocrelizumab) for Treatment of Adult Patients with Relapsing or Primary Progressive Forms of Multiple Sclerosis. https://accp1.org/Members/ACCP1/5Publications__News/FDA_Approves_OCREVUS_Ocrelizumab_.aspx.
Pontieri, L., 2022. Ocrelizumab treatment in multiple sclerosis: a Danish population-based cohort study. Eur. J. Neurol. 29 (2), 496–504.
Prockl, V., 2020. Real world application of ocrelizumab in multiple sclerosis: single-center experience of 128 patients. J. Neurol. Sci. 415, 116973.

Sempere, A.P., 2020. Ocrelizumab in Multiple Sclerosis: a Real-World Study From Spain. Front. Neurol. 11, 592304.
Swissmedic, 2018. In: AG, R.P.S. (Ed.), OCREVUS® (Ocrelizumab) Konzentrat zur Herstellung einer Infusionslösung, 300mg/10Ml Zul.-Nr. 66185. Editor.
Thompson, A.J., 2018a. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.
Thompson, A.J., 2018b. Multiple sclerosis. Lancet 391 (10130), 1622–1636.
Wolach, O., Bairey, O., Lahav, M., 2010. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. Medicine (Baltimore) 89 (5), 308–318.