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# Real-world experience of ocrelizumab in patients with multiple sclerosis: A single-center study

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### *Abstract*

*Objective:* We aimed in this study to obtain real-world data in MS patients treated with ocrelizumab at our center and examine the drug's efficacy, safety, and side effects. *Methods:* We conducted a retrospective study and included MS patients receiving at least one infusion therapy of ocrelizumab at our center. Demographic information, clinical and radiological course of the patients, whether they were infected with the COVID-19 virus, vaccination status, and drug-related safety data were collected and analyzed. *Results:* Two hundred and forty patients meeting the inclusion criteria were included. Before ocrelizumab treatment, the mean annualized relapse rate (ARR) was 0.816 (CI:0.66-0.99) in the RRMS group fell to 0.10 (CI: 0.06- 0.16) after the ocrelizumab initiation($p<0.001$). Similarly, ARR fell from 0.44 (CI:0.28-0.67) to 0.04 (CI:0.001-0.13) in the SPMS group after treatment initiation ($p<0.001$). The most common reason for the treatment change with ocrelizumab was increased disease activity (n:101, measured either clinically, radiological, or both ), disease progression (n:60), or the adverse effects (n: 23 ) of previous DMT. Infection was seen in 80 of 240 patients. The most frequent condition was COVID-19 infection (n=45) related to a pandemic, followed by urinary tract infection (n=18) and upper respiratory tract infection (n=14). While the cancer screening results of 1 patient were within normal limits at the beginning, breast cancer was detected six months after starting ocrelizumab. *Conclusions:* Our real-world data with ocrelizumab have shown that it is an effective and well-tolerated disease-modifying therapy supporting the results of pivotal studies.

*Keywords:* Ocrelizumab, real-world experience, multiple sclerosis

## INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated central nervous system disease involving inflammation, demyelination, and axonal damage. The most common form of MS, relapsing-remitting MS (RRMS), is marked by attacks (relapses) and periods of partial or complete recovery (remissions). In contrast, primary progressive MS (PPMS) is a less common form that progresses from the onset of the disease.[1] With the development of disease-modifying therapies, the course and management of MS have altered. Today, there are many agents approved for use by the EMA and FDA to treat MS.[2]

Disease-modifying therapies (DMTs) used in the treatment of MS act through suppression or modulation of immune and inflammatory responses.[3] Ocrelizumab is a humanized monoclonal antibody effective against CD20-positive B cells, approved by the FDA in 2017 to treat RRMS and PPMS. Ocrelizumab is a chimeric monoclonal antibody developed against the B-cell surface marker CD20 protein that binds to an epitope that overlaps with rituximab.[4] OPERA I and II studies have shown that ocrelizumab significantly reduces annualized relapse rates in RRMS patients compared to Interferon Ia.[5] The ORATORIO study in PPMS patients also demonstrated that ocrelizumab was superior to placebo in the progression of disability.[6] Despite these clinical studies, real-world data on ocrelizumab are limited. In this study, we aimed to evaluate the patient profiles of our clinic, drug

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efficacy during the treatment process, and side effects, if any.

## METHODS

We conducted a retrospective study at Uludag University Faculty of Medicine, Department of Neurology, MS Center. The study was approved by the local ethics committee of the university. We obtained medical record data of patients who received at least one infusion of ocrelizumab between July 2018 and February 2022 and were followed for one year before and after treatment. All participants on ocrelizumab treatment were aged 18–55 years, previously evaluated by an experienced specialist in MS and diagnosed with RRMS, active secondary progressive MS (aSPMS), and PPMS according to the 2017 McDonald criteria and included in the study.[7]

Before starting ocrelizumab therapy, patients were screened for hepatitis B virus, varicella-zoster virus, and other infections. The patients not immune to hepatitis B and VZV were included in the vaccination program. Before ocrelizumab treatment, patients were premedicated with intravenous methylprednisolone (100 mg), antihistamine, and paracetamol, and then ocrelizumab was administered according to the recommended protocol. The patients were followed up in the hospital during the administration of ocrelizumab and until 1 hour after its end. All adverse events occurring during ocrelizumab infusion and within the first 24 hours were recorded and classified as mild, moderate, severe, or life-threatening according to Common. Terminology Criteria for Adverse Events (CTCAE).[8] After starting ocrelizumab treatment, the patients were called for a visit every three months and evaluated for clinical and radiological (if any new symptoms or clinical signs are present), disease progression, EDSS, and possible side effects. We obtained the demographic, clinical, and radiological characteristics of the patients from the medical records. (Demographics: gender, age at diagnosis, age of disease. Clinical: ocrelizumab infusion number, last DMT used before ocrelizumab and reason for discontinuation of the treatment, EDSS scores before and after ocrelizumab treatment, the annualized number of relapses before and after ocrelizumab treatment. Radiological: number of gadolinium-enhancing lesions (GELs) or new/enlarged T2 lesions on the first MRI scan before ocrelizumab initiation (up to 3 months ago) and every year thereafter).

Clinical relapse was defined as new or recurrent symptoms and typical objective signs of MS with a duration of at least 24 h, in the absence of fever or infections.[7]

Patients underwent brain and spinal cord MRI with gadolinium before ocrelizumab initiation and after 12 months of the treatment initiation and every year following that. The presence of T1 gadolinium-enhancing lesions (GELs) or new/enlarged T2 lesions was defined as MRI activity.

Disability progression was defined as an EDSS score increase of $\geq 1$ point in patients with a baseline EDSS score of $\leq 5$ or an increase of $\geq 0.5$ points in an EDSS score in patients with a baseline EDSS score of >5.5 and assessed in patients with a follow-up period longer than one year.[9] No evidence of disease activity (NEDA) is a composite measure of the absence of confirmed EDSS, and of clinical as well as radiological disease activity, in relapsing multiple sclerosis (RMS).[10]

### *Statistics*

The data was examined by the Shapiro-Wilk test whether or not it presented a normal distribution. The results were presented as mean±standard deviation, median with interquartile range (IQR), or frequency and percentage. Normally distributed data were compared with independent samples t-test or one-way ANOVA. Kruskal Wallis and Mann Whitney U tests were used for nonnormally distributed data. The Bonferroni test was used as a multiple comparison test. Categorical variables were compared using Pearson's chi-square test and Fisher's exact test between groups. The annualized relapse rate (ARR) was calculated as the number of relapses divided by the total patient-years of exposure to ocrelizumab. Kaplan-Meier survival analysis was used to estimate the median follow-up time with progression on ocrelizumab using. The statistical significance level was considered as $p<0.05$. Statistical analyses were performed with IBM SPSS ver.23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

## RESULTS

The study included two hundred and forty patients (141 RRMS, 51 SPMS, and 48 PPMS) meeting the inclusion criteria. The demographic and clinical characteristics of the patients and their comparison with the primary research of ocrelizumab are summarized in Table 1. Of the patients, 165 were female, and 75 were male. The mean age at ocrelizumab initiation was 44.34 years for the

**Table 1: Comparison of baseline characteristics of our patients' group with OPERA 1-2 and ORATORIO studies**

| | Full cohort (n=240) | PPMS (n=48) | RRMS (n=141) | aSPMS (n=51) | OPERA-I[1] (n=410) | OPERA-II[1] (n=417) | ORATORIO (n=488) | RRMS vs OPERA-I | RRMS vs OPERA-II | PPMS vs ORATORIO |
|---|---|---|---|---|---|---|---|---|---|---|
| **Sex (Female), n (%)** | 165(68.75) | 26 (54.17) | 98 (69.5) | 41 (80.39) | 270 (65.9) | 271 (65.0) | 237 (48.6) | 0.427 | 0.327 | 0.459 |
| **Age (years), mean ± SD** | 45.31 ±10.53 | 45 ± 11.31 | 44.34 ± 10.49 | 48.29 ± 9.51 | 37.1 ± 9.3 | 37.2 ± 9.1 | 44.7 ± 7.9 | <0.001 | <0.001 | 0.810 |
| **MS duration, mean ± SD** | 10.02 ± 5.02 | 8.98 ± 5.25 | 8.82 ± 3.72 | 14.31 ± 5.68 | 6.74 ± 6.37 | 6.72 ± 6.10 | 2.9 ± 3.2 | <0.001 | <0.001 | <0.001 |
| **Previous DMT, n/total (%)** | 221/240 (92.08) | 31/48 (64.58) | 139/141 (98.58) | 51/51 (100) | 107/408 (26.2) | 113/417 (27.1) | 55/488 (11.3) | <0.001 | <0.001 | <0.001 |
| İnterferon B | 43 (17.92) | 8 (16.66) | 25 (17.73) | 10 (19.6) | 81/408 (19.8) | 80/417 (19.2) | - | 0.599 | 0.703 | - |
| GA | 27 (11.25) | 3 (6.25) | 19 (13.48) | 5 (9.8) | 38/408 (9.3) | 39/417 (9.4) | - | 0.163 | 0.166 | - |
| Teriflumomide | 22 (9.16) | 5 (10.42) | 11 (7.8) | 6 (11.76) | - | - | - | - | - | - |
| DMF | 8 (3.33) | 0 (0) | 8 (5.67) | 0 (0) | 1/408 (0.2) | - | - | <0.001 | - | - |
| Fingolimod | 70 (29.17) | 4 (8.33) | 48 (34.04) | 18 (35.29) | 1/408 (0.2) | 4/417 (1.0) | - | <0.001 | <0.001 | - |
| Mitoxantrone | 17 (7.08) | 10 (20.83) | 3 (2.13) | 4 (7.84) | - | - | - | - | - | - |
| Natalizumab | 8 (3.33) | 0 (0) | 6 (4.26) | 2 (3.92) | - | 1/417 (0.2) | - | - | 0.001 | - |
| Rituximab | 26 (10.83) | 1 (2.08) | 19 (13.48) | 6 (11.76) | - | - | - | - | - | - |
| Naive, n/total (%) | 19/240 (7.91) | 17/48 (35.42) | 2/141 (1.42) | 0 (0) | 301/408 | 304/417 | 433/488 | <0.001 | <0.001 | - |
| **Reason for treatment change** | | | | | | | | | | |
| Disease activity, n/total (%) | 101/221(45.7) | 0/31 (0) | 88/139 (63.3) | 13/51(25.5) | NA | NA | - | - | - | - |
| Disease progression, n/total (%) | 60/221 (27.1) | 22/31 (71) | 11/139 (7.9) | 27/51(52.9) | NA | NA | - | - | - | - |
| Side effects, n/total (%) | 23/221 (10.4) | 6/31 (19.4) | 16/139 (11.5) | 1/51(2) | NA | NA | - | - | - | - |
| PML risk, n/total (%) | 8/221 (3.6) | 0/31 (0) | 6/139 (4.3) | 2/51(3.9) | NA | NA | - | - | - | - |
| Others, n/total (%) | 29/221 (13.1) | 3/31 9.7() | 18/139 (12.9) | 8/51(15.7) | NA | NA | - | - | - | - |
| **Baseline EDSS, mean ± SD Median (IQR)** | 3.63 ± 1.43 3.5 (1-7) | 4 ± 1.01 4 (2-6.5) | 2.96 ± 1.25 3 (1-6.5) | 5.12 ± 0.95 5.5 (3.5-7) | 2.86 ± 1.24 | 2.78 ± 1.30 | 4.7 ± 1.2 4.5 (2.5-7.0) | 0.410 | 0.152 | <0.001 |
| **Relaps in last year, mean (SD)** | 0.47 ± 0.60 | 0.04 ± 0.2 | 0.65 ± 0.62 | 0.39 ± 0.57 | 1.31 ±0.65 | 1.32 ± 0.69 | - | <0.001 | <0.001 | - |
| **Baseline Gd+/T2 lesions, n/total (%) mean ± SD** | 105/240(43.75) | 2/48 (4.17) | 92/141(65.24) | 11/51(21.56) | 172/405 | 161/413 | 133/448 | <0.001 | <0.001 | <0.001 |

[1]OPERA-I ve 2 data adapted from Hauser, SL et al, NEJM, 2017.
PML: progressive multifocal leukoencephalopathy

RRMS patients, 48.29 years for the SPMS, and 45 years for the PPMS. The mean disease duration was 8.82 years for RRMS patients, 14.31 years for SPMS, and 8.98 years for PPMS.

Two hundred and twenty one patients were using DMT before and the DMT distributions they used were as follows; Fingolimod (n:70), beta-interferon (n:43), glatiramer acetate (n:27), rituximab (n:26), teriflunomide (n:22), mitoxantrone (n:17), dimethyl fumarate (n: 8), and natalizumab (n:8). The most common reason for the treatment change with ocrelizumab was increased disease activity (n:101, measured either clinically, radiological, or both) or disease progression (n:60). Twenty-three patients switched to ocrelizumab due to adverse effects of previous DMT (such as lymphopenia, prolonged flu-like syndrome, gastrointestinal side effects, and elevated liver enzymes). Treatment switches were made due to the increase in the JCV index over time in 8 patients who received natalizumab). Nineteen of the patients (19/240, 7.91%) had never undergone treatment before ocrelizumab (treatment-naive). When the patients were compared in terms of EDSS scores before the start of ocrelizumab treatment; Scores were higher in the SPMS group (median: 5.5, IQR: 3.5-7) compared to the RRMS (median: 3, IQR:1-6.5) and PPMS (median: 4, IQR: 2-6.5) groups. In the one year before ocrelizumab treatment initiation, the mean relapse rate of the whole cohort was 0.47 ± 0.60. Radiologically, one hundred five of the patients (43.75%) had gadolinium-enhancing lesions and/or new T2 lesions on MRI performed before starting ocrelizumab therapy.

The median follow-up was 13 months (range from 4 to 37) for RRMS patients, 14 months (range from 4 to 42) for SPMS patients, and 9 months (range from 4 to 41) for PPMS patients. The median number of infusions with ocrelizumab was 3 (range from 1 to 7), 3 (range from 1 to 8), and 2 (range from 1 to 7) for the RRMS, SPMS, and PPMS patients, respectively. After starting ocrelizumab treatment, 10 RRMS patients and 2 SMPS patients had a relapse. Relapses were evaluated by a neurologist and were considered as symptoms lasting longer than 24 hours in the absence of fever or infection. Before ocrelizumab treatment, the mean annualized relapse rate (ARR) was 0.816 (CI:0.66-0.99) in the RRMS group fell to 0.10 (CI: 0.06-0.16) after the ocrelizumab initiation ($p<0.001$). Similarly, ARR fell from 0.44 (CI:0.28-0.67) to 0.04 (CI:0.001-0.13) in the SPMS group after treatment initiation ($p<0.001$). After starting ocrelizumab treatment, 13 (5.4%) of all patients had radiological activation at 12 months on MRI, and all of these patients were in the RRMS group.

In our study, the evaluation of patients in terms of progression and NEDA-3 was performed only in patients who were followed up for at least 1 year after the start of ocrelizumab treatment. According to this; Of 145 patients followed for at least one year, 25 (17.2%) had disability progression (34.8%, n= 8/23 in the PPMS group, 13.3%, n= 12/90 in the RRMS group, and 15.6%, n= 5/32) in the SPMS group). The most disability progression was observed in the PPMS group (Figure 1a, 1b, 1c). Disability progression was not associated with gender, higher baseline EDSS, MS phenotype, or baseline radiologically activation. Finally, NEDA status was achieved in 86.4% of the RRMS patients and 80.4% of the SPMS patients who were follow-ups more than 12 months (Table 2).

*Adverse events*

Despite premedication with steroids, antihistamines, and antipyretic drugs before ocrelizumab infusion, some patients had an infusion-related reaction (IRR, calculated as every 15.01/100 PY).

The IRR was controlled by a reduction of the infusion rate; 3 patients required additional premedication. The infusion-related reaction was mild to moderate. Serious, life-threatening IRR was not seen in any patient (Table 3).

In our study, infection was seen in 80 of 240 patients. Since the study period coincided with the pandemic period, the most common infection was Covid-19 (n:45) infection, followed by urinary tract (n=18), upper respiratory tract (n:14), herpes zoster virus (n:2), and acute hepatitis B virus infection (n:1). (table 3) While 34 of 45 patients with COVID-19 infection recovered from the infection at home, six patients were hospitalized, and three patients required ventilatory support. Both patients treated with ocrelizumab and infected with Covid-19 unfortunately died. The first patient was a 37-year-old male with a 7-year history of RRMS, EDSS score of 5.5, psychiatric comorbidity, and was unvaccinated against COVID-19. The second patient was a 62-year-old male with a 19-year history of SPMS, EDSS score of 6, no other comorbidities, and was also unvaccinated against COVID-19. Patients with COVID-19 infection (n:45) had been receiving ocrelizumab treatment for an average of 11 months at the time of infection.

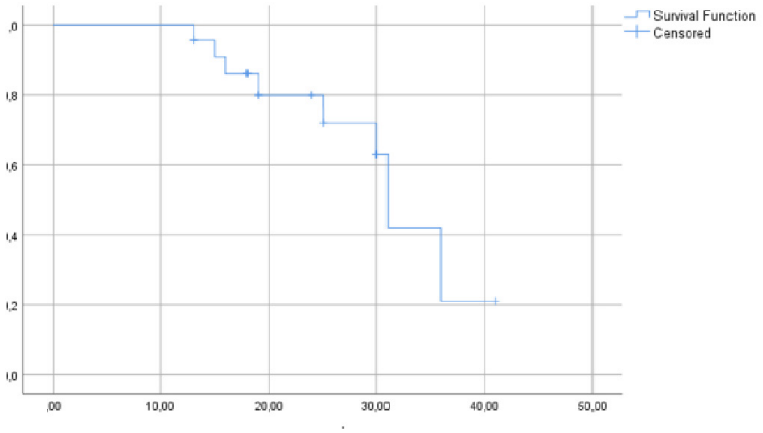


Fig. 1a: Time to CDP (months) in patients with PPMS

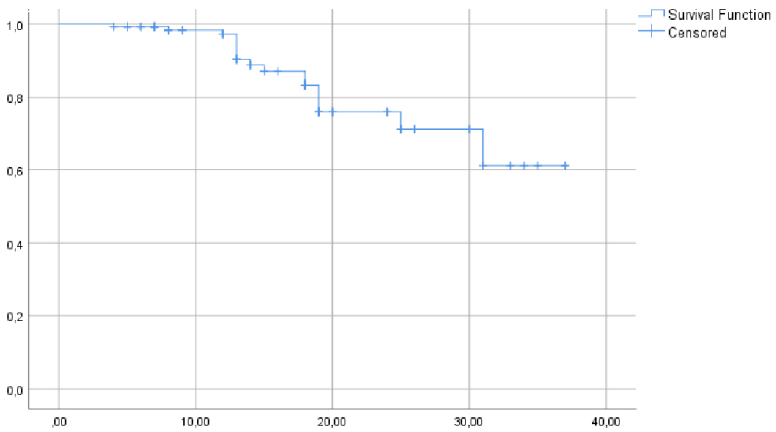


Fig. 1b: Time to CDP (months) in patients with RRMS

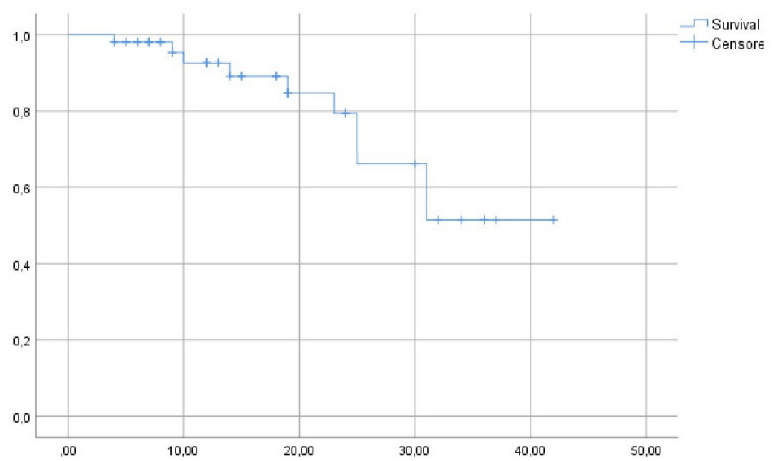


Fig. 1c: Time to CDP (months) in patients with SPMS

**Table 2: Clinical and radiological characteristics of the patients included in our study**

| | Full cohort (n:240) | PPMS (n=48) | RRMS (n=141) | aSPMS (n=51) |
|---|---|---|---|---|
| Follow-up (months), Mean (SD) | 14.90 ±8.77 | 15.73 ± 9.68 | 14.15 ± 7.55 | 17.16 ± 10.56 |
| Median (IQR) | 13 (4-42) | 9 (4-41) | 13 (4-37) | 14 (4-42) |
| Ocrelizuman infusion, Mean (SD) | 3.07±1.58 | 2.92 ± 1.78 | 3.01 ± 1.41 | 3.35 ± 1.83 |
| Median (IQR) | 3 (1-8) | 2 (1-7) | 3 (1-7) | 3 (1-8) |
| Relaps free, n/total (%) | | N/A | 131/141 (92.3) | 49/51 (96.08) |
| ARR post-OCR (95% CI) | 0.085 (0.05-0.13) | N/A | 0.10 (0.06-0.16) | 0.04 (0.001-0.13) |
| Post- treatment EDSS (12 months follow-up), Mean (SD) | 3.90 ± 1.48 | 4.31 ± 1.05 | 3.23 ± 1.33 | 5.36 ± 0.90 |
| Progression, n/total (%) | 25/145 (17.2) | 8/23 (34.8) | 12/90 (13.3) | 5/32 (15.6) |
| MRI activity, n/total (%) | 13 (5.4) | 0 (0) | 13/141 (9.22) | 0 (0) |
| NEDA-3, n/total (%) | 162/191 (84.8) | N/A | 121/140 (86.4) | 41/51 (80.4) |

As mentioned above, Herpes zoster virus infection developed in 2 patients, and hepatitis B virus infection developed in 1 patient. This patient was unvaccinated against HBV. Treatment with ocrelizumab was started due to the patient's refusal to be vaccinated against HBV, but acute HBV infection developed after the 4th cycle of treatment. Antiviral treatment was initiated in 14 out of 17 patients who were chronic Hepatitis B carriers prior to ocrelizumab treatment. As for the remaining 3 patients who declined antiviral treatment, they were clinically and laboratory-monitored for HBV reactivation. Breast cancer was detected in 1 of the patients in our study 6 months after starting ocrelizumab treatment, and the patient's breast cancer screening tests (breast USG and mammography) were normal before initiation of treatment.

The comorbidities of MS patients using ocrelizumab are summarized in Table 4. While no comorbidity was detected in 70% of the patients, 16.67% had cardiovascular (hypertension, type 2 diabetes, smoking), 9.17% had psychiatric, 7.08% had chronic hepatitis B virus carriers, and 3.75% had thyroid disease (Table 4).

**Table 3: Infection, infusion-related reaction, and other safety data observed in patients receiving ocrelizumab therapy**

| | Our Study (n=240) | OPERA I/II (n=825) | ORATORIO (n=488) |
|---|---|---|---|
| Total patient-years (PY) | 299 | 1448 | 1606 |
| Infections (rate per 100 PY) | 26.8 | 84.5 | 70.8 |
| Urinary tract infection, n/total, % | 18/240 (7.5) | 96/825 (11.6) | 195/488 (40.1) |
| Upper respiratory tract infection, n/total, % | 14/240 (5.8) | 125/825 (15.2) | 59/488 (12.1) |
| COVID-19, n/total, % | 45/240 (18.8) | - | - |
| Cellulitis, n/total, % | - | 17/825 (2.1) | - |
| Herpes zoster, n/total, % | 2/240 (0.8) | - | - |
| Gastroenteritis, n/total | - | - | - |
| Others, n/total, % | 1/240 (0.4) | - | - |
| Serious infections (rate per 100 PY) | - | 0.83 | 2.74 |
| Infusion-related reactions (rate per 100 PY) | 15.01 | 34.9 | 31.0 |
| Malignancies (rate per 100 PY) | 0.33 | 0.28 | 0.93 |
| Others (rate per 100 PY) | - | - | - |
| Deaths (rate per 100 PY) | 0.66 | 0.07 | 0.25 |

**Table 4: Comorbidities of patients treated with ocrelizumab**

| | PPMS (n=48) | | RRMS (n=141) | | aSPMS (n=51) | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| 0- no comorbidity | 31 | 64,58 | 104 | 73,76 | 33 | 64,71 | 168 | 70,00 |
| CVC | 9 | 18,75 | 20 | 14,18 | 11 | 21,57 | 40 | 16,67 |
| Mood disorder | 5 | 10,42 | 11 | 7,80 | 6 | 11,76 | 22 | 9,17 |
| Troid pathology | 1 | 2,08 | 5 | 3,55 | 3 | 5,88 | 9 | 3,75 |
| Chronic hepatitis B virus carriers | 4 | 8,33 | 10 | 7,09 | 3 | 5,88 | 17 | 7,08 |
| Others | 1 | 2,08 | 0 | 0,00 | 0 | 0,00 | 1 | 0,42 |

CVC: cardiovascular Comorbidities

## DISCUSSION

Although pivotal studies provide information about the drug's effectiveness, they may present some differences according to data obtained from real-world experiences. For instance, while most of the patients included in the OPERA I and II studies were treatment-naive patients, most of the patients included in our study consisted of patients who had used at least 1 DMT before. Also, the RRMS patients included in our cohort were older and had a longer disease duration than the pivotal study. This may be due to the requirement in our country that patients must have used one of the first-line treatments for at least one year before starting ocrelizumab treatment, potentially delaying the initiation of ocrelizumab therapy in RRMS patients. Despite these differences, the EDSS scores of the patients in our study and OPERA I/II were similar. In addition, NEDA was achieved in 86% of patients with RRMS and 80.4% of patients with SPMS at year 1. In our study, while 99 (44.79%) of 221 patients who switched to ocrelizumab were treated with first-line therapy (Interferon Beta, glatiramer acetate, teriflunomide, and DMF), 122 patients (55.2%) were treated with more potent therapies, such as fingolimod, natalizumab, rituximab, or mitoxantrone. In several other studies, patients received highly effective treatments before switching to ocrelizumab.[11,12] Despite this, ocrelizumab has similarly demonstrated its therapeutic efficacy not only after switching from primary care to ocrelizumab but also after highly effective treatments. We switched rituximab to ocrelizumab because the health authorities did not pay for the rituximab treatment in patients with RRMS in our country.

Compared to the OPERA study, our study had lower relapse rates one year before starting ocrelizumab (mean ± SD, 1.3 ± 0.6 vs. 0.7 ± 0.6)[5], which may be related to the older patient age (44.3 vs. 37.1), and longer disease duration (8.8 vs. 6.7). In addition, most patients used DMT before ocrelizumab treatment (98.5% vs. 26.2%) in our cohort. Detection of a lower relapse rate before ocrelizumab treatment than pivotal studies may suggest that the inflammatory process is more limited in patients due to the cohort characteristics listed above.

The disability progression rate in our PPMS patient group was higher than in the ORATORIO study (34.8% vs. 32.9%).[6] This can be explained by the quarantine measures applied during the COVID-19 infection making patients less physically active and also both effects of COVID-19 and quarantine on the mental health of patients. The safety and clinical efficacy data obtained from our study were consistent with both pivotal phase 3 trials and previously presented real-world data.[5,6,12,13] COVID-19 infection was the most common 18.8%) seen in our study, unlike the studies mentioned above. This may be related to the coinciding period of the study with the Covid-19 pandemic. Other infections (Upper respiratory tract and urinary tract infections) were observed at a lower rate compared to the pivotal studies. Similarly, no severe, life-threatening conditions related to opportunistic infections were encountered in our research. However, two patients developed respiratory failure and eventually succumbed to COVID-19 infection.

Because real-world trials include patients' comorbidities, complications related to these comorbidities, and drugs used, we may encounter different results from pivotal trials. In our study, the most common comorbidities were cardiovascular comorbidities, including HT, DM, and smoking. Mood disorders followed this. These findings aligned with the few real-world data available before.[5,12,13]

Anti-CD20 antibody therapy poses a risk of HBV reactivation in susceptible patients, but HBV antiviral prophylaxis has been shown

to prevent this in up to 98% of cases. Before initiating anti-CD20 antibody therapy, it's crucial to conduct HBV serology tests. ASCO recommends screening for HBsAg and HBcAb, with HBV antiviral prophylaxis initiation for HBsAg-positive patients, and either prophylaxis or regular monitoring for HBcAb-positive patients. HBV may cause liver cell damage for up to 12 months post-anti-CD-20 treatment, necessitating continued antiviral prophylaxis during this period[14]. In our study, contrary to other real-world data, chronic hepatitis B virus carrier status was notable among comorbidities, possibly due to our comprehensive serological testing, which included assessments for HBs antigen and anti-HBs, as well as anti-HBc total, HBe antigen, and anti-HBe serology. In this study, the incidence of side effects was higher in PPMS patients with comorbidities than in the RRMS group (p=0.008); that may be because the disability before treatment detected in these patients was higher than in the RRMS group. Comorbidities are often associated with faster worsening of existing disease and progression of disability. However, in our study, most RRMS and SPMS group patients achieved NEDA (for RRMS: 86.4%, and 80.4% SPMS).

In both the ocrelizumab pivotal studies and real-world data, IRRs were the most common adverse events. Prophylaxis with analgesics, antipyretics, and antihistamines was optional in the ORATORIO and OPERA studies. In our protocol, all of these drugs were routinely given to patients before the ocrelizumab infusion. In addition, in the routine protocol, the infusion rate starts from 40 ml/hour and is increased by 40 ml every 30 minutes, not exceeding 200 ml, and is completed in 3.5 hours. In our practice, the infusion rate is increased every 40 minutes, especially during the first two infusions (not in 30 minutes). We observed fewer IRRs in our study cohort (15%) compared to pivotal studies (OPERA: 34.3%, ORATORIO: 39.9%) and other real-world data.[6,15] The reason for this may be the administration of premedication in each patient and the slow infusion rate.

After the initiation of ocrelizumab treatment, a significant decrease was observed in the ARRs of both patients with RRMS (0.8 to 0.1) and SPMS (0.4 to 0.04). These findings were similar to OPERA and other real-world data.[5,13,16]

The limitations of our study are that it was a retrospective study and the short follow-up period. Moreover, the short follow-up period limited us to performing subgroup analysis in some treatment subgroups.

In conclusion, our real-world data with ocrelizumab therapy have shown that it is effective and well-tolerated, supporting the results of pivotal studies. Despite comorbidities, additional treatments, and previously used DMTs in patients in real-world studies, ocrelizumab-related reactions, development of side effects, and infections can be controlled with appropriate premedication protocols programmed clinical and laboratory follow-ups. In addition, thanks to the infusion rates that facilitate patient compliance with the drug, it may allow the control and minimization of possible treatment side effects.

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## DISCLOSURE

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