Two-year Assessment of the Efficacy and Safety of Ocrelizumab in Switching Patients from Other Disease Modifying Therapies

Terzi Murat[1]*, Boz Cavit[2], Demir Caner Feyzi[3], Cilingir Vedat[4], Helvaci Elif Merve[5]

[1]*Department of Neurology, Faculty of Medicine, Ondokuz Mayis University, Samsun, Turkey*

[2]*Department of Neurology, Faculty of Medicine, Karadeniz Teknik University, Trabzon, Turkey*

[3]*Department of Neurology, Faculty of Medicine, Firat University, Elazig, Turkey*

[4]*Department of Neurology, Faculty of Medicine, Van YuzuncuYil University, Van, Turkey*

[5]*Department of Neuroscience, Ondokuz Mayis University, Samsun, Turkey*

*Corresponding Author**

Terzi Murat,

Department of Neurology, Faculty of

Medicine, Ondokuz Mayis University, Samsun,

Turkey

E-mail: mterzi@omu.edu.tr

Received: 27-Nov-2022, Manuscript No: JMSO-22-81437; **Editor assigned:** 30-Nov-2022, PreQC No. JMSO-22-81437(PQ); **Reviewed:** 12-Dec-2022, QC No. JMSO-22-81437(Q); **Revised:** 14-Dec-2022, Manuscript No: JMSO-22-81437(R); **Published:** 19-Dec-2022, **DOI:** 10.35248/2376-0389.22.9.12.475

Abstract

Objective: To evaluate the efficacy and safety of OCR in a real-world setting.

Methods: Clinical data for patients aged ≥ 18 years with relapsing forms of MS or Primary Progressive MS (PPMS) were retrospectively collected from medical records. The main efficacy outcomes were several relapses and a proportion of patients free from relapses, disability progression, and brain MRI activity (gadolinium [gd+] enhanced and new t2 lesions).

Results: A total of 460 patients were included: 246 with relapsing-remitting MS (RRMS), 196 Progressive Relapsing MS (PRMS), and 18 PPMS. The patients were 58.6% females with a mean age of 46.8 years. Fingolimod was the most commonly used disease-modifying therapy (DMT; 35.2%), followed by interferon β 1a+1b+glatiramer acetate (23.9%), and teriflunomide (10.4%) before OCR. The mean Expanded Disability Status Scale (EDSS) was 4.91 in PPMS, 4.90 in PRMS, and 4.45 in RRMS and almost remained unchanged during treatment. The number of relapses was 2.04 and 1.01 at 12 months before OCR in PRMS and RRMS, respectively, and decreased to 0.30 at 6 months and 0.21 at 12 months in PRMS (p=0.000) and 0.13 at 6 months and 0.09 at 12-month in RRMS (p=0.000) after OCR initiation. The reduction in new T2 lesions was statistically significant. Infusion-related reactions (IRRs) occurred in 8.91% of the patients. OCR discontinuation rate due to IRRs was 2.83%.

Conclusions: This study showed that OCR was associated with a statistically significant reduction in the number of relapses and T2 lesions. However, the number of patients was low which led to a severely limited quantity of data collected and thus resulting in a limited informative value of the analysis results.

Keywords: Multiple sclerosis • Ocrelizumab • Relapse • Expanded disability status scale • T2 lesions • Switch

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease, characterized by inflammation of the central nervous system that leads to progressive neuro-axonal degeneration [1]. There is no established cure for MS however Disease-modifying Therapies (DMTs) are the cornerstone of long-term MS management. In general, DMTs act via suppression or modulation of immune and inflammatory responses [2].

Ocrelizumab (OCR) is a humanized anti-CD20 monoclonal antibody but the precise mechanism by which OCR exerts its clinical benefits in MS is not fully understood. Possibly it involves immunomodulation through a reduction in the number and function of CD20-expressing B cells. OCR binds to CD20 and selectively depletes CD20-expressing B cells through antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity, and apoptosis [3].

OCR was approved for the treatment of adult MS patients after the successful completion of the two identically designed phase III, 96-week Opera I (n=821) and Opera II (n=835) trials in Relapsing Multiple Sclerosis (RMS) patients [4]. Activity of OCR in patients with Primary Progressive Multiple Sclerosis (PPMS) was investigated in the ORATORIO phase III study [5]. In Opera studies, OCR significantly reduced annualized relapse rates versus interferon β-1a. In the ≥ 120-week ORATORIO trial in patients with PPMS, ocrelizumab significantly reduced the risk of≥12-week confirmed disability progression relative to placebo. OCR was effective at reducing clinical and Magnetic Resonance Imaging (MRI) activity in these studies. OCR was generally well tolerated in these studies, with infusion-related reactions and infections being the most common adverse events, which were mostly mild to moderate in severity.

OCR efficacy was sustained in the open-label extension phases of the pivotal trials, where Adverse Events (AEs) were generally consistent with those from the controlled periods and no new safety signals emerged with prolonged treatment [6, 7]. A recently published integrated safety analysis of the data from 11 clinical trials and open-label extension periods (up to 7 years of continuous ocrelizumab treatment) demonstrated a favorable and manageable safety profile. There was no indication of higher rates of malignancy compared with matched reference MS and general populations over 8 years [8].OCR is approved in the USA, EU, and many countries of the world for the treatment of RMS and PPMS. It is the only approved pharmacotherapy for PPMS.

In daily practice, MS patient population could be more diverse than in clinical trials. Therefore, we conducted this retrospective study designed to describe the MS-related disease activity against treatment based on relapse(s) that occurred and changes in MRI lesions during the Follow-Up (FU) period (at least for 12 months; a minimum of 2 FU visits were necessary) of treatment with ocrelizumab in Turkish patient population.

Materials and Methods

Study design and population

This was a retrospective, Secondary Data Use (SDU) non-interventional, national, multicenter study to be performed in Turkey. Data was collected from the IMED network of four major MS centers in Turkey. The IMED software collects patient data through a secure web-based data collection system worldwide. Physicians who treated MS patients entered their patients' data into this software prospectively as per their regular clinical practice after appropriately obtaining patient consent.

It was expected to include approximately 400 MS patients in this study who had switched their treatment from any DMT to OCR. The decision to treat patients with OCR had been taken before enrollment. Patients aged 18 years and older (with no age limit) at the time of inclusion with a diagnosis of relapsing forms of MS (relapse remitting MS [RRMS] and Progressive Relapsing MS [PRMS]) or PPMS were included in the study.

Data collection

Data were collected at enrollment and clinical visits were performed at 6-month intervals. Data extraction was performed between 31 March 2020 and 30 April 2020.

Baseline data collected included age, gender, comorbidities, previous DMT therapies, the reason for switching to OCR, MS phenotype, relapses in the 12 months and 24 months before starting OCR, Expanded Disability Status Scale (EDSS), and MRI results (number of gadolinium (gd) positive and new t2 lesions) at baseline. Variables and outcomes assessed during FU were relapses, EDSS, MRI results, Infusion-related Reactions (IRRs), the

reason for OCR discontinuation, and routine laboratory tests. The Timed 25 Foot Walk Test (T25FW) and Nine Hole Peg Test (9-HPT) were also implemented before OCR initiation at baseline, and every 6 months.

Statistical analysis

Statistical analysis was performed for this retrospective data collection study by using descriptive analytic methods. All statistical analyses and data processing were performed using STATA software, Version 14.0.

As the study was descriptive, there were no predefined hypotheses. No formal study sample size was calculated for this study. The study included data from all eligible MS patients in the registry database.

Primary efficacy analysis was based on the occurrence of clinically confirmed relapses which were analyzed periodically at 6-month intervals after the first OCR infusion and during the FU period. Secondary efficacy analyses were based on disability evolution as determined by the change of the EDSS score after 12 months, the number of Gd+ and t2 lesions after, and the reasons for discontinuation of OCR therapy. Subgroup analyses were performed on age groups (18-30, 30-50, and ≥ 50 years), baseline EDSS status (patients with EDSS scores<3 and ≥ 3), and MS phenotypes. For safety analysis, only the number and frequency of IRRs were documented.

For continuous variables, data are presented as the number of patients with valid/missing observations, mean, Standard Deviation (SD), median, and minimum and maximum values. For categorical variables, data are presented as frequencies and percentages. Missing data were not imputed.

In addition to the descriptive statistical methods, Pearson's chi-squared test for the comparison of normally distributed parameters in quantitative data, the Mann-Whitney U test for comparisons of non-normally distributed parameters between two groups, and Kruskal-Wallis in comparison between multivariate groups, Wilcoxon test for in-visit comparisons were also performed. The statistical significance was defined as a two-sided p-value <0.05.

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations, and ranges when parametric and median, and Inter-quartile Range (IQR) when data was found non-parametric. Also, qualitative variables were presented as numbers and percentages. The comparison between groups with qualitative data was done by using the Chi-square test. The comparison between two groups with quantitative data and parametric distribution was done by using an Independent t-test. While the comparison between two groups with quantitative data and non-parametric distribution was done by using the Mann-Whitney test. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

Results

Demographics and disease characteristics

A total of 460 patients fulfilling the inclusion criteria were included, of which 53.5% (n=246) had RRMS, 42.6% (n=196) PRMS, and %3.9 (n=18) PPMS. Patients had a mean (± SD) age of 46.8 years ± 10.7 years, and 58.6% were female. Baseline demographic and disease characteristics are summarized in Table 1.

Before the start of OCR treatment, 92 (37.4%) and 53 (21.5%) patients in the RRMS group and 70 (35.7%) and 53 (27.0%) in the PRMS group were being treated with fingolimod and interferon β 1a+1b+glatiramer acetate, respectively (Table 2). Forty-seven patients were treatment naïve or did not receive any specific MS therapy. The most common reasons for switching to OCR were ineffectiveness in 231 (50.2%), disease progression in 132 (28.7%), and AEs in 23 patients (5.0%); (Figure 1). A total of 94 relevant comorbidities were present in 76 patients (16.5%) which included hypertension as the most frequent one (25.5%) followed by diabetes (12.7%) and hypothyroidism (11.7%).

Efficacy of OCR

Mean EDSS scores were calculated for different categories: MS phenotypes, three age groups (18-30, 30-50, and ≥ 50 years), and baseline EDSS scores<3.0 and ≥ 3.0. Baseline EDSS scores in PPMS (4.91 ± 1.33) and PRMS (4.90 ± 1.43) groups were slightly higher than in RRMSgroup (4.45 ± 1.69), but not significant (p=0.058).EDSS scores significantly increased with increasing age (p=0.000). The mean (± SD) baseline EDSS was 2.48 ± 1.73 in patients aged 18 years-30 years, 4.48 ± 1.50 in patients aged 30 years-50 years, and 5.19 ± 1.35 in patients aged ≥ 50 years.

The mean EDSS score remained almost stable over one year of OCR treatment, and at 24-month there was a very slight worsening in EDSS scores in terms of both MS phenotypes and age groups (Figure 2).Patients with a baseline EDSS<3.0s showed EDSS improvements (from 1.68 to 1.59)

Table 1. Baseline and disease characteristics.

Variable	N=460
Gender, n (%)	
Female	271 (58.61)
Male	189 (41.09)
Age (years), n (%)	
18-30	30 (6.5)
30-40	89 (19.3)
40-50	147 (32.0)
50-60	139 (30.2)
60-70	53 (11.5)
70-80	2 (0.4)
Age (mean ± SD)	
18-30	25.64 (3.14)
30-40	35.71 (2.80)
40-50	44.42 (2.92)
50-60	54.58 (2.79)
60-70	63.07 (2.77)
70-80	71.26 (1.05)
MS phenotypes, n (%)	
RRMS	246 (53.5)
PRMS	196 (42.6)
PPMS	18 (3.9)
Age in MS phenotypes, n (%)	
RRMS	44.67 (11.20)
PRMS	49.50 (9.42)
PPMS	47.02 (11.54)
Comorbidities, n (%)	
Hypertension	24 (25.5)
Diabetes	12 (12.7)
Hypothyroidism	11 (11.7)
Restless leg syndrome	11 (11.7)
Trigeminal neuralgia	7 (7.4)
Herpes zoster virus	4 (4.2)
Baseline EDSS, mean (SD)	
RRMS	4.45 (1.6)
PRMS	4.90 (1.4)
PPMS	4.91 (1.3)
Relapse rate, mean (SD)	
Previous 12 months (n=432)	1.40 (1.9)
Previous 24 months (n=419)	2.17 (2.9)
Magnetic resonance imaging at baseline, n (%)	
Gadolinium+lesions	385 (83.7)
T2 lesions	385 (83.7)
Missing data	75 (16.3)

RRMS: Relapse Remitting MS; PRMS: Progressive Relapsing MS; PPMS: Primary Progressive MS; EDSS: Expanded Disability Status Scale.

Table 2. Disease-Modifying Therapies (DMT) before Ocrelizumab

	RRMS	PRMS	PPMS
Prior DMT		n (%)	
Fingolimod	92 (37.4%)	70 (35.7%)	-
Interferon β 1a+1b+Glatiramer acetate	53 (21.5%)	53 (27.0%)	4 (22.2%)
Teriflunomide	29 (11.8%)	18 (9.2%)	1 (5.6%)
Treatment-naïve / no specific MS treatment	25 (10.1%)	12 (6.1%)	5 (27.8%)
Dimethyl fumarate	21 (8.5%)	10 (5.1%)	-
Natalizumab	21 (8.5%)	7 (3.6%)	-
Rituximab	3 (1.2%)	4 (2.0%)	-
Azathioprine, Cyclophosphamide, Mitoxantrone	2 (0.8%)	17 (8.7%)	8 (44.4%)

DMT: Disease-Modifying Therapy

J Mult Scler 2022, Vol. 9, Issue 12, 475

whereas those with a baseline EDSS ≥ 3.0 experienced a small increase in EDSS scores (from 5.08 to 5.42) from baseline to 24 months.

In the RRMS+PRMS population, the number of relapses(mean ± SD) in the 12 months and 24 months before OCR treatment initiation was 1.40 ± 1.9 and 2.17 ± 2.9, respectively, and it was significantly higher in patients with PRMS compared to those with RRMS (2.04 vs. 1.01 and 3.08 vs. 1.66, respectively; p=0.000). The number of relapses at the 6-and 12-month OCR treatment in the RRMS+PRMS population was 0.20 ± 0.5 and 0.14 ± 0.4, significantly lower than the relapse rate in the previous year (p=0.000). The proportion of relapse-free patients at 12 months before starting OCR, and at 6 months and 12-months post-treatment was 44.6%, 82.8%, and 73.0%, respectively. The relapse-free rate decreased to 27.8% at 24 months because there was a considerable amount of missing data. The number of relapses was reduced from 0.30 ± 0.6 at 6 months to 0.21 ± 0.5 at 12 and 24 months in the PRMS group and from 0.13 ± 0.4 at 6 months to 0.09 ± 0.3 at 12 months and increased to 0.18 ± 0.4 at 24 months in RRMS group (all significant vs. 12-month before OCR; p=0.000). Similar reductions in relapse rates were also observed in patients with a baseline EDSS<3.0 and ≥ 3.0, and the difference between groups was not significant (Table 3).

At baseline (0-month) and 6 months, 83.7% and 37.8% of patients had gadolinium-enhancing (gd+) and t2 lesions on MRI. The mean number of new T2 lesions was 0.93 ± 1.2 (mean ± SD) at baseline, 0.11 ± 0.4 at 12 months, and 0.14 ± 0.4 after 24 months of OCR treatment (p=0.000 vs. baseline; (Table 4).

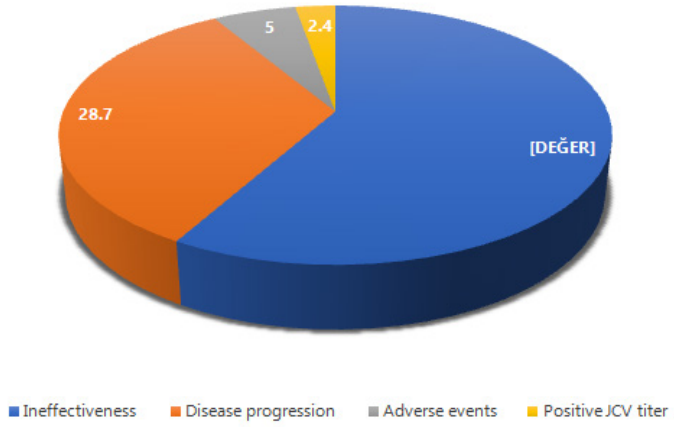

Figure 1. Reasons to switch to Ocrelizumab.

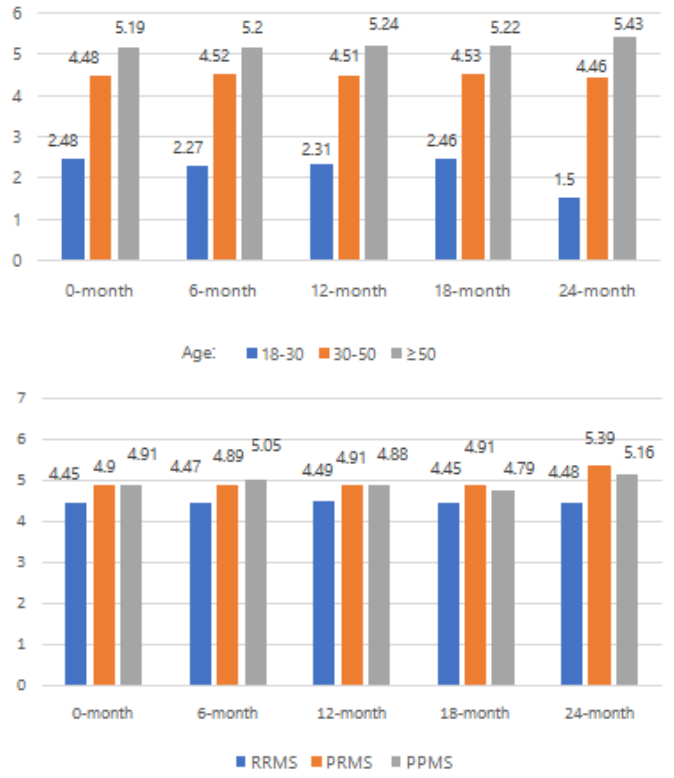

Figure 2. Mean EDSS scores by age and MS phenotypes.

Table 3. Relapse rates related to baseline EDSS scores (<3 and ≥ 3).

	Baseline EDSS <3	Baseline EDSS ≥ 3	P*
Relapse rate	**Mean (SD)**		
Previous 24-month	1.31 (1.1)	2.32 (3.1)	0.709
Previous 12-month	0.80 (0.6)	1.51 (2.0)	0.911
6-month	0.04 (0.1)	0.23 (0.5)	0.009*
12-month	0.11 (0.3)	0.14 (0.4)	0.595
18-month	0.10 (0.3)	0.14 (0.4)	0.804
24-month	0.15 (0.3)	0.19 (0.4)	0.991
30-month	0.33 (0.5)	0.33 (0.6)	0.88
*Mann-Whitney U Test			

Table 4. MRI activity baseline vs. post-treatment.

New t2lesion number	Mean	SD	p
0-month (baseline)	0.93	1.22	-
6-month	0.12	0.34	0.000*
12-month	0.11	0.41	0.000*
24-month	0.14	0.34	0.000*
** p<0.01; Wilcoxon test			

The mean score of T25FW decreased from 18.50 seconds ± 15.9 seconds at baseline to 13.19 seconds ± 12.6 seconds at 6 months and increased to 19.46 seconds ± 14.4 seconds at 12 months. Patients with a baseline EDSS<3.0 had almost stable T25FW scores during the FU period (range: 7.52 seconds-6.50 seconds). Patients with a baseline EDSS ≥ 3.0 showed slower (worsening) T25FW times at 12 months (20.5 ± 14.6) compared to baseline and 6 months (19.7 ± 16.3 and 14.0 ± 13.3, respectively). Patients with a baseline EDSS<3.0 had significantly better scores compared to another group of patients throughout the study. The mean scores at 9-HPT were 29.92 ± 16.9 for the right hand and 33.52 ± 23.9 for the left hand at baseline and remained almost unchanged up to 24 months for both hands (29.64 s ± 18.7 s and 32.53 s ± 19.6 s, respectively). Patients with a baseline EDSS ≥ 3.0 had improved 9-HPT scores in both hands compared to those with a baseline EDSS<3.0, and a statistically significant difference was observed for only the left hand between the groups (p<0.01).

Safety of OCR

In this study, no AEs were recorded except IRRs. Forty-one patients (8.91%) experienced a total of 86 IRRs. The proportion of patients discontinuing OCR treatment due to IRRs over the study was 2.83%. The most commonly reported IRRs during the study period were itchy ears (15.12%), followed by the itchy throat (11.63%) and burning sensation in the throat (9.30%). Neutrophil levels remained below the normal limit in approximately 20% of patients over up to 24 months of OCR treatment. Lymphocyte levels above the normal limit at baseline returned to the normal range over time. After OCR infusion, no drug-induced hepatotoxicity was recorded. There were 2 cases of pregnancy during the study leading to early discontinuation of OCR treatment. However, the outcomes of these cases were not recorded. Twelve patients discontinued OCR and the most common reasons were: patient withdrawal (n=3), pregnancy (n=2), disease progression (n=2), and (n=1). However, related data was only available for 12 patients.

Discussion

Real-world studies generally include diverse patient populations, reflecting features of daily clinical practice and providing data to further evaluate the risk/benefit profiles described for new therapies in Randomized Clinical Trials (RCT). To mitigate potential confounding factors, RCTs include selected patient populations. On the other hand, real-world populations may be more diverse than those included in randomized clinical trials, comprising patients with different prior MS-specific treatments, a longer duration of disease, increased physical disability, older age, or with comorbidities that may have an impact on the safety of on-going treatment [9, 10].

In line with the defined multifactorial outcomes, this study was designed as a retrospective secondary-data use to study, and previously collected patient data obtained from four MS centers across Turkey was extracted and analyzed.

In this real-world evidence study, this cohort showed that ocrelizumab

was associated with significantly lower annualized relapse rates and a confirmed lower rate of disability progression. Despite the higher EDSS scores and higher patient age observed in this cohort, the clinical effectiveness data was generally in line with those reported in the pivotal phase 3 clinical trials and in the few real-world studies conducted so far [11-15].

The relapse rate significantly decreased when the treatment was switched to OCR at 6 and 12 months. The overall relapse rate of the evaluated cohort was 0.20 ± 0.5 and this was lowered to 0.14 ± 0.4, which is significantly lower as compared to the relapse rate in the previous year (p<0.001). Since one of the main aims of MS treatment is to reduce relapses, we have shown a decrease in the overall relapse rate and this finding was in line with the findings of the main pivotal studies conducted with ocrelizumab.

We were not able to demonstrate a significant decrease in the mean EDSS score throughout the study. Although the mean EDSS scores in our cohort were found higher compared to phase III OPERA and ORATORIO trials [4, 5], EDSS scores remained almost stable over one year with OCR treatment, and at 24-month there was a very slight worsening in EDSS scores in terms of both MS phenotypes and age groups. However, our data for 50% of patients at 24 months were missing, indicating a drawback of retrospective data collection.

For efficacy, our retrospective data cohort showed an improvement in the number of new t2 lesions. The mean number of new t2 lesions was 0.93 ± 1.2 (mean ± SD) at baseline, 0.11 ± 0.4 at 12 months, and 0.14 ± 0.4 after 24 months of OCR treatment (p=0.000 vs. baseline). The reduction in new t2 lesions after OCR treatment was statistically significant (0.93 ± 1.2 at baseline, 0.11 ± 0.4 at 12 months, and 0.14 ± 0.4 at 24 months; p=0.000). The retrospective data were cross-checked with the MRI reports at the hospital archives, and confirmation of the reduction of t2 lesions was performed. Additionally, T25FW and 9-HPT scores remained relatively stable over the study period.

The analysis of this study represents a real-world cohort of patients with comorbidities and with no limits in inclusion and exclusion criteria such as age or comorbidities. MS is associated with numerous comorbidities such as cardiovascular disease, psychiatric and neurologic disturbances, restless leg syndrome, migraine, cancer, autoimmune diseases, and metabolic disorders. In the real-world MS cohorthypertension was the most frequent comorbidity (25.5%) followed by diabetes (12.7%) and hypothyroidism (11.7%), similar to the other real-world data of Hauer L, et al and Weber MS et al [16, 17].

IRRs were the most frequently reported adverse events related to OCR, which occurred in 34.3% and 39.9% of OCR-treated patients in the pooled analysis of OPERA [4] and ORATORIO trials [5], respectively. However, in our patient cohort IRR occurred less frequently, only in 8.91% of patients, which may be related to the lesser duration of infusions. Based on the results of the randomized, double-blind ENSEMBLE PLUS study, the Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) approved a shorter two-hour infusion time for ocrelizumab in patients with relapsing and progressive MS who have not experienced any previous serious IRRs [18].

Limitations

A major limitation of the study is the relatively small number of observed patients. Furthermore, as with any "as observed" analysis, there is a potential risk of bias due to missing outcome data, while the risk increases with a reduced number of patients observed over time. In this study, there is substantial missing data during the follow-up period of patients which may have a limiting effect on the generalizability of the results. Another limitation was missing source data verification due to the nature of data collection, however, the MRI evaluations were cross-checked with the MRI archive and confirmed.

Conclusion

This is a pooled analysis of patient-level data from the network of several MS centers in Turkey using "IMED" software. Despite the study population with higher EDSS scores and higher age compared to the above-mentioned Phase III trials, our study showed that ocrelizumab was associated with a statistically significant reduction in the number of relapses in the RRMS+PRMS population and a lower number of patients developed new T2 lesions in this patient cohort. Additionally, the safety profile of available ocrelizumab data and a lesser proportion of IRR were positive outcomes for this patient cohort.

Acknowledgements

The authors thank Assoc. Prof. Dr. Sedat Altug and Irem Unsal, DVM of Monitor CRO for medical writing and editing assistance and reviewing services for this manuscript.

References

1. McCool, Rachael, et al. "Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis." *Mult Scler Relat Disord* 29 (2019): 55-61.
2. Lehmann-Horn, K., et al. "Deciphering the role of B cells in multiple sclerosis—towards specific targeting of pathogenic function." *Int J Mol Sci* 18.10 (2017): 2048.
3. Sorensen, P.S., and Blinkenberg, M. "The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and prospects." *Ther Adv Neurol Disord* 9.1 (2016): 44-52.
4. Hauser, S.L., et al. "Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis." *N Engl J Med* 376.3 (2017): 221-234.
5. Montalban, X., et al. "Ocrelizumab versus placebo in primary progressive multiple sclerosis." *N Engl J Med* 376.3 (2017): 209-220.
6. Hauser, S.L., et al. "Five years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension." *Neurology* 95.13 (2020): e1854-e1867.
7. Wolinsky, J.S., et al. "Long-term follow-up from the ORATORIO trial of ocrelizumab for primary progressive multiple sclerosis: a post-hoc analysis from the ongoing open-label extension of the randomised, placebo-controlled, phase 3 trial." *Lancet Neurol* 19.12 (2020): 998-1009.
8. Hauser, S.L., et al. "Safety of ocrelizumab in patients with relapsing and primary progressive multiple sclerosis." *Neurology* 97.16 (2021): e1546-e1559.
9. Ziemssen, T., et al. "The importance of collecting structured clinical information on multiple sclerosis." *BMC Medicine* 14.1 (2016): 1-9.
10. Magyari, M., and Sorensen, P.S. "Comorbidity in multiple sclerosis." *Front Neurol* 11 (2020): 851.
11. Daniels, K., et al. "Real-world results of ocrelizumab treatment for primary progressive multiple sclerosis." *Mult Scler Int* 2020 (2020).
12. Prockl, V., et al. "Real world application of ocrelizumab in multiple sclerosis: Single-center experience of 128 patients." *J Neurol Sci* 415 (2020): 116973.
13. Sempere, A.P., et al. "Ocrelizumab in multiple sclerosis: a real-world study from Spain." *Front Neurol* (2021): 1816.
14. Einsiedler, M., et al. "Anti-CD20 immunotherapy in progressive multiple sclerosis: 2-year real-world follow-up of 108 patients." *J Neurol* (2022): 1-7.
15. Lanzillo, R., et al. "Prognostic Markers of Ocrelizumab Effectiveness in Multiple Sclerosis: A Real World Observational Multicenter Study." *J Clin Med* 11.8 (2022): 2081.
16. Hauer, L., et al. "A global view of comorbidity in multiple sclerosis: a systematic review with a focus on regional differences, methodology, and clinical implications." *J Neurol* 268.11 (2021): 4066-4077.
17. Weber, M.S., et al. "Safety, Adherence and Persistence in a Real-World Cohort of German MS Patients Newly Treated With Ocrelizumab: First Insights From the CONFIDENCE Study." *Front Neurol* 13 (2022): 863105-863105.
18. Hartung, H. P., et al. "Shorter infusion time of ocrelizumab: results from the randomized, double-blind ENSEMBLE PLUS substudy in patients with relapsing-remitting multiple sclerosis." *Mult Scler Relat Disord* 46 (2020): 102492.

Cite this article: Murat, T, et al. Two-year Assessment of the Efficacy and Safety of Ocrelizumab in Switching Patients from Other Disease Modifying Therapies. J Mult Scler, 2022, 9(12), 475.