# DOES PANDEMIC CHANGE THE OCRELIZUMAB THERAPY APPROACH? YES. – SINGLE CENTER OCRELIZUMAB EXPERIENCE

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**Background and purpose** – We know that treatment algorithms have changed in Multiple Sclerosis (MS) practice during the pandemic. In this study, we aimed to investigate whether there was a change in the patient population for ocrelizumab (OCR) treatment during the pandemic period, the treatment compliance of the patients, and the course of the Coronavirus Disease-19 (COVID-19) disease in the patients who received OCR.
**Methods** – Our study was designed as a survey study. A questionnaire was sent to the patients assessing whether they had COVID-19 infection, whether they received treatments regularly before and after the pandemic, vaccination status and duration of OCR treatment. Demographic characteristics of the patients, treatments they used before, MS type, Expanded Disability Status Scale (EDSS) scores were determined from the database. Each group of OCR started before pandemic and OCR started after pandemic were compared.
**Results** – We included into the study 86 patients who started OCR before pandemic period and 75 patients who started OCR after the pandemic. Demographic features were similar. EDSS scores were higher in the group that started OCR treatment before the pandemic ($p<0.0001$). The patients who started OCR treatment before the pandemic had more disruptions than which started during the pandemic ($p<0.0001$). No correlation was found between the duration of OCR treatment and COVID-19 infection ($p=0.940$). We observed that the patients who had severe

**MÓDOSULT-E A PANDÉMIA ALATT AZ OCRELIZUMABKEZELÉS? IGEN. – EGY KÖZPONTÚ TAPASZTALAT OCRELIZUMABKEZELÉSSEL**

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**Háttér és cél** – Tudjuk, hogy a sclerosis multiplex (SM) kezelési algoritmusai megváltoztak a pandémia alatt. Vizsgálatunk célja az volt, hogy elemezzük, megváltozott-e az ocrelizumabkezelésben (OCR) részesült betegpopuláció a pandémia alatt, milyen volt a betegek terápiás adherenciája, és milyen volt a Coronavirus Disease-19 (Covid-19) betegség lefolyása az OCR-kezelésben részesült betegek körében.
**Módszerek** – Kérdőíves vizsgálatot végeztünk. Kérdőívet küldtünk betegeinknek, és megkérdeztük, volt-e Covid-19 betegségük, részesültek-e rendszeres kezelésben a pandémia előtt és után, milyen a vakcinációs státuszuk, és milyen régóta részesülnek OCR-kezelésben. A betegek demográfiai jellemzőit, korábbi gyógyszerelésük adatait, SM-betegségük típusát, Expanded Disability Status Scale- (EDSS-) pontszámukat adatbázisunkból gyűjtöttük ki. Összehasonlítottuk azokat a betegcsoportokat, akik OCR-kezelése a pandémia előtt, illetve utána indult.
**Eredmények** – Nyolcvanhat olyan beteget vontunk be a vizsgálatba, akinek OCR-kezelése a pandémia előtt indult, és 75 olyan beteget, akinek utána. A két csoport demográfiai jellemzői megegyeztek. A pandémia előtt indult OCR-kezelésben részesültek EDSS-pontszámai magasabbak voltak ($p < 0,0001$), és több megszakítás volt a terápiájukban ($p < 0,0001$), mint azoknak, akik kezelése a pandémia indulása után kezdődött. Nem találtunk összefüggést az OCR-kezelés időtartama és a SARS-CoV-2-fertőzés bekövetkezte között ($p = 0,940$).

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COVID-19 infection had received OCR therapy for a longer period.
**Conclusion** – This retrospective study concluded that the OCR treatment approach in our center had changed during the pandemic period. OCR therapy was started in patients with less disability. The possible reasons for this situation include the proven relationship between high EDSS and serious COVID-19 infection, and that the patients who have higher EDSS score had troubles in reaching health institutions during the pandemic. The result that patients with severe COVID-19 infection received OCR treatment for a longer period necessitates more evidence-based research to investigate the relationship between treatment duration and disease severity.

***Keywords:*** *COVID-19, SARS-CoV-2, ocrelizumab, anti-CD20 therapies, multiple sclerosis*

Megfigyelésünk szerint azok a betegek, akik súlyos Covid-19 betegségben szenvedtek, hosszabb ideig részesültek OCR-kezelésben.
**Következtetés** – Retrospektív vizsgálatunk eredménye szerint központunkban a pandémia alatt módosult az OCR-kezelés megközelítése. Enyhébb betegséggel küzdő betegeknél indult OCR-kezelés. E szituáció lehetséges okai közé tartozik a magas EDSS-pontszám és a súlyos Covid-19 betegség közötti bizonyított kapcsolat, valamint az, hogy a magasabb EDSS-pontszámmal bíró betegek nehezebben érték el az egészségügyi intézményeket a járvány alatt. Eredményük, miszerint a súlyos Covid-19 betegségben szenvedők hosszabb ideig részesültek OCR-kezelésben, arra hívja fel a figyelmet, hogy több bizonyíték alapú kutatásra van szükség a kezelés időtartama és a betegségsúlyosság közötti összefüggés tisztázása érdekében.

***Kulcsszavak:*** *Covid-19, SARS-CoV-2, ocrelizumab, anti-CD20-terápiák, sclerosis multiplex*

With the onset of the Coronavirus Disease-19 (COVID-19) pandemic, patients and physicians were faced with socially and medically challenging problems. The fact that people with Multiple Sclerosis (pwMS) are under immunomodulatory and immunosuppressive drug treatments with different mechanisms has also raised many questions about the severity of COVID-19 infection.

At the beginning of the pandemic, it was reported that severe COVID-19 infection was associated with age, immunosuppression, and comorbidities such as hypertension, diabetes, smoking, obesity[1, 2]. With an increasing number of studies and observations, anti-CD20 treatments are discussed as the first among the treatments that may pose a serious risk of COVID-19 infection in the treatment of MS. Recent studies have shown that severity of COVID-19 infection in pwMS depend on age, presence of comorbid diseases, higher expanded disability status scale (EDSS) score, progressive MS course and longer disease duration[3]. In addition, use of metilprednisolone within 1 month and anti-CD20 treatments are reported to increase the risk[4].

Ocrelizumab (OCR) is an anti-CD20 treatment used in relapsing remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS) after its efficacy was shown by phase 3 OPERA and ORATORIO studies[5, 6]. It is reported that as of July 31, 2020, an estimated 174.508 people with MS worldwide have been treated with OCR, including approximately 167.684 in the commercial post-marketing setting, and 6.824 in clinical trials resulting in an exposure of 249.971 patient-years[7]. Especially for patients with high disease activity and PPMS, ocrelizumab treatment is important, but it has become challenging to initiate high-efficacy treatments, first of all, anti-CD20 therapies such as OCR, during the pandemic. At the same time, individuals who used OCR were concerned about whether their treatment would continue. However, treatment schedules were delayed in many clinics. This raised concerns about the risk of severe COVID-19 infection in individuals using OCR, as well as MS relapse in patients whose treatment was delayed.

The aim of this study was to investigate the treatment compliance, COVID-19 histories and vaccination status of the patients who started OCR before the pandemic and who started OCR during the pandemic period.

## Materials and methods

### PATIENTS

Patients who were followed up in our outpatient clinic and received OCR treatment were identified from the database. A questionnaire was sent to the patients assessing whether they had COVID-19 infection, whether they received treatments regularly before and after the pandemic, what was their

**Table 1.** *Demographic and clinical data of patient groups*

| | Before pandemic (n=86) | During the pandemic (n=75) | P value |
|---|---|---|---|
| Female, n (%) | 49 (57) | 41 (54.7) | 0.768 |
| Male, n (%) | 37 (43) | 34 (45.3) | |
| Age, year±SD | 43.5±9.3 | 43.2±10.8 | 0.831 |
| Disease duration, year±SD | 12.2±7.2 | 9.8±9.2 | 0.004 |
| EDSS, n (%) | | | <0.0001 |
| 0-4 | 18 (20.9) | 43 (57.3) | |
| >4 | 68 (79.1) | 32 (42.7) | |
| MS type , n (%) | | | 0.069 |
| RRMS | 33 (38.4) | 42 (56) | |
| SPMS | 34 (39.5) | 19 (25.3) | |
| PPMS | 19 (22.1) | 14 (18.7) | |

vaccination status and the duration of OCR treatment. Patients who did not answer were excluded. The data collection started on September 20, 2021 and closed for the analysis on December 23, 2021. Demographic characteristics of the patients who completed the questionnaire, treatments they used before, MS type, EDSS scores were determined from the database. Patients were divided into two groups: OCR started before pandemic and OCR started during the pandemic. In patient groups who started OCR before and after the pandemic, demographic features (age, gender, duration of disease, MS type), EDSS score, duration of OCR therapy, disease modifying therapies (DMTs) before OCR treatment (interferons, glatiramer acetate, teriflunamide, dimethyl fumarate grouped as first line treatment; fingolimod, cladribine, monoclonal antibody therapies and other immunosuppressive treatments like azathioprine, cyclophosphamide grouped as immunosuppressive-or second line treatments) were compared. Patients with and without COVID-19 infection were also compared in terms of MS type, EDSS scores, duration of OCR treatment, vaccination status. Patients who had COVID-19 were asked about COVID-19 severity.

Ethics committee approval was obtained. Each patient gave informed consent before answering the questionnaire.

### STATISTICAL ANALYSES

Numerical data were presented as mean ± SD (minimum-maximum) and categorical variables in n (%).

Chi-square test was used to compare categorical data. We determined whether the numerical data complied with the rules of normal distribution. T-test was used for independent groups when there was homogenous distribution, and Mann-Whitney U test was used for nonhomogeneous data.

Statistical analysis was done using IBM SPSS (version 20.0), p value was deemed <0.05.

## Results

Questionnaire was sent to 247 patients who were under OCR therapy. 161 patients who completed the questionnaire were included in the study. Groups were determined as OCR started before pandemic and OCR started after pandemic. **Table 1** shows the demographic and clinical characteristics of the groups.

There were 86 patients who started OCR before pandemic period and 75 patients who started OCR during the pandemic. Comparing these two groups, the patients were found to be similar in gender distribution and age. The mean age (mean±SD) was 43.5±9.3 years (range = 21-63) in the group of before the pandemic, 43.2±10.8 years (range = 21-68) in the group of during the pandemic. Disease duration was higher in the before-pandemic group (12.2±7.2 vs. 9.8±9.2, p = 0.004).

EDSS scores were categorized as 0-4 and >4. When EDSS scores were compared, it was found that EDSS scores were statistically significantly higher in the group that started OCR treatment before the pandemic (p<0.0001) **(Figure 1)**. There was no difference for MS type among the groups. Although it was not statistically significant, we

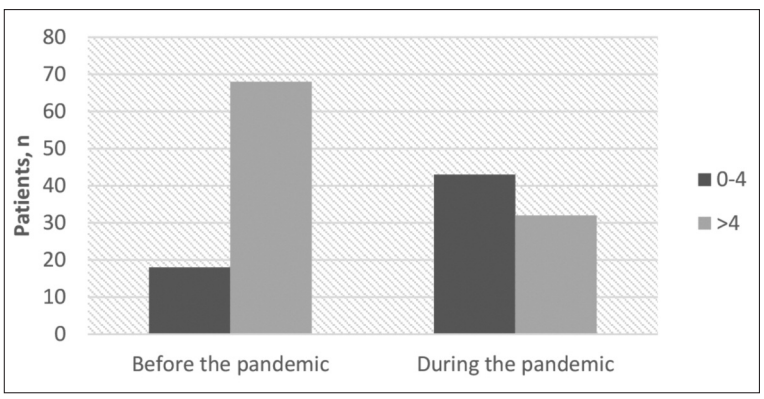


**Figure 1.** *Distribution of EDSS score of patients*

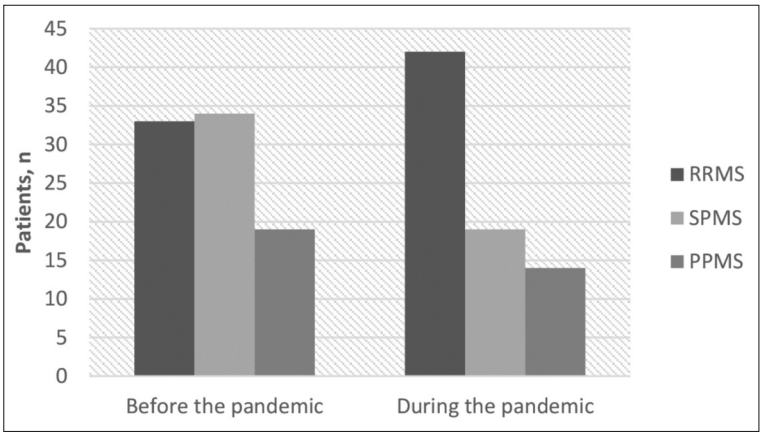


**Figure 2.** *MS types of the cohort*

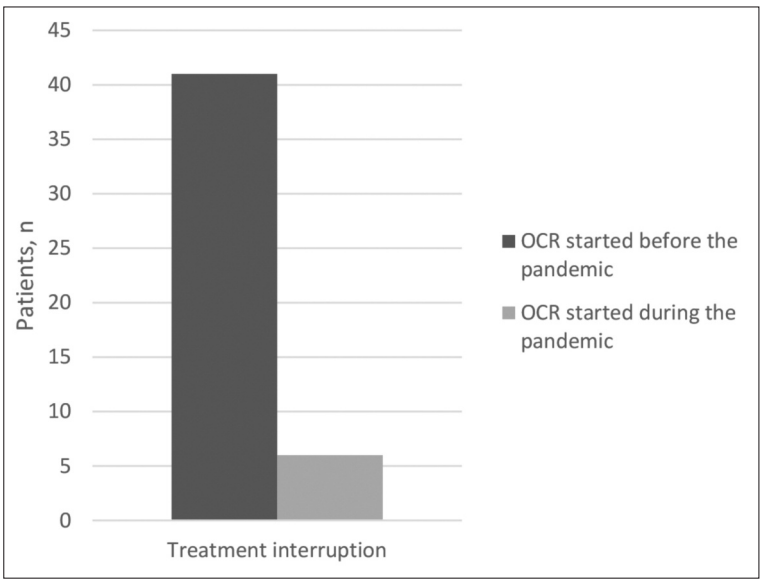


**Figure 3.** *Treatment interruptions among the patients before the pandemic vs. during the pandemic*

tended to start more OCR treatment in the RRMS group during the pandemic **(Figure 2)**.

One of the questions in our survey was whether patients were receiving OCR therapy regularly. It was observed that the patients who started OCR treatment before the pandemic period had significantly more disruptions than which started during the pandemic ($p<0.0001$) **(Figure 3)**.

34 of 161 patients had been infected with COVID-19 in our cohort. There was no significant difference among the groups who had and had not been infected with COVID-19 in terms of MS type, EDSS score and previous use of immunosuppressive therapy. Duration of OCR therapy was 22.3±13.3 months in the group of pwMS who had got infected with COVID-19, and 22.5±14.9 months in the group of who had not get infected. No correlation was found between the duration of OCR treatment and COVID-19 infection ($p=0.940$). However, it was found that patients with severe COVID-19 symptoms requiring intensive care were receiving OCR treatment for a statistically significantly longer period ($p=0.009$). **Table 2** shows the characteristics of the groups infected and not infected with COVID-19.

Eighteen patients were not vaccinated and 143 patients were vaccinated with at least two doses of inactivated vaccine (Sinovac) or mRNA vaccine (BioNTech). COVID-19 infection was higher in the unvaccinated group, but it was not statistically significant ($p=0.066$). In our cohort two patients had been lost due to COVID-19 infection. EDSS score of both patients was >4 and they were vaccinated. The age of the patients were 59 and 44 years. One of the patients had hypertension; the other patient did not have comorbid disease. The second patient had used immunosuppressive treatment before OCR therapy and the duration of OCR therapy were 39 and 45 months, respectively.

## Discussion

Since Multiple Sclerosis especially affects active, young adults and the treatment options include immunosuppressive drugs, developments related to COVID-19 are followed with curiosity and meticulousness by neurologists. Increasing number of studies had showed that the course of the COVID-19 disease in pwMS is similar to normal population with similar age and comorbidities, and there is no increase in the risk of developing the disease with effective preventive approaches[8, 9].

Although data are contradictory, COVID-19 infection can be a trigger for MS attacks[10]. Also, *Garjani* et al. reported that COVID-19 can worsen existing symptoms[10, 11]. Both situations can result in increased EDSS score. Just before this report *Etemadifar* et al. suggested that COVID-19 infec-

**Table 2.** *Comparison of patients with and without COVID-19 infection*

| | Covid-19 (+) (n=34) | Covid-19 (-) (n=127) | P value |
|---|---|---|---|
| Duration of OCR therapy, months (mean ± SD) | 22.3 ± 13.3 | 22.5 ± 14.9 | 0.940 |
| MS type, n | | | 0.059 |
| RRMS | 19 | 56 | |
| SPMS | 13 | 40 | |
| PPMS | 2 | 31 | |
| EDSS Score, n | | | 0.656 |
| 0-4 | 14 | 47 | |
| >4 | 20 | 80 | |
| Previous immunosuppressive treatment, n | 15/34 | 47/127 | 0.449 |

tion is not associated with MS relapses[11]. Prevention of COVID-19 infection is the primary goal, but effective treatment is also very important in case of infection. As a precaution against catching infection, there is no other option than social distance, hygiene rules and vaccination. The fact is that anti-CD20 therapies cause lower humoral immune response against vaccination, and recent reports show that anti-CD20 therapies are associated with severe COVID-19 infection[12, 13]. There is no guideline for anti-CD20 therapies during the pandemic. Experience of MS experts and patient selection may influence initiation of OCR therapy and following the patients who receive OCR therapy. So, we would like to share our OCR therapy experience comparing before the pandemic and during the pandemic period.

It is known that higher EDSS score is associated with poor outcomes for COVID-19 infection[4, 14, 15]. Some papers emphasize that there was no correlation between COVID-19 related mortality and DMTs in pwMS[9]. However, recent studies have shown that anti-CD20 therapies may be associated with severe COVID-19 infection and especially rituximab is associated with mechanic ventilation needs[3, 4]. Our tendency to initiate OCR therapy in patients with lower EDSS scores during the pandemic compared to the pre-pandemic period is also related to this data. In addition to this, duration of MS was higher in the before-pandemic group in our cohort. In the first years of OCR therapy, active progressive patients were treated even though their EDSS scores were high and the disease duration was longer. Later, it has been reported in post-marketing studies that OCR treatment is more effective in patients with low EDSS scores rather than progressive patients[16]. Our clinical practice also supports this data.

Roche – Genentech clinical research, post-marketing data and the OPTUM database provided that COVID-19 in pwMS treated with OCR was mild to moderate in most patients that would not require hospitalization[7]. These data are compatible with the general population's and COVID-19 MS data. Mortality rates for pwMS treated with OCR are within similar ranges as the general population and other MS cohorts, and in our study mortality rate was similar among the patients to whom we sent the questionnaire (n: 2/247). In our study there was no correlation between the duration of OCR treatment and COVID-19 infection, but patients who had required intensive care were using OCR for longer. This data is compatible with the literature, so while the limited number of cases is a limitation for the study, we can say that OCR treatment, especially long-term use, is associated with severe COVID-19 infection. Two patients in our cohort died due to COVID-19 infection. Based on our observations, the following comment can be made: Only two patients had mortal course, it might be related to the younger age of our patient group and to less comorbid diseases. On the other hand, deceased individuals had higher EDSS score so it was compatible with the literature.

We found that patients who started OCR therapy before pandemic had more interruptions for OCR doses. This can be explained by the fact that the patients in this group had higher EDSS scores and experienced transfer problems to the hospital. On the other hand, at the beginning of the pandemic, strict restrictions caused some troubles. After the organizations were arranged, infusions were started for the patients who deserved OCR treatment. Additionally, until the vaccine was developed, treatments were delayed for some patients who started OCR before the pandemic and had risk factors. For these reasons, it can be predicted that there will be fewer disruptions in the treatment of patients in the group in which OCR was started after the pandemic.

In a study on delaying OCR doses due to COVID-19, it was reported that none of the 33 patients whose treatment was delayed had a relapse. In our study, no recurrence was seen in patients whose treatment was delayed. This may suggest

that ocrelizumab is protective for longer than 6 months[17].

In a multicenter study comparing patients who underwent extended interval dosing (EID) and standard interval dosing (SID), no recurrence was observed in either group. No statistically significant difference was found in SID and EID groups when comparing three-month confirmed progression of disability. With these results, it is thought that EID may be a treatment strategy for anti-CD20 treatments in disaster situations such as pandemics. In our study, there was not observed different clinical and radiological course in patients whose treatment was delayed compared to those who received treatment within the standard practice[18].

LIMITATIONS

There was no control group that we would compare with patients receiving OCR treatment. Because of the small number of patients who were infected with COVID-19, it was difficult to comment on mortality. We sent the questionnaire to 247 patients via mobile phone, 161 patients answered. This is another limitation for this study.

## Conclusion

Identification of risk factors can improve the treatment of pwMS and COVID-19 by alerting clinicians requiring more careful treatment or monitoring. While the process of rapid normalization is being carried out all over the world with the vaccination, it is important that pwMS can get the treatments they deserve without delay. COVID-19 and its possible consequences should be kept in mind when deciding treatment. Especially for anti-CD20 treatments, in patient selection high EDSS score, comorbid diseases and age should be considered, which increase the risk of serious COVID-19 infection.

*AUTHOR CONTRIBUTIONS*
*Damla Cetinkaya Tezer: Conceptualization, methodology, investigation, writing - Original draft. Ipek Gungor Dogan: Methodology, investigation, writing - Review & editing. Murat Mert Atmaca: Formal analysis. Melek Colak Atmaca: Investigation, formal analysis. Serkan Demir: Conceptualization, writing - Review & editing, supervision.*

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*DATA AVAILABILITY STATEMENT*
*De-identified data will be shared by the corresponding author with any qualified investigator by request.*

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