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RISK OF COVID-19 INFECTION IN PATIENTS WITH MULTIPLE SCLEROSIS TREATED WITH OCRELIZUMAB – A SINGLE CENTER EXPERIENCE

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Ocrelizumab is a disease-modifying therapy (DMT) for active relapsing and early primary progressive multiple sclerosis (MS). During the COVID-19 pandemic, it was speculated that ocrelizumab might increase the risk of COVID-19 in patients with MS. The aim was to assess the risk of COVID-19 infection in MS patients treated with ocrelizumab. Our study included patients who met revised McDonald criteria and who were treated with ocrelizumab at the University Clinical Centre Niš. The diagnosis of COVID-19 was made by positive PCR (polymerase chain reaction) or antigen test. The severity of the disease was estimated based on the Australian guidelines for the clinical care of people with COVID-19. Out of 103 patients treated with ocrelizumab, 33 (32%) were found to be infected with COVID-19. Out of these, there were 10 (30.3 %) COVID-positive men and 23 (69.7%) women. The average age of affected patients was 43.9±9.1. Most of them had mild clinical presentation of COVID-19 infection (81.8%), 12.1% had moderate clinical presentation, 3% with severe clinical manifestation and one patient died. There was no significant impact of ocrelizumab administration in patients with MS on the increased risk of COVID-19 infection and the development of severe clinical manifestations of the disease. In our cohort, patients with moderate and severe COVID-19 disease were usually older than 50 (66.7%), although there were not many of those patients.*Acta Medica Medianae 2023;62(3):88-94.*

***Key words**: COVID-19, multiple sclerosis, ocrelizumab*

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Introduction

Multiple sclerosis is a chronic inflammatory autoimmune demyelinating disease of the central nervous system and is one of the leading causes of disability in the world. MS predominantly affects females aged between 20 and 50 (1). This inflammation can affect different parts of the brain and spinal cord and it can cause a wide range of neurological symptoms and signs. There are four recognized patterns of MS: 1) relapsing-remitting (RRMS), 2) secondary progressive (SPMS), 3) primary progressive (PPMS), and 4) progressive relapsing (PRMS). Relapsing-remitting disease is the most common form (70−80%) (2).

Ocrelizumab is an effective, humanized anti-CD 20, B cell-depleting, monoclonal antibody approved for treating relapse remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS). It achieves its effect by binding to the CD20 receptor on B lymphocytes and thus leads to their depletion, with spontaneous recovery afterward (3).

SARS-CoV-2 virus was first identified in Wuhan, China (4). The disease was first discovered in our country in March 2020, and restrictive measures were put in place by the Serbian government. This period brought a lot of difficulties in the organization of medical systems, including prescribing therapies for patients with MS. The period of the COVID-19 pandemic overlapped with the commencement of the treatment with ocrelizumab at the University Clinical Center Niš.

It is estimated that patients with MS could be at increased risk of severe COVID-19 infection. Patients with comorbidities, including those on immunosuppressive therapy might be more susceptible to COVID-19 infection (5).

Materials and methods

We conducted a cross-sectional cohort study in the period from March 2020 to November 2022. Our study included patients selected according to the revised McDonald criteria and who were treated with ocrelizumab at the University Clinical Centre Niš.

All patients were receiving disease-modifying therapy (ocrelizumab) at the time of assessments.

We analyzed demographic data (sex and age), clinical patterns of MS (PPMS and RRMS), incidence and severity of the clinical picture of COVID-19 infection, and vaccination status of patients.

COVID-19 infection was confirmed by positive PCR or antigen test.

The severity of the disease was estimated based on the Australian guidelines for the clinical care of people with COVID-19:

- mild illness: no symptoms, or mild upper respiratory tract symptoms, or cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation;
- moderate illness: prostration, severe asthenia, fever > 38 ^{O}C or persistent cough, clinical or radiological signs of lung involvement, no clinical or laboratory indicators of clinical severity or respiratory impairment; and
- severe illness: respiratory rate ≥ 30 breaths/min, oxygen saturation ≤ 92% at a rest state arterial partial pressure of oxygen (PaO_2)/inspired oxygen fraction (FiO_2) ≤300 (6).

All collected data were analyzed retrospectively.

Results

Out of 103 patient who were treated with ocrelizumab, 80 (77.7 %) patients had RRMS, and 23 (22.3%) patients had PPMS (Figure 1).

The investigated patients were aged between 23 and 64 (43.9±9.1). The most frequent age group included individuals in the fifth decade, from 41 to 50 years of age.

Fifty-seven patients (55.3%) were vaccinated, while the other 46 patients (44.7%) were not vaccinated.

COVID-19 infection was confirmed in 33 patients. Out of these, there were 10 (30.3 %) positive men and 23 (69.7%) women. Among the vaccinated patients, there were 23 patients (40.3%) who were confirmed to have COVID-19 infection, 15 of them being women (65.2%) and 8 men (34.8%).

Among the unvaccinated patients, COVID-19 was confirmed in 8 women (80%) and 2 men (20%).

The main clinical and social epidemiological characteristics, as well as the status of the COVID-19 infection are presented in Table 1.

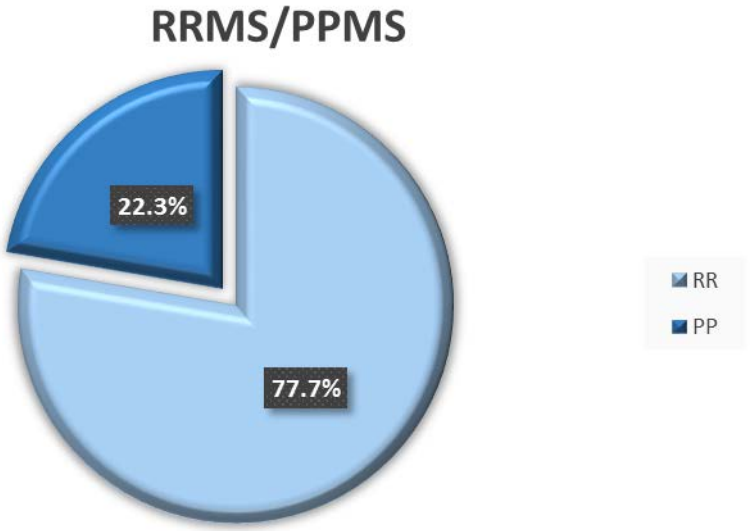

Figure 1. Number of patients with RRMS and PPMS treated with ocrelizumab

Table 1. The main characteristics of total patients treated with ocrelizumab

Characteristics	N° (%)
Gender	
Male	28 (27.2%)
Female	75 (72.8%)
Years	
23–30	8 (7.8%)
31–40	30 (29.1%)
41–50	43 (41.7%)
51–60	20 (19.4%)
>60	2 (1.9%)
Age, years, mean (SD)	43.9±9.1
The course of the disease	
RRMS	80 (77.7%)
PPMS	23 (22.3%)
COVID-19	33 (32%)
Vaccinated	57 (55.3%)
Confirmed COVID infection	23 (40.3%)
Male	8 (34.8%)
Female	15 (65.2%)
Unvaccinated	46 (44.7%)
Confirmed COVID infection	10 (21.7%)
Male	2 (20%)
Female	8 (80%)

We further compared patients with COVID-19 according to the severity of the disease. Most of them had mild clinical manifestation of COVID-19 infection (81.8%), 12.1% had a moderate clinical manifestation, and 3% had a severe clinical manifestation. One patient who had PPMS died (Figure 2).

Among those aged between 41 and 50, mild clinical manifestation was recorded in the largest number of COVID positive patients (11), while moderate and severe clinical manifestation was most common in middle-aged and elderly patients. We had 2 patients with moderate clinical presentation in the third decade, 2 patients in the sixth decade, while one patient in the sixth decade had severe clinical presentation and one died. In our cohort, patients with moderate and severe COVID-19 disease were usually older than 50 (66.7%), although there were not many of those patients.

The main comparative characteristics of our patients with COVID-19 in relation to the severity of the disease are presented in Table 2.

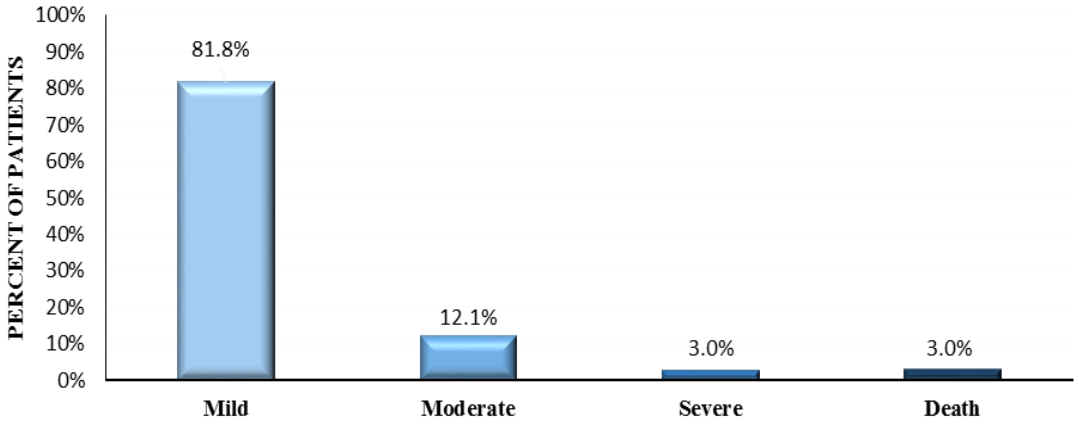

Figure 2. The severity of the COVID-19 disease

Table 2. Comparative characteristics of the patients with COVID-19 in relation to the severity of disease

Characteristics		**Mild** N° 27 (81.8%)	**Moderate** N° 4 (12.1%)	**Severe** N° 1 (3%)	**Death** N° 1 (3%)
Years	23–30	2 (7.4%)	0	0	0
	31–40	6 (22.2%)	2 (50%)	0	0
	41–50	11 (40.7%)	0	0	0
	51–60	6 (22.2%)	2 (50%)	1 (100%)	1 (100%)
	>60	2 (7.4%)	0	0	0

Discussion

There are now numerous disease-modifying therapies (DMT) that can slow down the progression of the disease successfully. These drugs have a different mechanism of action. Some of them act on B cells, some act on T cells, and some affect immunomodulation (7). Immunity to COVID-19 includes both cell immune responses. For this reason, the use of DMT during COVID-19 was controversial (8).

The beginning of the COVID-19 pandemic was a difficult period for organizing the administration of DMTs. Most of the patients were taking therapy in continuity. International data indicates that only 5% of the patients had significant reasons for therapy delays during the pandemic (9). All our patients started taking the therapy without delay, and the therapy was neither discontinued nor switched (except for one patient who died).

Current evidence does not indicate increased COVID-19 infection in MS patients (10). Prior to COVID-19 infection, it was considered that patients with MS have 2–4 more risk of being hospitalized with a serious infection (11). Some studies showed a higher risk of infection with COVID-19 if patients were female, younger and have other comorbidities. A possible additional reason for this was the greater number of social interactions (12). On the other hand, some other studies did not find any significant risk of infection with COVID-19 between MS and the general population (13, 14).

Two large cohort studies in China and Italy also did not show an increased impact of DMT use on the incidence of COVID-19 (15, 16).

Anti-CD20 monoclonal antibodies are widely used in MS therapy. Those drugs can increase the risk of contracting serious infections compared to other DMTs (17). Ocrelizumab is one of the most effective DMTs. According to many studies, it was shown to have significantly reduced relapses in RRMS patients and slowed down disease progression in PPMS patients. Considering that ocrelizumab acts on B cells, and that cells play an important role in the immune response to SARS-CoV-2 virus, it was thought that its use would increase the frequency of COVID-19. However,

this was not confirmed by many studies and it was proven that there was no association between the duration of ocrelizumab exposure and rates of COVID-19 infections (18). Taking into account risk factors for severe COVID-19 infection (older age, disability status, comorbidities), patients treated with ocrelizumab were considered to be at a high risk of being infected by COVID-19. Patients treated with ocrelizumab were compared with other MS cohorts, and it was noticed that less than one-fourth of patients developed moderate infection. This study delayed the suspicion that depleting drugs increased the risk for severe COVID-19 infection. In addition, it showed that the mortality rate was not higher in patients treated with ocrelizumab. Fatal cases occurred only in patients with multiple risk factors (19, 20, 21).

A group of authors in Scotland estimated the risk of infection with COVID-19 in patients with inflammatory rheumatic diseases (IRD) treated with immunosuppressive therapy. The study included 433 patients treated with immunosuppressive therapy and infected with COVID-19. They concluded that the risk of COVID-19 infection in these patients is higher than in the general population. Some drugs (methotrexate, hydroxychloroquine and TNF inhibitors) had a lower risk of COVID-19 disease, and the highest risk was associated with prednisolone (22).

Accordingly, several studies have shown that COVID-19 infection is more common in women, as well as in patients with a longer duration of pulse corticosteroid therapy (23).

The availability of recent data indicates that the reduction of the humoral response is not associated with a high risk of COVID-19, although both cellular and humoral immune responses play an important role in the prevention of virus infection. This is supported by the report of two patients with X-linked agammaglobulinemia, who had COVID-19 pneumonia, but fully recovered despite the absence of B cells in peripheral blood (24).

Conclusion

In conclusion, bearing in mind that ocrelizumab is an immunosuppressive therapy, our study showed that ocrelizumab administration had no significant impact on the increased risk of COVID-19 infection and the development of severe clinical manifestations of the disease. During the pandemic, managing MS patients should be done optimally, and treatment decisions should be made according to an individual benefit-risk profile.

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RIZIK OD COVID-19 INFEKCIJE KOD BOLESNIKA SA MULTIPLOM SKLEROZOM LEČENIH OKRELIZUMABOM – ISKUSTVO JEDNOG CENTRA

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Okrelizumab je terapija koja modifikuje prirodni tok bolesti u multiploj sklerozi (MS) i koristi se za lečenje aktivne relapsno remitentne i/ili primarno progresivne forme bolesti. Tokom pandemije virusa COVID-19 spekulisalo se da bi okrelizumab mogao povećati rizik od infekcije izazvane viursom COVID-19 kod bolesnika sa MS. Cilj rada je procena rizika od COVID-19 infekcije kod obolelih od multiple skleroze i lečenih okrelizumabom. Našom studijom obuhvaćeni su bolesnici koji su ispunjavali revidirane McDonald kriterijume, a koji su lečeni okrelizumabom u Univerzitetskom kliničkom centru Niš. Dijagnoza COVID-19 infekcije postavljena je pozitivnim PCR (lančanom reakcijom polimeraze) ili antigenskim testom. Težina COVID-19 infekcije procenjena je na osnovu australijskih smernica za kliničku negu osoba zaraženih COVID-19 viursom. Od 103 pacijenta lečena okrelizumabom, kod njih 33 utvrđeno je da su zaraženi COVID-19. Od toga je bilo 10 (30,3 %) pozitivnih muškaraca i 23 (69,7 %) žene. Prosečna starost obolelih bila je 43,9 godina ± 9,1 godina. Većina njih imala je blagu kliničku sliku COVID-19 infekcije (81,8%); 12,1% imao je umereno tešku kliničku sliku, 3% tešku kliničku manifestaciju, a jedan pacijent je preminuo. Nije bilo značajnog uticaja primene okrelizumaba kod bolesnika sa MS na povećan rizik od infekcije COVID-19 virusom i razvoj teške kliničke manifestacije bolesti. U našoj kohorti, bolesnici sa umerenom i teškom kliničkom slikom COVID-19 infekcije obično su bili stariji od 50 godina (66,7%), mada tih bolesnika nije bilo mnogo. *Acta Medica Medianae 2023; 62(3):88-94.*

***Ključne reči**: COVID-19, multipla skleroza, okrelizumab*