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Original article

Influence of delaying ocrelizumab dosing in multiple sclerosis due to COVID-19 pandemics on clinical and laboratory effectiveness

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ABSTRACT

Objective: To evaluate clinical and laboratory effects of delaying ocrelizumab infusions during the COVID-19 pandemics in people with multiple sclerosis (pwMS).

Methods: We have retrospectively searched our electronic database and identified 33 pwMS who had a delay in treatment due to COVID-19 pandemics. The following data were extracted: age, sex, multiple sclerosis (MS) phenotype: relapsing-remitting (RRMS) or primary progressive multiple sclerosis (PPMS), disease duration, Expanded Disability Status scale (EDSS), previous disease modifying therapy (DMT), number of ocrelizumab cycles prior to the lockdown, dates of first ocrelizumab infusion, last ocrelizumab infusion prior to the lockdown and delayed ocrelizumab infusion after the lockdown. Flow cytometry results, relapses and EDSS progression prior to the delayed ocrelizumab infusion after the lockdown were extracted.

Results: The mean time between two ocrelizumab infusion during the lockdown was 7.72±0.64 (range 6.07 to 8.92) months. The mean time between last ocrelizumab infusion and the lymphocyte sampling prior to post COVID infusion was 6.59±0.95 (range 5.18 to 8.49) months. In this period, none of the studied patients had a relapse. In a multivariable linear regression analysis, time from last ocrelizumab infusion to lymphocyte sampling prior to the next infusion was the only significant predictor for $CD19^{+}$ B cells count, when corrected for the number of previous ocrelizumab cycles and MS phenotype (RRMS or PPMS) (B=7.981, 95% C.I. 3.277-12.686, p=0.002).

Conclusions: We have not shown clinical consequences of delaying ocrelizumab due to COVID-19 pandemics. However, the delay in dosing of ocrelizumab was an independent predictor of repopulation of B cells.

Introduction

Ocrelizumab is a humanized anti-CD20 monoclonal antibody approved for the treatment of adults with relapsing-remitting multiple sclerosis (RRMS) or primary progressive multiple sclerosis (PPMS). (1) Ocrelizumab 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. (2) In people with RRMS, ocrelizumab has significantly reduced annualized relapse rates, while in people with PPMS, ocrelizumab significantly reduced the risk of ≥ 12-week confirmed disability progression. (3,4)

As ocrelizumab's mechanism of action is closely associated with depletion of B lymphocytes, it has been suggested that B-cell repopulation latency may serve as surrogate marker for individualized treatment strategies in people with MS (pwMS). (5) This may have significant implications on the effectiveness of treatment during the COVID-19 pandemics when many, especially second line disease modifying therapies (DMTs), have been postponed or delayed either due to COVID-19 infection in an individual patient or due to the worsening

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epidemiological situation in certain areas of the world. Furthermore, most of the international and national recommendations regarding DMT management during the COVID-19 pandemic, including recommendation from the Croatian neurological society, initially recommended considering the delay of dosing for cell-depleting therapies, including CD20 monoclonal antibodies. (6)

Therefore, the aim of this study was to evaluate clinical and laboratory effects of delaying ocrelizumab infusions during the COVID-19 pandemics.

Methods

Patients

All pwMS treated with ocrelizumab according to the local reimbursement guidelines at the University Hospital Center Zagreb were eligible for the study. The criteria for reimbursement for RRMS include only patients who failed 1st line treatment (interferons, glatiramer acetate, teriflunomide or dimethyl fumarate) or patients who had adverse event on any of the 2nd line treatments (natalizumab, fingolimod, alemtuzumab, cladribine). The diagnosis of PPMS and Expanded Disability Status scale (EDSS) <6.5 are criteria for the reimbursement of ocrelizumab in pwPPMS.

All patients received ocrelizumab 600 mg every 6 months (two 300 mg infusions 14 days apart for the first dose and a single 600 mg infusion thereafter).

The laboratory work-up before each scheduled ocrelizumab infusion consisted of complete blood count (CBC), IgG, IgM and IgA levels and flow cytometry data ($CD4^+$, $CD8^+$ and $CD19^+$ lymphocytes) performed at least 2 weeks prior to ocrelizumab infusion.

The first case of documented COVID-19 case in Croatia occurred in February 2020 (7), and very soon Croatian neurological society issued recommendations on the use of disease-modifying therapies in MS during the COVID-19 pandemics. (8) These guidelines recommended delaying the next ocrelizumab infusion during the pandemics, which resulted in stopping all ocrelizumab infusions in the period from March 16th to April 30th 2020.

We have retrospectively searched our electronic database and identified all patients who had a delay in treatment due to COVID-19 pandemics. The following data were extracted: age, sex, MS phenotype (RRMS or PPMS), disease duration, EDSS, previous DMT, number of ocrelizumab cycles prior to the lockdown, dates of first ocrelizumab infusion, last ocrelizumab infusion prior to the lockdown and delayed ocrelizumab infusion after the lockdown. Furthermore, flow cytometry results, relapses and EDSS progression prior the delayed ocrelizumab infusion after the lockdown were extracted.

Flow cytometry

The four-color flow cytometry analysis of peripheral blood samples was carried out by staining the cells with appropriate fluorochrome-conjugated antibodies in two separate tubes, one for T and one for B cells. The antibodies used were CD20-FITC (clone L27), CD45-PerCP (clone 2D1), CD19-APC (clone SJ25C1), CD8-FITC (clone SK1), CD4 -PE (clone SK3) and CD3-APC (clone SK7) purchased from BD Biosciences (San Jose, USA). One hundred microliters of whole blood per tube were stained for 15 min with fluorochrome-conjugated antibodies according to manufacturer's recommendations and were afterwards incubated for 10 min with BD FACS Lysing solution for lysing red blood cells (BD Biosciences, San Jose, USA). Finally, leukocytes were washed in phosphate-buffered saline (PBS) and resuspended in 300 μL of PBS. The FACS Lyric (BD Biosciences, San Jose, USA) was used for acquisition of samples and data were analyzed by FACSuite ver1.2 software (BD Biosciences, San Jose, USA). The absolute count of lymphocyte subsets (per μL of blood) was obtained by using absolute lymphocyte count (ALC) derived from the hematological analyzer Sysmex XN-3000 (Sysmex Corporation, Kobe, Japan).

Outcomes

The primary outcome was to investigate clinical effectiveness by assessing whether delaying ocrelizumab infusions has an impact on

a) Occurrence of relapse and
b) EDSS progression.

The secondary outcomes were to investigate laboratory effectiveness by assessing whether delaying ocrelizumab infusions has an impact on:

a) Repopulation of $CD19^+$ B cells
b) Repopulation of $CD19^+$ B cells depending on the number of prior ocrelizumab infusions
c) To investigate possible predictors of $CD19^+$ B cells count prior to next ocrelizumab infusion

Statistical analysis

Statistical analysis was performed with IBM SPSS 25 software. Due to relatively small number of participants, the differences between the two groups were assessed using the Mann-Whitney test, and the associations between the groups were determined with the Spearman's correlation analysis. Univariable and multivariable linear regression analysis was performed to determine which variables are independent predictors of the count of the $CD19^+$ B cells. P values of less than 0.5 were regarded as statistically significant.

Results

The electronic database retrieved 33 pwMS which fulfilled the inclusion criteria. The flow-chart of the study is provided in Figure 1. As some of the patients had flow cytometry performed in a period of 2 weeks prior to the lockdown, a 6.5 months delay in the laboratory was set as a cut-off value for further analysis. Demographic characteristics of the cohort are presented in Table 1.

Primary outcomes

The mean time between two ocrelizumab infusion during the lockdown was 7.72±0.64 (range 6.07 to 8.92) months. The mean time between last ocrelizumab infusion and the lymphocyte sampling prior to post COVID infusion was 6.59±0.95 (range 5.18 to 8.49) months.

In this period, none of the studied patients had a relapse. As well, none of the patients experienced worsening of the EDSS in the studied period.

Secondary outcomes

In 13 pwMS, $CD19^+$ B cell counts were determined in the period of <6.5 months and in 20 patients they were determined in the period of ≥6.5 months after the prior ocrelizumab infusion (Figure 1). In 20 patients, in which $CD19^+$ B cell counts were determined in the period of ≥6.5 months after the prior ocrelizumab infusion, we found no correlation between time of delay and number of $CD19^+$ B cells (r_s=0.191, p=0.420). The graphical presentation of $CD19^+$ counts depending on the time of the delay is presented in Figure 2.

We than divided the pwMS in the group which received 2nd cycle (Group 1) and group which received 3rd or subsequent cycle (Group 2). Values of $CD19^+$ lymphocytes depending on the cycle and time of sampling (<6.5 months vs ≥6.5 months after the prior ocrelizumab infusion) are presented in the Table 2. Group 2 had a statistically significant higher levels of $CD19^+$ lymphocytes, if measured ≥6.5 months after the last ocrelizumab infusion. For the group who received only 1

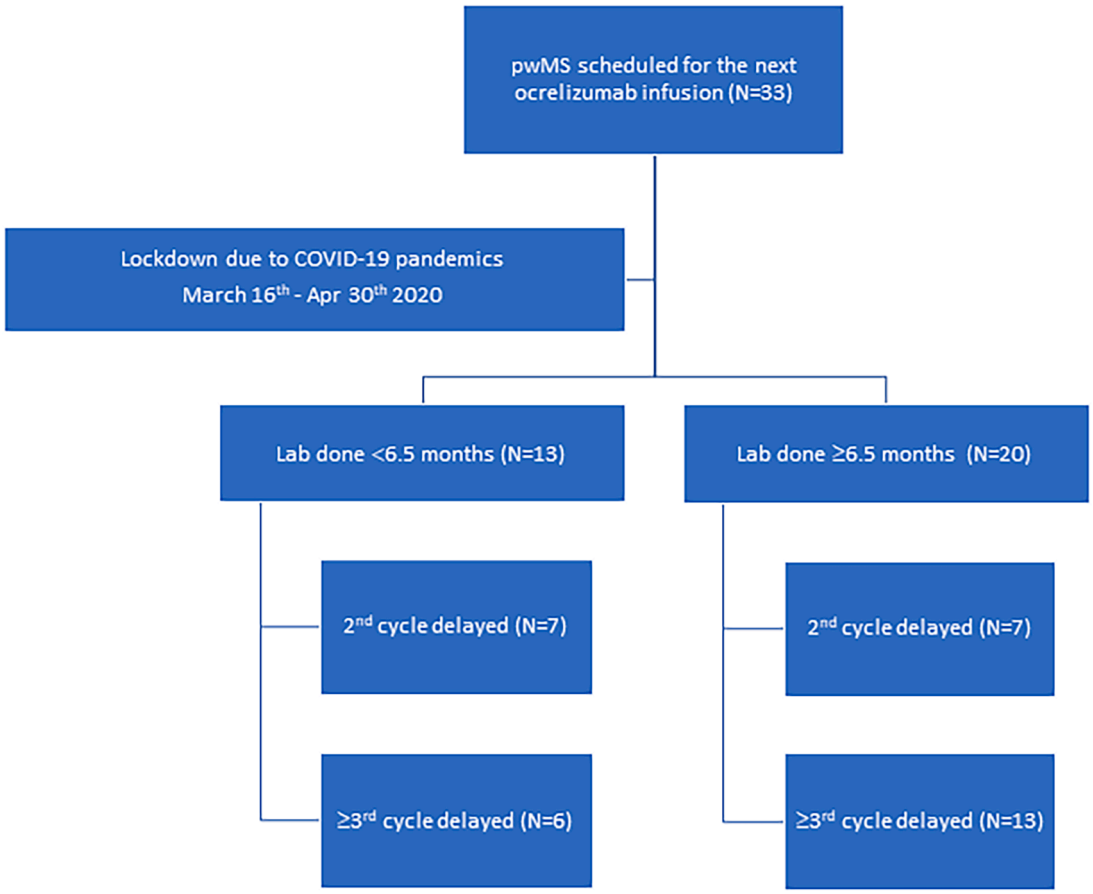

Figure 1. Flow chart of the study.

Table 1
Demographic characteristics of the cohort.

Age	42.2±10.4
Sex (females)	22 (66.7%)
MS phenotype	
RRMS	23 (69.7%)
PPMS	10 (30.3%)
Disease duration (years)	10.24±7.12
EDSS	4.5 (0-8.0)
Previous DMTs	
Treatment naïve	8 (24.2%)
1 previous DMT	16 (48.5%)
2previous DMTs	6 (18.2%)
≥3previous DMTs	3 (9.1%)
Previous DMTs	
1st line injectables	19 (57.6%)
1st line orals	7 (21.2%)
Fingolimod	4 (12.1%)
Natalizumab	2 (6.1%)
Alemtuzumab	1 (3.0%)
Number of ocrelizumab cycles prior to the lockdown	
1	14 (42.4%)
2	12 (36.4%)
3	6 (18.2%)
5	1 (3.0%)

prior cycle of ocrelizumab infusion and who had the time of lymphocyte sampling of ≥6.5 months (7 patients), we found positive correlation between the time of lymphocyte sampling and levels of $CD19^+$ B cells (r_s=0.847, p=0.016). No correlation was found between the time of lymphocyte sampling and the levels of $CD19^+$B cells for patients who received 3rd or subsequent cycle if measured ≥6.5 months after the prior ocrelizumab infusion (r_s=-0.148, p=0.630).

In order to investigate possible predictors of $CD19^+$ B cell count, univariable and multivariable linear regression analyses were performed (Table 3). Time from last ocrelizumab infusion to lymphocyte sampling prior to the next infusion was the only significant predictor for $CD19^+$ B cell count in a univariable linear regression analysis. In a multivariable linear regression analysis, this finding persisted when corrected for the number of previous ocrelizumab cycles and MS phenotype (RRMS or PPMS).

Discussion

Although delaying the next ocrelizumab dose did not have any effect on the relapses and EDSS progression, we have found significant effect on the repopulation of B cells. Similar finding was observed in a study which investigated the repopulation rate of peripheral $CD19^+$ B cells as a potential surrogate marker for individual application intervals in pwMS and neuromyelitis optica spectrum disorders treated with rituximab, another anti-CD20 monoclonal antibody. (5) Despite the fact that the therapeutic effect in their cohort has been closely associated with the absence of $CD19^+$ B cells, no correlation between B cell counts at the time-point of reinfusion and clinical course or MRI outcome in patients in whom relapses did occur were observed. (5) However, given the large inter-individual range of B cell recovery time, authors suggest that the $CD19^+$ B-cell repopulation rate may serve as surrogate marker to appraise individually adapted therapy intervals. (5) This is supported by the results of the recently published study which showed that the memory B cell–based rituximab reinfusion protocol is able to reduce the mean number of rituximab reinfusions with persistent reduction of disease activity. (9) Similar findings are observed in the present study, where we have not found increased occurrence of relapses despite higher repopulation of B cells.

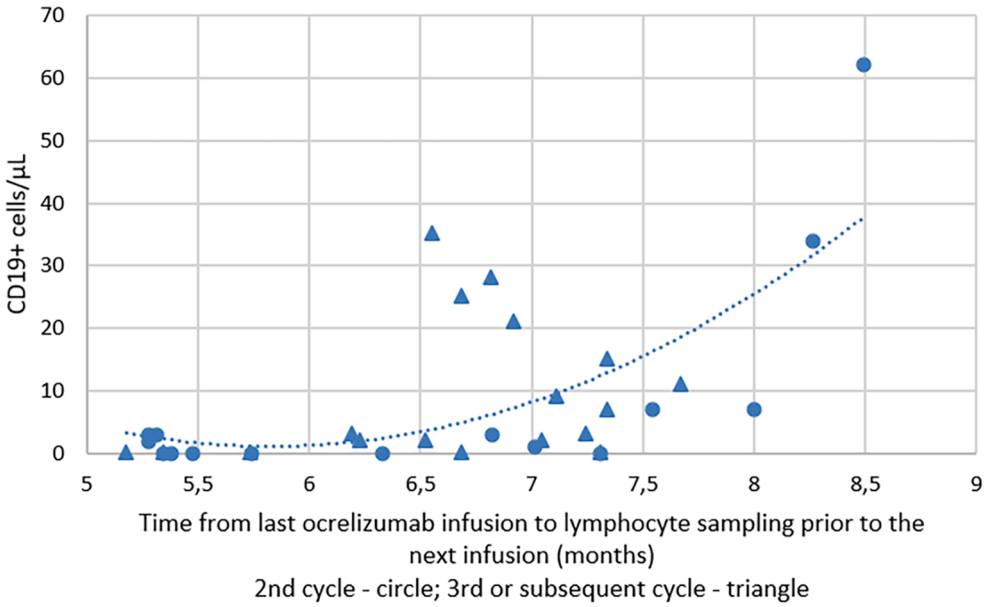

Figure 2. Graphical presentation of $CD19^+$ counts depending on the time of the delay.

Table 2
Comparison of values of $CD19^+$ B cells for Group 1 (2^{nd} cycle) and Group 2 ($\geq 3^{rd}$ cycle) depending on the time of sampling (<6.5 months vs ≥6.5 months after the prior ocrelizumab infusion).

Ocrelizumab cycle	Time of sampling	$CD19^+$ cells/µL, median (range)	p value
2^{nd}	<6.5 months	0 (0-3)	0.053
	≥6.5 months	7 (0-62)	
$\geq 3^{rd}$	<6.5 months	0 (0-3)	0.012
	≥6.5 months	9 (0-35)	

Table 3
Results of the univariable and multivariable linear regression model.

	Univariable linear regression			Multivariable linear regression		
	B	95% C.I. for B	p value	B	95% C.I. for B	p value
CD19+ B cell counts						
Age	0.079	-0.412-0.570	0.746			
Sex	-0.409	-11.102-10.283	0.938			
EDSS	1.081	-1.654-3.817	0.426			
MS phenotype (RRMS or PPMS)	-2.491	-13.422-8.440	0.645	-1.562	-11.110-7.985	0.740
Number of previous Ocrelizumab cycles (1 or >1)	-0.135	-10.335-10.064	0.979	-0.148	-9.012-8.715	0.973
$CD19^+$ B cells count prior to the last ocrelizumab cycle	-0.007	-0.060-0.046	0.784			
Time from last ocrelizumab infusion to lymphocyte sampling prior to the next infusion	8.025	3.486-12.564	0.001	7.981	3.277-12.686	0.002

Treatment regiments differ between rituximab and ocrelizumab, with ocrelizumab treatment having fixed 6 months intervals with a long-lasting depletive effect. Repopulation of B cells is defined when $CD19^+$ cells reach 1% of lymphocyte counts, after which a rapid increase occurs. (10,11) The median time to B-cell replenishment for ocrelizumab is about 62 weeks after 3 treatment cycles and 72 weeks after 4 treatment cycles. (12,13) In contrast, in rituximab-treated patients, B-cell repopulation has considerable intraindividual variation which may be a consequence of different regiments applied, with average intervals being 8.3 months. (14) Studies investigating repopulation of B cells in ocrelizumab treated patients are scarce. A recently published study observed a significant depletion of $CD19^+$ cells after six months and one year of treatment, but an incomplete depletion was detected in 41.8% of patients and in 24% of patients a significant reappearance of this B cells (2%) has been achieved. (15) One of the factors that may be responsible for these variations in repopulation of $CD19^+$ cells identified in this study is body mass index.

The COVID-19 pandemic has created concerns about immunosuppression in pwMS, leading to cessation or a delay in disease modifying treatments. Although most reports suggest that DMTs should not necessarily expose people to severe SARS-CoV-2-related issues, recently presented data has shown that compared with dimethyl fumarate, rituximab was associated with significantly higher risk of hospitalization, ICU admission, and ventilation. (16) Weaker but similar associations were seen for ocrelizumab, although these did not always reach statistical significance. Another potential problem with B-cell depleting therapies is formation of protective immunity following infections and vaccination. (12) Whether extended interval dosing or dosing interruption to allow vaccination, without compromising effectiveness, remains to be investigated.

The main limitations of this study are small number of participants and lack of MRI data. A study correlating MRI activity with repopulation of B cells would be of great interest.

In conclusion, we have not shown clinical consequences of delaying ocrelizumab due to COVID-19 pandemics. However, the delay in dosing of ocrelizumab was an independent predictor of repopulation of B-cells. Potential long-term clinical consequences of this association remain to be determined.

Authors' contributions

Study concept and design: Habek. Acquisition of data: Barun, Gabelić, Adamec, Babić, Lalić, Batinić, Krbot Skorić, Habek. Analysis and interpretation of data: Barun, Gabelić, Adamec, Babić, Lalić, Batinić, Krbot Skorić, Habek. Drafting of the manuscript: Krbot Skorić, Habek. Critical revision of the manuscript for important intellectual content: Barun, Gabelić, Adamec, Babić, Lalić, Batinić, Krbot Skorić, Habek. Administrative, technical, and material support: Barun, Gabelić, Adamec, Babić, Lalić, Batinić, Krbot Skorić, Habek.

Financial & competing interest disclosure

BB: Participated as a clinical investigator and/or received consultation and/or speaker fees from: Biogen, Sanofi Genzyme, Merck, Bayer, Novartis, Pliva/Teva, Roche, Alvogen, Actelion, Alexion Pharmaceuticals.

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