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Anti-severe acute respiratory syndrome coronavirus-2 antibody responses following Pfizer-BioNTech vaccination in a patient with multiple sclerosis treated with ocrelizumab: a case report

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Abstract
Patients with multiple sclerosis (MS) repeatedly receive therapies that cause B-lymphocyte depletion. This may lead to abnormal immune responses following coronavirus disease 2019 (COVID-19) vaccination, as has been suggested previously. We therefore evaluated post-vaccination immune responses in a patient with MS treated with ocrelizumab. The intervals between ocrelizumab infusions and vaccination were as recommended by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society. A reactive immune response was observed in this patient following vaccination. This suggests that appropriate intervals between ocrelizumab infusions and COVID-19 vaccinations may permit the generation of efficacious immune responses in patients receiving B-lymphocyte depleting therapies.

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Introduction

Multiple sclerosis (MS) was initially thought to be a T-cell mediated disease, but more recently B-cells have been considered central to the pathogenesis of the disease.[1] Therefore, therapies that result in B-cell depletion, such as ocrelizumab, have been increasingly popular for the treatment of MS.[2] The mechanism of action of ocrelizumab is to reduce production of pathogenic antibodies in MS.[1,2] However, depletion of B-lymphocytes can also lead to increased risks of severe infections and decreased production of non-pathogenic antibodies.[2,3] During the coronavirus disease 2019 (COVID-19) pandemic, therapies that result in B-lymphocyte depletion have received special attention: patients with MS receiving ocrelizumab may be at higher risks of infection and severe COVID-19.[4] It was also reported that patients with MS receiving anti-CD20 therapy, which also results in B-lymphocyte depletion, showed significantly impaired antibody responses during severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as well as following administration of vaccines.[5–8] COVID-19 vaccination campaigns are underway in many areas of the world. Currently, various vaccines are available.[5,9] Because of the mechanism of action of ocrelizumab and reports on this drug, a question arises regarding the potential impact of treatment on immune responses following COVID-19 vaccination. Khayat-Khoei et al. presented data on the immune response against COVID-19 mRNA vaccination in a patient with MS receiving ocrelizumab.[5] The patient, who had relapsing-remitting MS, did not produce a detectable antibody response over 27 days following administration of the Pfizer-BioNTech COVID-19 vaccine. Therefore, we evaluated anti-SARS-COV-2 spike (S) protein antibody titers following Pfizer-BioNTech COVID-19 vaccination in a patient with primary progressive MS receiving ocrelizumab. In a Letter to the Editor of the *Journal of Neurology*, we briefly reported our observations on the report by Khayat-Khoei et al.[10] In the letter we also mentioned the upcoming publication of a detailed case report of another patient with MS receiving ocrelizumab vaccinated with the Pfizer-BioNTech vaccine; this was the aim of the current manuscript. In the case described here, a post-vaccination antibody response was observed. Successful generation of immune responses in patients with MS receiving ocrelizumab may require the selection of appropriate time intervals between the last infusion of ocrelizumab and the first dose of vaccine as well as between the second dose of vaccine and the first infusion of ocrelizumab after vaccination.

Case presentation

The reporting of this study conformed to CARE guidelines.[11] The study was approved by the Bioethics Committee of the Medical University of Silesia in Katowice (No. PCN/CBN/0022/KB1/44/21). Written informed consent was obtained for the publication of this case report. A 23-year-old woman was diagnosed with primary progressive MS on 29 May 2019 based on clinical presentation and results of additional examinations according to the 2017 McDonald criteria.[12] She had an Expanded Disability Status Scale (EDSS) score of 4. Figure 1 shows patient characteristics and key information during the study timeframe. Table 1 shows the results of selected laboratory tests performed on 15 July 2019 before the first infusion of ocrelizumab. Following diagnosis, the patient
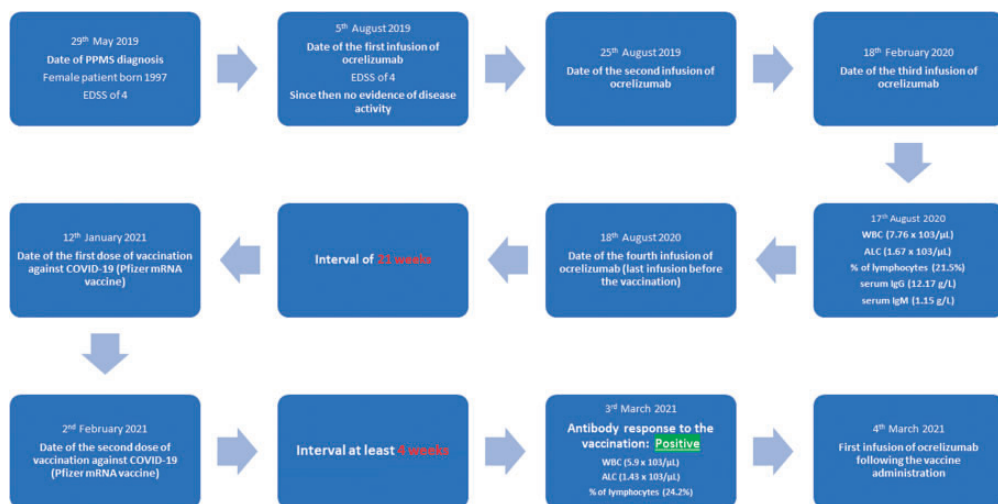
Figure 1. Patient characteristics and key information on the timeframe for ocrelizumab infusion and Pfizer-BioNTech vaccination. PPMS, primary progressive multiple sclerosis; EDSS, Expanded Disability Status Scale; COVID-19, coronavirus disease 2019; WBC, white blood cell; ALC, absolute lymphocyte count.

Table 1. Results of selected examinations before the first infusion of ocrelizumab.

Basic laboratory tests	
WBCs ($\times 10^3/\mu L$)	7.21
(normal range: 4–10.5 $\times 10^3/\mu L$)	
ALC ($\times 10^3/\mu L$)	2.14
(normal range: 1–3.3 $\times 10^3/\mu L$)	
Lymphocytes (%)	29.7
(normal range: 21%–51%)	
Lymphocyte immunophenotyping	
T cells (%)	77.1
(normal range: 67%–76%)	
B cells (%)	11.6
(normal range: 11%–16%)	
NK cells (%)	10.5
(normal range: 10%–19%)	
CD4 T cells (%)	72.9
(normal range: 38%–46%)	
CD8 T cells (%)	23.5
(normal range: 31%–40%)	
CD4/CD8 ratio	3.1
Activated T cells (%)	7.9
(normal range: 8%–15%)	

WBC, white blood cell; ALC, absolute lymphocyte count; NK, natural killer.

was treated with ocrelizumab at doses recommended by the manufacturer. No disease progression (as reflected by the EDSS score) was observed after the first dose of ocrelizumab. The patient did not develop symptoms of COVID-19 at any time since the beginning of the pandemic, nor was she diagnosed with COVID-19.

The patient was vaccinated with the Pfizer-BioNTech mRNA vaccine as part of the so-called "0" vaccination group in Poland. The patient was vaccinated 4 to 6 months after the last dose of ocrelizumab and the subsequent ocrelizumab infusion was administered at least 4 to 6 weeks after the second vaccine dose. These intervals were recommended in the statement of a working group convened by the Section of Multiple Sclerosis and Neuroimmunology (SMSN) of the Polish Neurological Society.[13]

The first three doses of ocrelizumab were administered on 5 August 2019,

25 August 2019, and 18 February 2020. No adverse events were reported. The results of blood tests performed on 17 February 2020 were as follows: white blood cell (WBC) count $5.81 \times 10^3/\mu L$ (normal range: 4–$10.5 \times 10^3/\mu L$); absolute lymphocyte count (ALC) $1.28 \times 10^3/\mu L$ (normal range: 1–$3.3 \times 10^3/\mu L$); and lymphocyte percentage 28% (normal range: 21%–51%). Serum levels of IgA (2.24 g/L), IgM (1.25 g/L) and IgG (11.26 g/L) were also determined on 17 February 2020. Lymphocyte immunophenotyping was performed the following day and showed a B-lymphocyte percentage of 0.3% (normal range: 11%–16%) and a B-lymphocyte count of $0 \times 10^3/\mu L$ (normal range: $0.2–0.4 \times 10^3/\mu L$). Contrast head and cervical spine magnetic resonance imaging was performed on 17 August 2020 and showed diffuse demyelinating lesions with no active plaques. No progression was observed compared with the previous examination.

Blood tests prior to the next dose of ocrelizumab (on 17 August 2020) showed a WBC count of $7.76 \times 10^3/\mu L$), ALC $1.67 \times 10^3/\mu L$, a lymphocyte percentage of 21.5%, serum IgG of 12.17 g/L, and serum IgM of 1.15 g/L. Detailed test results before the last infusion of ocrelizumab prior to vaccination are shown in Table 2.

On 18 August 2020, the fourth and last dose of ocrelizumab was administered prior to Pfizer-BioNTech COVID-19 vaccination. No adverse events were reported. The patient was given her first dose of Pfizer-BioNTech vaccine on 12 January 2021 and the second dose on 2 February 2021 (exactly 3 weeks after the first dose). Therefore, the intervals between the last infusion of ocrelizumab and the first and second vaccinations were 21 and 24 weeks, respectively. Quantitation of antibodies against the SARS-CoV-2 S protein receptor-binding domain was performed on 3 March 2021 (29 days following administration of the second vaccine dose).

Antibody titer quantitation was conducted in a laboratory accredited by the Polish Centre for Accreditation using a carbonyl metallo immunoassay (Abbott, Chicago, IL, USA). A reactive result (10.35) was observed (cut-off value ≥7.1). The results were expressed in binding antibody units (BAU) per mL in accordance with the World Health Organization International Standard (NIBSC code: 20/136). This test demonstrates the presence of antibodies following natural infection with SARS-CoV-2 or following vaccination against COVID-19 that are associated with protective immunity against COVID-19. A test for the presence of SARS-CoV-2 antigens was performed on the same day and the result was negative. The results of selected laboratory tests and post-vaccination immune responses at least 4 weeks after the second dose of Pfizer-BioNTech vaccine are shown in Figure 1 and Table 3. On 4 March 2021, more than 4 weeks after the second dose of vaccine, another infusion of ocrelizumab was administered. Following the infusion, lymphocyte immunophenotyping was performed (Table 3).

Discussion

Administration of ocrelizumab is of particular concern because of its immunosuppressive effects, especially during the COVID-19 pandemic.[4] Ocrelizumab is a humanized monoclonal antibody whose mechanism of action involves targeting the CD20 marker on B-lymphocytes.[14] Ocrelizumab results in depletion of B cells that are involved in the pathogenesis of MS by producing autoantibodies targeting specific tissues in the central nervous system, ultimately leading to demyelination.[1,2,15] B-cell depletion may also lead to IgM, IgA, and IgG deficiency and increased risks of severe infections.[2,3,16] Because of its mechanism of action, ocrelizumab could potentially cause attenuated antibody responses following COVID-19

Table 2. Results of selected examinations before the last infusion of ocrelizumab prior to Pfizer-BioNTech COVID-19 vaccination.

Basic laboratory tests	
WBCs ($\times 10^3/\mu$L)	7.76
(normal range: 4–10.5 $\times 10^3/\mu$L)	
ALC ($\times 10^3/\mu$L)	1.67
(normal range: 1–3.3 $\times 10^3/\mu$L)	
Lymphocytes (%)	21.5
(normal range: 21%–51%)	
Serum IgG (g/L)	12.17
Serum IgM (g/L)	1.15
Lymphocyte immunophenotyping	
T cells (%)	87.9
(normal range: 67%–76%)	
T cell count ($\times 10^3/\mu$L)	1.47
(normal range: 1.1–1.7 $\times 10^3/\mu$L)	
B cells (%)	0.2
(normal range: 11%–16%)	
B cell count ($\times 10^3/\mu$L)	0
(normal range: 0.2–0.4 $\times 10^3/\mu$L)	
NK cells (%)	11.3
(normal range: 10%–19%)	
NK cell count ($\times 10^3/\mu$L)	0.19
(normal range: 0.2–0.4 $\times 10^3/\mu$L)	
CD4 T cells (%)	65.4
(normal range: 38%–46%)	
CD4 T cell count ($\times 10^3/\mu$L)	1.09
(normal range: 0.7–1.1 $\times 10^3/\mu$L)	
CD8 T cells (%)	23.6
(normal range: 31%–40%)	
CD8 T cell count ($\times 10^3/\mu$L)	0.39
(normal range: 0.5–0.9 $\times 10^3/\mu$L)	
CD4/CD8 ratio	2.77
Activated T cells (%)	5.4
(normal range: 8%–15%)	
Lymphocyte count ($\times 10^3/\mu$L)	1.67
(normal range: 1–3.3 $\times 10^3/\mu$L)	
MRI scan with contrast	
Description of results	Diffuse demyelinating lesions. The numbers and morphology of lesions were similar to observations from an examination conducted 1 year previously. No active demyelinating lesions were observed.

COVID-19, coronavirus disease 2019; WBC, white blood cell; ALC, absolute lymphocyte count; NK, natural killer; MRI, magnetic resonance imaging.

vaccination.[17] Recent clinical trials have shown that during ocrelizumab treatment, humoral responses to some vaccines may be attenuated but still present.[18] For example, influenza vaccination is recommended in patients receiving ocrelizumab even if humoral responses are attenuated. However, an adequate interval between

Table 3. Results of selected examinations more than 4 weeks after the last dose of Pfizer-BioNTech COVID-19 vaccine.

Basic laboratory tests	
(performed before infusion of ocrelizumab following vaccine administration)	
WBCs ($\times 10^3$/µL)	5.9
(normal range: 4–10.5 $\times 10^3$/µL)	
ALC ($\times 10^3$/µL)	1.43
(normal range: 1–3.3 $\times 10^3$/µL)	
Lymphocytes (%)	24.2
(normal range: 21%–51%)	
Response to COVID-19 vaccination	
(assessed before infusion of ocrelizumab following vaccine administration)	
Antibodies to the SARS-CoV-2 spike protein receptor-binding domain (BAU/mL)	10.35
Note: <7.1 BAU/mL: negative, non-reactive; ≥7.1 BAU/mL: positive, reactive	
Lymphocyte immunophenotyping	
(performed after infusion of ocrelizumab following vaccine administration)	
T cells (%)	87.3
(normal range: 67%–76%)	
B cells (%)	0.1
(normal range: 11%–16%)	
NK cells (%)	12.3
(normal range: 10%–19%)	
CD4 T cells (%)	61.4
(normal range: 38%–46%)	
CD8 T cells (%)	26.8
(normal range: 31%–40%)	
CD4/CD8 ratio	2.29
Activated T cells (%)	6
(normal range: 8%–15%)	

WBC, white blood cell; ALC, absolute lymphocyte count; NK, natural killer; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; BAU, binding antibody units.

ocrelizumab administration and vaccination is recommended.[18,19] Khayat-Khoei et al. were the first to report a negative antibody response to COVID-19 vaccination in a patient with MS following intravenous administration of ocrelizumab.[5] In our opinion, the interval between the second dose of vaccine and the first infusion of ocrelizumab following vaccination may have been too short in the study by Khayat-Khoei et al. Nevertheless, the impact of ocrelizumab on antibody responses following COVID-19 vaccination is certainly not clear and further studies are warranted.

Bar-Or et al. indicated that to maximize the probability of eliciting effective antibody responses, patients should be vaccinated 3 months after the last ocrelizumab infusion.[18] The rationale for this interval was to allow sufficient time for reconstitution of the total lymphocyte count.[18]

In the patient described here, a detectable antibody response against SARS-CoV-2 S protein was observed following administration of the Pfizer-BioNTech vaccine with suitable time intervals between ocrelizumab infusions, as recommended by a statement of the SMSN of the Polish Neurological Society.[13] According to this

statement, the interval between the last infusion of ocrelizumab pre-vaccination and vaccine administration should be 4 to 6 months, while the interval between the second dose of vaccine and the next infusion of ocrelizumab should be at least 4 to 6 weeks.[13,19,20] It was previously demonstrated that an interval between the second dose of vaccine and the next ocrelizumab infusion of 4 weeks or less may inhibit antibody production. The current study showed that an anti-SARS-CoV-2 antibody response was observed when the recommended intervals between ocrelizumab administration and vaccination were followed. Our patient had a reactive response to COVID-19 vaccination, in contrast to the case reported by Khayat-Khoei et al.[5] However, comparison of the levels of antibodies in this patient with those of healthy controls is not informative because correlations between antibody concentrations or specific antibodies and protection against COVID-19 have yet to be established.[21]

Buttari et al. reported that an interval of 3 months between the last ocrelizumab infusion and the first vaccine dose yielded an immune response in a patient with MS, whereas an interval of 2 months in a second patient did not.[22] These results indicate that prolonging the time interval between ocrelizumab administration and vaccination may favor generation of a reactive immune response.

The results of Achiron et al. were less optimistic.[23] That study included 44 patients with MS receiving ocrelizumab. The minimum interval from the last ocrelizumab infusion to the first dose of COVID-19 mRNA vaccine was 3 months (median 4.9 months). A reactive immune response was observed in only 10 of 44 patients (22.7%).[23] That study also applied an interval of 4.5 to 6.5 weeks between the second dose of vaccine and the subsequent ocrelizumab infusion.[23] Those intervals were very similar to those used in the current study as

suggested by the SMSN of the Polish Neurological Society. However, the results of Achiron et al. suggest that the interval from the last ocrelizumab infusion to the first vaccine dose should perhaps be extended to 9 months or longer, which would require postponing one infusion of the drug.[23]

Gallo et al. studied four patients with MS receiving ocrelizumab.[24] An interval of at least 3 months between the last ocrelizumab infusion and the first vaccine dose was used. Seven days after the second dose of COVID-19 mRNA vaccine, a reactive antibody response was observed in two patients, although antibody titers were weaker than in healthy controls.[24] That study had several limitations. First, the post-vaccination antibody response was assessed 7 days and not 4 weeks after the second dose. Second, the interval from the second dose to the next ocrelizumab infusion was not stated. However, it is plausible to assume that the next ocrelizumab infusion had not yet been administered at the time that the immune response was assessed. The most significant result of that study was that the strongest immune response was observed in the patient with the longest interval from the last ocrelizumab infusion to the first vaccine dose (>6 months).[24]

As with ocrelizumab, it has been reported that COVID-19 vaccination is not effective in patients treated with another drug that causes B-lymphocyte depletion (rituximab).[25,26] Because of the mechanism of action of this drug, it is recommended to administer COVID-19 vaccines in patients with MS receiving rituximab at least 3 to 6 months after the last infusion of rituximab and at least 6 weeks before the next infusion.[27]

Based on the above results, we conclude that in patients with MS receiving B-lymphocyte depleting therapies, the intervals between drug administration and

vaccination recommended by the SMSN of the Polish Neurological Society should be followed.[13,27] However, in some patients it appears that a longer interval may be necessary. Currently only limited data are available and therefore it is necessary to conduct further studies of immune responses following COVID-19 vaccination in patients receiving B cell-depleting therapies.

Conclusions

An interval of at least 4 to 6 months (or perhaps even 9 months) between the last infusion of ocrelizumab and the first dose of Pfizer-BioNTech COVID-19 vaccine and an interval of at least 4 to 6 weeks between the second dose of vaccine and the next infusion of ocrelizumab, as recommended by the SMSN of the Polish Neurological seems, offers the best chance to elicit antibody responses in patients with MS. This is currently the most cautious strategy for patient management based on the limited available data.

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