Immunocompetence after SARS-CoV-2 Infection in a Patient with Multiple Sclerosis Treated with Ofatumumab: A Case Report

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Abstract
Ofatumumab is the first fully human anti-CD20 monoclonal antibody that, on March 26, 2021, was approved by the EMA to treat patients with relapsing multiple sclerosis. This paper aimed to present a case confirming the ability to produce and maintain anti-SARS-CoV-2 antibodies in a patient treated with ofatumumab for over 4 years. The course of the infection was moderate, and the patient did not require hospitalization. Antibody measurements were performed five times post-COVID-19 infection. The first test was performed in the fourth month (131 days), and the last, over 1 year after the infection. To date, only 2 cases have been published describing the ability of a patient treated with the same drug to produce antibodies against SARS-CoV-2, although the observation was conducted over a shorter period. In our case study, we have 15-month follow-up data. The patient was not vaccinated and additionally received suppressive steroid therapy due to the relapse. We observed an increase in antibodies up to 10 months from the infection. The case under analysis suggests that patients treated with ofatumumab, despite complete peripheral B-cell depletion, can produce and maintain a long-lasting immune response.
Introduction

The COVID-19 pandemic has changed our perception of the treatment of patients with multiple sclerosis (MS). Initial concerns were mainly about the safety of disease-modifying therapies (DMTs). However, guidelines for the use of specific drugs were developed relatively quickly. In contrast, the increasing number of SARS-CoV-2 infections and the advent of the availability of COVID-19 vaccines have made it necessary to evaluate the immune response in patients receiving immunomodulatory treatment. This issue is particularly relevant to therapies that reduce the level of B lymphocytes, i.e., cells involved in the humoral response.

Several publications evaluated the immune response in MS patients treated with anti-CD20 antibodies that deplete peripheral B-cell amount. Habek et al. [1] evaluated outcomes obtained in patients with MS – on ocrelizumab (OCR) therapy and treatment-naïve and also results from healthy controls. They noticed that OCR administration had led to a decrease in humoral immunity.

Similar results were observed by Kister et al. [2] in a study conducted on 154 patients on OCR and 177 patients on other DMTs. It was demonstrated that patients on OCR who have had a SARS-CoV-2 infection present lower antibody levels than patients on other DMTs (seropositivity for OCR was only 36%, while for non-OCR DMTs it was 83–100%) [2].

Evaluation of COMBAT-MS trial participants revealed that OCR and rituximab (RTX), other anti-CD20 antibody, did not prevent the production of SARS-CoV-2-specific antibody. Moreover, in reaction for acute COVID-19 infection, great majority of patients on RTX produced a functional T cell response regardless of B-cell depletion status. The strength of memory T cell response in the OCR/RTX group was comparable to that in other treatment groups or in healthy subjects [3].

In turn, Zabalza et al. [4] who examined humoral response to SARS-CoV-2 infection in patients on anti-CD20 therapy observed that although humoral response is impeded with anti-CD20 therapy, it is higher in those with severe course of COVID-19. Ofatumumab (OFA) is a new, fully human monoclonal antibody administered subcutaneously (20 mg) once a month. In August 2020, the Food and Drug Administration approved the drug, and in March 2021, it was approved to treat patients with RMS in Europe.

To date, only a few publications have assessed the ability to produce antibodies against SARS-CoV-2 virus infection in patients treated with OFA; however, so far, it has not been evaluated in long-term follow-up. It, therefore, is important to collect detailed data on the use of different anti-CD20 therapy and its effect on IgG antibody production and maintenance in light of the SARS-CoV-2 pandemic.

Case Report/Case Presentation

The female patient, now 42 years old, was diagnosed with RMS on July 7, 2017. Her comorbidities included bronchial asthma of mild symptoms and obesity, according to the BMI (32.6 kg/m²). The first relapse occurred in April 2017 and manifested as left-sided paresthesia. In the subsequent relapse, 2 months later, dizziness and diplopia appeared. The patient was hospitalized, and diagnostic tests were performed. The MRI imaging showed nine lesions typical for MS (the largest was 12 mm in diameter), one ring-enhancing lesion. Oligoclonal bands were detected in cerebrospinal fluid. The patient was qualified for treatment in the COMB study (157G2301) on August 2, 2017. During the randomization process, she was assigned to a group of patients who received 20 mg OFA via subcutaneous injection once a month. The patient’s treatment progressed with good tolerability and efficacy; and no relapses had occurred. The patient’s physical ability did not deteriorate, and the patient had no
complaints about the form of administration of the drug. From July 11, 2019, the patient was treated in an open-label phase of the study OMB157G2399. Since the beginning of OFA treatment, IgG remained within the average range (normal range: 5.65–17.65 g/L), while the level of IgM significantly decreased to more than 10% below the lower limit of normal (LLN) in March 2020 (normal range: 0.4–2.3 g/L). As IgM values increased within a month, OFA treatment was continued and IgM levels remained relatively low but stable above LLN (Table 1). The first symptoms of SARS-CoV-2 infection occurred in the patient during the second wave of the COVID-19 pandemic in Poland. On October 9, 2020, the patient reported malaise associated with flu-like symptoms (muscle pain, cough, and intermittent dyspnea). Due to present symptoms and the confirmation of SARS-CoV-2 infection among family members, the patient was tested for infection on October 14, 2020. The PCR test confirmed SARS-CoV-2 infection. Cough and dyspnea increased suddenly on October 21, 2020. The patient required bronchodilators with Alvesco® (ciclesonide) and antibiotic therapy with Cirprinol® (ciprofloxacinum). The symptoms gradually subsided with marked improvement until October 28, 2020.

Due to the symptoms of COVID-19 during the planned OFA administration period, the dose planned for October 28, 2020, was omitted. The previous dose was administered as planned, i.e., on September 30, 2020, and the following dose on November 27, 2020. Laboratory tests performed after the SARS-CoV-2 infection during the routine visit on November 25, 2020, showed an increase in white blood cells (WBC) (16.71 × 10^9/L; normal range: 4.0–10.0 × 10^9/L) and neutrophils (14.09 × 10^9/L; normal range: 2.4–7.0 × 10^9/L) and a twofold increase in IgM (0.83 g/L) compared to that tested previously (0.42 g/L), with full B-cell depletion (CD19 [%] 0.0; normal range: 6.5–27.0% and CD19 [Abs] 1; normal range: 107–698/µL).

On the subsequent visits, laboratory tests were repeated, and a gradual return to normal was observed over 1 month. The first follow-up examination was performed on December 18, 2020. The following values were noted: WBC 14.03 × 10^9/L, neutrophils 13.12 × 10^9/L. The values noted in the succeeding examination on December 22, 2020, are WBC 7.75 × 10^9/L, neutrophils 5.34 × 10^9/L.

The patient had a mild relapse of MS, with symptoms manifesting from February 2, 2021, to February 8, 2021 (dizziness, balance disorders, nystagmus). A 0.5-point increase in the Expanded Disability Status Scale (EDSS) associated with the relapse was recorded.

During the four follow-up visits performed in 2021 and one in 2022, anti-SARS-CoV-2 IgG antibodies were tested. The results revealed an increase in antibody levels up to 10 months from the SARS-CoV-2 infection. Having been assessed 12 and 15 months later, they slightly decreased to a level of 89.70 BAU/mL. However, they remained about 3× above LLN; the details are presented in Table 2. Currently, the patient continues treatment with OFA; EDSS values remain unchanged since the beginning of therapy.

| Date       | IgG, g/L | IgM, g/L | CD19, % | CD19 Abs, n/µL |
|------------|---------|---------|--------|----------------|
| Aug 6, 2019| 10.10   | 0.44    | 0.0    | 0              |
| Oct 4, 2019| 9.86    | 0.42    | 0.0    | 0              |
| Dec 13, 2019| 9.18   | 0.43    | 0.0    | 0              |
| Mar 19, 2020| 10.70 | 0.36    | 0.0    | 0              |
| Apr 15, 2020| 10.20 | 0.42    | not assessed | |
| Jun 8, 2020 | 11.60 | 0.42    | 0.0    | 1              |
| Nov 25, 2020| 10.9  | 0.83    | 0.0    | 1              |
Discussion/Conclusion

The COVID-19 pandemic has focused global attention on the possibility of an increased risk of infection in patients treated with immunomodulation. When administering DMTs for MS, we are constantly looking to improve patient safety. There is a need to identify factors that affect the ability of patients undergoing DMTs for MS to produce and maintain an immune response, as viral infections are one of the major risk factors for relapse.

According to Xiao et al. [5], who described the profile of specific antibodies to SARS-CoV-2 in a general group of patients, IgM and IgG were confirmed in all patients 3 weeks after the onset of symptoms. At the fourth week after the onset of symptoms, IgM levels began to decrease, while IgG levels increased until the end of the study, at week 7. These results indicate a humoral immune response to protect the body from the SARS-CoV-2 virus [5].

To date, isolated publications supported the ability of patients receiving anti-CD20 therapy to produce antibodies. However, it has been suggested that serum antibody levels do not reflect the patient’s ability to respond to renewed exposure to the antigen. In the ASCLEPIOS phase-3 trial, no apparent association was observed between decreased Ig levels and increased risk of serious infection in MS patients treated with OFA up to 96 weeks [6]. Based on the known biology of autoimmunity and COVID-19, it is hypothesized that even though B-cell depletion should not necessarily expose patients to severe SARS-CoV-2-related issues, it may blunt protective immunity following infection and vaccination [7].

During the observation of our patient, we were able to evaluate the immune response in a patient treated with OFA after SARS-CoV-2 infection. Despite prolonged and complete depletion of CD19, the patient maintained the ability to produce antibodies against SARS-CoV-2. However, it should be emphasized that the data are fragmentary, and the patient requires further observation.

In addition to our observation, only in 2 cases of patients treated with OFA and infected with SARS-CoV-2, the presence of antibodies was confirmed. One of them was treated with OFA for 42 months and showed complete B-cell depletion with preserved normal serum IgG and IgM levels (it needs to be noted that in the case of the patient described herein, lower IgM levels were recorded). Despite being infected, the patient did not develop symptoms of infection. She showed a humoral response, and antibodies to SARS-CoV-2 remained positive for 3 months after initial serologic testing [8]. In the case of the patient described by Ivan Adamec as patient No. 3, symptoms of infection such as muscle pain and fever occurred in the 18th month of OFA treatment, and the authors confirmed the presence of antibodies after SARS-CoV-2 infection. However, this patient had a 28-week break in the intake of OFA caused by lower IgM levels. The level of CD19 before infection was 6.4% [9].

Table 2. The characteristics and results of anti-SARS-CoV-2 IgG antibodies determinations

| Date       | Result | Interpretation | Unit | Test type                                                                 |
|------------|--------|----------------|------|---------------------------------------------------------------------------|
| Feb 22, 2021 | 53     | Negative <12   | AU/mL| Chemiluminescence immunoassay LIAISON® SARS-CoV-2 S1/S2IgG (DiaSorin S.p.A.) |
| May 14, 2021 | 123.24 | Positive ≥15   | BAU/mL| Chemiluminescence immunoassay LIAISON® SARS-CoV-2 TrimericS IgG assay (DiaSorin S.p.A.) |
| Aug 6, 2021  | 128    | Negative <33.8 | BAU/mL|                                                                          |
| Oct 25, 2021 | 110    | Positive ≥33.8 | BAU/mL|                                                                          |
| Jan 17, 2022 | 98.70  |                |      |                                                                          |

AU, arbitrary units; BAU, binding antibody units (WHO International Reference Standard).
The patient presented in this publication developed symptoms of COVID-19 in the 68th week of the OMB157G2399 study after 37 months of OFA treatment. The PCR test confirmed the infection. The IgG level was normal while IgM decreased but remained slightly above the LLN. Complete CD19 depletion was confirmed, and the final testing of the anti-SARS-CoV-2 antibodies levels was performed 15 months post-infection. The patient’s recovery and subsequent antibody tests confirmed the ability of the patient treated with immunomodulatory therapies to produce and maintain long-term antibodies to SARS-CoV-2. By performing multiple measurements during follow-up, for the first time, it was possible to provide some insight on the sustainability of the humoral response over time in a B-cell depleted patient. Such long-term persistence of anti-SARS-CoV-2 antibody levels in a patient treated with OFA has not been described before. When administering anti-CD20 therapy, it appears necessary to identify the group of patients capable of producing antibodies and determine how long anti-SARS-CoV-2 antibodies will persist.

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Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local and national guidelines. Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest Statement

Elżbieta Jasińska reports advisory boards for Biogen; speaker fees from Biogen, Novartis, Roche, and Sanofi.

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Author Contributions

Elżbieta Jasińska is the single author of this publication and was solely involved in the case management, data acquisition, and manuscript editing and review.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the author.
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