

# Negative Anti-SARS-CoV-2 S Antibody Response Following Pfizer SARS-CoV-2 Vaccination in a Patient on Ocrelizumab

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## Case Report

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# Abstract

Several vaccines for novel Coronavirus (SARS-CoV-2) are now available. In Multiple Sclerosis (MS) patients on anti-CD20 therapy, blunted antibody responses to SARS-CoV-2 infection and to some vaccines have been reported. However, there is no data on immune response to mRNA vaccines against SARS-CoV-2 in patients on anti-CD20 therapies. We present a patient with MS on ocrelizumab, who received the Pfizer mRNA COVID-19 vaccine, and did not seroconvert 27 days after the second vaccine dose as measured by an FDA approved Anti-SARS-CoV-2 S assay.

## Case Presentation

A 44-year-old Caucasian male presented 4 years ago with symptomatic myelitis and multifocal demyelinating T2 and T1 Gadolinium contrast enhancing (T1Gd+) lesions throughout brain and spinal cord. He was diagnosed with Relapsing Remitting MS (RRMS), initiated on semi-annual ocrelizumab therapy and had no evidence of disease activity (NEDA) for 3.5 years. He had been repeatedly tested for presence of SARS-CoV2 by RT-PCR through the institutional research program (Figure 1). He received his first dose of SARS-CoV-2 (Pfizer) vaccine 5 months after ocrelizumab infusion, followed by the second dose 21 days later. There was a moderate post-vaccination systemic reaction with myalgias and fatigue. He received another ocrelizumab infusion 9 days after the second dose of vaccine (Figure 1). The decision to receive treatment on schedule was made considering his excellent therapeutic response to date with on-label use of ocrelizumab. On the day of infusion, he had complete depletion of CD19+ and CD20+ but Immunoglobulin G (IgG) level and Absolute Lymphocyte Count (ANC) were normal (Figure 1). At the time of infusion he tested negative for antibodies to the SARS-CoV-2 nucleoplasmid antigen (Roche Elecsys Anti-SARS-CoV-2), an assay that interrogates for a humoral immune response to SARS-CoV-2 indicating prior infection [6]. This assay does not reflect immune response from the mRNA vaccines, directed against virus spike but not nucleocapsid protein.

27 days after the second vaccine dose and 18 days after Ocrelizumab infusion, the patient was tested using the Roche Elecsys Anti-SARS-CoV-2 S assay (Figure 1). This assay is intended for qualitative and semiquantitative detection of antibodies to the SARS-CoV-2 spike (S) protein receptor binding domain. It is designed to detect adaptive immune response indicating prior infection, and to uniquely detect SARS-Cov-2 anti-S antibodies post mRNA vaccination [7]. Based on manufacturer's internal studies in healthy subjects and patients infected with with SARS-CoV-2 (positive RT-PCR), the assay is highly specific with negative predictive value (NPV) of 99.98, while its sensitivity increases from 90.6% 0-7 days after confirmed infection to 96.6%  $\geq$ 15 days after positive RT-PCR [8].

The result of this spike antibody assay was negative in our patient indicating no measurable post-vaccination immunity (negative results  $<0.80$  U/mL).

## Discussion

To our knowledge, this is the first report of SARS-CoV-2 vaccine response in a patient with multiple sclerosis on intravenous anti-CD20 therapy. There are cases of negative SARS-CoV-2 IgG assays in MS patients with PCR-confirmed COVID-19 infection on Ocrelizumab [2–4]. A recent publication of persistent anti-SARS-CoV-2 IgG antibodies following COVID19 infection in patient on ofatumumab, suggests a detectable humoral response to SARS-CoV-2 [9]. Another investigation indicates that binding titers to spike receptor–binding domain (RBD) protein as assessed on enzyme-linked immunosorbent assay (ELISA) are significantly increased on day 15 post initial 100-µg dose of mRNA-1273 vaccination [10]. Further, unpublished internal validation studies in 24 healthy volunteers for Anti-SARS-CoV-2 S assay at our institution (Dr. Petr Jarolim) suggest positive immunity after the first dose of mRNA vaccine in all subjects, with some showing titers greater than 250 U/mL (analytical measurement range).

The VELOCE trial in RRMS patients showed attenuated but present humoral responses following pneumococcal, influenza and tetanus toxoid vaccinations upon initiation of ocrelizumab. [5]. Blunted immunity to hepatitis B vaccine has been observed in patients on rituximab [11, 12]. Ocrelizumab does not affect plasma cells directly and naïve B-cells generally recover significantly faster than memory B-cells [12].

Our patient did not seroconvert when tested 27 days after the second dose of the Pfizer mRNA vaccine. It is likely that antibody response would have been generated after the 1<sup>st</sup> and the 2<sup>nd</sup> vaccine doses, 5 months after the prior infusion, despite re-treatment with ocrelizumab on day 9 post-vaccination (Figure 1). However, it is possible that early re-treatment with ocrelizumab may have further dampened post-vaccination immunity.

Our case documents insufficient humoral response after mRNA SARS-CoV-2 vaccination in a B-cell depleted patient, and this is potentially concerning. However, the clinical relevance of this result is unclear as it may not indicate a complete absence of immunity to the wild type SARS-CoV-2 infection [2, 10]. In this setting, formation of antigen-specific cytotoxic anti-viral T cells may help provide some protection. It is not known if the absence of Anti-SARS-CoV-2 S antibodies reflects suboptimal vaccine response and whether delaying anti-CD20 treatments to allow B cell reconstitution before administering COVID-19 mRNA vaccine may be warranted in some patients [2,9].

Larger studies investigating COVID-19 mRNA vaccine response in patients on anti-CD20 treatments are essential to define the optimal “vaccination window.”

## Declarations

**Funding:** not applicable.

**Conflicts of interest/competing interests:** authors have no conflict of interest.

**Ethics approval:** All studies performed at the Brigham and Women’s Hospital are approved by the appropriate ethics committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Consent:** Patient signed informed consent regarding publishing his data.

**Data and/or Code availability:** not applicable

**Authors’ contribution statements:**

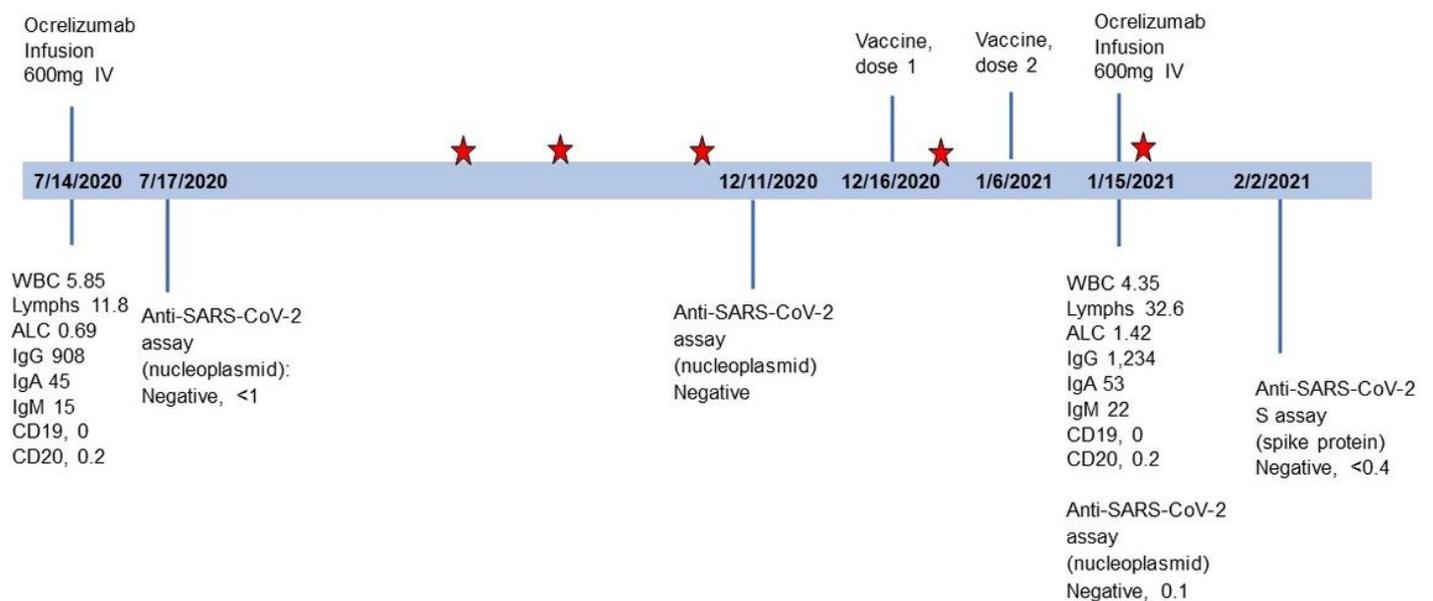
All authors contributed to the study conception and design. The first draft of the manuscript was written by Mahsa Khayat-Khoei and all authors edited subsequent versions of the manuscript. All authors read and approved the final draft.

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## Figures



**Figure 1**

Timeline of patient's ocrelizumab infusions, vaccination and SARS-CoV-2 test and lab results. Patient had serial SARS-CoV-2 PCR tests (negative) through the institutional research program. The red stars indicate negative SARS-CoV-2 PCR tests. Reference range for Anti-SARS-CoV-2 assay (nucleoplasmid) <1.00 COI, Anti-SARS-CoV-2 spike (S) <0.8 U/mL, WBC 4.00 - 10.00 K/uL, Lymphocytes 18.0 - 41.0%, ALC 0.72 - 4.10 K/uL, IgG 700 - 1,600 mg/dL, IgA 70 - 400 mg/dL, IgM 40 - 230 mg/dL, CD19 7.0-27.0 % lymphocytes, CD20 3.0-20.0 % lymphocytes