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Negative SARS-CoV-2 antibody testing following COVID-19 infection in Two MS patients treated with ocrelizumab

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SUMMARY

Background: It is unknown whether MS disease modifying therapies impact ability to mount an antibody response to SARS-CoV-2.

Methods: Case series and literature review. We report a series of two MS patients who developed COVID-19 while on Ocrelizumab therapy and subsequently exhibited negative SARS-CoV-2 serology.

Results: A 42-year-old man and 39-year-old woman with MS developed COVID-19 while on Ocrelizumab therapy. Neither patient required hospitalization. The man exhibited negative serology at 7- and 9-weeks post-infection. The woman exhibited negative serology at 6- and 12-weeks post-infection.

Conclusions: Large studies are essential to determine whether certain DMTs may blunt SARS-CoV-2 antibody production.

1. Introduction

The emergence of SARS-CoV-2 has produced numerous questions surrounding immunomodulatory management of patients with autoimmune conditions like multiple sclerosis (MS). Treatment of MS is complex, relying on a variety of disease modifying therapies (DMTs) with myriad mechanisms of action. Each DMT, therefore, may impact response to the virus in a different manner (Berger et al., 2020).

As the majority of patients with coronavirus disease-19 (COVID-19) recover and the world moves to the next phase of the pandemic, COVID-19 antibody testing has emerged as a useful tool in determining prior infection and potential immunity. Several serological assays have been granted “Emergency Use Authorization” (EUA) by the FDA for this purpose. While the specificity of these assays is of concern with regards to false-positives, the sensitivity and negative predictive value are high (FDA.gov, “EUA Authorized Serology Test Performance”). The sensitivity may be diminished by inadequate timing of testing following an infection, but the most recent literature suggests that the vast majority of patients with symptomatic COVID-19 produce antibodies within the first two to three weeks after symptom onset (Long et al., 2020).

In MS, a possible concern is the impact of certain DMTs, such as CD-20 monoclonal antibodies and Sphingosine 1-Phosphate receptor modulators, on the ability of patients to mount an antibody response to SARS-CoV-2. This question is not only pertinent post-infection, but is also of paramount importance with regards to eventual vaccine production. Studies have demonstrated that use of B-cell depleting therapies like Rituximab (Assen et al., 2010; Bingham et al., 2010) and Ocrelizumab (Stokmaier et al., 2018) is associated with blunted humoral response to certain vaccinations. It remains to be seen whether patients on B-cell therapies who develop COVID-19 mount a detectable antibody response.

In this article, we report serology results from the first two patients at our center to have undergone SARS-CoV-2 antibody testing after developing COVID-19 while on Ocrelizumab therapy.

2. Methods

Case report, literature review.

3. Case histories

3.1. Case 1

A 42-year-old man with relapsing remitting (RR) MS treated with Ocrelizumab developed symptomatic COVID-19 infection. He was diagnosed with MS four years prior, had no comorbidities, and was a non-smoker. He began Ocrelizumab treatment nine months prior to infection, with the last infusion occurring two months prior contracting the disease. Initial symptoms of COVID-19 included fever, cough, and impaired taste. This progressed over several days to involve dyspnea on exertion. However, he did not exhibit shortness of breath at rest and did not require hospitalization. He underwent nasopharyngeal testing which confirmed SARS-CoV-2 infection. The patient's respiratory symptoms resolved after two weeks, while dysgeusia persisted >1 month. The patient underwent SARS-CoV-2 serology testing at 7-weeks post-infection (BioReference Laboratories, using either the DiaSorin Liaison Sars-CoV-2 S1/S2 assay) and again at 9-weeks post-infection (Northwell Health Laboratory, using the Roche Elecsys Anti-Sars-CoV-2 assay), both yielding a negative result (Table 1). At the time of the second negative result, his absolute CD-19 count was 30 cells/uL (3%), absolute lymphocyte count (ALC) was 1260 cells/uL, and an immunoglobulin panel was within normal limits.

3.2. Case 2

A 39-year-old woman with RRMS treated with Ocrelizumab developed symptomatic COVID-19 infection. She was diagnosed with MS five years prior, had no comorbidities, and was a non-smoker. She received her first Ocrelizumab infusion four months prior to infection. A health-care worker, she developed only a mild cough after a close contact with

Table 1
Testing characteristics.

	Case 1 1 st Test <u>DiaSorinLIAISON SARS-CoV-2</u>	2 nd Test <u>RocheElecsysAnti-SARS-CoV-2</u>	Case 2 1 st Test <u>Abbott Architect SARS-CoV-2</u>	2 nd Test <u>Ortho-Clinical Diagnostics VITROS Anti-SARS-CoV-2</u>
Antibody Target	IgG Spike	Pan-Ig Nucleocapsid	IgG Nucleocapsid	IgG Spike
Technology	High Throughput CMIA	High Throughput ECLIA	High Throughput CMIA	High Throughput CLIA
Location	BioReference Labs	Northwell Labs	Quest Labs	Northwell Labs
Estimate Interval After Symptom Onset	7 weeks	9 weeks	6 weeks	12 weeks
Sensitivity*	97.6% (40/41)	100% (29/29)	100% (88/88)	90% (36/40)
NPV at 5% Prevalence*	99.9%	100%	100%	99.5%
Specificity*	99.3 (1082/1090)	99.8% (5262/5272)	99.6% (1066/1070)	100% (407/407)
PPV at 5% Prevalence*	88.0%	96.5%	92.9%	100%

Abbreviations: Chemiluminescence Microparticle Immunoassay (CMIA), Electrochemiluminescence Immunoassay (ECLIA), Chemiluminescence Immunoassay (CLIA), Estimated Disability Status Scale (EDSS), Disease Modifying Therapies (DMT), Negative Predictive Value (NPV), Positive Predictive Value (PPV). *Estimates as provided on FDA.gov website.²

someone in her care who tested positive for SARS-CoV-2. She underwent nasopharyngeal swab that confirmed SARS-CoV-2 infection. She had a mild course and her respiratory symptoms lasted only two days. The patient underwent SARS-CoV-2 serology testing at 6-weeks post-infection (Quest Laboratories, using the Abbott Architect SARS-CoV-2 IgG assay) and again at 12-weeks post-infection (Northwell Health Laboratory, using the Ortho-Clinical Diagnostics VITROS Anti-SARS-CoV-2 IgG assay), both yielding a negative result (Table 1). At the time of the first negative result, absolute CD-19 count was 2 cells/uL (0.06%), ALC was 3900 cells/uL, and an immunoglobulin panel was within normal limits.

4. Discussion

In this case series, we present negative results from the first two MS patients at our site who underwent SARS-CoV-2 antibody testing after developing PCR-confirmed COVID-19 while on Ocrelizumab. While accuracy of individual assays is a potential concern, the results are strengthened by the fact that each patient underwent two separate assays granted EUA by the FDA, performed at two separate labs, several weeks apart (Table 1). Furthermore, negative testing over two time-points greatly limits the possibility that timing was a significant factor. As most people infected with COVID-19 are expected to produce antibodies (Long et al., 2020), we posit that Ocrelizumab played a role in dampening the antibody response.

Anti-CD20 monoclonal antibodies impair the humoral arm of the immune system by removal of nearly all circulating B-cells. This results in dampened humoral responses (Assen et al., 2010; Bingham et al., 2010; Stokmaier et al., 2018). However, as evidenced by our series and by reassuring preliminary data on recovery of the vast majority of MS patients from COVID-19 (Safavi et al., 2020; Sormani et al., 2020), an intact humoral response may not be strictly necessary for virus clearance. Further support for this assertion comes from a report of two patients with X-linked Agammaglobulinemia, a genetic disease characterized by lack of B-cells, who developed a mild COVID-19 infection and recovered fully (Soresina et al., 2020). Therefore, a functioning innate immune and an intact antigen-specific cytotoxic T-cell response may be sufficient for virus clearance.

Following COVID-19, short-term re-infection rates in the general population are low (Kirkcaldy et al., 2020). It is thought that immunity is mediated by both the synthesis of neutralizing antibodies and formation of antigen-specific cytotoxic T-cells directed against the virus, but it is currently unknown whether either is essential or sufficient. Therefore, the failure of our patients to produce antibodies to SARS-CoV-2 may or may not indicate a higher risk of re-infection, and further research is necessary. Large studies are essential to conclusively determine whether certain DMTs may blunt SARS-CoV-2 antibody production, and whether this may increase re-infection risk in MS patients.

Declaration of Competing Interests

Jeanine Rempe Thornton reports no disclosures.

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