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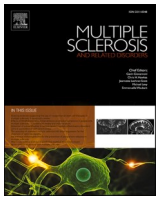

Original article

Attenuation of antibody response to SARS-CoV-2 infection in patients with multiple sclerosis on ocrelizumab: A case-control study

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ABSTRACT

Objective: Ocrelizumab (OCR) is a monoclonal antibody directed at B-cells that is FDA approved for treatment of RRMS and PPMS. Prior studies have raised concerns about patients' ability to form antibodies in response to various antigens, especially SARS-CoV-2. The objective of this study is to determine whether OCR attenuates the antibody response to SARS-CoV-2 in patients with MS as compared with other disease modifying therapies.
Methods: This is a case-control study looking at the odds of developing antibodies to SARS-CoV-2 in patients treated with OCR versus other disease modifying therapies. From May 13, 2020 through March 1, 2021, patients with a RT-PCR-confirmed infection to SARS-CoV-2 were tested for presence of antibodies and the data was recorded. Outpatients with MS at the Methodist Hospitals Comprehensive MS Center were selected who had a prior infection with COVID-19 as demonstrated by RT-PCR in the electronic health records. Odds ratios were calculated to compare rates of antibody formation with OCR exposure vs other DMT.
Results: 24 patients had evidence of COVID-19 and had antibody testing available at the time of analysis. Patients who received OCR had decreased odds of forming antibodies (OR 0.045, $p = 0.011$, 95% CI (0.004,0.488)).
Conclusions: Patients who received OCR within the prior 6 months of COVID-19 infection had decreased odds of developing antibodies as compared with other DMTs. This suggests that OCR may attenuate the antibody response to SARS-CoV-2. Additional studies should analyze the odds of spike protein antibody formation in response to SARS-CoV-2 vaccines for patients on OCR.

1. Introduction

Ocrelizumab (OCR) is a monoclonal antibody directed against CD20+ B-cells. It is approved for both relapse-remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS) in the United States (Hauser et al., 2017; Montalban et al., 2017). I previously reported a case of a patient on OCR with hypogammaglobulinemia who did not have detectable antibodies to SARS-CoV-2 after a course of COVID-19 (Conte, 2020). Since then, other case reports have emerged regarding various antibody responses after OCR exposure. Lucchini and colleagues reported two patients without SARS-CoV-2 antibodies following OCR exposure, with one patient having hypogammaglobulinemia (Lucchini et al., 2020). Thornton and Harel reported an additional two cases of negative antibody testing, but with normal immunoglobulin levels (Thornton and Harel, 2020). However, not all case reports have shown negative antibodies. Flores-Gonzalez and associates reported a case of a patient on ofatumumab, which is another B-cell-depleting agent similar to OCR, with normal immunoglobulin levels and evidence of B-cell depletion who did in fact develop antibodies to SARS-CoV-2 (Flores-Gonzalez et al., 2021). A recent study showed that only 17.6% of patients on OCR developed antibodies and another study found that in their cohort, 90% of those that tested negative for antibodies were on CD20 modulators (Zabalza et al., 2021; Wallach and Picone, 2021).

Since my first study, I began to collect data on other patients' antibody status after various disease modifying therapies (DMT) within my center. The objective of the present study was to determine whether OCR reduces antibody production in response to SARS-CoV-2 as compared to other DMTs.

2. Methods

This study design was a case-control study. Starting in May 2020, patients with MS who had a confirmed infection of COVID-19 were tested for antibodies to SARS-CoV-2 IgG. Patients were considered positive for COVID-19 if they had a prior positive RT-PCR test. In

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addition, a chart review was performed to record age, race, gender, type of MS, MS disease onset, current DMT, and time between infection and testing of antibodies. For patients on OCR, immunoglobulin levels were tested if not tested within the last month. A variety of assays were used to test for antibodies to SARS-CoV-2, and included assays from Alverno Laboratories, Quest Diagnostics, and Labcorp.

Statistics were performed in Stata 14. Logistic regression was used to obtain the odds ratio of having an antibody response while on OCR vs other DMT. p-values less than 0.05 were considered significant.

2.1. Data availability

Individual, deidentified participant data is available on request.

3. Results

Twenty-four patients with MS at The Methodist Hospitals Comprehensive MS Center were infected in the community with SARS-CoV-2 as demonstrated by RT-PCR testing before the time of analysis and had SARS-CoV-2 IgG testing available. Fifteen patients were on OCR and 9 patients were on other DMTs. "Other" DMTs included fingolimod (2), ozanimod (2), teriflunomide (2), alemtuzumab (1), natalizumab (1) and oral cladribine (1). Baseline characteristics are reported in Table 1, which were similar between the two groups. Ages ranged between 21 and 65. There were 22 females and 2 males.

Overall, 4 out of 15 patients on OCR developed antibodies (0.27), while 8 out of 9 patients on other DMTs developed antibodies (0.89). Patients who received OCR had decreased odds of forming antibodies (OR 0.045, $p = 0.011$, 95% CI (0.004,0.488)). Only one patient in the OCR group had hypogammaglobulinemia (IgG 538 mg/dl (normal 700–1600 mg/dl), IgM <25 mg/dl (normal 40–230 mg/dl), and IgA 161 mg/dl (normal 70–400 mg/dl)), and she had tested negative for antibodies. The majority of patients were considered to have a mild course of COVID-19 regardless of DMT, although two patients on OCR had a moderate course of COVID-19 (requiring hospitalization) and three patients on other DMTs had a moderate course of COVID-19.

Age independent of DMT was not associated with attenuation of antibody response (OR 1.06, $p = 0.134$, 95% CI (0.983,1.14)). Similarly, longer duration of disease was not associated with attenuation of antibody response (OR 1.08, $p = 0.129$, 95% CI (0.977,1.20.).

4. Discussion

There exists a concern about the immunogenicity of SARS-CoV-2 in patients on FDA-approved B-cell depleting agents such as OCR, rituximab, and ofatumumab. I had previously postulated in a single case report that hypogammaglobulinemia could drive the attenuation of the antibody response. However, in the current study, immunoglobulin levels did not influence antibody status. Indeed, this study shows that mere exposure to OCR significantly attenuates the antibody response to SARS-CoV-2.

With the exception of one patient, all the non-OCR DMTs showed antibody formation. The one patient was on ozanimod. This could have been a scenario where she did not produce antibodies naturally, as a previous study showed a 93.1% seroconversion rate for SARS-CoV-2 antibodies for normal patients (Zhao et al., 2020). There was another patient in the cohort who was on ozanimod and did in fact develop antibodies.

It should be noted that absence of antibody production in response to a COVID-19 infection should not be equated to predicting whether or not there would be a humoral response to a vaccine. In the recently published VELOCE trial, patients were able to mount a humoral response to various antigens although the response was attenuated (Bar-Or et al., 2020).

This study is limited by a relatively small sample size and that not all FDA-approved DMTs were included. There is also no information about other B-cell depleting agents such as rituximab and ofatumumab. Data will continue to be collected as more patients are infected with SARS-CoV-2. An additional study should be undertaken to measure antibody levels to the spike protein following vaccination.

Table 1
Patient characteristics.

		Overall	OCR	Other DMT	p-value
N		24	15	9	
Age, mean (SD), y		46.1 (12.49)	42.6 (12.12)	52.0 (11.38)	0.073
Sex, n (%)	Female	21 (92)	14 (93)	8 (89)	0.70
	Male	2 (8)	1 (7)	1 (11)	
Race, n (%)	White	21 (88)	13 (87)	8 (89)	0.69
	Black	2 (8)	1 (7)	1 (11)	
	Hispanic	1 (4)	1 (7)	0 (0)	
MS subtype, n (%)	RRMS	22 (92)	13 (87)	9 (100)	0.52
	PPMS	1 (4)	1 (7)	0 (0)	
	SPMS	1 (4)	1 (7)	0 (0)	
Onset of disease, mean (SD), y		11.6 (8.95)	9.8 (7.05)	14.6 (11.29)	0.21
Time between infection and testing, mean (SD), months		2.85 (2.90)	2.97 (2.79)	2.67 (3.23)	0.81

Author statement

WLC performed the writing of the manuscript, data collection, data analysis, and statistics.

Conflicts of interest

Research funding from Novartis unrelated to the current study. Consultant fees from Bayer, Biogen, Bristol Meyers Squib, Genentech, Novartis, and Sanofi Genzyme. Speaking fees from Allergan, Alexion, Biogen, Bristol Meyers Squib, EMD Serono, Genentech, Janssen, Novartis, and Sanofi Genzyme.

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