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Tixagevimab and Cilgavimab (Evusheld) boosts antibody levels to SARS-CoV-2 in patients with multiple sclerosis on b-cell depleters

William L. Conte [a,b,*], Lilian Golzarri-Arroyo [c]

[a] *Comprehensive MS Center, Methodist Hospitals, Merrillville, IN 46410, United States of America*
[b] *School of Medicine, Indiana University, Bloomington, IN, United States of America*
[c] *Department of Epidemiology and Biostatistics, School of Public Heath Bloomington, Indiana University, Bloomington, IN, United States of America*

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ABSTRACT

Background and objectives: B-cell-depleting therapies may affect the development of a protective immune response following vaccination against SARS-CoV-2. It is important to have a different strategy for creating immunity in this patient population. The objective of this study was to evaluate whether Evusheld (tixagevimab co-packaged with cilgavimab) affects the antibody response to SARS-CoV-2 following an attenuated response to the vaccines against SARS-CoV-2 in patients on b-cell depleters who have multiple sclerosis.
Methods: This was a single-center cohort study performed at Methodist Hospitals in Merrillville, IN, USA. It included patients with multiple sclerosis treated with ocrelizumab and ofatumumab. Patients had already received the mRNA vaccinations against SARS-CoV-2 and had demonstrated an attenuated response on baseline antibody testing. All participants received 150 mg of Evusheld. Follow-up antibody levels were measured at least two weeks following Evusheld injections.
Results: All patients (100%) developed the highest level of antibodies possible at least two weeks following Evusheld injections.
Discussion: In this study, patients with MS who had an attenuated antibody response to the COVID-19 vaccines due to exposure to b-cell depleters now had the highest antibody response possible after receiving Evusheld. This is important as it provides a different strategy for protection against COVID-19.

1. Introduction

Although vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed, immunocompromised patients or patients who are on medications that blunt the humoral response to vaccination remain a challenge. Multiple studies have shown that b-cell depleters, such as ocrelizumab (OCR) and ofatumumab (OFA) attenuate the humoral response to SARS-CoV-2 vaccines in patients with multiple sclerosis (MS) (Achiron et al., 2021; Apostolidis et al., 2021; Brill et al., 2021; Conte, 2022; Gallo et al., 2021; Georgieva et al., 2022; Jakubecz et al., 2022; Katz et al., 2022; Mariottini et al., 2022; Novak et al., 2021; Sormani et al., 2021; Tallantyre et al., 2022).

On December 8, 2021, the Food and Drug Administration (FDA) authorized Evusheld (tixagevimab co-packaged with cilgavimab) for pre-exposure prophylaxis in certain individuals. The indication includes patients who are immunocompromised, either due to a medical condition or due to taking medications that causes people to not mount an adequate immune response to vaccines. The authorization was based on the PROVENT study, which was a double-blind trial comparing Evusheld to placebo (Levin et al., 2022). The primary endpoint (symptomatic COVID-19) occurred in 8 patients who received antibodies and in 17 who received placebo which amounted to a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness (relative risk reduction 76.7%, $p<0.001$) (FDA, 2021; Levin et al., 2022).

2. Methods

2.1. Study participants

Patients with MS were recruited at the Comprehensive MS Center at Methodist Hospitals, in Merrillville, IN, USA. Patients who were vaccinated against SARS-CoV-2 and were exposed to b-cell depleters (OCR and OFA) during their vaccination period were recruited. Patients were

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* Corresponding author at: Comprehensive MS Center, Methodist Hospitals, 200 E 89th Ave, Merrillville, IN 46410, USA
E-mail address: Billy.conte@gmail.com (W.L. Conte).

Table 1
Baseline characteristics.

	Overall (N=18)
Age	
Mean (SD)	49.9 (13.6)
Median [Min, Max]	50.0 [27.0, 72.0]
Gender	
Female	10 (55.6%)
Male	8 (44.4%)
Race	
Black	1 (5.6%)
White	17 (94.4%)
Type of MS	
PPMS	3 (16.7%)
RRMS	15 (83.3%)
Med	
Ocrelizumab (OCR)	17 (94.4%)
Ofatumumab (OFA)	1 (5.6%)
Onset of Disease (years)	
Mean (SD)	12.1 (9.02)
Median [Min, Max]	10.0 [3.00, 40.0]
Lymph <1.2	
Mean (SD)	1.55 (0.620)
Median [Min, Max]	1.45 [0.600, 2.70]
Time from infusion (m)	
Mean (SD)	4.32 (2.49)
Median [Min, Max]	4.00 [0.500, 11.0]
Missing	1 (5.6%)
time from injection (d)	
Mean (SD)	22.1 (7.78)
Median [Min, Max]	18.0 [14.0, 38.0]
Vaccine	
Moderna	5 (27.8%)
Pfizer	13 (72.2%)
Boosted	
No	1 (5.6%)
Yes	17 (94.4%)

tested for antibodies against SARS-CoV-2, and if less than 150 U/mL (50% of the maximum assay value) were offered Evusheld. Post-Evusheld antibody testing was performed at least two weeks following injections of Evusheld.

2.2. Antibody testing

The immunoassay for the detection of IgG antibodies was performed using the Labcorp anti-SARS-CoV-2 semi-quantitative IgG ECLIA assay against the spike protein receptor binding domain. The assay ranged from <0.4 to >250 U/mL. Titers <0.8 U/mL were considered negative.

2.3. Evusheld injection

150 mg of tixagevimab and 150 mg of cilgavimab were given as an intramuscular injection (note that this study was completed prior to the FDA's update to 300 mg each of tixagevimab and cilgavimab).

2.4. Data collection

The study was approved by the institutional review board at Methodist Hospitals. Individual, deidentified participant data is available on request.

2.5. Statistical analysis

Descriptive statistics were calculated for demographic variables. To compare the difference on frequency pre and post Evusheld for antibodies higher or lower than 0.8 U/mL, a McNemar's test was performed. Additionally, Paired Wilcoxon test and permutation tests were performed to compare the level of antibodies pre and post Evusheld. All analyses for this project were run in R version 4.0.3 (R Core team, 2020) using RStudio (RStudio Team, 2020).

3. Results

3.1. Demographic characteristics

Baseline characteristics are reported in Table 1. Eighteen patients were recruited, with 17 patients on OCR and 1 patient on OFA. The majority of patients were female (55.6%) and received the Pfizer vaccine (72.2%).
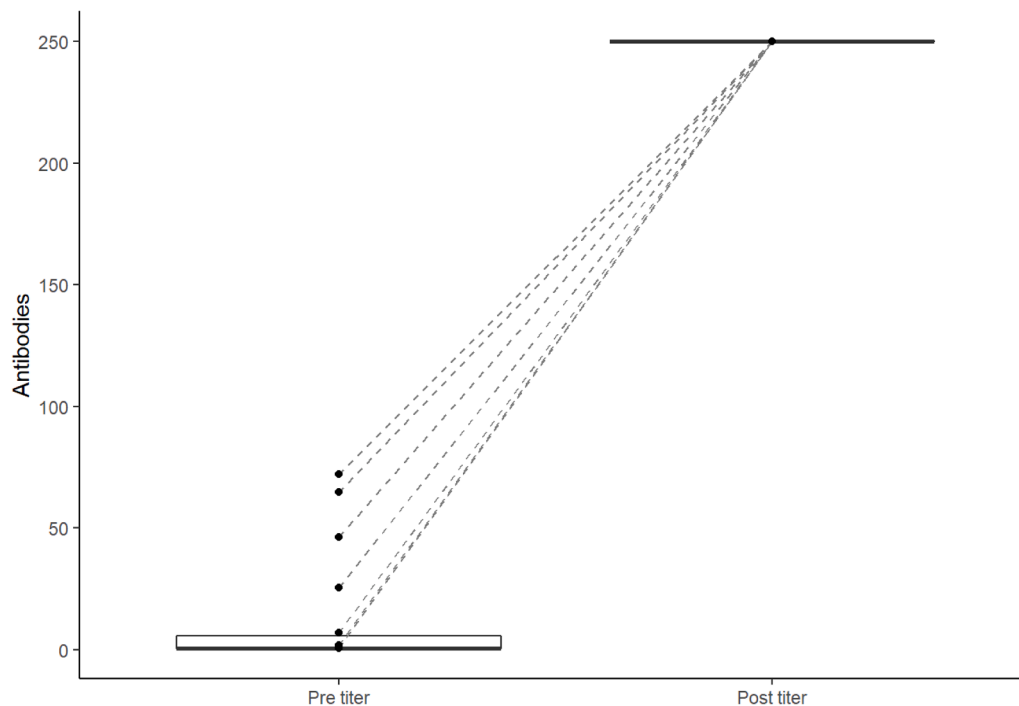

Fig. 1. Paired plot showing pre- and post-titer.

3.2. Level of SARS-CoV-2 antibody response

Prior to Evusheld, the mean antibody level was 12.38 U/mL and 12 patients had undetectable antibody levels (66%). At least two weeks following Evusheld injection, all patients in this cohort had an antibody response. Specifically, all patients had aa >250 U/mL level of antibody, which is the highest level the assay measures.

To compare the level of antibodies, it can be seen in Fig. 1 that all values increased to the highest level that can be recorded.

At baseline there were 12 patients lower than 0.8 U/mL and 6 higher than the threshold. After Evusheld, all 18 subjects were above the threshold. When comparing the frequencies of samples higher or lower than 0.8 U/mL, there were significant differences between pre and post frequencies ($p = 0.001$) with McNemar's test.

When comparing the ranks of the level of antibodies between pre and post using a paired Wilcoxon test, there was a statistical difference ($p<0.001$). To look into the difference further and see how extreme the change was prior and after Evusheld injection, a Permutation Test was performed, where the mean observed difference in our sample was 237.62, which was statistically significant ($p<0.001$).

4. Discussion

It is concerning that certain medications, such as b-cell depleters, attenuate the antibody response to SARS-CoV-2. Therefore, it is important to have other options that do not depend on the humoral immune system. As demonstrated in the data, we have shown that Evusheld creates a 100% antibody response in this patient population.

This study is limited by a relatively small sample size. It is also worth mentioning that it is still unknown what antibody level denotes immunity to SARS-CoV-2. Further, due to time constraints, we did not measure clinical outcomes after Evusheld. A future study should look at clinical outcomes following Evusheld in patients with MS on b-cell depleters. In addition, we will continue to monitor patients' antibody levels in order to assess the longitudinal effects of Evusheld on antibody levels in this patient population.

CRediT authorship contribution statement

William L. Conte: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Lilian Golzarri-Arroyo:** Formal analysis.

Declaration of Competing Interest

WLC: Research funding from Novartis and Sanofi Genzyme, unrelated to the present study. Consultant fees from Bayer, Biogen, Bristol Meyers Squib, Genentech, Novartis, and Sanofi Genzyme. Speaker fees from AbbVie, Alexion, Biogen, Bristol Meyers Squib, EMD Serono, Genentech, Horizon, Janssen, and Sanofi Genzyme

LGA: None pertinent.

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