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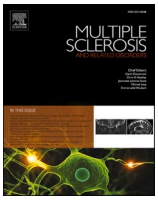

The humoral response to SARS-COV-2 vaccines in MS patients: A case series exploring the impact of DMT, lymphocyte count, immunoglobulins, and vaccine type

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ABSTRACT

Background & Objectives: Certain disease modifying therapies may negatively impact the humoral response to SARS-CoV-2 vaccines. Many MS related clinical, demographic, and immunological characteristics can also affect vaccine response but those have not been fully explored. This study aimed to investigate potential correlations between clinical, demographic, and immunological variables in MS patients to post-vaccination spike protein antibody positivity rates and levels.

Methods: Patients with MS and related neuroimmunological disorders who requested verification of the immune response to the SARS-COV-2 vaccine were tested for the spike protein antibody from January to October 2021. We performed an exploratory analysis to compare patients with positive versus negative spike protein antibody.

Results: Fifty patients (mean age 53 ±12, 78% females) were included. There were 29 patients with positive post-vaccination spike protein antibody (58%) and 21 with negative antibody (42%). Patients with negative antibody were more likely to have been on B-cell therapy (86% vs 31%, P=.001) while positive patients were more likely to have been on a fumarate (31% vs 4.8%, P=.03). Thirty percent of positive patients on fumarate therapy had mild lymphopenia. No differences existed between groups in gender, age, race, disease phenotype, vaccine brand, and lymphocyte counts. Among patients on B-cell therapy, 33% had a positive spike protein antibody. There was an association between detectable CD19 cells at time of vaccination and positive humoral response to vaccination (P=0.049). There was no relationship between subgroups in terms of vaccine timing relative to B-cell therapy dose. Hypogammaglobulinemia was not associated with seroconversion rates, however it was associated with decreased quantitative spike protein antibody levels (p=0.045).

Discussion: B-cell therapy is associated with a negative humoral response to SARS-COV-2 vaccines. Patients on B-cell depleting therapy with detectable CD19 counts at the time of vaccination were associated with a positive humoral response. There was no relationship between hypogammaglobinemia and seroconversion rate, however it was associated with decreased spike protein antibody levels. The fumarates are associated with positive humoral response even in the presence of mild lymphopenia.

1. Introduction

The US Food and Drug administration has authorized the use of both mRNA (Moderna and Pfizer/BioNTech) and adenovirus vector (Janssen) vaccines to combat the ongoing COVID-19 pandemic. These vaccines have proven to be a useful resource to curb the viral spread and severity of SARS-CoV2 infection. Evidence supports a robust immune response and high COVID-19 spike antibody titers that correlate with high clinical vaccine efficacy in the overall population (Baden et al., 2021; Polack et al., 2020; Sadoff et al., 2021; Steensels et al., 2021). In the setting of multiple sclerosis (MS), patients on certain disease modifying therapy (DMT) are more vulnerable to progression to severe COVID-19, making

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vaccination particularly important for MS patients. Emerging evidence suggests that patients receiving DMT with B-cell depleting agents such as ocrelizumab, rituximab, and ofatumumab, may have a weakened immune response to COVID-19 infection and vaccination and subsequent diminished or absent spike antibody titer (Bigaut et al., 2021). However, questions remain surrounding the role of absolute lymphocyte count (ALC), CD19 cell concentrations, and immunoglobulin concentrations at the time of vaccination and their relationship with the humoral response to SARS-CoV2 vaccines.

2. Methods

This single center study was completed at University Hospitals Health System in Cleveland, Ohio. All study procedures and a request for waiver of informed consent were reviewed and approved by the local ethical standards committee. Patients were considered for inclusion in this study if they were at least 18 years of age, had a diagnosis of MS, neuromyelitis optica spectrum disorder (NMOSD), CNS vasculitis, or other related neurological disorders and were vaccinated against COVID-19 with an mRNA (Pfizer/BioNTech or Moderna) or viral vector (Janssen) based vaccine. After a thorough discussion of testing implications, patients were included if they elected to receive a SARS-CoV2 spike antibody test after completion of COVID-19 vaccination series. Patients were vaccinated between December 2020 and October 2021, including booster or additional doses for some patients meeting authorization criteria. Patients were permitted to be included in the analysis regardless of DMT status and class.

Blood samples were collected by venipuncture at least 14 days after the second dose of mRNA vaccines (Pfizer/BioNTech and Moderna) and at least 14 days after the first dose of adenovirus vector vaccine (Janssen).

Serological testing for SARS-CoV2 total spike antibody was conducted at the University Hospitals Cleveland Medical Center core laboratory which is certified under the Clinical Laboratory Improvement Amendments (CLIA) of 1988, 42 U.S.C 263a, to perform high complexity testing. The testing was performed on Siemens Atellica immunoassay analyzers using a chemiluminescent microparticle immunoassay that measures total antibodies against the spike protein receptor binding domain. This assay has been approved by the FDA for use under an Emergency Use Authorization. Test results were interpreted as positive or negative based on index values using a cutoff of $\geq$1.0 (index value) per the manufacturer's instruction. The index values correlate with antibody levels and the upper limit of reported range was 10.0 (index value). Any value reported as >10 was imputed to a continuous value of 10 for inclusion in the quantitative analysis.

The primary objective of this study was to identify factors affecting humoral immune response to vaccination. We collected data on demographics, disease phenotype, DMT class, vaccine class, vaccine brand, and vaccine timing relative to B-cell therapy. Laboratory data including ALC, immunoglobulins, and CD19 cell concentrations were also collected. A subgroup analysis of patients receiving B-cell therapy was also conducted to examine factors associated with a positive humoral response.

Statistical analysis was completed using a *t*-test for continuous variables and Chi-squared test or Fisher's exact test, as appropriate, for categorical variables. Continuous data is reported as mean and standard deviation (SD) and categorical data is reported as percentages unless otherwise specified. Results were considered statistically significant if less than a pre-specified alpha level of 0.05. Due to the exploratory nature of the analysis and the small sample size, we did not adjust for multiple variables.

3. Results

A total of 50 patients were included for analysis. Among the patients included, 39/50 (78%) were white, 39/50 (78%) were female, and the mean age was 53±2 years old. Twenty-five patients (50%) had relapsing-remitting MS (RRMS), eight patients (16%) had secondary progressive MS (SPMS), 7 patients (14%) had NMOSD, and six patients (12%) had primary progressive MS (PPMS). Of the four remaining patients three had central nervous system vasculitis and one had chronic relapsing inflammatory optic neuropathy.

Forty-six patients (92%) received an mRNA vaccine (30 Pfizer/BioNTech and 16 Moderna) and four patients (8%) received the viral vector based vaccine (Janssen).

Twenty-seven patients (54%) were receiving B-cell therapy including ocrelizumab (n=18), rituximab (n=8), and ofatumumab (n=1) at the time of vaccination. Ten patients (20%) were receiving fumarates, 4 patients (8%) receiving sphingosine-1-phosphate (S1P) modulators including fingolimod (n=1) and siponimod (n=3), and 6 patients (12%) were receiving other immunomodulators including mycophenolate (n=3), glatiramer acetate (n=1), cladribine (n=1), and satralizumab (n=1). Three patients were not receiving DMT at the time of vaccination. One of these patients discontinued dimethyl fumarate six months prior to vaccination, one patient received the vaccine three months after discontinuing mycophenolate and two months prior to initiating ocrelizumab, and one patient initiated ofatumumab one month after vaccination.

Overall, 29/50 vaccinated patients (58%) tested positive for SARS-CoV2 spike antibody after vaccination with an mRNA or viral vector vaccine. On average patients were tested for SARS-CoV2 spike antibody 104 ±66 days from last dose of vaccine. Among the patients with a positive response to vaccination, 21/29 (72%) had an antibody index >10 (index value). Mean antibody index among negative patients was 0.4 ± 0.22. Two patients (one in the positive group and one in the negative group) had a pre-vaccine PCR-confirmed COVID-19 infection. Supplementary table S1 contains detailed clinical data of the entire cohort.

In the qualitative analysis (Table 1), lymphopenia, hypogammaglobulinemia (IgG <600 mg/dL), S1P modulators, non-selective immunosuppressants, vaccine class, and vaccine brand did not differ significantly among the positive and negative response populations. Among patients with RRMS, 72% of patients had a positive humoral response to vaccination. Among the entire cohort, RRMS patients accounted for 62% of all antibody positive patients and 33% of negative patients (p=0.04). Most patients (90%) receiving fumarates had a positive humoral response to vaccination. Patients receiving fumarate therapy accounted for 31% of patients with a positive vaccine response compared to 4.8% of patients with a negative immune response (p=0.03). Thirty percent of positive patients on fumarate therapy had lymphopenia, however none of these patients had an ALC $<0.8 \times 10^9$/L. There was no relationship between ALC and humoral response to vaccine in the fumarate patients (p=0.83). Among patients receiving B-cell therapy (Table 2), 33% had a positive humoral response to vaccination, while 77% had a negative humoral response, which accounted for 86% of the overall negative response population(p=0.01). A subgroup analysis of patients receiving B-cell therapy was also completed. Patients with a detectable CD19 cell population at the time of vaccination were associated with a positive humoral response (p=0.049). Mean immunoglobulin G levels were numerically lower in the negative vaccine response group, however this did not reach statistical significance (p=0.29).

Mean interval from last B-cell therapy infusion to first vaccine dose was 3.3±1.0 months in the positive response group and 3.1±1.9 months in the negative response group (p=0.81). Mean interval from second vaccine dose (or first if viral vector) until next B-cell therapy infusion was 2.1 ± 1.0 months in the positive response group and 2.5±1.5 months in the negative response group (p= 0.52).

In our quantitative analysis of spike protein antibody levels (Table 3), detectable B-cells at the time of vaccination was associated with significantly higher antibody levels than those without detectable B cells (p<0.001). Patients receiving S1P modulators had similar levels to

Table 1
Clinical Factors in MS patients with positive and negative spike antibody response.

Clinical factors, n (%)	Positive SARS-CoV-2 spike protein antibody (n=29)	Negative SARS-CoV-2 spike protein antibody (n=21)	Statistical test	P-value
Female	24 (83%)	15 (71%)	X^2 = 0.9112	0.34
White	23 (79%)	16 (83%)	X^2 = 0.0691	0.79
Relapsing remitting course (RRMS)	18 (62%)	7 (33%)	X^2 = 4.02	**0.04**
Primary progressive course (PPMS)	4 (14%)	2 (10%)	X^2 = 0.2102	0.65
mRNA vaccine (Pfizer/ BioNTech, Moderna)	27 (93%)	19 (90%)	Fisher's Exact	1.00
Viral vector vaccine (Janssen)	2 (7%)	2 (10%)	Fisher's Exact	1.00
Pfizer vaccine*	15/24 (63%)	12/17 (71%)	X^2 = 0.29	0.59
Moderna vaccine*	9/24 (35%)	5/17 (29%)	X^2 = 0.55	0.59
Lymphopenia (<1 × 10^9/L)	6 (21%)	5 (24%)	X^2 = 0.069	0.79
B-cell therapy	9 (31%)	18 (86%)	X^2 = 14.66	**0.001**
Fumarates	9 (31%)	1 (4.8%)	Fisher's Exact	**0.0313**
S1P modulators	3 (10%)	1 (4.8%)	Fisher's Exact	0.63
MMF/cladribine	3 (10%)	1 (4.8%)	Fisher's Exact	0.63
Average age	50.52 ± 12.30	55.14 ± 11.94	t= 1.33	0.19
Average absolute lymphocyte count	1.19 ± 0.68	1.23 ± 0.69	t= 2.16	0.83

*n=46, comparing Moderna to Pfizer vaccine. 4 patients received Janssen vaccine and were not included in the analysis.

Table 2
Clinical Factors in the B-cell therapy patients with positive and negative spike antibody response.

Clinical factors, n (%)	Positive SARS-CoV-2 spike protein antibody (n=9)	Negative SARS-CoV-2 spike protein antibody (n=18)	Statistical Test	p-value
Detectable CD19 cells (≥1%)at vaccination	4 (44%)	2 (11%)	Fisher's Exact	**0.049**
CD19 cells (%) at time of vaccination	4.1 ± 4.8	0.17 ± 0.51	t=3.42301	**<0.001**
Hypogammaglobinemia (IgG <600 mg/dL)	1 (11.1%)	3 (17.6%)#	X^2 = 0.1931	0.66
Average IgG level (mg/dL)	1063.4 ± 522.3	895.5 ± 271.1	t= 1.09	0.29
Average absolute lymphocyte count (x10^9 cells/L)	1.3 ± 0.34	1.5 ± 0.66	t= 0.61	0.55
Average interval from last B-cell therapy dose to first vaccine dose in months	3.3 ± 1.0	3.1 ± 1.9	t= 0.23	0.81
Average interval from second vaccine dose to the next B-cell therapy dose in months	2.1 ± 1.0	2.5 ± 1.5	t= 0.65	0.52

n=17, one patient in negative group did not have IgG collected.

Table 3
Quantitative Analysis of Spike Antibody levels in Select Populations.

	Spike Antibody level (index value)	Statistic	p-value
B-Cell Therapy (n=27) No B-Cell Therapy (n=23)	2.67 ± 3.80 7.78 ± 4.09	t=-4.7011	**<0.001**
S1P Modulators (n=4) No S1P Modulators (n=46)	5.54 ± 5.17 4.91 ± 4.54	t=0.2611	0.795
Undetectable CD19 cells (<1%) at vaccination (n=22) Detectable CD19 cells (≥1%) at vaccination (n=10)	1.66 ± 2.85 7.16 ± 3.88	t=4.51203	**<0.001**
Hypogammaglobulinemia (IgG < 600 mg/dL) (n=5) No Hypogammaglobulinemia (IgG ≥ 600 mg/dL) (n=28)	0.68 ± 0.31 4.12 ± 4.32	t=-1.75538	**0.045**
Lymphopenia (<1 × 10^9/L) (n=11) No Lymphopenia (≥1 × 10^9/L) (n=39)	4.49 ± 4.78 5.08 ± 4.53	t=-0.36298	0.359

those in the overall population (p=0.795). Hypogammaglobulinemia (IgG <600 mg/dL) was associated with lower mean antibody levels (p=0.045) despite being noncontributory to positive/negative vaccine response. We found no relationship between lymphopenia and average antibody level (p=0.359).

Most patients (98%), including those with negative humoral response, did not develop confirmed or suspected COVID19 infection after vaccine completion over an average follow-up of 3.7 ±2.5 months. In the second half of 2021, the average weekly COVID19 infection rate in Cleveland, Ohio was 395.8 per 100,000 residents (coronavirus.ohio.gov/accessed 2/18/2022). Two patients developed symptomatic non-complicated COVID19 infection between the first and second vaccine doses. One of these patients was not on DMT at the time of vaccination however stopped mycophenolate 3 months prior to vaccination and started ocrelizumab two months after vaccination then eventually developed positive post-vaccination humoral response. The second patient was receiving rituximab at the time of vaccination and did not develop the antibody after the second vaccine dose. One patient on ocrelizumab received two doses of the Pfizer/BioNTech vaccine without spike antibody response 30 days after the second dose of the series. This patient received a third dose of the Pfizer/BioNTech vaccine six months after completing the initial series, however contracted a symptomatic non-complicated COVID-19 infection six weeks after the vaccine's third dose. Interestingly, this patient was tested for SARS-CoV2 spike protein antibody two weeks after recovery from the natural infection and had seroconverted to positive antibody status.

4. Discussion

In this study, we found that treatment with the fumarates is associated with a positive SARS-CoV2 spike protein antibody response even in patients with mild lymphopenia. This is possibly driven by the dominance of patients receiving B cell therapies in the comparator group and rarity of other DMT classes in our cohort. Of note, none of the fumarate patients in our cohort had moderate to severe lymphopenia (<0.8 × 109/L) so we cannot generalize our findings to all patients on fumarates. About 8% of patients on fumarates develop severe lymphopenia and the humoral vaccine response in this subset of patients remains unknown (Fox et al., 2016).

Similar to prior studies, the patients receiving B-cell therapy were associated with diminished humoral response to vaccination (Sormani et al., 2021; Meca-Lallana et al., 2020). However, we did not find an association between timing of vaccination relative to B-cell therapy dose

and the humoral response. This comes in partial agreement with the finding by Tallantyre and colleagues that timing of vaccine administration in relation to B-cell therapy infusions did not impact SARS-CoV2 spike protein antibody seroconversion (albeit it impacted antibody titers with lower titers in those vaccinated closer to the time of B-cell therapy infusion and in those who have been on treatment longer) (Tallantyre et al., 2021). Since B-cell repopulation rate is different from one patient to another, B-cell (CD19) counts may be more relevant to vaccination than timing in relation to infusions. We found a significant association between a positive antibody response and patients with a CD19 percentage of $\geq$1% of the total B-cell population around the time of vaccination. This study adds to some limited data on CD19 cell percentages and immunoglobulin levels and their role in the humoral response to COVID-19 vaccination. A previously published report found increasing serologic response to vaccination with increasing time from last B-cell depleting infusion and increasing concentration of B-cells (Brill et al., 2021; Disanto et al., 2021). It is worth noting that our mean interval from last B-cell depleting infusion was only 3.1 months, which was comparatively shorter than the median 7.1 months observed by DiSanto, et al and may account for the lack of association between seroconversion and vaccination timing in our study. Another important limitation to our study is that we did not evaluate the T-cell response in our patients. Several recent studies found that the T-cell response to vaccination is preserved among patients on B-cell therapy and may even be accentuated, so vaccination is likely partially protective in those patients regardless of the humoral response (Apostolidis et al., 2021; Gadani et al., 2021). Additionally, a threshold for determining protective antibody level is not established yet.

Our quantitative analysis of antibody levels largely supported our findings on humoral response rates in patients receiving B-cell therapy and among patients with detectable B-cell concentrations at the time of vaccinations. However, our quantitative analysis revealed that hypogammaglobulinemia may be a potential risk factor for low antibody level after vaccination. This finding suggests that, in addition to CD19 counts, collection of serum immunoglobulins prior to vaccination may be a useful tool to identify those at very high risk for decreased vaccine response and to guide optimal timing for vaccination.

Booster and additional doses of COVID-19 vaccines have become increasingly important among certain high-risk patient populations, including those moderately to severely immunocompromised due to DMT (Barda et al., 2021). Although, B-cell therapy has been linked to reduced post-infectious and post-vaccination humoral response to SARS-CoV2, we encountered one patient on ocrelizumab who initially tested negative for the spike protein antibody after completing two mRNA vaccine doses but eventually seroconverted after a third vaccine dose and a natural COVID19 infection. This suggests that repeated exposure to viral antigens may improve humoral responses in patients on B-cell therapy. It remains unclear whether booster or additional doses of vaccine will consistently lead to higher seroconversion rates among immunocompromised patients but this could be the set of future investigation.

Similar to the study by Conte, we did not find an association between S1P modulators and the humoral vaccine response (Conte, 2022). However, we only included four patients on S1P modulators so we cannot draw any strong conclusions in regards to this medication class. Several prior studies have suggested low vaccine responses in patients treated with S1P modulators (Achiron et al., 2021). We also did not find an association between mRNA vaccine brand and the humoral vaccine response unlike the findings by Sormani and colleagues (Sormani et al., 2021). However, we had a substantially smaller number of patients who received the Moderna vaccine and we did not correct for the respective DMT when investigating vaccine effect. This limits our ability to draw conclusions regarding the impact of vaccine brand on the humoral response in our cohort.

Our results showed that patients with RRMS were associated with a positive response to vaccination compared to other MS subtypes and related neuroinflammatory disorders. However, this result is likely confounded by the fact that patients with a progressive disease course or NMOSD were more likely to be receiving B-cell therapy. Of note, 10/25 (40%) of patients with RRMS included in the study were on B cell depleting therapy, as opposed to 5/6 (83%) of patients with PPMS and 5/6 (83%) of patients with NMOSD.

In addition to the limitations mentioned above, there were also no standardized intervals of laboratory collection relative to vaccination, which limits the comparability of the data with other studies. The narrow reportable range of the assay utilized to measure spike protein antibody concentrations required multiple imputation of values above the limit of detectability which introduced bias into the model and limited our ability to directly analyze the relationship between antibody concentration and immune globulin-G concentration, B-cell concentration, absolute lymphocyte count and DMT class. Additionally, the heterogeneity of diagnoses and disease modifying therapies limits the ability of this study to draw strong conclusions about the variables investigated.

5. Conclusions

Among patients on B-cell depleting therapy, those with detectable CD19 cells at the time of vaccination were associated with higher rates of positive humoral response. We did not find a relationship between hypogammaglobulinemia or absolute lymphopenia and positive humoral response rate to vaccination. However, hypogammaglobulinemia was associated with decreased post-vaccination antibody levels. Testing CD19 counts and immunoglobulin levels prior to vaccination may be more important than coordinating timing of vaccination in relation to B-cell therapy infusions, especially since B-cell repopulation rates vary from one individual to another. Individualized decisions on vaccine timing may be better guided by CD19 and immunoglobulin levels. Patients with undetectable CD19 counts and/or low immunoglobulin-G levels at the time of vaccination could be considered a high priority for booster or additional vaccine doses. The fumarates are associated with positive humoral response even in the presence of mild lymphopenia but the impact of moderate and severe lymphopenia on vaccine response needs further research.

CRediT authorship contribution statement

Collin Jakubecz: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Xiaochun Susan Zhang:** Data curation, Methodology, Formal analysis, Writing – review & editing. **Sophia Woodson:** Data curation, Writing – review & editing. **Alessandro Serra:** Data curation, Writing – review & editing. **Hesham Abboud:** Conceptualization, Data curation, Formal analysis, Supervision, Writing – review & editing.

Declaration of Competing Interest

CJ has no conflicts of interest to disclose. XZ has no conflicts of interest to disclose. SW is a consultant for Biogen, Genentech, and Novartis. AS is a consultant for Biogen and BMS. He is supported in part by Career Development Award #IK2RX001180 from the US Department of Veterans Affairs, Rehabilitation Research and Development Service. HA is a consultant for Biogen, Genentech, BMS, Alexion, and Horizon. He receives research support from Genentech, BMS, Novartis, and Sanofi-Genzyme.

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Supplementary materials

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