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RESEARCH LETTER

SARS-CoV-2 Vaccine Response in Patients With Antineutrophil Cytoplasmic Autoantibody–Associated Vasculitis

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INTRODUCTION

The development of COVID-19 vaccines and mass vaccination is a landmark achievement of modern medicine. Management of patients with antineutrophil cytoplasmic autoantibodies–associated vasculitis (AAV) during the pandemic has been challenging. Immunosuppressive medications to control vasculitis are associated with severe COVID-19 infection and may impair immune response to the vaccine.

During the course of the pandemic, the treatment of patients with AAV has varied across the world with regard to both induction of remission and maintenance treatments.[1,2]

COVID-19 vaccination has been successfully implemented among patients with AAV given their vulnerability to severe infection. In our study, we aim to identify correlations between serologic tests carried out for anti–SARS-CoV-2 spike antibodies and immunosuppressive medications used in the management of AAV.

RESULTS

A total of 159 patients were included with a mean (SD) age of 65 (14) years. The average time from diagnosis of AAV was 7 years (±6). Most patients had AAV with multisystem involvement. Clinical characteristics, comorbidities, and correlation with anti–SARS-CoV-2 spike antibodies are illustrated in Table 1.

In total, 155 patients (97%) received full immunization with 1 dose of the Johnson & Johnson or both doses of Oxford-AstraZeneca, Pfizer-BioNTech, or Moderna mRNA vaccines. The mean time between the first and second doses of Pfizer-BioNTech mRNA or Moderna mRNA vaccines was 33.7 ± 19.9 days, whereas it was 75 ± 25.9 days for Oxford-AstraZeneca vaccines. The mean duration between the second vaccine dose and anti–SARS-CoV-2 spike antibody measurement was 49.8 ± 29.4 days across all centers.

Determinant of Humoral Response to the SARS-CoV-2 Vaccinations

There were 87 patients (55%) who developed detectable anti–SARS-CoV-2 spike antibodies. Of those with available quantitative antibody values ($n = 48$), the median antibody titer was 1192 U/ml (interquartile range: 109.3–2461.5 U/ml). We did not find any significant correlation between humoral response and age, sex, race, antineutrophil cytoplasmic autoantibody type, type of vaccine received, co-morbidities, or renal impairment (Table 1).

A total of 144 patients received immunosuppression during the time of their vaccination. Among those, 129 patients were treated with rituximab and half ($n = 64$, 49.6%) of these developed anti–SARS-CoV-2 spike antibodies (Table 1).

Rituximab and Cluster of Differentiation 19

The use of rituximab was significantly associated with poor humoral response to the COVID-19 vaccine and the absence of anti–SARS-CoV-2 spike antibodies (odds ratio [OR]: 0.31, CI: 0.12–0.74, $P = 0.01$), as found in Table 2. In univariate analysis, therapy with rituximab was strongly associated with poor antibody

Table 1. Demographic and clinical characteristics versus antispike antibody status after SARS-CoV-2 vaccination

Variables	Overall ($N = 159$)	Undetectable antispike antibodies ($n = 70$)	Detectable antispike antibodies ($n = 87$)	*P* value
Demographics				
Age, yr, mean (SD)	65.5 (13.6)	66.7 (12.5)	64.2 (14.4)	0.33
Sex, females, *n* (%)	79 (49.7)	35 (50.0)	44 (50.6)	1.00
Race, *n* (%)				
White	145 (91.2)	61 (87.1)	82 (94.3)	0.16
Black	7 (4.4)	5 (7.1)	2 (2.3)	0.24
Other	7 (4.4)	4 (5.7)	3 (3.4)	0.70
AAV disease characteristics, *n* (%)				
ANCA type				
PR3	73 (45.9)	34 (48.6)	38 (43.7)	0.63
MPO	83 (52.2)	36 (51.4)	46 (52.9)	0.87
ANCA negative	3 (1.9)	0 (0)	3 (3.4)	0.25
Active disease	13 (8.2)	4 (5.7)	8 (9.2)	0.55
Organ involvement, *n* (%)				
Renal	141 (88.7)	63 (90.0)	76 (87.4)	0.80
Respiratory	90 (56.6)	39 (55.7)	49 (56.3)	1.00
Sinuses	69 (43.4)	27 (38.6)	41 (47.1)	0.33
Ophthalmic	19 (11.9)	5 (7.1)	14 (16.1)	0.14
Neural	20 (12.6)	12 (17.1)	8 (9.2)	0.15
Gastrointestinal	3 (1.9)	2 (2.9)	1 (1.1)	0.59
Cardiac	7 (4.4)	4 (5.7)	3 (3.4)	1.00
Cutaneous	21 (13.2)	7 (10.0)	13 (14.9)	0.47
Renal limited disease	25 (15.7)	13 (18.6)	12 (13.8)	0.51
Co-morbidities, *n* (%)				
Hypertension	112 (70.4)	52 (74.3)	58 (66.7)	0.38
Diabetes mellitus	21 (13.2)	10 (14.3)	11 (12.6)	0.82
Cardiovascular disease	39 (24.5)	17 (24.3)	21 (24.1)	1.00
Respiratory disease	**27 (17.0)**	14 (20.0)	13 (14.9)	0.52
Renal transplant	10 (6.3)	6 (8.6)	4 (4.6)	0.34
ESKD	24 (15.1)	13 (18.6)	9 (10.3)	0.17
eGFR	46.5 (26.5)	44.2 (23.4)	49.3 (28.3)	0.30
Vaccination characteristics, *n* (%)				
Vaccine type				
Oxford-AstraZeneca	34 (21.4)	16 (22.9)	16 (18.8)	0.69
Johnson & Johnson	5 (3.1)	4 (5.7)	1 (1.2)	0.17
Moderna	31 (19.5)	12 (17.1)	19 (22.4)	0.55
Pfizer-BioNTech	89 (56.0)	38 (54.3)	49 (57.6)	0.75
Days between first and second Vaccine	43.2 (25.3)	43.2 (24.7)	43.2 (25.8)	0.92
Current immunosuppression, *n* (%)				
CNI	10 (6.3)	6 (8.6)	4 (4.6)	0.34
MMF	21 (13.2)	9 (12.9)	12 (13.8)	1.00
Azathioprine	4 (2.5)	2 (2.9)	2 (2.3)	1.00
Methotrexate	1 (0.6)	0 (0)	1 (1.1)	—
Cyclophosphamide	1 (0.6)	0 (0)	1 (1.1)	—
IVIG	2 (1.3)	1 (1.4)	1 (1.1)	1.00
Steroid	51 (32.1)	20 (28.6)	30 (34.5)	0.49
Rituximab therapy, *n* (%)				
Use of RTX	129 (81.1)	63 (90.0)	64 (73.6)	0.01
Vaccination within 6 mo of RTX	69 (43.4)	48 (68.6)	20 (23.0)	<0.001
Days from last RTX to first vaccine, median (IQR)	164 (84–426)	104 (49–167)	374 (163–954)	<0.001
Cumulative RTX dose before vaccine (g), mean (SD)	4.42 (3.35)	5.11 (3.16)	3.91 (3.43)	0.01
CD19 reconstitution	64 (40.3)	8 (11.4)	56 (64.4)	<0.001

AAV; antineutrophil cytoplasmic autoantibodies–associated vasculitis; ANCA, antineutrophil cytoplasmic autoantibodies; CD19; cluster of differentiation 19; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate (ml/min per 1.73 m^2); ESKD, end-stage kidney disease; IQR, interquartile range; IVIG; i.v. immunoglobulin; MMF, mycophenolate mofetil; MPO; myeloperoxidase; PR3; proteinase 3; RTX, rituximab.

response among those patients treated within 6 months before the first vaccine dose (OR: 0.12, CI: 0.06–0.25, $P < 0.001$).

There were 107 patients who had cluster of differentiation 19 (CD19) counts checked around the time of vaccination with 64 having CD19 reconstitution, and all

Table 2. Multivariate analysis of age, sex, eGFR, cumulative rituximab dose, time from rituximab to initial vaccination, and presence of CD19 reconstitution on the probability of developing a humoral response to the SARS-CoV-2 vaccination

Model 1			Model 2			Model 3		
Variable	OR 95% CI	*P* value	Variable	OR 95% CI	*P* value	Variable	OR 95% CI	*P* value
Age	0.99 (0.96–1.02)	0.68	Age	0.98 (0.94–1.01)	0.19	Age	1.02 (0.96–1.08)	0.49
Male vs. female	1.12 (0.57–2.21)	0.75	Male vs. female	1.49 (0.67–3.39)	0.33	Male vs. female	2.47 (0.83–8.10)	0.11
eGFR	1.00 (0.99–1.02)	0.54	eGFR	1.00 (0.98–1.02)	0.86	eGFR	1.02 (0.99–1.05)	0.19
Cumulative RTX dose $<$ 6 g	2.61 (1.21–5.83)	0.02	Cumulative RTX dose $<$ 6 g	2.10 (0.88–5.22)	0.1	Cumulative RTX dose $<$ 6 g	3.03 (0.94–10.76)	0.07
			Months from RTX to vaccine	1.08 (1.04–1.13)	$<$0.001	Months from RTX to vaccine	0.99 (0.96–1.03)	0.62
						CD19 reconstitution	49.85 (11.89–273.33)	$<$0.001

CD19; cluster of differentiation 19; eGFR; estimated glomerular filtration rate (ml/min per 1.73 m^2); OR, odds ratio; RTX, rituximab.

these patients developed detectable antispike antibodies. In univariate analysis, CD19 reconstitution was significantly associated with the likelihood of a positive humoral vaccine response (OR: 29.37, CI: 11.71–85.89, $P < 0.001$).

The median cumulative dose of rituximab was 4000 mg (interquartile range: 2583–6770 mg). Patients with a humoral response had received a lower dose of rituximab (3.91 g vs. 5.11 g, $P = 0.01$) (Table 1). For every 1 g increase in the cumulative dose of rituximab given before vaccination, there was a 10% reduction in the probability of anti–SARS-CoV-2 spike seroconversion (OR: 0.89, CI: 0.79–0.99, $P = 0.05$) (Supplementary Table S1).

Multivariate Analysis

When adjusting for age, sex, and estimated glomerular filtration rate, the effect of a cumulative dose of rituximab on the humoral response to the vaccine had moderate significance. In model 1, a cumulative dose of rituximab $<$ 6 g was associated with developing a humoral response (OR: 2.61, CI: 1.21–5.83, $P = 0.02$) (Table 2). In model 2, when including the time between rituximab administration and vaccination, the cumulative dose effect of rituximab lost statistical significance ($P = 0.10$). For every month between before rituximab therapy and vaccination, seroconversion rate increased by 8% (OR: 1.08, CI: 1.04–1.13, $P < 0.001$). In the final multivariable analysis (Table 2, model 3), we further adjusted for CD19 reconstitution. Our analysis reveals that regardless of cumulative dose or duration between last rituximab administration and vaccination, CD19 reconstitution was the best predictor for a humoral response to the vaccine (OR: 49.85, CI: 11.89–273.33, $P < 0.001$).

DISCUSSION

In this multicenter study, we reveal a diminished immune response to the COVID-19 vaccine in patients with AAV after immunosuppression. Approximately half of our study participants developed no humoral antibody response to the COVID-19 vaccination. B cell-depleting therapy with rituximab was associated with the poorest response. The CD19 count was the strongest predictor for seroconversion, with depletion conferring a low likelihood of antibody formation. In line with this, the cumulative dose and timing of vaccination were both significant factors. Every additional gram of rituximab given conferred a poorer response with a dose limit effect of 6 g, and dosing >6 months before vaccination was associated with a 7-fold increase in the odds of seroconversion.

Similar findings with regard to vaccine timing in the context of rituximab therapy have been found by Prendecki *et al.*[3]

In our cohort, the cumulative dose of rituximab has a significant effect on humoral response to COVID-19 vaccination. For every 1 g increase in rituximab administered, the chance of serologic conversion after vaccination reduced by 11%. This reveals that cumulative dosing affects humoral immunity and is an important factor in patients receiving maintenance rituximab treatment.

CD19 counts are used clinically as a measure of B cell depletion.[4,5] In our patient cohort, we found a significant relationship between B cell depletion at time of vaccination and lack of antibody production after vaccination, whereas patients with CD19 reconstitution were nearly 30 times more likely to respond to vaccination. Similar findings were recently reported in 2 smaller cohorts.[6,7] In our cohort, this relationship remained significant irrespective of cumulative dose or timing of rituximab infusion in relation to the vaccination.

Impaired humoral response to other vaccines, such as Haemophilus influenza B, pneumococcus, and hepatitis B, has been found in rituximab-treated patients, and blunted immune response to vaccines has been found to persist for up to 6 months after rituximab infusion.[8,9,S1] A similar finding was found in our cohort with less than a quarter (23%) of those who received rituximab within 6 months from their initial vaccine mounting a humoral response to the vaccine. Nevertheless, those patients treated with rituximab >6

months before vaccination had significantly higher chances of developing antibodies.

The study was limited by its relatively small sample size, differences in cumulative immunosuppressive doses, type of vaccinations, and serologic assays. Furthermore, T cell response to vaccination could not be determined. Despite this, our study cohort represents the so far largest study on humoral response to COVID-19 vaccine in patients with AAV, most of whom were treated with B cell-depleting therapy.

Our study reveals a significant negative impact of the therapy with the B cell-depleting agent, rituximab, on the anti–SARS-CoV-2 spike antibody response after vaccination. CD19 reconstitution was the most predictive marker of humoral response to the vaccine regardless of dose or duration of rituximab treatment. On the basis of these findings, it is reasonable to propose that CD19 counts can be used as a marker to aid decisions on timing and anticipated response to other vaccines in patients receiving rituximab.

DISCLOSURE

DG reports serving as a consultant to ChemoCentryx and funded by Jerome L. Greene discovery award. AD reports receiving fees for lecturing for Merck Sharp & Dohme and travel support from Pharmacosmos. US reports receiving grants and nonfinancial support from Alexion Pharma, Ablynx/Sanofi, ChemoCentryx/Vifor, and Allena Pharmaceuticals. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Table S1. Impact of AAV disease characteristics, comorbidities, and immunosuppression on the presence of antispike antibodies after SARS-CoV-2 vaccination.

Supplementary Reference S1.

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