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Impact of rituximab on humoral response to COVID-19 booster vaccine and antibody kinetics in patients with anti–neutrophil cytoplasmic antibody vasculitis

To the editor: The advent of vaccines has resulted in mitigation of severe disease as a consequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There is notable absence of humoral response after 2 doses of mRNA vaccines in rheumatic and musculoskeletal diseases.[1] There has been evidence that the administration of a third dose of vaccine leads to augmentation of a humoral response in kidney transplant recipients.[2] In addition, there is increasing evidence that neutralizing antibody titers correlate with reduction in breakthrough infections in vaccinated individuals.[3] To further understand these aspects in patients with anti–neutrophil cytoplasmic antibody–associated vasculitis (AAV) on immunosuppression, we elucidated antibody response to booster doses of the coronavirus disease 2019 (COVID-19) vaccine, and sought to ascertain the effect of rituximab on SARS-CoV-2 antibody titers, given immunosuppression is known to alter immunogenicity of a vaccine.

Patients with AAV attending the vasculitis clinic at Johns Hopkins on rituximab therapy were screened for a completion of vaccine series and associated antibody response between April 2021 and June 2021. IgG antibodies to the spike protein S1 subunit of SARS-CoV-2 were measured using enzyme-linked immunosorbent assay (Clinical Immunology Laboratory of the Johns Hopkins Hospital) at least 1 month after completion of a vaccination series and then after 1 month after rituximab administration. Clinical demographics and immunologic data were retrieved after review of the electronic health record. Four patients with demonstrable antibody levels due to receive rituximab therapy were included. In addition, we identified a separate cohort of patients who lacked humoral response to the initial vaccine administration and received a booster dose. Antibody responses to the spike protein of SARS-CoV-2 were measured 4 weeks after the booster dose of the respective vaccines. This study was approved by the Johns Hopkins Institutional Review Board.

Three patients with AAV received booster doses of the COVID-19 vaccine. The age range was 67–80 years, with 2 being female and all White ethnicity. Two patients each had microscopic polyangiitis phenotype and received rituximab as induction therapy, whereas all patents were on rituximab maintenance. Only 1 patient was on steroid maintenance therapy (prednisone, 2.5 mg once a day). The duration that elapsed between the last dose of rituximab and the first dose of vaccine ranged between 3 and 5 months. Two patients with B cells measured at the time of the booster dose showed B-cell depletion, and in the third patient, B-cell measurement 8 weeks before the vaccine administration demonstrated B-cell depletion. Among 2 patients who received the Johnson & Johnson vaccine first devoid of any resultant antibody response, the booster dose was associated with humoral response in 1 patient, whereas the other patient did not mount an antibody response. The third patient initially received 2 doses of the Pfizer–BioNTech vaccine and received a third dose of Johnson & Johnson vaccine and did not mount a humoral response. None of the patients had previous COVID-19 infection or required dialysis during periods of vaccination. Patient characteristics, immunosuppressive regimen, immunologic data, and vaccine administration details are presented in Table 1.

With regard to patients screened for antibody titers after rituximab, all 4 patients had a >50% decline in antibody titers 1 month after drug administration. The age range of the patients was 36–years, with 1 being female. Two patients each had the microscopic polyangiitis and granulomatosis with polyangiitis phenotype, with 3 showing continued presence of detectable respective anti–neutrophil cytoplasmic antibody subtypes. The range of cumulative rituximab dose in these patients was 4–12 g, correlating with a higher decline in antibody titers. Two patients received concomitant cyclophosphamide for episodes of refractory vasculitis. All patients received the Pfizer–BioNTech vaccine. Patient characteristics, immunosuppressive regimen, immunologic data, and details of vaccine administration are presented in Table 2.

To our knowledge, this is the first elucidation of antibody response after a booster dose of COVID-19 vaccine in patients with AAV on maintenance immunosuppression. It is being increasingly recognized that patients on immunosuppression are less likely to have a detectable antibody response to the spike protein to SARS-CoV-2 after the initial dose of vaccine administration.[1] Three doses of the vaccine have been utilized to aid in the increment or development of antibodies in kidney transplant recipients, with moderate success.[2] In our series, the booster dose resulted in a humoral response in 1 of 3 patients. Patients with AAV receiving rituximab have been shown to have a suboptimal response to the vaccine, with duration elapsed between rituximab and vaccine administration having a significant bearing on eventually developing

Table 1 | Patient characteristics, immunosuppressive regimen, immunologic data, and details of vaccine administration

Patient no.	Age, yr	Sex	Ethnicity	Disease phenotype	ANCA type and titer at the time of booster, U/ml	eGFR at the time of booster, ml/min per 1.73 m^2	Proteinuria at the time of booster, mg	Induction IS	Maintenance IS	Cumulative RTX dose, g	Interval between last RTX and first vaccine dose, mo	CD19 count, cells/ml (%)	Time point of CD19 measurement	Vaccine types	SARS-CoV-2 spike protein IgG titer (immunoassay), AU
1	67	Male	White	GPA	PR3 (30.8)	68	91	RTX + steroids	RTX	8.2	4	<20 (0)	2 wk before second vaccine dose	JNJ and then Pfizer–BioNTech series	>12
2	80	Female	White	MPA	MPO (<9)	34	307	RTX + steroids	RTX	9	5	<20 (0)	1 wk before second vaccine dose	JNJ and then Moderna series	<12 (DiaSorin Liaison)
3	70	Female	White	MPA	MPO (NA)	44	219	Cyclophosphamide + steroids	RTX	3	3	<20 (0)	1 mo after second vaccine dose	Pfizer–BioNTech and then JNJ	<1 (Roche Elecsys)

ANCA, anti–neutrophil cytoplasmic antibody; AU, arbitrary unit; eGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; ID, identifier; IS, immunosuppression; JNJ, Johnson & Johnson; MPA, microscopic polyangiitis; MPO, myeloperoxidase; NA, not available; PR3, proteinase 3; RTX, rituximab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

antibodies.[4] It has been previously suggested that a delay in vaccine administration for at least 6 months after rituximab administration or B-cell reconstitution should be considered to maximize efficacy of vaccines.[5] Another pertinent aspect that warrants discussion is the the immunogenicity of viral vector-based COVID-19 vaccines. In accordance with our series, the antibody response after viral vector COVID-19 vaccines may be suboptimal for immunocompromised patients, as has been demonstrated in a previous study.[4] This finding does require more robust investigation to clarify which type of COVID-19 vaccine yields the most efficacious immune response.

Although the focus of the medical community is to enhance the immunogenicity of the vaccines to aid in the protection of this vulnerable population, the effect of immunosuppression on patients with established generation of SARS-CoV-2 antibodies is unknown. In addition, rituximab has been known to be associated with reduced humoral response to pneumococcal and influenza vaccines.[6] To our knowledge, this is the first elucidation of the effect of rituximab on SARS-CoV-2 antibodies in vaccinated patients with AAV, demonstrating a precipitous decline in antibodies 1 month after administration of the drug. This finding, albeit preliminary and in a small subset of patients, may be of significance to a large number of patients with autoimmune disease, given rituximab is one of the most widely prescribed disease-modifying therapies. Because neutralizing antibody titers against SARS-CoV-2 correlate with reduced risk of breakthrough infections, it may be important to continue personal protective measures in the immediate period after rituximab administration, despite previous evidence of robust antibody response to vaccines, given the demonstrated decline in antibody titers.[3] Also, alternate immunosuppression may need to be considered during periods of high community transmission, given the detrimental effect of rituximab on antibody titers.

To our knowledge, these data are the first demonstration of antibody development after a booster dose of the COVID-19 vaccine in patients with AAV on rituximab maintenance therapy. It is of paramount importance that larger studies be convened to investigate the effects of the administration of a booster dose of the vaccine to this vulnerable population. This intervention may have far-reaching effects in alleviating morbidity and mortality arising from COVID-19, the biggest public health crisis of our generation. In addition, future studies assessing immunogenicity of vaccines in patients who are immunocompromised should consider incorporating this aspect of decline of antibody titers and measure T-cell and memory B-cell responses, because generation of antibodies may not be the only paradigm that determines durable success of the vaccine in this population.

DISCLOSURE

DG is a consultant to ChemoCentryx and Aurinia Inc. The other author declared no competing interests.

Table 2 | Patient characteristics, immunosuppressive regimen, immunologic data, and details of vaccine administration

Patient no.	Age, yr	Sex	Ethnicity	Disease phenotype	ANCA type and titer at the time of second vaccine dose, U/ml	eGFR at the time of last RTX, ml/min per 1.73 m^2	Proteinuria at the time of last RTX, mg	IS	Cumulative RTX dose, g	Vaccine type	Pre-RTX spike protein antibody titers, AU (negative, <1.24 AU)	Post-RTX spike protein antibody titers, AU (negative, <1.24 AU)	Duration elapsed between RTX and second antibody measurement, mo
1	57	Male	White	MPA	MPO (>100)	19	241	Induction: RTX + steroids; CYC + PLEX for refractory vasculitis (new diagnosis)	4	Pfizer–BioNTech	8.35	3.02	1
2	49	Female	White	MPA	MPO (>100)	39	1024	Induction: CYC + steroids Maintenance: RTX Relapse (3 mo after vaccine): RTX, CYC, and steroids	12	Pfizer–BioNTech	20	4.39	1
3	36	Male	White	GPA	PR3 (4.4)	96	190	Induction: CYC + steroids Maintenance: RTX	9	Pfizer–BioNTech	66	21.4	1
4	60	Male	White	GPA	MPO (<3.2)	50	130	Induction: RTX + steroids Maintenance: AZA transitioned to RTX	4.5	Pfizer–BioNTech	7.29	4.23	1

ANCA, anti–neutrophil cytoplasmic antibody; AU, arbitrary unit; AZA, azathioprine; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; ID, identifier; IS, immunosuppression; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PLEX, plasma exchange; PR3, proteinase 3; RTX, rituximab.

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Risk factors associated with poor response to COVID-19 vaccination in kidney transplant recipients

To the editor: The case fatality ratio of coronavirus disease 2019 (COVID-19) in kidney transplant recipients is between 10% and 30%,[1,2] underscoring the importance of vaccination to prevent COVID-19. However, kidney transplant recipients have a reduced response to COVID-19 vaccines (18%–54%).[3,4] We determined severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike IgG (anti–spike IgG) responses to COVID-19 vaccination in 65 kidney transplant recipients who received BNT162b2 (Pfizer–BioNTech), 29 who received mRNA-1273 (Moderna), and 4 who received Janssen Ad26.CoV2.S (Johnson & Johnson) vaccines at a median of 4 years (range, 3 mo–22 yr) after transplantation (Supplementary Table S1). Twenty-one patients had prior COVID-19 infection, and 11 (52%) had SARS-CoV-2 nucleocapsid IgG (anti–nucleocapsid IgG) before vaccination, of whom 20 (95%) generated anti–spike IgG. However, only 24 (32%) of 76 patients without a previous history of COVID-19 and a negative anti–nucleocapsid IgG before vaccination generated an anti–spike IgG response. The median anti–spike IgG level was significantly higher in those with prior COVID-19 (median signal-to-cutoff ratio, 13.3 [95% CI, 7.59–16.20] vs. 6.3 [95% CI, 1.22–15.6]; $P < 0.01$). African Americans, those on full-dose anti-metabolite therapy, and those with lower median CD3 and CD4 T-cell and serum IgM levels had reduced responses (Table 1). A total of 65% of those with CD4 counts >400 and 57% of those with CD3 counts >1000 responded, but only 17% and 13%, respectively, of those with CD4 counts <400 and CD3 counts <500 responded (Supplementary Figure S1A and S1B). In summary, a lack of response to COVID-19 vaccines was associated with African American race; being on high-dose anti-metabolite therapy; and having lower prevaccination CD3, CD4 T-cell, and serum IgM levels.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1A. Antibody response rate to vaccination per CD3 cell counts.

Figure S1B. Antibody response rate to vaccination per CD4 cell counts.

Table S1. Baseline demographics of kidney transplant recipients with and without previous history of coronavirus disease 2019 (COVID-19).

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