Original Article
Yonsei Med J 2025 May;66(5):259-268
https://doi.org/10.3349/ymj.2024.0129
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Immunologic Response and Effects of COVID-19 Vaccines in Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

Ki Hyun Lee[1*], Hyunsue Do[2*], Jun Yong Choi[1], Yong-Beom Park[2,3], Sinyoung Kim[4], Sang-Won Lee[2,3], and Su Jin Jeong[1]

[1]Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul;
[2]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul;
[3]Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul;
[4]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea.

Purpose: The immunological response and adverse effects of antineutrophil cytoplasmic antibody-associated vasculitis (AAV) in patients receiving coronavirus disease-2019 (COVID-19) vaccines remain unclear. We aimed to evaluate the effects of these vaccines on AAV disease activity.

Materials and Methods: We reviewed the medical records of 52 patients with AAV who had received at least second doses of the COVID-19 vaccine and evaluated their immunogenicity by measuring the anti-spike (S) antibody (Ab) titer levels using the Roche Elecsys® immunoassay. Responses to the Birmingham Vasculitis Activity Score (BVAS) tool and 36-Item Short Form Survey before and after vaccination were obtained to assess AAV disease activity. Vaccine reactivity was measured using a standardized questionnaire.

Results: We enrolled 52 patients with AAV. No differences were found between those who received second and third doses of vaccination in terms of AAV type, disease activity, vaccine type, or the use of immunosuppressive agents, including steroids. The median anti-S Ab titer was 3967.0 after third doses compared to 419.0 after second doses (p=0.001). Except for mycophenolate mofetil (MMF), when immunosuppressants were administered in conjunction with steroids, the Ab titer was higher after the third vaccination than that after the second dose. The BVAS remained unchanged before and after second and third doses. No life-threatening adverse events were reported.

Conclusion: Although COVID-19 vaccine may not produce sufficient antibodies in patients taking MMF, the vaccine did not exacerbate disease activity or cause severe side effects. Therefore, COVID-19 vaccines should be considered in patients with AAV.

Key Words: COVID-19, vaccination, antineutrophil cytoplasmic antibody, vasculitis

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic has fueled research on therapeutics and vaccines. Notably, vaccine research on the receptor-binding domain (RBD) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike

Received: May 24, 2024 **Revised:** September 12, 2024 **Accepted:** September 27, 2024 **Published online:** January 3, 2025
Co-corresponding authors: Su Jin Jeong, MD, PhD, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: JSJ@yuhs.ac and
Sang-Won Lee, MD, PhD, Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: sangwonlee@yuhs.ac

*Ki Hyun Lee and Hyunsue Do contributed equally to this work.
•The authors have no potential conflicts of interest to disclose.

(S) protein has reached phase 3 clinical trials at an unprecedented pace, showing exceptional progress.[1] The phase 3 clinical data on BNT162b2 (BNT, Pfizer-BioNTech) and mRNA1273 (m1273, Moderna), which utilize messenger ribonucleic acid (mRNA), demonstrated efficiencies of 95% and 94.5%, respectively. ChAdOx1 nCov-19 (ChAd, Oxford-AstraZeneca), a viral vector vaccine, and Ad26.COV2-S (Ad26, Janssen) also demonstrated efficiencies of 62%–90%, meeting the vaccine Emergency Use Authorization criteria set by the United States Food and Drug Administration.[2-5] Ensuring safe vaccination for high-risk groups remains crucial. However, data on effectiveness, safety, and immune responses of the COVID-19 vaccine in specific groups, especially those with rare autoimmune diseases including vasculitis, are lacking.[6-9] Additionally, immunosuppressive therapy inhibits humoral responses to vaccinations, such as influenza and pneumococcal vaccines.[10,11] Similar to other vaccines, the COVID-19 vaccine may be less effective in patients taking immunosuppressants, such as steroids, biologics, or antirheumatic drugs.[12] Rituximab, used for managing antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), can affect vaccine efficacy for up to 6 months. However, precise vaccine administration guidelines for patients with AAV receiving immunosuppressants are lacking.

Synthetic antigen vaccines against COVID-19 may induce B cells to produce ANCAs via antigen mimicry. Furthermore, neutrophils could react to inflammatory signals by excessively releasing pro-inflammatory cytokines in response to vaccine-related inflammation, a phenomenon known as neutrophil priming.[13] This suggests that COVID-19 vaccines can cause AAV in healthy individuals, a hypothesis supported by previously published case reports.[14,15] Hence, this study investigated the effect of COVID-19 vaccines on the disease course of AAV and the effect of AAV itself or immunosuppressive drugs for AAV treatment on the effectiveness of these vaccines.

This study aimed to evaluate the changes in disease activity, immunogenicity, and adverse effects (AEs) after COVID-19 vaccination in patients with AAV.

MATERIALS AND METHODS

Study participants (study design and population)

Fifty-two patients with AAV were selected from the Severance Hospital ANCA-associated VasculitidEs (SHAVE) cohort. The clinical data and medical records were reviewed. The SHAVE cohort was an observational cohort of patients established in November 2016. The study included patients: 1) with AAV classified based on the classification algorithm for AAV and polyarteritis nodosa proposed by the European Medicine Agency in 2007 (the 2007 algorithm) and the revised nomenclature of vasculitides suggested by the Chapel Hill Conference Consensus in 2012 (the 2012 definitions);[16,17] 2) with AAV classified at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital; and 3) aged 18 years or older enrolled in the AAV cohort. The patients received at least second doses of BNT, m1273, and ChAd vaccines or an additional first dose of mRNA vaccine following the initial dose of Ad26 vaccine. Patients previously infected with COVID-19, indicated by a positive anti-nucleocapsid (anti-N) antibody (Ab), were excluded from the study due to its potential effects on the anti-S Ab titers. Those who received rituximab were also excluded as this treatment was discontinued at least 1 month before and after the COVID-19 vaccination. The medical records included the necessary data for the clinical record form, such as clinical data, laboratory tests results, AAV-specific data, and medications used.

This study was approved by the Institutional Review Board of Yonsei University Health System, Severance Hospital (Seoul, Republic of Korea 4-2021-1329) and was conducted in accordance with the Declaration of Helsinki.

Vaccination schedules

All study participants received at least second doses of mRNA (BNT or m1273) with a 3- to 4-week interval between the first and second doses. For the ChAd vaccine, a second dose was administered at 8- to 12-week intervals, in accordance with the domestic guidelines. After the second dose of the mRNA vaccine or the second dose of ChAd and the initial dose of Ad26, booster doses were administered 3 months later, following the domestic guidelines. The Ab levels were measured before the first vaccination and after the second or third dose.

Study outcomes and covariates

We evaluated the demographic and clinical characteristics of patients with AAV. We used the Birmingham Vasculitis Activity Score (BVAS) tool to assess AAV disease activity and the Short Form-36 (SF-36) to evaluate the functional activity of AAV before and after vaccination. Disease activity was evaluated on the day of sampling. Routine laboratory tests, including assessments of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), P-ANCA, C-ANCA, MPO, and PR3 levels, were performed before and after vaccination. To evaluate the immunogenicity of the vaccination, we quantitatively analyzed the anti-SARS-CoV-2 S Ab (anti-S Ab) levels using blood samples collected at least 7 days after vaccination. We also investigated the type of immunosuppressive medications used.

Immunogenicity assessment

The presence of anti-N Ab was used as a surrogate marker to confirm a history of COVID-19. The Elecsys® Anti-SARS-CoV-2 N protein assay (Roche Diagnostics, Mannheim, Germany) was performed on baseline samples to exclude participants with a history of COVID-19, with a cut-off value of ≥1.0 indicating a positive result. The presence of antibodies against the RBD of the S protein (anti-S Ab) was determined using Elecsys® Anti-SARS-CoV-2 S immunoassay on a Roche Cobas e411 analyzer

https://doi.org/10.3349/ymj.2024.0129

(Roche Diagnostics). This one-step double-antigen sandwich assay was developed to quantitatively assess the levels of total anti-SARS-CoV-2 RBD antibodies in human serum and plasma specimens. Results ranged from 0.4 (lower limit of detection, ≤0.40 U/mL) to 250 U/mL (extensible to 2,500 U/mL with a 1:10 sample dilution and up to 25,000 U/mL with onboard 1:100 dilution). Titer values above 0.8 U/mL indicated a positive result.[18]

AEs according to reactogenicity

AEs associated with vaccine reactogenicity within 7 days following each vaccine dose were collected using a standardized questionnaire, either during a hospital visit or over the phone. The questionnaire consisted of questions that assessed both local and systemic symptoms, including injection site swelling, pain, erythema, fever, headache, diarrhea, fatigue, arthralgia, and myalgia.[19] The participants reported the duration and severity of each symptom and the corresponding severity ratings. The cumulative symptom scores were calculated by summing the individual scores and categorizing them according to symptom severity: asymptomatic (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3), and potentially life-threatening (grade 4).

Statistical analysis

All statistical analyses were performed using SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient demographics. Categorical variables were compared among AAV subtypes using the Kruskal–Wallis test, χ^2 test, or Fisher's exact test. An analysis of covariance (ANCOVA) was employed to correct the gap between vaccination and blood sampling. The amount of anti-S Ab produced was compared between the second and third doses of the COVID-19 vaccine. Wilcoxon signed rank, t-test, and McNemar's tests were used to evaluate the changes in disease activity and laboratory findings before and after the second or third dose of the vaccines. Statistical significance in the multivariate logistic regression analysis was defined as $p<0.05$.

RESULTS

Demographic and clinical characteristics

We analyzed the baseline clinical characteristics during blood sampling. We enrolled 52 patients, 31 (59.6%) of whom were only vaccinated with BNT or m1273 mRNA. According to the number of doses completed, 33 patients received the second dose, while 19 patients received the third dose.

When comparing the clinical data of the three AAV subtypes, 26 patients had microscopic polyangiitis (MPA), 16 had granulomatosis with polyangiitis (GPA), and 10 had eosinophilic granulomatosis with polyangiitis (EGPA). The participants' median ages were 68.5, 62.0, and 51.5 years, respectively. The proportions of male were 12 (46.2%), 6 (37.5%), and 3 (30.0%). A total of 48 patients (92.3%) were taking immunosuppressants: 23 patients (88.5%) with MPA, 16 patients (100%) with GPA, and 9 patients (90.0%) with EGPA were taking prednisolone at doses of 5 mg [interquartile range (IQR): 2.5–7.5], 5 mg (IQR: 3.1–6.9), and 5 mg (IQR: 1.9–7.5) per day, respectively (Table 1).

Immunologic response of vaccinated patients with AAV

The baseline characteristics of the second- and third-dose vaccination groups were analyzed. No significant differences were observed between these groups according to AAV type, baseline disease activity, vaccine type, or use of immunosuppressive agents, including steroids. The median age of the third-dose group was 67.0, which was higher than that of the second-dose group (60.0); however, the difference was not significant.

When immunogenicity was compared between the second- and third-dose vaccination groups, the time from the last vaccination day to the measurement of anti-S Ab titer levels was 30.0 days in the third-dose vaccination group, which was shorter than that in the second-dose vaccination group (68.0). The median anti-S Ab titer was 3967.0 in the third-dose vaccination group, which was higher than that in the second-dose vaccination group (419.0%; $p=0.001$). Even when the sampling interval was adjusted using ANCOVA, the Ab titer level was significantly higher in the third-dose vaccination group ($p=0.002$) (Table 2).

Anti-S Ab titer levels according to the use of immunosuppressants

Steroid combination therapy involved the use of azathioprine (AZA), mycophenolate mofetil (MMF), tacrolimus, methotrexate, or cyclophosphamide combined with steroids. The group treated with MMF plus steroids showed lower anti-S Ab titer levels at the second and third doses compared to the group treated with steroids alone ($p=0.011$ and $p=0.014$, respectively). In the group that received the third vaccine dose, single steroid users showed a higher median anti-S Ab titer level; however, the difference was not significant ($p=0.439$) as only three patients received steroids alone. Except for those who received MMF, the anti-S Ab titer level was higher in the group that received the third vaccine dose compared to the group that received the second dose, particularly participants who received AZA ($p=0.021$) (Fig. 1).

Immunogenicity and changes in AAV disease severity before and after the second or third vaccination according to the AAV subtype

Patients who completed the second-dose vaccination were analyzed according to AAV subtype. In patients with MPA, the median anti-S Ab titer level was 84.30. In patients with GPA and EGPA, the median anti-S Ab titer levels were 1456.50 and 816.00, respectively. The anti-S Ab titer levels were significantly different among the three groups ($p=0.027$) (Table 3, Supplementary

Fig. 1, only online). Conversely, no significant differences were found in the anti-S Ab titer levels between the MPA and GPA groups (p=0.010). No significant differences were also found between the MPA and EGPA group and between the EGPA and GPA group (p=0.135 and p=0.364, respectively) (Supplementary Table 1, only online).

Patients who completed the third-dose vaccination were analyzed according to AAV subtype. In patients with MPA, GPA, and EGPA, the median anti-S Ab titer levels were 4537.50, 4310.82, and 3336.33, respectively. No significant differences were observed among the three groups (p=0.907) (Table 3, Supplementary Fig. 1, only online). No significant differences were also observed between MPA and GPA, MPA and EGPA, or EGPA and GPA (p=0.875, p=0.692, and p>0.999, respectively) (Sup-

Table 1. Demographic and Clinical Characteristics of Patients with ANCA-Associated Vasculitis

	All (n=52)	MPA (n=26)	GPA (n=16)	EGPA (n=10)	*p* value
Sex, male	21 (40.4)	12 (46.2)	6 (37.5)	3 (30.0)	0.650
Age, yr	64.0 (52.5–71.0)	68.5 (64.0–74.0)	62.0 (51.0–70.5)	51.5 (47.8–56.5)	0.001
BMI, kg/m^2	23.0 (20.8–24.2)	23.0 (21.3–24.1)	23.3 (20.3–25.2)	21.3 (18.3–24.0)	0.465
Vaccination					0.890
Second doses	33 (63.5)	16 (61.5)	10 (62.5)	7 (70.0)	
BNT/BNT	19 (36.5)	8 (30.8)	6 (37.5)	5 (50.0)	
m1273/m1273	1 (1.9)	0 (0.0)	1 (6.3)	0 (0.0)	
ChAd/ChAd	10 (19.2)	7 (26.9)	3 (18.8)	0 (0.0)	
Ad26/m1273	2 (3.8)	0 (0.0)	0 (0.0)	2 (20.0)	
ChAd/BNT	1 (1.9)	1 (3.8)	0 (0.0)	0 (0.0)	
Third doses	19 (36.5)	10 (38.5)	6 (37.5)	3 (30.0)	
BNT/BNT/BNT	11 (21.2)	5 (19.2)	3 (18.8)	3 (30.0)	
ChAd/ChAd/BNT	4 (7.7)	4 (15.4)	0 (0.0)	0 (0.0)	
ChAd/ChAd/m1273	4 (7.7)	1 (3.8)	3 (18.8)	0 (0.0)	
Disease activity					
BVAS	4.0 (2.0–6.0)	4.0 (2.0–8.3)	3.5 (1.0–6.0)	4.5 (3.0–7.3)	0.765
SF-36 MCS	66.5 (53.4–78.7)	63.9 (53.3–75.8)	74.4 (58.3–84.4)	68.7 (52.3–80.0)	0.307
SF-36 PCS	67.2 (51.3–84.1)	64.8 (50.6–72.2)	75.8 (57.0–88.3)	69.7 (50.2–86.0)	0.163
Underlying disease					
Hypertension	27 (51.9)	14 (53.8)	10 (62.5)	3 (30.0)	0.262
Diabetes mellitus	18 (34.6)	9 (34.6)	8 (50.0)	1 (10.0)	0.114
Cerebrovascular accident	8 (15.4)	4 (15.4)	4 (25.0)	0 (0.0)	0.241
Cardiovascular disease	3 (5.8)	2 (7.7)	0 (0.0)	1 (10.0)	0.576
Chronic kidney disease	17 (32.7)	11 (42.3)	5 (31.3)	1 (10.0)	0.178
End stage renal disease	7 (13.5)	6 (23.1)	1 (6.3)	0 (0.0)	0.158
Dyslipidemia	11 (21.2)	4 (15.4)	6 (37.5)	1 (10.0)	0.216
ILD	7 (13.5)	6 (23.1)	1 (6.3)	0 (0.0)	0.158
Hypothyroidism	5 (9.6)	3 (11.5)	1 (6.3)	1 (10.0)	0.999
Solid cancer	5 (9.6)	2 (7.7)	2 (12.5)	1 (10.0)	0.840
Hematologic malignancy	2 (3.8)	2 (7.7)	0 (0.0)	0 (0.0)	0.686
Solid organ transplantation	1 (1.9)	1 (3.8)	0 (0.0)	0 (0.0)	0.999
Immunosuppressants	48 (92.3)	23 (88.5)	16 (100)	9 (90.0)	0.395
Steroid	47 (90.4)	23 (88.5)	16 (100)	8 (80.0)	0.150
AZA	25 (48.1)	9 (34.6)	9 (56.3)	7 (70.0)	0.120
MMF	9 (17.3)	5 (19.2)	3 (18.8)	1 (10.0)	0.898
Tacrolimus	5 (9.6)	4 (15.4)	0 (0.0)	1 (10.0)	0.318
MTX	2 (3.8)	0 (0.0)	2 (12.5)	0 (0.0)	0.124
CYC	1 (1.9)	1 (3.8)	0 (0.0)	0 (0.0)	0.999

ANCA, antineutrophil cytoplasmic antibody; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; BMI, body mass index; BNT, BNT162b2 (Pfizer-BioNTech); m1273, mRNA1273 (Moderna); ChAd, ChAdOx1 nCov-19 (Oxford-AstraZeneca); Ad26, Ad26.COV2-S (Janssen); BVAS, Birmingham Vasculitis Activity Score; SF-36, Short Form-36; MCS, mental component summary; PCS, physical component summary; ILD, interstitial lung disease; AZA, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; CYC, cyclophosphamide.
Data are expressed as the median (interquartile range) or n (%) of patients, unless otherwise indicated.

https://doi.org/10.3349/ymj.2024.0129

Table 2. Demographics and Immunogenicity According to Vaccination Dose

	All (n=52)	Second dose (n=33)	Third dose (n=19)	*p* value
Age, yr	64.0 (52.5–71.0)	60.0 (48.0–70.0)	67.0 (59.0–73.0)	0.058
Type of AAV				0.890
MPA	26 (50.0)	16 (61.5)	10 (38.5)	
GPA	16 (30.8)	10 (62.5)	6 (37.5)	
EGPA	10 (19.2)	7 (70.0)	3 (30.0)	
Disease activity†				
BVAS	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–7.0)	0.487
SF-36 MCS	70.1 (59.3–78.2)	69.7 (58.8–84.8)	70.3 (63.4–73.7)	0.427
SF-36 PCS	68.1 (55.9–79.0)	69.1 (56.6–82.0)	67.2 (55.6–76.3)	0.256
Type of vaccination				0.848
mRNA	31 (59.6)	20 (60.6)	11 (57.9)	
Other viral vector or mixed	21 (40.4)	13 (39.4)	8 (42.1)	
Duration of sample collection from vaccination, days	63.0 (27.5–89.3)	68.0 (34.5–116.5)	30.0 (15.0–69.0)	0.019
Seroconversion	49 (94.2)	30 (90.9)	19 (100.0)	0.291
Anti-S Ab titer, U/mL	1134.5 (83.9–3943.5)	419.0 (31.9–1546.0)	3967.0 (1245.0–7419.0)	0.002*
Immunosuppressants	48 (92.3)	32 (97.0)	16 (84.2)	0.132
Steroid (prednisolone), mg/day	5.0 (2.5–7.5)	5.0 (2.5–7.5)	5.0 (2.5–7.5)	0.897
COVID-19 infection after vaccination	13 (25.0)	9 (27.3)	4 (21.1)	0.746

AAV, antineutrophil cytoplasmic antibody-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; BVAS, Birmingham Vasculitis Activity Score; SF-36, Short Form-36; PCS, physical component summary; MCS, mental component summary.
Data are expressed as the median (interquartile range) or n (%) of patients, unless otherwise indicated.
*Using an analysis of covariance to adjust for the gap in time from vaccination to blood sampling; †Disease activity, estimated at the time of sampling after vaccination.

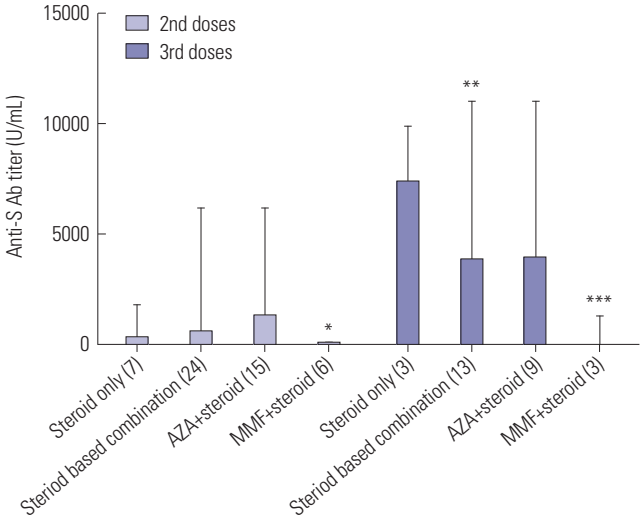

Fig. 1. Anti-S Ab titer according to the use of immunosuppressants in patients receiving second and third doses of COVID-19 vaccine. Boxes and bars indicate the median (interquartile range) of the anti-S Ab titer, parentheses indicate the n (%). Steroid-based combination means AZA, MMF, tacrolimus, MTX, CYC combined with steroid use. *p<0.011 compared to the steroid-based combination group in second dose; **p<0.026 compared to the steroid-based combination group in second dose; ***p<0.014 compared to the steroid-based combination group in third dose. S, spike; Ab, antibody; AZA, azathioprine; MMF, mycophenolate mofetil; other s, tacrolimus, methotrexate (MTX), and cyclophosphamide (CYC).

plementary Table 1, only online).

Regardless of the number of vaccinations, the median BVAS score was 4.0, which remained unchanged before and after vaccination (p=0.343 and p=0.092, respectively) (Table 4). In patients who completed the second-dose vaccination, the median SF-36 physical component summary (PCS) scores were 65.63 and 69.06 pre- and post-vaccination, respectively. Meanwhile, the median SF-36 mental component summary (MCS) scores were 61.88 and 69.69 pre- and post-vaccination, respectively; these changes were not considered significant (p=0.597, 0.088) (Table 4). In patients who completed the third-dose vaccination, the median SF-36 PCS scores were 68.75 and 67.19 pre- and post-vaccination, respectively. The median SF-36 MCS scores were 69.69 and 70.31 pre- and post-vaccination, respectively. No significant differences were found between the groups (p=0.936, 0.778) (Table 4).

Comparison of laboratory findings pre- and post-vaccination

In patients who completed the second vaccination, the median ESR values pre- and post-vaccination were 13.00 and 19.50, respectively (p=0.041). The median CRP levels were 1.150 and 3.250, respectively (p=0.010). In patients who completed the third vaccination, the median ESR value was 12.00 pre- and post-vaccination (p=0.522). The median CRP levels were 1.00 and 2.30 pre- and post-vaccination, respectively (p=0.013). MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) positivity did not

change significantly pre- and post-vaccination, regardless of the number of vaccinations (Table 4).

AEs according to the reactogenicity after COVID-19 vaccination in patients with AAV

Forty-nine out of the 52 individuals who received the second dose of the COVID-19 vaccine and 16 out of the 19 who received the third dose responded to the vaccine (Table 5). Injection site pain was the most common local AE after the second and third vaccinations in all AAV groups (75.5% and 68.8% of patients, respectively). Most of the patients experienced grade 1 pain and did not require any special type of analgesic. Six patients

Table 3. Comparison of Follow-Up Duration and Anti-S Ab Titer among MPA, GPA, and EGPA

	MPA	GPA	EGPA	*p* value
Variables (after second dose)				
Total subjects	16 (48.48)	10 (30.30)	7 (21.21)	
Duration of pre-vaccination to final sampling, days	183.50 (168.00–357.00)	178.50 (175.00–273.00)	264.71±91.47	
Duration of vaccination to final sampling, days	76.88±54.95	103.10±73.41	57.00 (40.50–65.50)	
Presence of anti-S Ab	13	10	7	
Anti-S Ab titer, U/mL	84.30 (5.67–444.00)	1456.50 (899.00–2794.00)	816.00 (253.50–1265.00)	0.027
Steroid (prednisolone), mg/day	6.09±4.18	5.00±2.04	4.29±3.45	0.492
MMF administration	4 (25.00)	1 (10.00)	1 (14.30)	0.841
MMF dose, mg/day	218.75±406.97	100.00±316.23	35.71±94.49	0.445
Variables (after third dose)				
Total subjects	10	6	3	
Duration of pre-vaccination to final sampling, days	353.50 (341.00–358.00)	188.50 (176.00–350.00)	245.00±103.12	
Duration of vaccination to final sampling, days	56.10±35.00	25.33±13.65	45.33±44.43	
Presence of anti-S Ab	10	6	3	
Anti-S Ab titer, U/mL	4537.50 (1245.00–9882.00)	4310.82±4356.67	3336.33±1646.94	0.907
Steroid (prednisolone), mg/day	4.38±3.69	7.08±6.41	5.83±1.44	0.523
MMF administration	1 (10.00)	2 (33.30)	0 (0.00)	0.536
MMF dose, mg/day	50.10±158.08	166.67±258.20	0.00±0.00	0.373

MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MMF, mycophenolate mofetil.
Values are expressed as a median (interquartile range), mean±standard deviation, or n (%).

Table 4. Comparison between Pre- and Post-Vaccination Conditions after the Second and Third Vaccine Doses

	Pre-vaccination	Post-vaccination	*p* value
Variables (after second vaccination)			
BVAS	4.0 (2.0–6.0)	4.0 (2.0–6.0)	0.343
SF-36 PCS	65.63 (50.62–86.10)	69.06 (56.57–82.04)	0.597
SF-36 MCS	61.88 (52.14–83.44)	69.69 (58.75–84.85)	0.088
Serum albumin, g/dL	4.42±0.29	4.34±0.24	0.164
ESR, mm/hr	13.00 (6.00–27.50)	19.50 (6.00–47.50)	0.041
CRP, mg/L	1.150 (0.50–2.85)	3.250 (1.00–6.85)	0.010
MPO-ANCA (or P-ANCA) positivity	19 (57.58)	16 (48.48)	0.375
Interval to vaccination, days	107.00 (60.00–139.00)	68.00 (35.00–87.00)	0.015
Variables (after third vaccination)			
BVAS	4.00 (2.50–10.50)	4.00 (2.00–6.50)	0.092
SF-36 PCS	68.75 (54.68–76.88)	67.19 (55.63–76.25)	0.936
SF-36 MCS	69.69 (58.85–78.13)	70.31 (63.44–73.65)	0.778
Serum albumin, g/dL	4.38±0.31	4.22±0.25	0.010
ESR, mm/hr	12.00 (5.50–19.00)	12.00 (6.00–20.00)	0.522
CRP, mg/L	1.00 (0.50–2.40)	2.30 (1.20–5.00)	0.013
MPO-ANCA (or P-ANCA) positivity	14 (73.68)	13 (68.42)	0.999
Interval to vaccination, days	146.00 (101.00–157.50)	30.00 (18.50–66.00)	<0.001

BVAS, Birmingham Vasculitis Activity Score; MCS, mental component summary; PCS, physical component summary; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; MPO, myeloperoxidase; ANCA, antineutrophil cytoplasmic antibody.
Values are expressed as median (interquartile range), mean±standard deviation, or n (%).

https://doi.org/10.3349/ymj.2024.0129

Table 5. Reactogenicity of the COVID-19 Vaccine in Patients with ANCA-Associated Vasculitis

Second doses	All (n=49)	Grade 1	Grade 2	Grade 3	Grade 4
Local adverse events					
Pain at the injection site	37 (75.5)	31 (63.6)	6 (12.2)	0 (0.0)	0 (0.0)
Redness at the injection site	1 (2.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling at the injection site	1 (2.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic adverse events					
Myalgia	3 (6.1)	2 (4.1)	0 (0.0)	1 (2.0)	0 (0.0)
Fatigue	5 (10.2)	4 (8.2)	0 (0.0)	1 (2.0)	0 (0.0)
Headache	2 (4.1)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)
Joint pain	2 (4.1)	1 (2.0)	1 (2.0)	0 (0.0)	0 (0.0)
Fever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Third doses	**All (n=16)**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Local adverse events					
Pain at the injection site	11 (68.8)	10 (62.5)	1 (6.3)	0 (0.0)	0 (0.0)
Redness at the injection site	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling at the injection site	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic adverse events					
Myalgia	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Joint pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

ANCA, antineutrophil cytoplasmic antibody.
Data are presented as n (%) of patients.

(12.2%) who received the second dose and one patient (6.3%) who received the third dose achieved pain relief using non-narcotic methods. None of the patients experienced severe AEs, including death, life-threatening events, or hospitalizations.

DISCUSSION

Vaccines play a crucial role in combating the COVID-19 pandemic, especially in immunocompromised patients who are at high risk of developing severe disease.[12,20-23] In autoimmune patients, the COVID-19 vaccine is recommended as a preventive measure given that the disease disrupts the immune system, which is further compromised by immunosuppressive medications.[12] Most patients with AAV require hospitalization and have a higher mortality rate than the general population, with rates comparable to those of solid organ transplant recipients (mortality rates: 20%–25%).[24,25] The American College of Rheumatology (ACR) provides detailed clinical guidance on COVID-19 vaccination for patients with rheumatic diseases. However, patients with autoimmune diseases have expressed concerns and hesitancy toward COVID-19 vaccination owing to fears of disease flares, reactions, or side effects.[7]

Many studies have examined the efficacy and immunogenicity of COVID-19 vaccines in autoimmune diseases, reaching similar conclusions. Consistent with our study's findings, the anti-S Ab index and neutralizing antibodies increased significantly when the third dose was administered compared with the second dose.[26] In patients taking immunosuppressants, the anti-S Ab titer level or the neutralizing function of antibodies was reduced compared to that of the general population or the same AAV cohort, especially those treated with rituximab.[26,27] Subgroup analysis based on the presence of seroconversion in patients with AAV showed a significant difference in those taking immunosuppressive drugs, especially MMF. Neutralizing antibodies were significantly lower in the rituximab group.[28]

Some studies described the de novo development of vasculitis associated with COVID-19 vaccination.[14,15] However, the current study found no worsening of disease activity in patients with AAV after COVID-19 vaccination, and the AEs were similar to those in the general population. Excluding injection site pain, the vaccine-related AEs were fewer than the reported adverse reactions to the COVID-19 vaccine in the general Korean population.[29,30]

The levels of inflammatory markers remained unchanged in patients with AAV after the second and third doses, with the median values remaining within normal ranges, indicating the absence of disease worsening. Although the ESR level increased after the second dose, it did not provide explicit evidence of AAV worsening and remained within the normal range. The mini-

mal differences in ESR and CRP levels pre- and post-vaccination could be attributed to the immune response stimulated by the vaccine. In addition, the albumin levels decreased after the third dose. None of the patients experienced disease worsening during the evaluation of disease activity or inflammatory markers.

In this study, the median anti-S Ab titer level was higher after the third dose than that after the second dose in patients with AAV. Among the participants, six with MPA, four with GPA, and three with EGPA were infected with COVID-19 after vaccination; however, all cases were mild and did not require hospitalization. Moreover, considering that the nationwide vaccination rate in Korea was approximately 88% and the proportion of cumulative confirmed cases was 30% (during the study period), the incidence of breakthrough infection was relatively low compared to the general population in Korea.[31]

After the third dose, the anti-S Ab production increased significantly compared to that after the second dose, regardless of the medication used for AAV treatment, except for MMF. MMF is one of the primary medications used to alleviate AAV; however, it may impair COVID vaccine responses. Although our sample size was small and heterogeneous, our results contradict the ACR guidelines, which do not impose special restrictions on MMF use.[12]

According to previous studies, MMF inhibits purine synthesis, impairing both B and T cells, thereby preventing lymphocyte proliferation. Additionally, it induces apoptosis in T cells and affects both cytotoxic T cells and Th1 and Th2 cells. This impairment is likely due to the dysfunction of B-cell and Th cell activities. MMF has also been shown to affect immune responses in the lymph nodes. Hence, MMF can potentially result in an impaired response to vaccines by inhibiting antibody production.[32]

Therefore, further research is warranted, and patients with AAV receiving MMF should exercise caution regarding the risk of developing COVID-19, even after sufficient vaccination.

Anti-S Ab production increases after the second dose in patients with GPA. Additionally, the median anti-S Ab titer level after the second dose was lower in patients with MPA than that in other groups. However, after the third dose, all patients showed high anti-S Ab production regardless of the AAV subtype. We examined the incidence of steroid use and MMF at the time of the second and third COVID-19 vaccine administrations, as well as the presence and dosage of these medications. During the second vaccination, the average steroid dose administered in the MPA group was 6.09±4.18, which was higher than that in the GPA group (5.00±2.04) and EGPA group (4.29±3.45). Although this difference was not significant (p=0.492), the trend in steroid dosage, which affects antibody production, could explain the lower Ab titer levels observed in the MPA group after the second vaccination. Furthermore, a higher proportion of patients were using MMF during the second vaccination, and the dosage was higher than that in other groups. This may have also contributed to the lower antibody production observed in the MPA group after the second vaccination. This trend was not observed after the third vaccination, and no significant difference was found in anti-S Ab levels among the three groups. This lack of difference may be due to the small sample size during the third vaccination, which could present limitations in the descriptive statistics (Table 3).

This study had several limitations. We only investigated the presence of anti-S Ab rather than assessing the presence of neutralizing antibodies. The actual immune responses were more complex owing to the involvement of T cells.[33] Therefore, it was difficult to evaluate the efficacy of COVID-19 vaccination in patients with AAV based on anti-S Ab levels. However, multiple studies have indicated that anti-S Ab and S1 RBD together account for nearly 90% of the neutralizing activity.[34-36] Therefore, the anti-S Ab titer can partially reflect the efficacy of vaccines.

Rituximab, which primarily affects B-cell immunity and antibody production, was not included since the participants did not receive it for 1 month before and after vaccination. Finally, this retrospective cohort study, which was conducted only in Korea using a small sample size, showed variabilities in the period from COVID-19 vaccination to blood sampling, the type of vaccine administered, and the immunosuppressant used. However, this study is the first to comprehensively investigate the ability of patients with AAV to produce anti-S Abs according to the type of immunosuppressant used and the changes in immunogenicity and disease activity using BVAS and SF-36. The COVID-19 vaccine may not produce sufficient antibodies in patients receiving MMF. However, since the vaccine did not exacerbate disease activity or cause severe side effects, and booster shots increased the anti-S Ab levels, COVID-19 vaccines should be considered in patients with AAV.

AVAILABILITY OF DATA

All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

ACKNOWLEDGEMENTS

This work was funded by Chong Kun Dang Pharmaceutical Corp, Seoul, Republic of Korea (4-2022-1351).

AUTHOR CONTRIBUTIONS

Conceptualization: Ki Hyun Lee and Hyunsue Do. Data curation: Ki Hyun Lee and Hyunsue Do. Formal Analysis: Ki Hyun Lee and Hyunsue Do. Funding acquisition: Sang-Won Lee. Investigation: Jun Yong Choi, Sinyoung Kim, and Yong-Beom Park. Methodology: Ki Hyun Lee and Hyunsue Do. Project administration: Sang-Won Lee and Su Jin Jeong. Resources: Sang-Won Lee and Su Jin Jeong. Supervision: Sang-Won Lee and Su Jin Jeong. Validation: Sang-Won Lee and Su Jin Jeong. Visualization: Yong-Beom Park. Writing—original draft: Ki Hyun Lee and Hyunsue Do. Writing—review & editing: Sang-Won Lee and Su Jin Jeong. Approval of final manuscript: all authors.

https://doi.org/10.3349/ymj.2024.0129

ORCID iDs

Ki Hyun Lee https://orcid.org/0000-0002-3138-6685
Hyunsue Do https://orcid.org/0000-0002-9550-1048
Jun Yong Choi https://orcid.org/0000-0002-2775-3315
Yong-Beom Park https://orcid.org/0000-0003-4695-8620
Sinyoung Kim https://orcid.org/0000-0002-2609-8945
Sang-Won Lee https://orcid.org/0000-0002-8038-3341
Su Jin Jeong https://orcid.org/0000-0003-4025-4542

REFERENCES

1. Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: the status and perspectives in delivery points of view. Adv Drug Deliv Rev 2021;170:1-25.
2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-15.
3. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403-16.
4. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99-111.
5. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med 2021;384:2187-201.
6. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 5. Arthritis Rheumatol 2023;75:E1-16.
7. Felten R, Dubois M, Ugarte-Gil MF, Chaudier A, Kawka L, Bergier H, et al. Vaccination against COVID-19: expectations and concerns of patients with autoimmune and rheumatic diseases. Lancet Rheumatol 2021;3:e243-5.
8. Terracina KA, Tan FK. Flare of rheumatoid arthritis after COVID-19 vaccination. Lancet Rheumatol 2021;3:e469-70.
9. Izmirly PM, Kim MY, Samanovic M, Fernandez-Ruiz R, Ohana S, Deonaraine KK, et al. Evaluation of immune response and disease status in systemic lupus erythematosus patients following SARS-CoV-2 vaccination. Arthritis Rheumatol 2022;74:284-94.
10. Fomin I, Caspi D, Levy V, Varsano N, Shalev Y, Paran D, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNFα blockers. Ann Rheum Dis 2006;65:191-4.
11. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2014;66:1016-26.
12. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 3. Arthritis Rheumatol 2021;73:e60-75.
13. Konstantinov KN, Ulff-Møller CJ, Tzamaloukas AH. Infections and antineutrophil cytoplasmic antibodies: triggering mechanisms. Autoimmun Rev 2015;14:201-3.
14. Mai AS, Tan EK. COVID-19 vaccination precipitating de novo ANCA-associated vasculitis: clinical implications. Clin Kidney J 2022;15:1010-1.
15. Shakoor MT, Birkenbach MP, Lynch M. ANCA-associated vasculitis following Pfizer-BioNTech COVID-19 vaccine. Am J Kidney Dis 2021;78:611-3.
16. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1-11.
17. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007;66:222-7.
18. Roche Diagnostics International Ltd. Elecsys® Anti-SARS-CoV-2 S [accessed on 2023, January 2]. Available at: https://diagnostics.roche.com/content/dam/diagnostics/Blueprint/en/pdf/cps/Elecsys-Anti-SARS-CoV-2-S-factsheet-SEPT-2020-2.pdf.
19. U.S. Food and Drug Administration. Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials [accessed on 2023, January 2]. Available at: https://www.fda.gov/media/73679/download.
20. Baang JH, Smith C, Mirabelli C, Valesano AL, Manthei DM, Bachman MA, et al. Prolonged severe acute respiratory syndrome coronavirus 2 replication in an immunocompromised patient. J Infect Dis 2021;223:23-7.
21. Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, et al. Persistence and evolution of SARS-CoV-2 in an immunocompromised host. N Engl J Med 2020;383:2291-3.
22. Nakajima Y, Ogai A, Furukawa K, Arai R, Anan R, Nakano Y, et al. Prolonged viral shedding of SARS-CoV-2 in an immunocompromised patient. J Infect Chemother 2021;27:387-9.
23. Tarhini H, Recoing A, Bridier-Nahmias A, Rahi M, Lambert C, Martres P, et al. Long-term severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectiousness among three immunocompromised patients: from prolonged viral shedding to SARS-CoV-2 superinfection. J Infect Dis 2021;223:1522-7.
24. Kronbichler A, Geetha D, Smith RM, Egan AC, Bajema IM, Schönermarck U, et al. The COVID-19 pandemic and ANCA-associated vasculitis – reports from the EUVAS meeting and EUVAS education forum. Autoimmun Rev 2021;20:102986.
25. Rutherford MA, Scott J, Karabayas M, Antonelou M, Gopaluni S, Gray D, et al. Risk factors for severe outcomes in patients with systemic vasculitis and COVID-19: a binational, registry-based cohort study. Arthritis Rheumatol 2021;73:1713-9.
26. Speer C, Töllner M, Benning L, Klein K, Bartenschlager M, Nusshag C, et al. Third COVID-19 vaccine dose with BNT162b2 in patients with ANCA-associated vasculitis. Ann Rheum Dis 2022;81:593-5.
27. Speer C, Töllner M, Benning L, Bartenschlager M, Kim H, Nusshag C, et al. BA.1/BA.5 immunogenicity, reactogenicity, and disease activity after COVID-19 vaccination in patients with ANCA-associated vasculitis: a prospective observational cohort study. Viruses 2023;15:1778.
28. Pereira RMR, Dagostin MA, Caparbo VF, Sales LP, Pasoto SG, Silva CA, et al. Anti-SARS-CoV-2 inactivated vaccine in patients with ANCA-associated vasculitis: immunogenicity, safety, antibody decay and the booster dose. Clinics (Sao Paulo) 2022;78:100150.
29. Choi YY, Kim MK, Kwon HC, Kim GH. Safety monitoring after the BNT162b2 COVID-19 vaccine among adults aged 75 years or older. J Korean Med Sci 2021;36:e318.
30. Jeon M, Kim J, Oh CE, Lee JY. Adverse events following immunization associated with coronavirus disease 2019 vaccination reported in the mobile vaccine adverse events reporting system. J Korean Med Sci 2021;36:e114.
31. Korea Disease Control and Prevention Agency. COVID-19 outbreak and vaccination status in Korea [accessed on 2023, January 2]. Avail-

able at: https://www.kdca.go.kr/board/board.es?mid=a20501010000&bid=0015&list_no=719440&cg_code=&act=view&nPage=29.
32. Fatly ZA, Betjes MGH, Dik WA, Fouchier RAM, Reinders MEJ, de Weerd AE. Mycophenolate mofetil hampers antibody responses to a broad range of vaccinations in kidney transplant recipients: results from a randomized controlled study. J Infect 2024;88:106133.
33. Vardhana S, Baldo L, Morice WG 2nd, Wherry EJ. Understanding T cell responses to COVID-19 is essential for informing public health strategies. Sci Immunol 2022;7:eabo1303.
34. Dolscheid-Pommerich R, Bartok E, Renn M, Kümmerer BM, Schulte B, Schmithausen RM, et al. Correlation between a quantitative anti-SARS-CoV-2 IgG ELISA and neutralization activity. J Med Virol 2022;94:388-92.
35. Piccoli L, Park YJ, Tortorici MA, Czudnochowski N, Walls AC, Beltramello M, et al. Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology. Cell 2020;183:1024-42.e21.
36. Premkumar L, Segovia-Chumbez B, Jadi R, Martinez DR, Raut R, Markmann A, et al. The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. Sci Immunol 2020;5:eabc8413.

https://doi.org/10.3349/ymj.2024.0129