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ORIGINAL ARTICLE

Efficacy of coronavirus disease 2019 vaccines in patients with rheumatic diseases

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ABSTRACT

Objectives: In this study, we report the immune response to the BNT162b2 vaccine and CoronaVac vaccine after a two-dose vaccination and the effects of conventional drugs, immunosuppressive drugs, and new-generation therapies on vaccine responses in patients with rheumatic and musculoskeletal diseases (RMDs).

Patients and methods: This is a prospective observational study conducted with 94 patients (65 males, 29 females; mean age: 42.7±12.1 years; range, 19 to 69 years) between May 2021 and January 2022. The immunogenicity of the two-dose regimens of the BNT162b2 and CoronaVac vaccines in adult patients with RMD was analyzed according to disease and treatments. Serum immunoglobulin G antibody levels against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike proteins were measured four weeks after the second dose of vaccines.

Results: Patients on regimens including mycophenolate, rituximab, and steroids were less likely to develop an antibody response (p=0.001, p=0.06, and p=0.001, respectively). Impairment of vaccine response by other conventional disease-modifying antirheumatic drugs and by anti-tumor necrosis factor treatments was not shown. Younger participants appeared more likely to develop an antibody response. The CoronaVac vaccine was less likely to develop an antibody response compared to the BNT162b2 vaccine (p=0.002). Systemic lupus erythematosus and vasculitis had the lowest antibody titers compared to other RMDs.

Conclusion: Patients receiving mycophenolate mofetil, rituximab, and steroids should be warned about the risk of a suboptimal vaccine response. If possible, vaccination strategies should be changed, and the dose modification of drugs should be made during the vaccination. Further studies are required to determine the responses to SARS-CoV-2 vaccination and optimization of vaccine response in patients with RMDs.

Keywords: Antibody formation, CoronaVac vaccine, Coronavirus disease 2019 vaccines, BNT162 vaccine, rheumatic diseases.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was detected for the first time in China and caused significant morbidity and mortality, quickly turned into a pandemic and became an important health problem. Social distancing, quarantine, and isolation measures are essential in preventing dissemination as the pandemic continues and the majority of the population is at risk of encountering the disease.[1] Currently, the most effective approach to reducing the spread of the disease and the development of morbidity and mortality when encountered is to control the pandemic with vaccines, particularly in patients with comorbidities since the disease may have a severe course in the patients.[2] In addition, the disease may have a severe progression in patients with rheumatic and musculoskeletal diseases (RMDs) due to both the

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immunomodulatory effects of their underlying diseases and immunomodulating treatments.[2] In Türkiye, the CoronaVac vaccine produced by the Chinese Sinovac company and the BNT162b2 vaccine produced by Pfizer-BioNTech have been administered according to priority groups in line with the national vaccine program.[3] As the coronavirus disease 2019 (COVID-19) vaccines are new on the market, studies addressing their efficacy in special groups, such as patients with RMDs receiving immunosuppressive medications, are needed. The current approach to COVID-19 vaccination of patients with RMD is mainly based on the data extrapolated from studies on other vaccines and limited COVID-19 vaccine studies. Herein, we report the immune response to COVID-19 vaccines and the effects of disease-modifying antirheumatic drugs (DMARDs), immunosuppressives, and biologic agents on vaccine responses in patients with RMD.

PATIENTS AND METHODS

This prospective observational study was conducted with 94 patients (65 males, 29 females; mean age: 42.7±12.1 years; range, 19 to 69 years) at the Ege University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology between May 2021 and January 2022. Patients with RMDs followed up by the rheumatology clinic who received two doses of the SARS-CoV-2 vaccine were recruited to participate in this study. RMD patients were recruited based on the following inclusion criteria: *(i)* individuals aged >18 years; *(ii)* vaccination with two doses of either the Pfizer-BioNTech BNT162b2 or the CoronaVac vaccine, with both vaccinations by the same brand; *(iii)* established diagnosis with RMD as defined by international disease classification criteria (the final classification criteria determined by The American College of Rheumatology (ACR) and The European Alliance of Associations for Rheumatology (EULAR) were used in the diagnosis of diseases); *(iv)* a negative history for SARS-CoV-2 infection. Exclusion criteria were as follows: *(i)* a history of SARS-CoV-2 infection; *(ii)* acute illness or fever within 72 h before vaccination; *(iii)* pregnancy; *(iv)* a history of cancer, chronic kidney failure, and chronic liver failure.

Demographic characteristics, diagnoses, and treatment regimens were collected from patient records. Twenty-eight days after the second dose of the COVID-19 vaccine, blood samples were obtained, centrifuged at 800×g for 12 min, and stored at -20°C. Then all the specimens were analyzed using an enzyme-linked immunosorbent assay (ELISA; Euroimmun AG, PerkinElmer Germany Diagnostics GmbH, Lübeck, Germany) [Euroimmun Medical Laboratory Diagnostics AG, Lübeck, Germany] that tests for anti-spike immunoglobulin (Ig) G-type antibodies against the SARS-CoV-2 spike protein. Anti-spike IgG-type antibodies were quantitatively measured by the ELISA method according to manufacturer's protocol. Seropositivity was defined as IgG ≥11 binding antibody units/mL.

Patients were instructed to continue their medication during the vaccination period, using the recommendations in the second version of the ACR guide and in line with our clinical experience.[2] Vaccines were administered at least six months after the last rituximab treatment. All the patients in this research were taking 2 g of rituximab. Mycophenolate mofetil was given to patients at a dose of 2 g. Azathioprine was provided to patients at a dose of 2 mg/kg. Mycophenolate mofetil and azathioprine treatments were interrupted for two weeks after vaccination. Methotrexate was administered to patients at a dose of 10-15 mg. Methotrexate treatments were interrupted for one week after vaccination. Leflunomide was delivered to patients at a dose of 20 mg. Sulfasalazine was administered to patients at a dose of 2 g. Hydroxychloroquine was given to patients at a dose of 200 mg. Colchicine was given to patients at a dose of 1-2 g, and ≤7.5 mg/day prednisone and equivalent steroid intakes were accepted as low dose, whereas >7.5 mg intakes were considered as medium or high doses. Post-vaccine leflunomide, sulfasalazine, hydroxychloroquine, anti-tumor necrosis factor (TNF), colchicine, and steroid treatments were not interrupted. In addition, all treatments were in use for more than one month.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Patient characteristics were summarized using means, standard deviation (SD), ranges,

Table 1. Demographic and clinical characteristics of the study population and vaccine type

				Age category				Sex					Vaccine type			
				<50		>50		Male		Female		Disease duration	BNT-162b2		CoronoVac	
	n	%	Mean±SD	n	%	n	%	n	%	n	%	Mean±SD	n	%	n	%
Total	94		42.7±12.1	63	62.7	30	32.3	29	30.9	65	69.1	11.1±8.0	43	45.7	51	54.3
Rheumatoid arthritis	16	17	50.6±12.5	6	37.5	10	62.5	2	12.5	14	87.5	13.6±8.6	10	62.5	6	37.5
Spondyloarthritis	21	22	42.3±10.7	16	76.2	5	23.8	10	47.6	11	52.4	11.9±8.2	5	23.8	16	76.2
Familial mediterranean fever	9	9	36.1±10.1	8	89.9	1	11.1	3	33.3	6	66.7	14±5.7	2	22.2	7	77.8
Systemic lupus erythematosus	22	23	39.7±11.5	15	71.4	6	28.6	4	18.2	18	81.8	11.7±9.2	11	50	11	50
Skleroderma	6	6	41.6±12	5	83.3	1	16.7	1	16.7	5	83.3	6.6±5.2	6	100	0	0
Vasculitis*	16	17	42.4±12.9	11	68.8	5	31.3	7	43.8	9	56.3	7.4±6.2	7	43.8	9	56.3
Others**	4	4	47.7±13.3	2	50	2	50	2	50	2	50	8.0±7.7	2	50	2	50

SD: Standard deviation; Ig: Immunoglobulin; * Others: Myosistis, Ig G4 related diseases; ** Vasculitis: Takayasu anca-vasculitis, IgA vasculitis, Behçet's disease.

and percentages as appropriate. Chi-square tests of independence and Fisher exact test were used for categorical data. For continuous variables, normality was tested with the Shapiro-Wilk test and the Mann-Whitney U test (Wilcoxon rank sum test), or a t-test was applied appropriately. Comparison among several groups was based on Kruskal-Wallis with post hoc analysis after testing the normality of the variables. A one-way analysis of variance was used for the comparison of three or more independent groups. A p value <0.05 was accepted as statistically significant.

RESULTS

The most common diagnosis was systemic lupus erythematosus (SLE; 23%), followed by spondylarthritis (22%), vasculitis (17%), and rheumatoid arthritis (RA) (17%; Table 1). DMARDs were used by 59.5% of the patients, 35.1% were using immunosuppressives, and 22.2% were using biologic agents (Table 2). The most common medications were hydroxychloroquine (25.5%), colchicine (20.2%), and mycophenolate mofetil (19.1%). Thirty (31.9%) patients were using corticosteroids, with 22 (23.4%) using a low dose and eight (8.5%) using a medium or high dose. Vaccines were administered at least six months after the last rituximab treatment. Forty-three (45.7%) patients received the BNT162b2 vaccine (Pfizer-BioNTech), and 51 (54.3%) patients received the CoronaVac vaccine.

Table 2. Therapies received

	n	%
DMARDs	56	59.5
Immunsupresives	33	35.1
Biologics		
Anti-TNF	13	13.8
Rituximab	7	7.4
Jak inhibitor	1	1
Steroid		
Low dose	22	23.4
Medium or high dose	8	8.5
None	64	68.1

DMARDs: Disease modifying antirheumatic drugs, Anti-TNF: Anti-tumor necrosis factor.

Table 3. Seroconversion rates by age and vaccine type

	Seroconversion (+)		Seroconversion (–)		
	n	%	n	%	*p*
Under 50 years	58	90.6	6	9.4	0.004
Over 50 years	20	66.7	10	33.3	
BNT162b2 vaccine	48	94.1	3	5.9	0.002
CoronaVac vaccine	30	69.8	13	30.2	

Table 4. Seroconversion rates by disease

	Seroconversion (+)		Seroconversion (–)		
	n	%	n	%	*p*
Rheumatoid arthritis	13	86.7	2	13.3	0.59
Ankylosing spondylitis	20	95.2	1	4.8	0.092
Familial Mediterranean fever	9	100	0	0	0.53
Systemic lupus erythematosus	16	69.6	7	30.4	0.036
Skleroderma	5	83.3	1	16.7	0.28
Vasculitis	11	68.8	5	31.3	0.98
Others	4	100	0	0	0.35

Ig: Immunoglobulin; * Others: Myosistis, IgG4 related diseases; ** Vasculitis: Takayasu, anca-vasculitis, IgA vasculitis.

Table 5. Seroconversion rates by receiving therapies

	Seroconversion (+)		Seroconversion (–)		
	n	%	n	%	*p*
Methotrexate	10	71.4	4	28.6	0.21
Leflunomide	7	87.5	1	12.5	0.72
Hydroxychloroquine	21	87.5	3	12.5	0.49
Sulfasalazine	9	90	1	10	0.53
Azathioprine	11	78.6	3	21.4	0.63
Mycophenolate mofetil	10	55.6	8	44.8	0.001
Colchicine	18	94.7	1	5.3	0.12
Rituximab	4	57.1	3	42.9	0.06
Anti-TNF	12	92.3	1	7.7	0.33
Steroid					
Low dose	13	59.1	9	40.9	0.001
Medium or high dose	5	62.5	3	37.5	0.005
Steroid	18	19.1	12	12.8	0.001

Anti-TNF: Anti-tumor necrosis factor.

Table 6. Combination therapies and the effects of combination therapies on seroconversion

Combination therapies	n	Seroconversion (+)	Seroconversion (–)	*p*
Methotrexate	4	2	2	
Methotrexate-hydroxychloroquine	4	4	0	
Methotrexate-sulfasalazine	1	1	0	
Methotrexate-hydroxychloroquine-sulfasalazine	1	1	0	0.40
Methotrexate-leflunomide	1	0	1	
Methotrexate-anti-TNF	1	1	0	
Methotrexate-rituximab	2	1	1	
Total	14			
Leflunomide	2	2	0	
Leflunomide-hydroxychloroquine	3	3	0	
Leflunomide-methotrexate	1	0	1	0.13
Leflunomide-rituximab	1	1	0	
Leflunomide-anti-TNF	1	1	0	
Total	8			
Mycophenolate mofetil	11	7	4	
Mycophenolate mofetil-hydroxychloroquine	4	2	2	0.64
Mycophenolate mofetil-rituximab	3	1	2	
Total	18			
Azathioprine	7	6	1	
Azathioprine-hydroxychloroquine	2	1	1	
Azathioprine-sulfasalazine	1	1	0	0.74
Azathioprine-anti-TNF	4	3	1	
Total	14			
Rituximab-mycophenolate mofetil	3	1	2	
Rituximab-methotrexate	2	1	1	
Rituximab-leflunomide	1	1	0	0.59
Rituximab-hydroxychloroquine	1	1	0	
Total	7			
Anti-TNF	5	5	0	
Anti-TNF-methotrexate	1	1	0	
Anti-TNF-leflunomide	1	1	0	0.62
Anti-TNF-azathioprine	4	3	1	
Total	11			

Anti-TNF: Anti-tumor necrosis factor.

Considering the antibody results according to age, younger participants appeared more likely to develop an antibody response. A significant difference was found between those under 50 years of age and those over 50 years of age (p=0.004).

A significant difference was found in favor of vaccine type. The CoronaVac vaccine was less likely to develop an antibody response (p=0.002, Table 3).

SLE had the lowest seroconversion rate when compared to other RMDs (p=0.036).

After two doses of vaccination, seroconversion was not observed in seven of 23 patients with SLE (Table 4).

The serologic response 28 days after the two doses of COVID-19 vaccines was assessed by quantifying serum IgG antibodies to the SARS-CoV-2 spike protein. Patients on regimens including mycophenolate mofetil, steroids, and rituximab were less likely to develop seroconversion (p=0.001, p=0.001, and p=0.06, respectively). When compared according to antibody titer, it was found that there was significantly less vaccine response in rituximab users (p=0.032). Impairment of the vaccine response by other DMARDs, immunosuppressive drugs, and anti-TNF treatments was not shown (Table 5).

Combination uses are given in Table 6. When the effect of combinations on seroconversion rates was examined, it was observed that there was no significant difference in terms of seroconversion rates between the use of treatments in combination or alone.

DISCUSSION

Since having an RMD is an exclusion criterion in phase I-III studies, there is no published data on the vaccine responses of RMD patients in SARS-CoV-2 vaccine studies. We could not provide clear answers to patients who were confused about getting vaccinated and how to manage their treatments during vaccination. Consequently, we studied the antibody response in patients with RMD who completed the second dose of the SARS-CoV-2 vaccination to determine the immune response to vaccination in this patient population.

After a literature search, a few studies about the immunogenicity of SARS-CoV-2 vaccines were identified.[2,4] The lowest seroconversion rates were observed with methotrexate, rituximab, mycophenolate mofetil, and steroids.[2,4]

Although methotrexate has been shown to reduce humoral response after vaccination in most of the studies,[4-7] it has been shown that it does not affect the vaccine response in some publications.[8,9] In our study, when the postvaccine seroconversion was evaluated, four of the 14 patients using methotrexate had a negative value. The patients with one negative result were also using rituximab, and patients with two negative results were also using a steroid. No significant results were observed considering the antibody levels. This result may be due to the low number of patients using methotrexate or patients' interruption of the drug for vaccination according to the ACR guidelines.[2]

In the literature, treatment with rituximab was associated with a significantly reduced immunogenicity after COVID-19 vaccinations.[4,8-17] Sakuraba et al.[16] found in their review that anti-CD20 therapy was associated with a lower response to vaccines. Additionally, in other type vaccine studies, it has been shown that rituximab has a negative effect on the response of pneumococcal and influenza vaccines.[18-22] In our study, consistent with these studies, the rate of antibody formation after COVID-19 vaccines was significantly reduced with the use of rituximab compared to other treatments (p=0.036). On the other hand, with rituximab, seroconversion rate was reduced markedly compared to other treatments, but this was not statistically significant (p=0.06). These decreases are associated with the critical role of B cells in antibody formation after vaccination. Despite this, attention to the timing of vaccination after rituximab administration may have contributed to the lack of significant results in terms of seroconversion.

We found that patients on mycophenolate mofetil were less likely to develop an antibody response to vaccination. In the literature search, there were studies that reached similar results with ours.[4,8,10,12,14,17,23-26] However, in one study, no significant effect of mycophenolate mofetil on antibody formation was demonstrated.[27] Patients receiving mycophenolate mofetil should be warned about the suboptimal vaccine response as similar results were also found in our study. If it is believed that the disease will not exacerbate, interruption of the drug should be considered. How long the drug should be interrupted may become clear with future studies.

In our study, azathioprine usage was not significantly associated with reduced immunogenicity after COVID-19 vaccinations. However, Sieiro Santos et al.[28] found that the effect of azathioprine on vaccine's immunogenicity was higher than observed with mycophenolate mofetil.

In our study, we found that using steroids has a negative effect on immunogenicity of vaccination, in line with most of the literature ($p<0.05$).[7,9,10,12,17,23] In addition, it has been shown that steroids have a negative effect on the response of pneumococcal and influenza vaccines.[29,30] However, in some studies, using steroids had no negative effects on immunogenicity of vaccination.[31] However, in our opinion, steroids should be discontinued or the dose should be minimized during vaccination if possible.

Seroconversion rates was not significantly affected by anti-TNF usage similar to most publications in the literature.[4,8,9,15,16,27,28] However, in one study, anti-TNF treatment was significantly associated with reduced immunogenicity after vaccinations.[12] When other vaccine type responses were examined, Hua et al.[32] found that anti-TNF treatment did not affect the immunogenicity of the pneumococcal vaccine in RA patients. França et al.[33] showed that the influenza vaccine response was lower in spondylarthritis patients receiving anti-TNF agents (infliximab and adalimumab) compared to healthy individuals and patients receiving conventional DMARDs but was similar to RA patients. Furthermore, it was observed that the effectiveness of the vaccine did not decrease in the etanercept group. However, in the meta-analyses of Gelinck et al.[21] and Hua et al.,[32] it was found that receiving anti-TNF treatment did not make a difference to the influenza vaccine response compared to the healthy population. In our study, we found that anti-TNF treatment was not significantly associated with reduced immunogenicity after COVID-19 vaccinations.

Boekel et al.[15] found that after the first dose of vaccination, the decrease in the vaccine response in patients using antirheumatic drugs increases after the second dose of vaccination, except for those treated with anti-CD20 therapies. Therefore, booster vaccine doses could be administered to nonresponding patients, except for those treated with anti-CD20 therapies. Further research is required to clarify this subject.

In multivariate analysis, a negative correlation between vaccine response and age (>50 years) was found. It has also been found in other publications that lower antibody titer rates are seen in older patients after vaccination.[10,12,13,23,28]

In our study, seroconversion rates in RMDs after the CoronoVac and BNT162b2 vaccines were 69.8% and 94.1%, respectively. In a study examining immunogenicity of the CoronaVac vaccine, the seroconversion rate was found to be 97% at the end of 28 days after two doses of the CoronoVac vaccine in the healthy population.[34] In another study, the seroconversion rate was 97.4% after two doses of the BNT162b2 vaccine in the healthy population.[35] When the data in our study is compared with the literature, the seroconversion rate appears to be reduced in patients with RMDs. As a similar result, in a previous study, the seroconversion rate was found to be 54% after hepatitis B vaccination in patients with rheumatic disease.[36] Moreover, a significant difference was found in favor of vaccine type in our study. Receiving the BNT162b2 vaccine was more likely to develop an antibody response than the CoronaVac vaccine ($p=0.002$). This shows that the use of mRNA (messenger ribonucleic acid) vaccines in RMD patients may be more effective.

In this study on COVID-19 vaccination, the seroconversion rate was 82.9%. Patients with SLE and vasculitis had the lowest antibody titers compared to other RMDs. The result could be associated with the underlying treatment regimes in SLE and vasculitis. In addition, interferon plays an important role in the vaccine response. It is thought that because of the defect in the formation of interferon, impaired response to the vaccine may be observed in patients with SLE.[37]

In our study, it was determined that the use of combination therapies did not make a statistically significant difference in vaccine responses compared to the use of drugs alone. However, the increase in the number of patients may change this situation with drugs that have a synergetic effect; in this respect, studies with a larger number of patients are required. The possibility of lower seroconversion should be considered, particularly in the case of concomitant use of drugs that are thought to affect the vaccine response.

Limitations of this study include the small sample size, nonrandomized design, lack of serial measurements, and lack of assessment of T-cell responses. Additionally, prevaccine serologies

of the patients participating in the study were not available; however, patients with a history of SARS-CoV-2 infection were excluded when selecting the patients.

In conclusion as the data in the literature continues to accumulate, our knowledge about immunogenicity after vaccinations in RDM patients will increase. According to current data, there is a decrease in antibody formation rates after COVID-19 vaccination in patients receiving mycophenolate mofetil, rituximab, and steroids. Patients receiving these treatments should be warned about the risk of suboptimal vaccine response. If possible, the treatments should be interrupted or adjusted during the vaccination period. The choice of vaccine type should be made according to the results in RMD patients. Older patients should also be warned about the possible decrease in vaccine response. As a result, risky groups that may have low seropositivity rate should be evaluated, antibody controls could be performed, and if necessary, the vaccination could be repeated. Additional research is required to determine the responses to SARS-CoV-2 vaccinations and the optimization of the vaccine response in patients with RMDs. It is also thought that the use of mRNA-type vaccines will become widespread. This study also contributes to the literature in terms of the use of these vaccines in immunosuppressed patients.

Ethics Committee Approval: The study protocol was approved initially by the Ethics Committee of Ege University dated and numbered decision of 22/06/2021, 21-6.3/5 and Turkish Ministry of Health, Turkish Medicines and Medical Devices Agency dated and numbered decision of 01.07.2021, E-85521274-000-991053. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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