



Immunogenicity and safety of the CoronaVac and BNT162b2 Covid-19 vaccine in patients with inflammatory rheumatic diseases and healthy adults: comparison of different vaccines

Sevilay Batıbay¹ · Rezan Koçak Ulucaköy² · Zafer Günendi¹ · Işıl Fidan³ · Gülendamar Bozdayı³ · Feride Nur Göğüş¹

Received: 19 July 2022 / Accepted: 16 October 2022 / Published online: 25 October 2022
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

Abstract

Objectives To determine the seroconversion (SC) rate after CoronaVac and BNT162b2 vaccines in adults with inflammatory rheumatic disease (IRD).

Methods Patients who were followed up with IRD and who received two doses of either CoronaVac or BNT162b2 vaccines were included in this prospective observational single-center study. Subjects with two doses of CoronaVac or BNT162b2 without known IRD were included in the healthy controls. The blood samples were taken at a minimum of two and a maximum of 12 weeks after the second dose of vaccine.

Results A total of 81 patients with IRD (61 CoronaVac, 20 BNT162b2) and 100 healthy controls (70 CoronaVac, 30 BNT162b2) were included. The SC rate was slightly lower among patients with IRD versus controls (84 vs 97%, $p=0.002$). The SC rate was 100% in all participants who received BNT162b2 both in the patient and control group. The IgG antibody level after CoronaVac in the patient group was significantly lower than both the BNT162b2 ($p=0.031$) and the healthy group ($p<0.001$). Among patients with IRD, those on rituximab (RTX) (12/81, 14.8%) had significantly less SC rate (5/12, 41.7%). The median neutralizing antibody titers were significantly higher in patients with BNT162b2 compared with CoronaVac (1.97 vs. 16.34, $p<0.001$).

Conclusions This study showed that all patients with BNT162b2 vaccine developed immunogenicity in patients with IRD, while there was a decreased antibody response with CoronaVac vaccine compared to that of BNT162b2. In particular, RTX significantly reduces the SC rate.

Keywords Covid-19 · SARS-CoV-2 · Vaccine · CoronaVac · BNT162b2 · Rheumatology · Inflammatory rheumatic disease

Introduction

The development and application of vaccines against coronavirus disease 2019 (COVID-19) have been important steps in controlling the pandemic. Although having an inflammatory rheumatic disease (IRD) is an exclusion criterion

in the efficacy and safety studies of vaccines, the American College of Rheumatology (ACR) recommended that patients with IRD be offered and receive vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Thomas et al. 2021; Tanriover et al. 2021; Curtis et al. 2021).

Vaccination in patients with IRD has always been an interesting and researched topic. Dysregulation in the immune system that develops due to the underlying immune-mediated disease, the effect of immunosuppressive agents, existing rheumatic disease activation, the type and dose of vaccine, are some of the factors that can affect the immunogenicity of vaccines (Arnold et al. 2021; Pugès et al. 2016; Furer et al. 2021a). Simon et al. showed that SARS-CoV-2 vaccination worked in patients with immune-mediated inflammatory disease, but there was a decreased and delayed response (Simon et al. 2021).

✉ Sevilay Batıbay
sevilaycucen@windowslive.com

¹ Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Gazi University Hospital, Çankaya, Ankara, Turkey

² Department of Internal Medicine, Division of Rheumatology, Ministry of Health Ankara City Hospital, Ankara, Turkey

³ Medical Microbiology, Gazi University Hospital, Ankara, Turkey

With the ongoing vaccination process, data on the immunogenicity and safety of COVID-19 vaccines in patients with IRD has been published (Furer et al. 2021b; Seyahi et al. 2021; Boekel et al. 2021; Medeiros-Ribeiro et al. 2021). However, there is a paucity of data about which type of vaccine is more effective or safe. Most studies in the current literature evaluated the efficacy of a single vaccine type, and a comparison of CoronaVac (Sinovac) and BNT162b2 (BioNTech) vaccines in these patients is not yet available.

The primary endpoint in the present study was to assess the seroconversion (SC) rate, IgG and neutralization antibody titers after CoronaVac and BNT162b2 vaccines in adults with IRD and to compare it with healthy controls. The secondary endpoints were to evaluate whether there were efficacy differences in the two vaccine types, both within and between groups, to determine adverse effects after both vaccines in the patient group, and to investigate the effects of medications used in the patient group on vaccine immunogenicity.

Methods

Study design and participants

This prospective observational single-center study was conducted at the Division of Rheumatology, Department of Physical Medicine and Rehabilitation of Gazi University Hospital, Ankara, Turkey, between June and September 2021.

The research protocol for this study was approved by the ethics committees of Gazi University Hospital (decision number: 19) and Turkish Medicines and Medical Devices Agency (E-66175679-514.04.03-486,228).

Patients with IRDs ($n = 81$) including rheumatoid arthritis (RA), spondyloarthritis (SpA), connective tissue diseases (CTD) (e.g., Sjögren syndrome, systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease), familial Mediterranean fever (FMF), vasculitis, and those who received one of the two doses of CoronaVac or BNT162b2 vaccines were included in the study. The healthy control group ($n = 100$) comprised participants without known IRD and who received two doses of CoronaVac or BNT162b2 vaccine.

Participants who had COVID-19 infection as confirmed in a reverse transcriptase-polymerase chain reaction (RT-PCR) test before or during vaccination, and patients with symptoms suggestive of COVID-19 but with negative PCR tests were excluded.

All patients provided written informed consent for inclusion in the study. Demographic characteristics of the participants including age, sex, body mass index (BMI), smoking status, and clinical characteristics such as diagnosis,

duration of disease, medication status, and comorbidities were recorded.

Vaccine procedure

As of January 2020, the CoronaVac vaccine, which was the only option in the vaccination program in Turkey; by March 2020 both CoronaVac and BNT162b2 were offered. In the routine vaccination program, the interval between two doses was 4 weeks. During vaccination, the medications of the patients were arranged in line with the recommendations of the ACR COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases, Version 2.

Blood samples

The blood samples of the patient group and the control group were taken at a minimum of two and a maximum of 12 weeks after the second dose of the vaccine. Serum fractions were separated from the blood within 1–3 h using centrifugation at 360 g for 15 min at room temperature. Collected samples were frozen at $-80\text{ }^{\circ}\text{C}$ until required for analysis. In the control group, only IgG antibodies against the receptor-binding domain protein of the SARS-CoV-2 spike protein were studied. In the patient group, a neutralization assay was also evaluated. Anti-S antibodies against SARS-CoV-2 spike proteins were evaluated using the SARS-CoV-2 IgG II Quant assay (Abbott), and neutralization antibody titers were evaluated using the ACE2-RBD neutralization assay (DIA.PRO). A value above 50 arbitrary unit/mL (AU/mL) was considered positive according to the manufacturer's instructions. The ACE2-RBD neutralization assay cut-off sample (Co/S) was above 1.

Safety of the vaccine

Adverse events (AEs) that developed after both doses in the patient group were evaluated using a questionnaire.

All patients whose blood samples were collected were called by phone and asked whether they had a COVID-19 infection within 3 months of being included in the study.

Statistical analysis

Descriptive statistics are reported as the mean \pm standard deviation (SD) or median (interquartile range, IQR), minimum (min) and maximum (max) values for numeric variables. Categorical results were expressed as frequency and proportions. The distribution of data was evaluated with the Kolmogorov Smirnov test. Continuous variables were compared using Student's t test or the Mann–Whitney U test and categorical variables using Fisher's Chi-square

test. Spearman's correlation test was used to investigate the association between antibody titer, time of sample collection and age. Additionally, IgG antibody titer was analyzed using a covariance model (ANCOVA) to correct for antibody screening time after vaccination. All statistical analyses were performed using the IBM SPSS Statistics 21 software (SPSS, Inc., Chicago, IL, USA). *P* values less than 0.05 were considered statistically significant.

Results

Study population

A total of 81 patients with IRD vaccinated using the two-dose regimen (61 CoronaVac, 20 BNT162b2) and 100 controls (70 CoronaVac, 30 BNT162b2) were analyzed in the study. The mean age for patients and controls was 50.65 ± 1.37 and 49.79 ± 1.20 years, respectively. Sex distribution was similar in both groups (71.6 vs. 65% female). Forty-six (56.8%) of the patients had one or more comorbid diseases, respectively listed as hypertension ($n = 23$, 28.4%) diabetes mellitus ($n = 12$, 14.8%), hypothyroidism ($n = 12$, 14.8%), pulmonary disease ($n = 9$, 11.1%), cardiac disease ($n = 9$, 11.1%), gastrointestinal system disease ($n = 6$, 7.4%), renal disease ($n = 6$, 7.4%), central nervous system disease ($n = 4$, 4.9%), and malignancy ($n = 7$, 8.6%).

The most common IRD among the patients was RA ($n = 35$), followed by CTD ($n = 20$), SpA ($n = 14$), vasculitis ($n = 3$), and FMF ($n = 4$). The median weeks between second-dose vaccination and sampling was 4 (4-4) (min 2-max 12).

A total of 40 (49.4%) patients with IRD were treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (methotrexate $n = 13$, leflunomide $n = 17$, sulfasalazine $n = 4$, and combination therapy $n = 6$). Hydroxychloroquine was used in 28 (34.6%) patients, colchicine in 12 (14.8%), glucocorticoid (GC) in 35 (43.2%) at a mean prednisolone dose of 4.97 ± 1.38 mg/day, non-steroidal anti-inflammatory drugs (NSAIDs) in 12 (14.8%), azathioprine in four (4.9%), mycophenolate mofetil in five (6.2%), and tofacitinib in one (1.2%) patient. Biologic DMARDs were used as a monotherapy or in combination with csDMARDs in 23 (28.4%) patients (rituximab $n = 12$, infliximab $n = 4$, etanercept $n = 2$, adalimumab $n = 2$, tocilizumab $n = 2$ and anakinra $n = 1$).

The median time to collect blood samples after the second dose of vaccination was 7 weeks in the patient group and 4 weeks in the healthy control group. Vaccine type distributions were similar between the groups (Table 1).

Seroconversion rates, IgG and neutralization antibody titers

SC rates after the second dose of CoronaVac or BNT162b2 vaccines were significantly lower in the patient group compared with the healthy control group (84 vs. 97%, χ^2 : 9.45, $p = 0.002$).

Although SC rate was similar for both vaccine types in the control group (95.7 vs. 100%, $p = 0.552$), it was significantly higher with BNT162b2 in the patient group than in the CoronaVac group (100 vs. 78.7%, $p = 0.031$).

The median IgG antibody titers in patients with IRD were significantly lower than that of controls (414.7 vs. 1140.5 AU/mL, $p < 0.001$). While the median values of IgG antibodies after BNT162b2 vaccination did not differ between patients and controls (4007.2 vs. 5792.3 AU/mL, $p = 0.277$); patients receiving CoronaVac vaccine had significantly lower titers compared with controls (275.8 vs. 1116.7 AU/mL, $p < 0.001$). However, post vaccination sample collection time was longer in the patient group than that in the control group. A further covariance analysis for the difference in time of sample collection found no difference in IgG antibody titers between the patient and control groups ($p = 0.127$, $F = 2.35$). When the two vaccine types were compared within the group, the titers after CoronaVac were significantly lower in both the patient and control groups than those after the BNT162b2 vaccine ($p < 0.001$ for both groups).

The median neutralization antibody titers against SARS-CoV-2 were significantly higher in patients with BNT162b2 compared with CoronaVac (1.97 vs. 16.34, $p < 0.001$).

Effect of immunosuppressive treatments on immunogenicity

The rate of SC was 89.7% (52/58) in non-bDMARD users, 41.7% (5/12) in RTX users, and 100% (11/11) in anti-cytokine users. The median IgG antibody titers and neutralization antibody levels were significantly lower in those receiving RTX than in those not using bDMARDs. Anti-cytokine therapies had no effect on the SC rate. The median IgG antibody titers were significantly lower in RTX users than those using anti-cytokines ($p = 0.012$). There was no significant difference in neutralization antibody levels between RTX and anti-cytokine users ($p = 0.035$) (Table 1).

Effect of age and time of sample collection on the immunogenicity

IgG antibody levels were found to decrease with age in the patient group ($r = -0.42$, $p < 0.001$), but no correlation was found in the healthy control group. In the analysis including all participants, it was observed that IgG antibody titers

Table 1 Demographic characteristics of the patients with IRD and healthy controls and immunogenicity of the CoronaVac and BNT162b2 vaccines

	Patients with IRD <i>n</i> :81	Healthy controls <i>n</i> :100	<i>P</i> value	χ^2
Age, years mean \pm SD	50.65 \pm 1.37	49.79 \pm 1.20	0.657	
Sex, female (%)	58 (71.6%)	65 (65%)	0.344	0.897
Disease duration, months mean \pm SD	152.34 \pm 104.45	N/A		
Body mass index, kg/m ² mean \pm SD	27.32 \pm 5.16	N/A		
Diagnosis, <i>n</i>				
RA	35	N/A		
SpA	14			
CTD	20			
FMF	4			
Vasculitis	8			
Vaccine, <i>n</i> (%)				
CoronaVac	61 (75.3%)	70 (70%)	0.427	0.631
BNT162b2	20 (24.7%)	30 (30%)		
Weeks between vaccine and sample collection, median (IQR)	7 (4–9.5) (min 2- max 12)	4 (4–4) (min 3- max 12)	<0.001	
Seroconversion rate (%)				
CoronaVac	68/81 (84%)	97/100 (97%)	0.002	9.45
	48/61 (78.7%)	67/70 (95.7%)		
BNT162b2	20/20 (100%)	30/30 (100%)	0.002	8.59
	<i>p</i> * 0.031	<i>p</i> * 0.552		
IgG, AU/ml median (IQR)	414.7 (106.8–1597.7)	1140.5 (674.3–5388.7)	<0.001	
CoronaVac	275.8 (68.95–916.70)	1116.7 (477.70–2074.18)	<0.001	
BNT162b2	4007.20 (1904.65–10,415.25)	5792.30 (3696.42–9419.85)	0.277	
	<i>p</i> * <0.001	<i>p</i> * <0.001		
Neutralization, median (IQR)				
CoronaVac	1.97 (0.92–6.82)	N/A		
BNT162b2	16.34 (13.85–16.67)			
	<i>p</i> * <0.001			
bDMARD/Seroconversion rate (%)				
Naive	52/58 (89.6%)	N/A		
RTX	5/12 (41.7%)			
Anti-cytokine	11/11 (100%)			

N/A not assessed, χ^2 chi square test, IQR interquartile range, SD standard deviation

*p** intragroup comparison

decreased as the sample time after vaccination increased (r : -0.31 , $p < 0.001$) (Table 2).

Safety of the CoronaVac and BNT162b2 vaccines

The most common adverse event in both vaccine types in the patient group was local pain (Corovac 21/61 at the first dose, BNT162b2 12/20, CoronaVac 14/61 at the second dose, BNT162b2 12/20). No serious adverse effects were observed. Table 3 shows the local and systemic reactions after the first and second-dose vaccines in the patient group.

Five patients had positive RT-PCR tests for COVID-19 infection after their two doses of vaccination. Only one

patient required hospitalization and oxygen support. The demographic and clinical characteristics of the patients are shown in Table 4.

Discussion

This study investigated the efficacy of two different types of COVID-19 vaccines among patients with IRD in comparison to healthy controls. The SC rate was lower in the patient group with IRD than the healthy controls. SC developed in all participants with BNT162b2 vaccine in both patient and healthy controls, however, SC with the CoronaVac

Table 2 Correlation of IgG antibody level with age and time of sample collection after vaccination

	<i>r</i>	<i>p</i>
Age		
Total (<i>n</i> :181)	- 0.26	<0.001
Patients (<i>n</i> :81)	- 0.42	<0.001
Healthy controls (<i>n</i> :100)	- 0.10	0.322
CoronaVac		
Total (<i>n</i> : 115)	- 0.08	0.36
Patients (<i>n</i> :48)	0.29	0.02
Healthy controls (<i>n</i> :67)	- 0.01	0.96
BNT162b2		
Total (<i>n</i> :50)	- 0.16	0.283
Patients (20)	- 0.02	0.93
Healthy controls (<i>n</i> :30)	0.01	0.96
Time of sample collection		
Total (<i>n</i> :181)	- 0.31	<0.001
Patients (<i>n</i> :81)	- 0.17	0.14
Healthy controls (<i>n</i> :100)	- 0.01	0.33
Coronavac total (<i>n</i> :115)	- 0.39	<0.001
BNT162b2 total (<i>n</i> : 50)	- 0.30	0.04

vaccine was lower than that of BNT162b2 in the patients with IRD. CoronaVac vaccine induced SC at a lower rate in the patient group than in the healthy control group. However, sample collection time post vaccination was longer in the patient group than in the control group (7 vs. 4 weeks); additional analysis revealed that there was no difference in

IgG antibody titers with CoronaVac vaccine between the two groups after adjusting for the time of sample collection. The study revealed a negative association between age and antibody titer. In addition, antibody titers decreased with increasing time after vaccine administration.

In a multicenter study, the IgG titers after two doses of BNT162b2 were significantly lower in patients with IRD compared with controls (86 vs. 100%) (Furer et al. 2021b). In another study including patients with RA and SpA, the rate of SC after the first dose of mRNA vaccine was found to be lower in the patient group than the healthy controls (52.5% with RA and 54.8% with SpA), but the rate of SC after the second dose was 100% in all patients (Simader et al. 2022). A similar result was reported by Boekel et al.; SC was 49% in patients with autoimmune disease after the first dose of vaccination (with four different COVID-19 vaccines), whereas it was 73% in healthy controls (Boekel et al. 2021). We reported that the rate of SC was 100% in all participants with the two doses of the mRNA vaccine, and there was no significant difference in IgG antibody levels between the patient and control groups.

In a phase four study that investigated the immunogenicity and safety of the CoronaVac vaccine in patients with autoimmune rheumatic diseases, it was reported that it had a good safety profile, but lower immunogenicity compared with the control group (Medeiros-Ribeiro et al. 2021). Seyahi et al. reported that a significant humoral response occurred after two doses of CoronaVac in the majority of patients with immune-mediated diseases, but patients using immunosuppressive treatments and

Table 3 Adverse events both for CoronaVac and BNT162b2 vaccine in patients with IRD

	After first vaccine		After second vaccine	
	CoronaVac <i>n</i> :61	BNT162b2 <i>n</i> :20	CoronaVac <i>n</i> :61	BNT162b2 <i>n</i> :20
Local reactions (<i>n</i>)				
Pain	21 (%34)	12 (%60)	14 (%23)	12 (%60)
Erythema	1	0	2	0
Swelling	4	2	3	0
Systemic reactions (<i>n</i>)				
Fever	2	1	2	0
Headache	4	3	4	2
Arthralgia	3	1	2	2
Myalgia	3	1	2	1
Nausea	0	1	1	2
Vomiting	0	1	0	0
Malaise	4	4	1	2
Rhinorrhea	1	1	1	0
Taking NSAID	3	1	0	1
Sweating	2	0	2	0
Dizziness	1	1	0	1
Palpitation	0	0	0	1
Nose bleeding	0	1	0	1

Table 4 Clinical characteristics and outcomes of the patients with IRD who had confirmed COVID-19 infection after their second vaccine dose

	Age	Sex	Diagnosis	Comorbidities	Medications	COVID-19 related symptoms	Hospitalization time (days)	Vaccine type	IgG antibody (AU/ml)
1	41	M	SpA	–	Etanercept 50 mg/week	Headache	–	CoronaVac	247
2	72	F	RA	HT, hypothyroidism	Leflunomide 20 mg/day, prednisolone 5 mg/day	Asymptomatic	–	CoronaVac	115.6
3	55	F	SjS	HT, DM, CHF	HCQ 200 mg/day	Cough, dyspnea	11	CoronaVac	145.1
4	22	M	SpA	–	Sulfasalazine 2 g/day	Cough, nasal congestion	–	BNT162b2	8429.4
5	21	F	SLE+APS	–	HCQ 400 mg/d, prednisolone 5 mg/d, methotrexate 10 mg/d	Cough, mild fever, arthralgia	–	BNT162b2	12,560.1

SpA Spondyloarthritis, CHF congestive heart failure, DM diabetes mellitus, F female, M male, HCQ hydroxychloroquine, HT hypertension, RA rheumatoid arthritis, SLE systemic lupus erythematosus, SjS Sjögren's syndrome, APS Antiphospholipid syndrome

the elderly had reduced antibody levels (Seyahi et al. 2021). Similarly, in our study as age increased in patients with IRD, the antibody titers after CoronaVac vaccine decreased, and the SC rate and IgG antibody levels were lower in the patient group after two doses of the CoronaVac vaccine compared with the control group. However, there was no difference between the two groups in the additional analysis performed according to the corrected time because the time of sample collection for antibody test was longer in the patient group after vaccination.

A head-to-head comparison study of CoronaVac and BNT162b2 vaccines in healthy adults aged between 18 and 79 years who had not had a previous COVID-19 infection showed that BNT162b2 induced higher levels of SARS-CoV-2-specific binding and neutralization antibody responses (Mok et al. 2022). For the first time, we compared two vaccine types in terms of efficacy in patients with IRD and found that the IgG and neutralizing antibody titers after CoronaVac were lower than those of BNT162b2. A systematic review and network meta-analysis evaluating the clinical efficacy of COVID-19 vaccines, including eight phase 3 randomized controlled trials, showed that mRNA vaccines reduced the risk of symptomatic COVID-19 more than other vaccines, but there was no difference in preventing severe disease (Rotshild et al. 2021). However, this was an indirect comparison between vaccines, and study protocols differed widely. Although it was not the aim of our study, when we screened the patients in terms of COVID-19 infection after blood samples were collected, two patients in the BNT162b2 vaccine group and three patients in the CoronaVac group had COVID-19 infection. While four of them had mild disease, one patient who received CoronaVac vaccine required hospitalization and oxygen support. These data are insufficient to suggest that one vaccination type is superior to another in terms of COVID-19 prevention in patients with IRD.

Furer et al. reported that the lowest SC rate was in patients with antineutrophil cytoplasmic vasculitis and idiopathic inflammatory myositis among the patients with IRD (Furer et al. 2021b). In a study conducted on patients with RA, the BNT162b2 vaccine produced an antibody-specific response in almost all patients, but antibody levels were lower in patients using abatacept or interleukin (IL)-6 inhibitors compared to healthy controls (Picchianti-Diamanti et al. 2021). A previous study compared 90 patients with SLE and 20 healthy controls after COVID-19 vaccine (mRNA and viral vector) (Izmirly et al. 2022). Antibody levels were significantly lower in patients with SLE compared to healthy controls (Izmirly et al. 2022). Independent risk factors for poor response to the COVID-19 vaccine were any immunosuppressant other than antimalarials and, contrary to expectations, having normal anti-dsDNA levels prior to vaccination (Izmirly et al. 2022). Ferri et al. found that autoimmune systemic disease-related interstitial lung disease was associated with decreased antibody response after mRNA-based COVID-19 vaccines (Ferri et al. 2021). In our study, no analysis could be performed according to the diagnosis subgroups due to the small sample size.

Failure to achieve an antibody response to the COVID-19 vaccine has been reported to be associated with ongoing treatments such as glucocorticoids, mycophenolate mofetil, and rituximab (Ferri et al. 2021). Results of two prospective cohort studies indicated that patients who received MTX or anti-CD20 therapy had significantly lower SC rates but not prednisone or tumor necrosis factor (TNF) inhibitors (Boekel et al. 2021). In this study SC developed in three of seven patients (43%) who received anti-CD20 therapy (Boekel et al. 2021). This result is also compatible with our study (5 of 12, 41.3%). In another study, it was reported that GC, rituximab, and abatacept in combination with MTX and the use of mycophenolate mofetil decreased immunogenicity after vaccination (Furer, et al. 2021b). Recently it has

been reported that the use of MTX and targeted biologics (inhibitors of TNF, IL-17, and IL-23) following the second dose of BNT162b2 in patients with psoriasis did not impair functional humoral immunity, but no T cell response was detected in some patients using immunosuppressives (Mahil et al. 2022). Haberman et al. reported that in patients with immune-mediated inflammatory disease using MTX, the rate of immunogenicity was 62% with BNT162b2 mRNA vaccination; however, more than 90% immunogenicity was achieved with anti-cytokine therapy and this was similar to healthy controls (Haberman et al. 2021). The same result was valid in our study, and the rate of SC in patients receiving anti-cytokines was similar to that of healthy controls at 100%.

In the EULAR Coronavirus Vaccine (COVAX) physician-reported registry, which included 5121 participants from 30 countries, the safety profiles of SARS-CoV-2 vaccines in subjects with inflammatory/autoimmune rheumatic and musculoskeletal diseases (IRMD) were reassuring and similar to participants with non-inflammatory RMDs. Most patients tolerated their vaccines well, with rare reports of IRMD flare-ups and very rare reports of serious adverse events (Machado et al. 2021). In this registry, the most frequently reported early adverse events were pain at the injection site (19%), fatigue (12%), general muscle pain (7%), and fever (7%) (Machado et al. 2021). In our study, similarly SARS-CoV-2 vaccines were well tolerated, and the most common adverse event in both vaccine types was local arm pain.

The limitations of our study are the inability to evaluate the vaccine response according to disease subgroups and treatment types due to the small sample size. Other limitations are that it has a non-randomized design, non-assessment of disease activity status at the time of vaccination, and the time to collect blood samples after vaccination is different between the patients and healthy controls. Finally, we did not evaluate the response of SARS-CoV-2-specific T cells, which may add to the immune relevance of protection. Despite the non-randomized design, there was no difference between the patient and control groups in terms of age and sex. To rule out the effect of sample collection time, we re-analyzed IgG levels by performing a time-adjusted analysis. To our knowledge, this is the first study to compare the CoronaVac and BNT162b2 mRNA vaccines in patients with IRD and healthy controls. Our findings will provide insight into vaccine recommendations in patients with IRD. Although both vaccine types appear to be effective, immunogenicity appears to be better with the mRNA vaccine in both patients with IRD and healthy adults.

In addition to evaluating humoral vaccine response and T-cell-mediated immunity in future studies, there is a need for longer term studies investigating the severity and clinical features of the infection when COVID-19 is detected in vaccinated patients compared with the general population.

Conclusion

BNT162b2 vaccine resulted in an increased antibody response compared to that of CoronaVac vaccine in patients with IRD. Moreover, SC developed in all patients with IRD after the BNT162b2 vaccination. RTX treatment was closely associated with decreased antibody response. Both vaccine types appear to be safe and effective in patients with IRD.

Funding This study was supported by TLAR (Turkish League Against Rheumatism). The funders were not related in the design of the study, data collection, analysis, and interpretation of the data, writing, or submitting it for publication.

Data availability The data underlying this article are available in the article.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

References

- Arnold J, Winthrop K, Emery P (2021) COVID-19 vaccination and antirheumatic therapy. *Rheumatology (oxford)* 60:3496–3502
- Boekel L, Steenhuis M, Hooijberg F et al (2021) Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: a substudy of data from two prospective cohort studies. *Lancet Rheumatol* 3:e778–e788
- Curtis JR, Johnson SR, Anthony DD et al (2021) American college of rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 1. *Arthritis Rheumatol* 73:1093–1107
- Ferri C, Ursini F, Gragnani L et al (2021) Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. High prevalence of non-response in different patients' subgroups. *J Autoimmun* 125:102744
- Furer V, Rondaan C, Agmon-Levin N et al (2021a) Point of view on the vaccination against COVID-19 in patients with autoimmune inflammatory rheumatic diseases. *RMD Open* 7(1):e001594
- Furer V, Eviatar T, Zisman D et al (2021b) Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis* 80:1330–1338
- Haberman RH, Herati R, Simon D et al (2021) Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease. *Ann Rheum Dis* 80(10):1339–1344.
- Izmirly PM, Kim MY, Samanovic M et al (2022) Evaluation of immune response and disease status in systemic lupus erythematosus patients following SARS-CoV-2 vaccination. *Arthritis Rheumatol* 74:284–294
- Machado PM, Lawson-Tovey S, Strangfeld A et al (2022) Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus

- vaccine (COVAX) physician-reported registry. *Ann Rheum Dis* 81(5):695–709
- Mahil SK, Bechman K, Raharja A et al (2022) Humoral and cellular immunogenicity to a second dose of COVID-19 vaccine BNT162b2 in people receiving methotrexate or targeted immunosuppression: a longitudinal cohort study. *Lancet Rheumatol* 4:e42–e52
- Medeiros-Ribeiro AC, Aikawa NE, Saad CHS et al (2021) Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial. *Nat Med* 27:1744–1751
- Mok CKP, Cohen CA, Cheng SMS et al (2022) Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong. *Respirology* 27(4):301–310
- Picchianti-Diamanti A, Aiello A, Laganà B et al (2021) Immunosuppressive therapies differently modulate humoral- and T-cell-specific responses to COVID-19 mRNA vaccine in rheumatoid arthritis patients. *Front Immunol* 12:740249
- Pugès M, Biscay P, Barnetche T et al (2016) Immunogenicity and impact on disease activity of influenza and pneumococcal vaccines in systemic lupus erythematosus: a systematic literature review and meta-analysis. *Rheumatology (oxford)* 55:1664–1672
- Rotshild V, Hirsh-Racah B, Miskin I et al (2021) Comparing the clinical efficacy of COVID-19 vaccines: a systematic review and network meta-analysis. *Sci Rep* 11:22777
- Seyahi E, Bakhdiyarli G, Oztas M et al (2021) Antibody response to inactivated COVID-19 vaccine (CoronaVac) in immune-mediated diseases: a controlled study among hospital workers and elderly. *Rheumatol Int* 41:1429–1440
- Simader E, Tobudic S, Mandl P et al (2022) Importance of the second SARS-CoV-2 vaccination dose for achieving serological response in patients with rheumatoid arthritis and seronegative spondyloarthritis. *Ann Rheum Dis* 81:416–421
- Simon D, Tascilar K, Fagni F et al (2021) SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. *Ann Rheum Dis* 80:1312–1316
- Tanriover MD, Doğanay HL, Akova M et al (2021) Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* 398:213–222
- Thomas SJ, Moreira ED Jr, Kitchin N et al (2021) Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. *New Engl J Med* 385:1761–1773

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.