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ORIGINAL ARTICLE

How do COVID-19 vaccines affect rheumatic diseases?

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ABSTRACT

Objectives: This study aims to investigate the effects of novel coronavirus disease 2019 (COVID-19) vaccines administered in Türkiye on disease activity and the side effects in the patients with inflammatory rheumatic disease (IRD).

Patients and methods: Between September 2021 and February 2022, a total of 536 patients with IRD (225 males, 311 females; mean age: 50.5±12.6 years; range, 18 to 93 years) who were vaccinated against COVID-19 and followed in the outpatient setting were included in the study. Vaccination status of the patients and whether they had COVID-19 were questioned. All patients were asked to rate their anxiety about the vaccination on a scale of 0-10 before and after the shots. They were asked whether they experienced any side effects and an increase in IRD complaints after vaccination.

Results: A total of 128 (23.9%) patients were diagnosed with COVID-19 before the first vaccination. Totally, 180 (33.6%) patients were vaccinated with CoronaVac (Sinovac) and 214 (39.9%) patients with BNT162b2 (Pfizer-BioNTech). Also, 142 (26.5%) patients were given both vaccines. When the anxiety level of the patients before the first vaccination was questioned, 53.4% reported that they had no anxiety. The rate of patients without any anxiety after vaccination was 67.9%. Comparison of pre- (median Q3=6) and post-vaccine (median Q3=1) anxiety values showed a statistically significant difference ($p<0.001$). A total of 283 (52.8%) patients reported side effects after vaccination. When both vaccines were compared with each other, the rate of the side effects was higher in the BNT162b2 group ($p<0.001$) and also in the CoronaVac plus BNT162b2 group ($p=0.022$). There was no statistically significant difference between BNT162b2 and CoronaVac plus BNT162b2 in terms of side effects ($p=0.066$). Forty-five (8.4%) patients had increased rheumatic complaints after vaccination.

Conclusion: The lack of a significant increase in disease activity after COVID-19 vaccination in patients with IRD and the absence of serious side effects requiring hospitalization support the safety of vaccines in this patient group.

Keywords: Anxiety, COVID-19 vaccines, rheumatic diseases, SARS-CoV-2.

Novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and emerged in China at the end of 2019 and quickly became a global health problem, has affected more than 250 million individuals worldwide and the number of deaths has exceeded five million until the date of this manuscript.[1]

Impaired immune response and immunosuppressive drugs render patients with inflammatory rheumatic disease (IRD) more vulnerable to COVID-19.[2] The rapid development of vaccines by scientists and their availability with the quick approval of official authorities has been a ray of hope for the exit from the pandemic. However, the relatively short phase studies

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and the rapid approval of the vaccines have contributed to the existing negative perception of the vaccines. In addition, since vaccine studies are mostly performed in healthy people, safety and efficacy data on the patients with IRD are limited. Therefore, the efficacy and safety data of a wide variety of existing vaccines in patients with rheumatic diseases would only be possible by compiling real-life data.

The first data on this subject have been published by Sattui et al.[3] The authors investigated patients' beliefs about the vaccine, drug (disease modifying anti-rheumatic drugs [DMARDs]) discontinuation during vaccination, and patient-reported side effects. They reported that patients usually tended to discontinue their DMARDs to improve the efficacy of the vaccine and also reported that the rate of vaccine-related side effects was similar to those observed in the healthy population.

The COVID-19 vaccination program in Türkiye started on January 13th, 2021. The first wave of vaccination targeted the people working in the healthcare services and other high-risk occupations and, then, the patients with chronic serious health problems. Those who did not have any chronic disease began to receive vaccine shots starting with the elderly population. Vaccination was not mandatory, but the Republic of Türkiye, Ministry of Health emphasized the importance of vaccination and started an information campaign encouraging people to get the shots to protect themselves and their families. With the vaccination program, the opposition to the vaccine emerged in the society. The use of the vaccine via the pre-approval process before the completion of all phases of the vaccine studies caused skepticism toward the vaccine in the society. In addition, prejudices and beliefs without scientific support in the society affected participation in the vaccination program.

In the present study, we aimed to investigate the effect of the use of vaccines available in our country in rheumatic diseases. During the study period, two types of vaccines, an inactivated whole virion vaccine developed by Sinovac (CoronaVac) and messenger ribonucleic acid (RNA) vaccine developed by Pfizer-BionTech (BNT162b2) were available in the vaccination program. The aim of this study was to determine the compliance of patients followed up in three centers for rheumatic diseases with the vaccination program and to investigate the effects of two COVID-19 vaccines administered in Türkiye on disease activity and the side effects in the patients with IRD.

PATIENTS AND METHODS

This cross-sectional study was conducted at rheumatology outpatient clinics of three centers between September 2021 and February 2022. A total of 536 patients with IRD (225 males, 311 females; mean age: 50.5±12.6 years; range, 18 to 93 years) who were followed in the outpatient setting were included in the study.

Vaccination status of the patients and whether they had COVID-19 were questioned. Patients included in a vaccination program were included in the study group. The patients who had never been vaccinated or could not remember information about the vaccine were excluded from the study. The rheumatological diagnosis, demographic data, vaccination type, and date of vaccine shots were recorded. Anxiety regarding COVID-19 vaccines, severity of rheumatic disease, and side effects of COVID-19 vaccines were determined by the patient's self-assessment. All patients were asked to rate their anxiety about the vaccination on a scale of 0-10 before and after the shots.[4] They were asked whether they experienced any side effects after vaccination and, if so, what they were. The anxiety levels of the patients reported by the patients before and after the first vaccination were statistically investigated. In addition, both vaccines were statistically compared with each other in terms of side effects after vaccination. Finally, the patients were asked whether there was an increase in IRD complaints after vaccination and which complaints increased.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean ± standard deviation (SD) or median (Q1-Q3), while categorical data were expressed in number and frequency. The Shapiro-Wilk test was used to determine whether the data were in normal distribution. Since the

data distribution was not normal, the Mann-Whitney U test was used for independent group comparisons and Wilcoxon test for dependent group comparisons. The McNemar-Bowker test was used to compare dependent categorical variables. The chi-square test, Fisher exact test, and Fisher-Freeman-Halton tests were used to compare categorical data between groups. A *p* value of <0.05 was considered statistically significant.

RESULTS

While there was no comorbidity in 277 (51.7%) patients, the remaining patients had at least one of the conditions of hypertension, diabetes mellitus, cardiovascular disease, and respiratory diseases. Demographic and clinical characteristics of all patients are given in Table 1.

Table 1. Demographic and clinical characteristics of all patients (n=536)

Medications	n	%	Mean±SD
Age (year)			50.5±12.6
Sex			
Male	225	42	
Female	311	58	
Rheumatic disease diagnosis			
Ankylosing spondylitis	313	58.4	
Rheumatoid arthritis	191	35.6	
Psoriatic arthritis	17	3.2	
Enteropathic arthritis	7	1.3	
Others*	8	1.5	
Medications†			
Infliximab	32	6.0	
Etanercept	53	9.9	
Adalimumab	69	12.9	
Certolizumab pegol	20	3.7	
Golimumab	38	7.1	
Secukinumab	30	5.6	
Rituximab	15	2.8	
Tocilizumab	15	2.8	
JAK inhibitors (Tofacitinib, Baricitinib)	12	2.2	
Glucocorticoid	63	11.8	
NSAIDs	218	40.7	
Leflunomide	44	8.2	
Methotrexate	110	20.5	
Sulfasalazine	51	9.5	
Hydroxychloroquine	51	9.5	

SD: Standard deviation; JAK: Janus kinase inhibitors; NSAIDs: Non-steroidal anti-inflammatory drugs; * Sjögren syndrome, systemic sclerosis, systemic lupus erythematosus, familial Mediterranean fever. † Participants may indicate more than one antirheumatic medication.

A total of 128 (23.9%) patients were diagnosed with COVID-19 before the first vaccination. Vaccination status inquiry revealed that 25 (4.7%) patients received a single dose, 302 (56.3%) patients two doses, and 209 (39%) patients three doses. A total of 180 (33.6%) patients were vaccinated with CoronaVac (Sinovac) and 214 (39.9%) patients with BNT162b2 (Pfizer-BioNTech). One hundred and forty-two (26.5%) patients were given both vaccines. When the anxiety level of the patients before the first vaccination was questioned, 53.4% (n=286) had no anxiety. The anxiety score of 93 (17.4%) patients was ≥7. The rate of patients without any anxiety after vaccination was 67.9%. The number of patients with a post-vaccine anxiety score of ≥7 was 21 (3.9%). Comparison of pre- (median Q3=6) and post-vaccine (median Q3=1) anxiety values showed a statistically significant difference (p<0.001). Anxiety levels before and after COVID-19 vaccination are given in Table 2.

A total of 283 (52.8%) patients reported side effects after vaccination. The most common side effect was arm pain (25.4%). Other side effects were fever (2.1%), joint pain (3.2%), fatigue (2.6%), and headache (1.9%). When the vaccines were evaluated separately for side effects, 40% in the CoronaVac (Sinovac) group, 62.6% in the BNT162b2 (Pfizer-BioNTech) group, and 54.2% in the CoronaVac (Sinovac) plus BNT162b2 (Pfizer-BioNTech) group had at least one of the side effects. When both vaccines were compared with each other, the rate of the side effects was higher in the BNT162b2 (Pfizer-BioNTech) group (p<0.001) and also in the CoronaVac (Sinovac) plus BNT162b2 (Pfizer-BioNTech) group (p=0.022). There was no statistically significant

Table 2. Anxiety levels before and after COVID-19 vaccination

	n	%	*p*
Before COVID-19 vaccination			
No	286	53.4	
Yes	250	46.6	
Score ≥7	93	17.4	<0.001
After COVID-19 vaccination			
No	364	67.9	
Yes	172	32.1	
Score ≥7	21	3.9	

p<0.05 statistical significance level.

Table 3. Adverse events after COVID-19 vaccination

	All		CoronaVac (Sinovac)		BNT162b2 (Pfizer-BioNTech)		CoronaVac (Sinovac)+ BNT162b2 (Pfizer-BioNTech)		
	n	%	n	%	n	%	n	%	*p*
Number of cases	536	100	180	33.6	214	39.9	142	26.5	
Any adverse events	283	52.8	72	40	134	62.6	77	54.2	<0.001* 0.022† 0.066§
Local arm pain	136	25.4	38	21.1	60	28	38	26.8	
Fever	11	2.1	3	1.7	6	2.8	2	1.4	
Muscle/joint pain	17	3.2	8	4.4	5	2.3	4	2.8	
Fatigue	14	2.6	4	2.2	8	3.7	2	1.4	
Headache	10	1.9	4	2.2	4	1.9	2	1.4	
Multiple adverse events	83	15.5	12	6.7	46	21.5	25	17.6	
Other adverse events**	12	2.2	3	1.7	5	2.3	4	2.8	

* CoronaVac (Sinovac) *vs.* BNT162b2 (Pfizer-BioNTech); † CoronaVac (Sinovac) *vs.* CoronaVac (Sinovac)+BNT162b2 (Pfizer-BioNTech); § BNT162b2 (Pfizer-BioNTech) *vs.* CoronaVac (Sinovac)+ BNT162b2 (Pfizer-BioNTech), p<0.05 statistical significance level; ** Including sleepiness, nausea or vomiting, diarrhea, other allergic reactions and rash.

difference between BNT162b2 (Pfizer-BioNTech) and CoronaVac (Sinovac) plus BNT162b2 (Pfizer-BioNTech) in terms of side effects (p=0.066). Adverse events after COVID-19 vaccination are given in Table 3.

Forty-five (8.4%) patients in total reported that their rheumatic complaints increased after vaccination. While 34 (6.34%) patients reported that their complaints related to their disease increased after the first dose of vaccination and four (0.74%) patients reported that their complaints decreased. There was no change in the complaints related to the disease in 498 (92.9%) patients. The number of patients whose complaints increased after the second and third dose vaccination was 35 (6.9%) and 17 (8.3%), respectively. Most of the patients (95.6%) reported an increase in pain, while 4.4% had an increase in morning stiffness. A total of 97.8% of the patients did not make any change in their ongoing medication after vaccination.

DISCUSSION

With the development and widespread distribution of COVID-19 vaccines, there has also been substantial research on the effectiveness of vaccination in the patients with IRD, the side effects, the impact of vaccines on disease activity, and the possible reservations of patients about being vaccinated.

Patients with a diagnosis of IRD are at a higher risk of COVID-19 viral infection than the general population due to their disease and the immunosuppressive drugs they use.[5,6] Patients have a relatively high risk of hospitalization, respiratory distress requiring oxygen support, and admission to the intensive care unit. The mortality rate (7%) is also higher than the normal population (3.4%) according to the World Health Organization (WHO) data.[2] Therefore, the American College of Rheumatology (ACR) guidelines recommend that patients with IRD should be given priority for COVID-19 vaccination.[5]

In Türkiye, the vaccine came into use with a few months delay compared to the Western countries. During that period, hospital admissions of patients with rheumatic diseases decreased due to the outbreak. After the vaccination program was started, it became possible to reach the vaccine easily, and most of the population were vaccinated with two types of vaccines (CoronaVac (Sinovac) and BNT162b2 (Pfizer-BioNTech)).

When the anxiety levels of the patients included in our study were questioned before vaccination, 53.4% of them reported that they had no worries and were willing to be vaccinated. In the study of Gaur et al.,[7] the willingness to be vaccinated was 67% in the control group and 54% in those with systemic autoimmune rheumatic disease. In our study, the rate of those who did not have any pre-vaccination worries was found to be similar to this study. In the study conducted by Yurttas et al.[8] in Türkiye, vaccine willingness rates were found to be similar in the group of general population (34.6%) and those with rheumatic disease (29.2%), while it was found to be higher among hospital workers (52.5%). The researchers also reported that the rate of people who were undecided about getting vaccinated was higher in the rheumatic disease group than in the normal population. In these two studies, the main reasons for vaccine-related anxiety were stated as fear of possible side effects, distrust toward vaccines, and fear of exacerbation of the rheumatic disease.[7,8] In our study, the percentage of patients with a vaccine anxiety score of ≥7 decreased from 17.4 to 3.9% following the vaccine. This statistically significant decrease may be explained by the better information and personal experience of the patients on the possible side effects of vaccines, and their effects of the current disease and the drugs used. These results support the importance of IRD patients being well informed before vaccination. As a matter of fact, in the ACR vaccine guideline, the importance of including patients with IRD in a joint decision-making process is emphasized.[5]

Since all patients in our study were vaccinated with CoronaVac (Sinovac) and BNT162b2 (Pfizer-BioNTech), we were only able to evaluate the side effects of these two vaccines. In the BNT162b2 (Pfizer-BioNTech) placebo-controlled safety and efficacy study, the most common post-vaccine side effects were short-term mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and similar in the vaccine and placebo groups.[9] Similarly, side effects were reported to be mild-to-moderate in CoronaVac (Sinovac) Phase 3 studies and the most common side effects were pain at the injection site and myalgia.[10] However, only healthy individuals were included in these studies and the patients with chronic diseases including IRD were strictly excluded.[9,10] In few studies on the side effects of COVID-19 vaccines in IRD patients, no adverse events were found serious enough to require hospitalization.[11,12] In one of these studies, Esquivel-Valerio et al.[11] investigated six different vaccines and found the rates of side effects to be 80% in the BNT162b2 group and 54.5% in the CoronaVac group. The most common side effect was localized injection site pain. In our study, side effect rates were similarly higher in the BNT162b2 (Pfizer-BioNTech) and CoronaVac (Sinovac) plus BNT162b2 (Pfizer-BioNTech) group compared to the CoronaVac (Sinovac) group. The most frequently reported side effect was arm pain at the local injection site, and none of the patients required hospitalization due to side effects. The combination of CoronaVac (Sinovac) and BNT162b2 (Pfizer-BioNTech) vaccination is the result of national health policy and it has given us the chance to investigate the overall effects of such combination which is unique in the literature.

Another reason of vaccine hesitancy is the concern that the vaccine may cause exacerbation of rheumatic disease in IRD patients. In our study, we found relatively low rates of disease exacerbation. Forty-five (8.4%) of our patients reported an increase in rheumatic complaints, but only 12 (2.2%) patients required a change in their routine medication. None of our patients were hospitalized for any condition arising from exacerbation of IRD after vaccination. There are few studies regarding this subject and they have also found low rates of exacerbation of the disease after vaccination.[3,5-7,13,14] In one of these studies, Connolly et al.[13] evaluated disease exacerbation and post-vaccination reactions following two doses of messenger ribonucleic acid (mRNA) vaccine in 1,377 rheumatic and musculoskeletal disease patients. They found that only 11% of participants reported flare requiring treatment following vaccination. Most of the them reported worsening of existing symptoms. No participant had severe exacerbation requiring hospitalization. More commonly reported symptoms were worsening joint pain, swelling of the joint, stiffness, fatigue, and myalgia. In our study, the most common complaint was increased joint pain. It is difficult to determine whether this result is due to a possible post-vaccine joint pain

side effect or a rheumatic disease exacerbation based on patient reports alone.

In the study of Sattui et al.,[3] including the early experience of vaccination conducted with online international survey, rheumatic disease exacerbations requiring medication change were found at a rate of 4.6%. In the study of Gaur et al.,[7] whose primary aim was to investigate vaccine hesitancy, only one rheumatoid arthritis patient requiring short-term prednisolone administration was reported. Since our study was a cross-sectional study, the evaluation of patients' disease activity before and after vaccination was only performed by the patient's statement and it was not possible to evaluate with objective scales or laboratory parameters. While this is a limitation of our study, the results show that vaccines do not cause a significant exacerbation in rheumatic diseases, consistent with the studies that conducted with similar methods mentioned above. Another important limitation is that the majority of our patients had ankylosing spondylitis or rheumatoid arthritis which makes it difficult to interpret our results across a wide range of IRD.

Nevertheless, we believe that our study provides additional contribution to the literature in that it is one of the few studies on the effects of COVID-19 vaccines on IRDs and includes data on both mRNA and inactivated vaccines.

In conclusion, the lack of a significant increase in disease activity after COVID-19 vaccination in patients with IRD and the absence of serious side effects requiring hospitalization support the safety of vaccines in this patient group. The lack of significant side effects with the administration of two different types of COVID-19 vaccines for the same patient supports the safety of the vaccines in patients with IRD. We believe that patients should be adequately informed about their diseases, medication and vaccines by physicians to prevent vaccination reservations, which may become an important problem during the pandemic period.

Ethics Committee Approval: The study protocol was approved by the Marmara University Ethics Committee (date/no: 03.09.2022/09.2021.1072). 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.

Author Contributions: All authors contributed equally to the article.

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