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Single-center experience of COVID-19 vaccine in patients with inflammatory rheumatic disease: Real-life data

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Ethics Committee Approval
The study was approved by the ethics committee at Istanbul Health Sciences University, Umraniye Research and Training Hospital (Date: 21/04/2022 No.148).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Patients with rheumatic disease are at high risk of infection complications, and vaccines are essential to prevent these diseases. Moreover, biologic disease-modifying/targeted synthetic anti-rheumatic drugs (b/tsDMARDs) have been shown to reduce the immunogenicity of vaccines, although their effectiveness, side effects, and effects on disease activity are not yet clear. In this study, we aimed to investigate the incidence of post-vaccine side effects, disease exacerbation, and COVID-19 infection despite vaccination in patients with inflammatory rheumatic disease; the difference in vaccination effects between patients who received and did not receive b/tsDMARD treatments.

Methods: Patients received b/tsDMARD (i.e., biologic group (BG)) (n = 194) who were admitted to the rheumatology outpatient clinic, were included in this study. All patients with inflammatory rheumatological disease, who did not receive b/tsDMARD (n = 185), but who applied to the rheumatology outpatient clinic during this time, were included in the non-biologic group (NG). Patients followed were included and evaluated cross-sectionally. Clinical and demographic characteristics, as well as type of COVID-19 vaccination, post-vaccine side effects, COVID-19 infection status before and after vaccination, and post-vaccine rheumatological disease exacerbation, were also evaluated.

Results: In BG, 92.2% of patients were vaccinated, but for NG, 82.7% were vaccinated against COVID-19 patients with BG, 46.2% were vaccinated with CoronaVac vaccine alone, 51.4% with Pfizer/BioNTech BNT162b2 vaccine alone, and 37.4% with a combination of CoronaVac and BNT162b2 vaccines. In the NG, 53.8% of patients were vaccinated with CoronaVac vaccine alone, 48.6% with BNT162b2 vaccine alone, and 36.2% with a combination of CoronaVac and BNT162b2 vaccines. There was a significant difference between groups, according to vaccine types (P = 0.040), as this difference was due to a larger number of patients vaccinated with the CoronaVac + BNT162b2 combination for BG. Adverse effects were detected in 99 patients (55.9%) with BG and 95 patients (62.5%) with NG post-vaccination. There was no difference between BG and NG vaccines (CoronaVac, BNT162b2, or their combination) for adverse effects (P > 0.05 for all). The vaccine with the most common adverse events was BNT162b2, for both BG and NG. The most common side effect was arm pain, significantly higher in BG (P = 0.014). Fever and rash were more common for NG (P = 0.017). Disease exacerbation was not observed with BG, whereas it was detected in 5 (1%) patients for NG that was different (P = 0.021). SARS-COV-2 infection was also significantly less common for BG vs. NG (15.3% vs. 20.3%) (P = 0.017). Despite COVID-19 vaccinations, 56 patients with BG and 62 patients with NG had COVID-19 (P = 0.005).

Conclusion: Standardized vaccination comparisons could not be achieved, as patients using b/tsDMARD were vaccinated for fewer COVID-19 infections. Additionally, COVID-19 vaccines are well-tolerated in patients with rheumatological disease, with vaccine-related disease activity at 1%, only seen in those not using b/tsDMARDs.

Keywords: COVID-19, Biologic / targeted synthetic DMARD, Conventional synthetic DMARD, Vaccination

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Introduction

COVID-19 disease is caused by the SARS-COV-2 virus, detected in Wuhan, China in December 2019, causing millions of deaths worldwide from developing acute respiratory failure syndrome. After the rapid spread of COVID-19, studies to create vaccines started in our country and globally. However, patients with inflammatory rheumatic diseases were not included in them. Information about vaccine efficacy and side effects in this group were obtained after their introduction. Vaccination is an effective tool to prevent infections for those with autoimmune and inflammatory rheumatic diseases, as well as the general population [1]. In autoimmune inflammatory rheumatic disease, the risk of infection may be higher due to underlying disease, chronic inflammatory processes, and immunosuppressive drug use. It is controversial if inflammatory rheumatic disease increases risk of severe COVID-19 [2-4]. Yet, those with inflammatory rheumatic diseases were at higher risk for hospitalization and severe COVID-19 vs. the general population: vaccination is critical in preventing disease [5]. Previous vaccinations showed that immunosuppressive therapy inhibited the humoral response to influenza and pneumococcal vaccines in rheumatologic patients [6]. Immunosuppressive therapy was shown to reduce and delay COVID-19 vaccine response in this patient group [7-9].

In one of the earliest studies conducted on 2,860 patients with a diagnosis of rheumatic disease, the first and most common side effects of vaccination were found to be fatigue, headache, muscle and joint pain, and fever. Also, side effects were similar in these patients vs. healthy population controls [10]. Another issue is post-vaccine disease exacerbation: there are studies about other routine vaccines, with disease exacerbation reported at a rate of 4.6 -5% after COVID-19 vaccines [10, 11].

When the current study was conducted, there were 2 different types of COVID-19 vaccines, one of which was CoronaVac, inactive for SARS-CoV-2, and the other Pfizer-BioNTech, a BNT162b2 messenger RNA (mRNA) vaccine. In most COVID-19 vaccine studies for rheumatic patients, we had Pfizer-BioNTech BNT162b2, viral vector vaccines, Oxford/AstraZeneca, and Janssen/Johnson & Johnson, plus Moderna mRNA. There is very little information about CoronaVac, one of the vaccines first used in our country, and the rheumatological patient group. Most patients used with the same type of vaccine, whereas many were inoculated with a combination of CoronaVac and BNT162b2 vaccines.

There is hesitation about vaccination for patients with inflammatory rheumatic diseases [12]. In the VAXICOV study [13], it was reported that 30% of patients with systemic autoimmune or inflammatory rheumatic diseases were hesitant to get vaccinated for COVID-19. In this cross-sectional study, considering apprehension about vaccination, we aimed to investigate the incidence of post-vaccine side effects, disease exacerbation, and COVID-19 infection despite vaccination in patients with inflammatory rheumatic disease; the difference was noted in effects between patients who received and those who did not receive biologic/targeted synthetic DMARD treatment.

Materials and methods

Study design and data collection

This is a single-center, cross-sectional, observational study conducted at the Ümraniye Training and Research Hospital. In our study, volunteers who applied to our rheumatology outpatient clinic between May 1-30, 2022 were diagnosed with inflammatory rheumatic diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), connective tissue disease (systemic lupus erythematosus, Sjogren's syndrome, myositis), familial Mediterranean fever (FMF), Behcet's disease, and vasculitis – so were included. Patients refusing to participate or those with neuropsychiatric diseases preventing communication or those with mental retardation or pregnancy, were followed without medication and noninflammatory issues such as osteoarthritis and fibromyalgia, but were excluded. During data collection, 432 patients were evaluated and 53 were excluded, as they did not meet eligibility criteria. In total, 379 patients were included in the study.

Those included were split in two groups, i.e., receiving biologic/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARD), and the biologic group (BG), or the non-biologic group (NG) – vs, patients with BG, using TNFi, (etanercept, adalimumab, infliximab, golimumab, and certolizumab), Interleukin-6 inhibitor (IL-6- tocilizumab), Interleukin-17A inhibitor (IL-17A- secukinumab), CTLA4-Ig (abatacept), JAK inhibitor (JAKi-tofacitinib), Interleukin-1 antagonists (IL-1- anakinra, canakinumab), and CD20 inhibitors (rituximab). NG patients used conventional synthetic DMARDs (csDMARD): methotrexate, leflunomide, hydroxychloroquine, colchicine, azathioprine, mycophenolate mofetil, and sulfasalazine, or anti-inflammatory drugs (NSAIDs).

An evaluation about COVID-19 vaccination was used with patients in the study as clinic controls. This consisted of information regarding patient age, gender, disease duration, comorbidities (hypertension, diabetes mellitus, cerebrovascular diseases, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), asthma, malignancy). Their medications and steroid doses, if any, were noted.

Assessment of vaccination

The COVID-19 vaccine status, vaccination time, doses and type of vaccines were recorded. Those who passed more than three months after the last vaccine, those vaccinated less than twice, or those with disease in the first 14 days after vaccination were considered to not have completed the protocol. Side effects in the first 7 days after vaccination were grouped as local and systemic side effects, and evaluated for each dose.

Local side effects were redness, warmth, regional arm pain, and axillary lymphadenopathy. Systemic side effects were weakness, fatigue, drowsiness, headache-dizziness, joint-muscle pain, fever, allergic complaints (itching, rash, shortness of breath), nausea-vomiting, or loss of appetite. Additional side effects were classified as *"other effects."*

Increase of disease activity at more than 2 days post-vaccination was vaccine-related exacerbation [10]. Unvaccinated patients were evaluated for not being vaccinated, which was also noted. COVID-19 infection status before and after the vaccine

was assessed. Vaccination timing was noted for those with COVID-19 infection.

Symptoms of COVID-19 and treatments were also considered. Use of immunomodulatory or immunosuppressive medications for COVID-19 were questioned for all patients. Clinical characteristics of COVID-19, pharmacological therapy in treatment, presence of lung involvement, and clinical outcomes (hospitalization, intensive care admission, length of stay, use of noninvasive mechanical ventilation) were each evaluated.

Ethical approval

This study was approved by the Ethics Committee at Ümraniye Training and Research Hospital (Date 21/04/2022, No. 148) and conducted as per the Helsinki Declaration and Good Clinical Practices guidelines. All patients had given oral and written consent.

Statistical analysis

The Statistical Package for Social Science (IBM-SPSS Statistics, v. 20.0, Armonk, NY, USA) was performed with statistical analyses. Descriptive statistics were reported as means (SD) for continuous variables and as number and frequency for binary and categorical variables. Comparing these variables was conducted with the Mann-Whitney U test for continuous variables, as data distribution was non-parametric, while the Chi-square test was used for categorical variables: this test was performed to compare COVID-19, symptoms, and disease between BG and NG. $P < 0.05$ held statistical significance.

Results

Demographic and clinical characteristics

The mean age of 379 patients in the study was 48.22 (13.05) years, with 58.8% male. While 194 (51.2%) patients were in the BG, 185 (48.8%) were in the NG. Table 1 shows demographic and clinical data of the overall study population and its subgroups.

BG consisted of patients on only b/tsDMARD (n = 101, 52%) or the combination of b/tsDMARD and csDMARD (n = 94, 47.9%), whereas NG consisted of patients who received csDMARD (n = 158, 85.4%) and no DMARDs (n = 27, 14.5%). Distribution of biologic drugs were: TNFi, (n = 142, 73.2%), JAKi (n = 13, 6.7%), IL-17 inhibitors (n = 13, 6.7%), rituximab (n = 18, 9.3%), IL-1 inhibitors (n = 2, 1%), CTLA4 inhibitor (n = 1, 0.5%), and IL-6 blockers (n = 5, 2.6%). For 142 patients receiving TNFi, 7 (3.6%) were treated with infliximab, 26 (13.4%) with etanercept, 42 (21.6%) with adalimumab, 38 (19.6%) with golimumab, and 29 (14.9%) with certolizumab. Seventy-three patients (37.6%) for BG used steroids. Drug distributions in NG were: methotrexate (n = 62, 33.5%), leflunomide (n = 38, 20.5%), hydroxychloroquine (n = 46, 24.9%), sulfasalazine (n = 24, 13%), azathioprine (n = 6, 3.2%), mycophenolate mofetil (n = 2, 1%), colchicine (n = 20, 10.8%) and NSAIDs (n = 27, 14.5%): 88 NG patients existed on steroids (47.6%).

COVID-19 vaccination status

One-hundred seventy-nine patients (92.2%) in BG and 153 patients (82.7%) in NG were vaccinated against COVID-19 ($P = 0.005$). For the BG, 36 patients were vaccinated only with CoronaVac (46.2%) and 76 patients with BNT162b2 vaccine (51.4%). Sixty-seven patients (37.4%) were vaccinated with a combination of CoronaVac and BNT162b2. For NG, 42 patients (27.6%) were vaccinated with CoronaVac, 72 patients (47.4%) with only BNT162b2, and 38 (25%) with a combination of CoronaVac and BNT162b2.

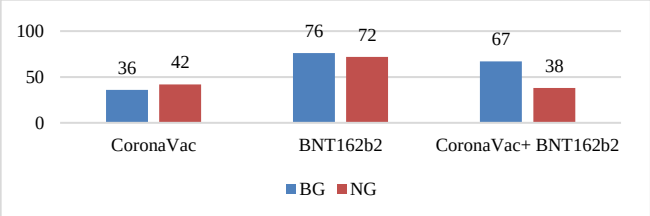
Table 1: Demographic and clinical data.

	Biologic group (n = 194)	Non biologic group (n = 185)	*P*-value	Overall (n = 379)
Female/Male (n)	98/96	58/127	<0.001	156/223
Age (years)	47.57 (12.19)	48.89 (13.89)	0.084	48.22 (13.05)
Disease duration (mo)	128.17 (81.60)	85.33 (84.95)	<0.001	107.32 (85.86)
Disease			<0.001	
Rheumatoid arthritis (n)	75	85	0.151	160
Spondyloarthropathies (n)	82	43	<0.001	125
Psoriatic arthritis (n)	31	13	0.007	44
Connective tissue disease (n)	7	21	0.004	28
FMF/BD/vasculitis (n)	8	20	0.013	28
Seropositivity (RF, anti-CCP + n)	42	52	0.050	94
HLAB27 positivity (+ / n)	45	24	0.596	69
Comorbidities (n)	70	70	0.723	140
Diabetes mellitus (n)	21	17	0.596	38
Hypertension (n)	37	34	0.863	71
Cerebrovascular accidents (n)	4	3	0.656	7
Cardiovascular disease (n)	12	8	0.418	20
COPD/Asthma/ILD (n)	11	10	0.910	21
Chronic Renal Failure (n)	2	5	0.227	7
Malignancy (n)	2	3	0.614	5
Inflammatory bowel disease (n)	10	2	0.024	12
Rheumatologic medications (n)			<0.001	
Only b/tsDMARD	101	0		101
b/tsDMARD + csDMARD	93	0		93
Only csDMARD	0	158		158
No DMARD	0	27		27

FMF: Familial Mediterranean Fever, BD: Behcet's disease, COPD: Chronic Obstructive Pulmonary Disease, b/tsDMARD: Biologic/ targeted synthetic disease-modifying anti-rheumatic drugs, csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs. RF: rheumatoid factor, Anti-CCP: Anti-Cyclic Citrullinated Peptide

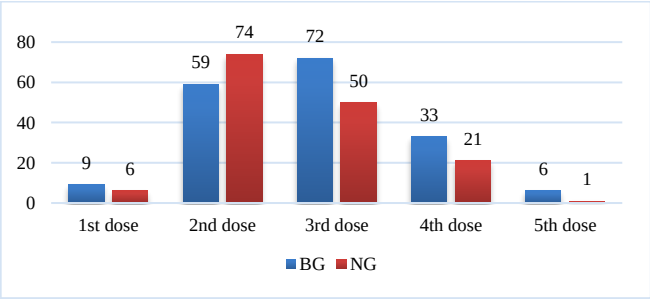
A significant difference was found between groups for vaccination rates ($P = 0.040$). There was no difference between patients vaccinated with only CoronaVac and only BNT162b2 ($P > 0.05$). However, there was a significant difference between groups vaccinated with a combination of CoronaVac and BNT162b2, only CoronaVac, or with only BNT162b2 ($P = 0.017$ and $P = 0.049$, respectively). This difference was ostensibly due to a combination of CoronaVac and BNT162b2 in BG (Figure 1A).

Figure 1A: Distribution of vaccine types among groups.



Vaccination doses are shown in Figure 1B. There was a significant difference between the two groups in terms of vaccine dose ($P = 0.035$). Pairwise comparison revealed that a significant difference was found between those who received 2 doses of vaccine and those who received 3, 4, and 5 doses ($P = 0.019$; $P = 0.038$; $P = 0.032$, respectively).

Figure 1B: Variation of vaccine dosages between groups



The rate of unvaccinated patients was 0.7% for BG, vs. 17.2% for NG (P = 0.005). No vaccination included fear of side effects (35.2%), not wanting to be vaccinated (18.9%), not trusting the vaccine (16.2%), indecisiveness about it (18.9%), and the disease (10.8%).

Side effects of COVID-19 vaccine

Post-vaccine side effects were detected in 99 (55.9%) patients in the BG Group and 95 (62.5%) patients in the NG Group. When side effects for all vaccines were evaluated, no difference was found between BG and NG. There was also no difference in side effects according to vaccine types (CoronaVac, BNT162b2, and the CoronaVac-BNT162b2 combination) for BG and NG (P > 0.05). The vaccine with the most common adverse events was BNT162b2 in both BG and NG. Evaluation of side effects due to each vaccine is shown in Table 2. The most common side effect, arm pain, was significantly higher in BG (P = 0.014). Fever and rash were more common in NG (P = 0.017), but there was no difference between BG and NG groups in terms of other side effects (P > 0.05).

Table 2: Vaccine side effects and their frequency.

	Biologic group	Non-biologic group
Rash-Swelling-pain the arm (n)	78	62
Lymphadenopathy (n)	4	4
Fatigue (n)	28	25
Headache-drowsiness (n)	12	10
Joint-muscle pain (n)	21	27
Fever-rash (n)	10	22
Anaphylaxis (n)	1	2
Nausea- vomiting- loss of appetite (n)	2	5
Runny nose (n)	1	0
Conjunctivitis (n)	0	1
Sore throat (n)	0	1
Chest pain (n)	1	0
Vaginal bleeding (n)	1	0

Among those with side effects in first dose vaccines (n=107), 73 (68%) had BNT162b2 while 34 (32%) had CoronaVac. Side effect rates were found to be significantly higher in patients vaccinated with BNT162b2 in BG and NG groups (P = 0.001 and P = 0.001, respectively). Distribution of side effects after the first vaccine dose were 49 (46.2%) local, 35 (33%) systemic, and 22 (20.8%) local + systemic.

Of those with side effects after the second vaccine dose (n = 104), 81 (77.9%) had BNT162b2 and 23 (22.1%) had CoronaVac. Side effects were significantly higher in BNT162b2 patients for BG and NG groups (P = 0.001 and P = 0.001, respectively). After the second vaccine dose, 48 (46.2%) of the side effects were local, 30 (28.8%) were systemic, and 26 (25%) were local with systemic side effects.

Among those with third vaccine doses (n = 80), 77 (96.3%) had BNT162b2 and 3 (3.6%) had CoronaVac. Side effects were significantly higher after BNT162b2 in BG and NG groups (P = 0.001 and P = 0.001, respectively). Side effects after the third vaccine dose were 46 (57.5%) local, 16 (20%) systemic, and 18 (22.5%) both local + systemic. Among those who had a fourth dose (n = 27), 24 (88.9%) had BNT162b2, whereas 3 (11.1%) had CoronaVac. There was no difference in side effects following the fourth dose of BNT162b2 and CoronaVac between BG and NG (P > 0.05). For vaccine effects after this dose, 15 (55.6%) were local, 5 (18.5%) were systemic, and 7 (25.9%) were local + systemic. Side effects after the fifth dose were noted in 2 patients (33%) for BG, but not for NG. Side effects were no different between BG and NG for vaccine doses, P > 0.05).

Disease exacerbation after COVID-19 vaccine

Disease exacerbation after vaccination was significantly different between BG and NG groups (P = 0.021). While no exacerbation of disease was observed in BG, it was detected in 5 patients (1%) for NG. The median disease duration with exacerbation was 172.80 (106.18) months: 2 patients with exacerbation had RA, 2 had AS, and 1 FMF. While 1 patient with RA was treated with methotrexate and steroids and the other was treated with leflunomide, patients with AS received NSAIDs, while those with FMF received colchicine. Vaccinations for exacerbated patients were BNT162b2 (n = 1), CoronaVac (n = 1), and 3 vaccinated with a combination of CoronaVAC and BNT162b2.

COVID-19 infection status

In the study, 135 patients (18%) were infected with SARS-COV-2. The frequency of infection was significantly lower in BG vs. NG (15.3 vs. 20.3%, P < 0.017). In patients with COVID-19, 96% with BG and 80.5% with NG were vaccinated (P = 0.005). Fifty-nine (18%) had at least one dose and 28 (8%) were fully vaccinated, even with COVID-19 infection. Headache and loss of smell, among clinical symptoms of COVID-19, were found to be significantly higher in BG (P = 0.012 and P = 0.023, respectively). Clinics with treatments for those with COVID-19 are listed in Table 3.

Table 3: Vaccination status of patients with COVID-19 with clinical characteristics and treatments for COVID-19.

	Biologic group (n = 58)	Non-biologic group (n = 77)	*P*-value
Vaccination (+ / n)	56	62	0.005
Post-vaccine COVID-19 positivity (+ / n)	30	29	0.389
Fully vaccinated (+ / n)	17	11	0.150
Interval time between the vaccine and COVID-19 infection (day)	92.93 (72.93)	81.40 (67.93)	0.740
Symptoms			
Asymptomatic (n)	8	9	0.723
Fever (n)	17	20	0.725
Dyspnea (n)	15	21	0.787
Cough/sputum (n)	20	29	0.620
Myalgia/weakness (n)	34	49	0.493
Loss of appetite (n)	13	20	0.574
Arthralgia (n)	20	23	0.628
Headache (n)	17	9	0.012
Sore throat (n)	7	9	0.989
Vomiting (n)	3	3	0.749
Diarrhea (n)	6	2	0.062
Loss of smell (n)	21	14	0.023
Loss of taste (n)	17	16	0.303
Lung involvement (n)	13	9	0.138
Hospitalization (yes, n)	10	11	0.680
Duration of hospital stay (day)	6.45 (4.50)	5.29 (4.44)	0.546
ICU stay (yes, n)	1	0	0.253
Non-invasive mechanical ventilation	1	0	0.363
COVID-19 Medication			
Favipiravir (n)	25	25	0.377
Hydroxychloroquine (n)	3	2	0.815
Azithromycin (n)	1	2	0.444
Steroids (n)	5	7	0.321
Anti-cytokine-IVIG (n)	1	0	0.363
Antibiotics	8	6	0.864

Data are presented as mean (SD). ICU: Intensive Care Unit, IVIG: intravenous immunoglobulin

The rate of patients with COVID-19 despite being vaccinated, were no different between BG (n = 30) and NG (n = 29) (P > 0.05). One patient completing the vaccination scheme was hospitalized with severe COVID-19 infection: this was a 56-year-old woman with a diagnosis of RA on rituximab and methotrexate. She did not need intensive care with hospitalization. Data regarding treatment for all patients with COVID-19 infection and those with COVID-19 after at least one vaccine are shown in Table 4. Fifty-nine patients (15.5%) with COVID-19 were infected after at least one vaccine dose, whereas

28 patients (7%) had the infection despite completing the vaccination regimen. There was no statistically significant difference between treatments for those with COVID-19 in both BG and NG ($P > 0.05$).

Table 4: Treatment for people with COVID-19 infection.

	All COVID-19 positive (n = 135)	COVID-19 positive + vaccinated (n = 59)
Biologic group	58 (43)	30 (50.8)
TNFi, n (%)	43 (74.1)	24 (80)
JAKi, n (%)	3 (5.2)	1 (3.3)
IL-17A inhibitor, n (%)	5 (8,6)	2 (6.7)
Rituximab, n (%)	6 (10.3)	2 (6.7)
IL-1 inhibitor, n (%)	-	-
CTLA4 Ig, n (%)	-	-
IL-6 inhibitor, n (%)	1 (1.7)	1 (3.3)
Non-biologic group	77 (57)	29 (49.2)
Methotrexate, n (%)	24 (31.2)	12 (41.4)
Leflunomide, n (%)	13 (16.9)	7 (24.1)
Hydroxychloroquine, n (%)	20 (26)	13 (44.8)
Sulfasalazine, n (%)	13 (16.9)	3 (10.3)
Azathioprine, n (%)	3 (3.9)	3 (10.3)
Colchicine, n (%)	10 (13)	2 (6.9)
Steroids, n (%)	35 (45.5)	14 (48.3)
NSAID, n (%)	10 (13)	-
Mycophenolate mofetil, n (%)	-	-

TNFi: Tumor Necrosis Factor Inhibition, JAKi: Janus Kinase Inhibitor, IL: Interleukin, NSAID: Non-steroidal anti-inflammatory drugs

Discussion

In our study, vaccination was more frequent for BG. There was no difference between BG and NG with all vaccine side effects. However, when side effects were evaluated, arm pain was more common with BG, whereas fever and rash were more common with NG. Side effects were higher in BNT162b2 vaccine with BG and NG. Vaccine-related disease exacerbation was seen at a rate of 1% for NG. Frequency of those infected with COVID-19 was lower for BG, but no difference was found in those vaccinated, or those who still had COVID-19 for BG and NG.

In a survey study conducted in those with inflammatory rheumatic disease, rates of vaccination for COVID-19 were 54% [12]. It was observed that they were willing to be vaccinated to protect themselves and their relatives, even without severe COVID-19. This increased to 67% if the doctor recommended it [13]. We saw a high vaccination rate of 92% in BG and 82% in NG. We suspect this was due to briefing about the vaccination for BG patients with close follow-up. Patients with BG were commonly vaccinated with a combined vaccine, and BNT162b2 was more common in NG. Patients on biological treatment had priority with vaccinations, with only CoronaVac vaccine available then.

In the literature, side effects ranging from 30 to 89% related to mRNA vaccine were reported, but most were not serious. The most common were pain and fatigue at the injection site [11, 14-17]. In the phase 4 immunogenicity study, conducted with Coronavac for inflammatory rheumatic patients, adverse effects were seen in 50% of inflammatory patients, with induration, headache, malaise, and sweating in the inflammatory group for the first dose (higher in the inflammatory group than the control group [18]). We found the frequency of vaccine side effects at 58%, which did not reach a significant difference between BG and NG in terms of side effects. Along with our study, another conducted in a pediatric patient group from Turkey, still no difference was found between BG, NG, and healthy control groups for all side effects [19]. Apart from these findings, analysis of side effects revealed that arm pain was more common in BG, while fever and rash were more common in NG. This may pertain to how treatments for BG can reduce fever. As stated, there are few studies evaluating differences between BG and NG in the literature.

The rate of side effects for vaccines shows differences between studies. In those given both mRNA and CoronaVac vaccines, side effects were more frequent after the first dose, with the rate decreasing after the second dose [15, 18]. In another study with a small number of patients, side effects were found at a higher rate after the second vs. the first dose [20]. In our study, there were patients with up to five doses of vaccine. We did not detect any differences in side effects after each dose between BG and NG. In a study of 225 patients with autoimmune rheumatic disease [21], side effects of 6 different COVID-19 vaccines were assessed: BNT162b2 was one with the highest frequency vs. the number of patients vaccinated, and localized pain was the most common. Side effects were less common in CoronaVac [21]. When BNT162b2 and CoronaVac were compared, the rate of side effects was highest in BNT162b2 for all doses. We did not find differences between groups with local, systemic, and local + systemic side effects evaluating doses individually, but local side effects were reported to be more common in the literature [16].

Inflammatory rheumatic diseases were excluded from the initial phase 3 studies of COVID-19 vaccines; this created hesitation in patients and clinicians. Vaccine reactogenicity was studied in inflammatory rheumatic diseases, and although this was higher, it was not more severe than healthy controls [14]. Our study included only patients with inflammatory rheumatic disease, with side effects from all vaccines; this profile was found to be similar to studies of both BNT162b2 and CoronaVac groups [22, 23].

Different results were found in studies for disease activity after vaccination. In a series of 1,101 patients [24], most were vaccinated with mRNA vaccines, but 15% reported worse rheumatologic disease status, experienced as moderate to severe. In another study of 5,121 patients [11], 4.4% of disease was detected, so treatment was changed in 1.5% of patients. There are smaller-scale studies in which there is no increase in disease activity after vaccination, or those with less than 1% activity [25, 26]. In our cohort, we identified 1% with increased disease after vaccination, and all were in the group not receiving BG.

In studies investigating indecisiveness about getting vaccinated, no consensus was established about a common cause. The far most common seemed to be fear of the vaccine, fear of side effects, and worsening of the disease, as well as safety concerns about the speed of vaccine production and doubts about its effectiveness [12, 27]. In this study, 11.8% of patients were not vaccinated, the most common reason being fear of side effects. The ratio of patients with COVID-19 infection after full dose vaccination was 0.6% in a systemic review [16]. In another multicenter study of 5121 patients, the rate of infection after full vaccination was 0.7% in patients with inflammatory rheumatological disease, as per the previous study [11]. In our study, the rate of COVID-19 infection was higher after one dose of vaccination or completing the vaccination scheme vs. in other studies. This may be due to the cross-sectional nature of our study, lack of standardization of the interval between doses,

variety of vaccines, and initial use of inactivated vaccine in our country.

It was reported that more than half the patients with rheumatological disease, hospitalized for COVID-19 after a full dose vaccination, used mycophenolate mofetil and B cell depletion therapy [28]. We did not detect any difference between treatment of patients with COVID-19 after vaccination with BG and NG. This may be the inhomogeneity of treatment in our population. For example, the number of patients using rituximab in BG and mycophenolate mofetil in NG was lower than other medications. These groups may not be complete enough to reach adequate sample size: 1 patient who received a full dose was hospitalized for severe COVID-19 after rituximab, a B-cell depletion therapy. In the NG group, about half the patients vaccinated with COVID-19 received steroid therapy, with a similar proportion taking hydroxychloroquine and methotrexate. No one in this group received mycophenolate. In accord with the data, when the antibody response after a single dose of BNT162b2 was assessed, it was shown that steroid and methotrexate can affect the vaccine response in chronic inflammatory diseases [29].

Limitations

This study has some limitations. Vaccination doses and intervals between doses were not standard in our country. In this study, people were vaccinated with different doses, from one to five. The CoronaVac was the only option available in our country when vaccination was given to patients receiving biological therapy for the first time. Since the BNT162b2 vaccine became available later, patients with BG were largely vaccinated with a combination of CoronaVac and BNT162b2. Since the interval time between doses depended on the person having it, it could not be standardized. Another limitation was a difference in the distribution of diseases and genders for BG and NG. We included all patients with inflammatory diseases who applied to our clinic at a certain time interval, as per our study design. Another limitation was that vaccine evaluation was performed only in clinical cases of COVID-19, as humoral and cellular immune response could not be evaluated in the laboratory. Disease activity was not evaluated for activity indices in the initial stage, with disease activity post-vaccine, not assessed for activity indices.

There are predominantly studies on mRNA vaccines in the literature, with the number of studies for other types of vaccines continuing to increase. Our study is important for evaluating two different groups of vaccines, or for groups with combined vaccinations, with real-life results, as well as to assess differences between BG and NG.

Conclusion

Patients with inflammatory rheumatic disease on b/tsDMARDs were vaccinated more often than others, and side effects were not different between BG and NG. Adverse effects were common in BNT162b2. Despite that COVID-19 infection occurred less in BG independent of vaccination, there was no difference between BG and NG in post-vaccine COVID-19 infection. Vaccine-related disease activity was as low as 1% in this study.

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