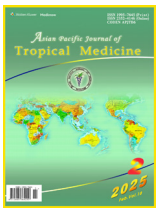

Original Article

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/apjtm.apjtm_253_24

COVID-19 vaccination in patients on biologic or targeted-synthetic disease modifying anti-rheumatic drug therapy: A multi center real-world data

Tuba Demirci Yildirim[1]✉, Cansu Akleylek[2], Derya Yıldırım[3], Haluk Cinakli[4], Selda Hakbilen[5], Belkıs Nihan Coşkun[6], Burak Okyar[7], Özlem Özdemir Işık[8], Rabia Pişkin Sağır[9], Hakan Apaydın[10], Ali Karakaş[1], Yeşim Erez[1], Tuba Yüce İnel[1], Semih Gülle[1], Abdurrahman Tufan[3], Servet Akar[4], Sema Yılmaz[5], Neslihan Yılmaz[2], Yavuz Pehlivan[6], Gözde Yıldırım Çetin[7], Ayşe Çefle[8], Süleyman Serdar Koca[9], Şükran Erten[10], Ediz Dalkılıç[6], Ayten Yazıcı[8], Gerçek Şen[1], İsmail Sarı[1], Ahmet Merih Birlik[1], Fatoş Onen[1]

[1]*Dokuz Eylul University Faculty of Medicine, Rheumatology, Izmir, Turkey*

[2]*Demiroglu Bilim University Faculty of Medicine, Rheumatology, Istanbul, Turkey*

[3]*Gazi University Faculty of Medicine, Rheumatology, Ankara, Turkey*

[4]*Izmir Katip Celebi University, Rheumatology, Izmir, Turkey*

[5]*Selcuk University Faculty of Medicine, Rheumatology, Konya, Turkey*

[6]*Bursa Uludag University Faculty of Medicine, Rheumatology, Bursa, Turkey*

[7]*Kahramanmaras Sutcu Imam University Faculty of Medicine, Rheumatology, Kahramanmaraş, Turkey*

[8]*Kocaeli University Faculty of Medicine, Rheumatology, Kocaeli, Turkey*

[9]*Firat University Faculty of Medicine, Rheumatology, Elazığ, Turkey*

[10]*Ankara City Hospital, Clinic of Rheumatology, Ankara, Turkey*

ABSTRACT

Objective: To assess the effectiveness of COVID-19 vaccination in patients with rheumatic diseases undergoing biologic (bDMARDs) or targeted-synthetic disease-modifying anti-rheumatic drugs (tsDMARDs).

Methods: This cross-sectional study was conducted at ten rheumatology clinics in Turkey between May 1, 2021, and October 30, 2022. Patients with rheumatic diseases on bDMARD or tsDMARD therapy who received at least two doses of an mRNA or inactivated SARS-CoV-2 vaccine were included. After vaccination, COVID-19 infection rates, adverse events, and rheumatic disease flares were recorded. Data were collected *via* face-to-face or telephone interviews.

Results: A total of 963 participants were included in the final analysis; 44% were male, and the median age was 49 years. The most frequently observed rheumatic diseases were ankylosing spondylitis and rheumatoid arthritis, accounting for 37.2% and 32.6% of cases, respectively. Adalimumab (19.2%) and infliximab (17.8%) were the most commonly used bDMARDs. Of the participants, 634 (65.9%) received an inactivated vaccine (CoronaVac) and 329 (34.1%) an mRNA vaccine (BioNTech). A total of 502 (52.1%) patients received a booster dose. Following the first, second, and third vaccine doses,

Summary

Question: What is the impact of COVID-19 vaccination on patients receiving biologic (bDMARDs) or targeted-synthetic disease-modifying anti-rheumatic drugs (tsDMARDs)?

Findings: In this multi-center study, two-thirds of the 963 bDMARDs/tsDMARD users were vaccinated with an inactivated vaccine, and one-third with an mRNA vaccine. COVID-19 occurred in 8.2% of the participants, with most cases being symptomatic but not requiring hospitalization.

Meaning: The findings suggest that COVID-19 vaccination is generally safe and effective in this population, highlighting the importance of vaccination for patients undergoing bDMARDs/tsDMARDs therapy.

✉To whom correspondence may be addressed. E-mail: tubademirci87@gmail.com

How to cite this article: Yildirim TD, Akleylek C, Yıldırım D, Cinakli H, Hakbilen S, Coşkun BN, et al. COVID-19 vaccination in patients on biologic or targeted-synthetic disease modifying anti-rheumatic drug therapy: A multi center real-world data. Asian Pac J Trop Med 2025; 18(2): 77-83.

Article history: Received 21 April 2024 Revision 19 February 2025
Accepted 24 February 2025 Available online 28 February 2025

adverse event rates were 19.9%, 15.9%, and 26.7%, respectively. Forty-two (4.4%) patients experienced a disease flare within six months after their first vaccination dose. COVID-19 infection occurred in 79 participants (8.2%) after two vaccine doses; most cases were symptomatic but did not require hospitalization. The COVID-19 infection rate was lower in participants who received a booster dose than those who did not (3.4% *vs.* 8.2%, $P<0.001$).

Conclusions: Our study indicates that both mRNA and inactivated SARS-CoV-2 vaccines are effective in preventing severe COVID-19 outcomes, with an acceptable rate of adverse events and disease flares among patients with rheumatic diseases on bDMARD or tsDMARD therapy.

KEYWORDS: bDMARDs; Rheumatic diseases; Vaccination; COVID-19; Adverse events; Flares

1. Introduction

Coronavirus disease-19 (COVID-19) has affected 770 million people and caused 7 million deaths globally[1]. Advanced age, comorbid conditions, and use of immunosuppressive drugs have been associated with worse outcomes[2-4]. Patients with rheumatic diseases are at an increased risk of COVID-19 and have a higher mortality rate than patients without rheumatic diseases due to the chronic inflammatory nature of their diseases[5]. Additionally, the use of biologic/targeted-synthetic disease-modifying anti-rheumatic drugs (bDMARDs/tsDMARDs) may increase the risk of mortality in patients with rheumatic diseases[5-7].

Vaccination against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been shown to decrease infection, hospitalization, and mortality in phase 3 trials and in real-life settings[8-12]. However, patients receiving immunosuppressive treatment, which may influence vaccine responses were excluded from phase 3 trials. Rituximab treatment was associated with an unfavorable vaccine response and a lower rate of measurable antibodies after two doses of mRNA vaccine[13]. Despite a reduced immune response to vaccines in patients who received bDMARDs/tsDMARDs, mRNA vaccines were reported effective against SARS-CoV-2 infection[14-16]. However, the effectiveness of inactivated vaccines in the rheumatic population receiving bDMARDs or tsDMARDs remains uncertain. Additionally, disease flares after vaccination are a significant concern for this group of patients, with previous studies reporting flare rates ranging from 0.4% to 20%[17-20].

The COVID-19 vaccination campaign began in Turkey on January 13, 2021. The inactivated vaccine (Sinovac-CoronaVac) became available on that date, and the BNT162b2 mRNA vaccine (Pfizer-BioNTech) became available in April 2021[21]. Both vaccines have been available since April 2021, and there are no restrictions on vaccine preference.

This study aimed to determine the effectiveness of both vaccines (inactivated and mRNA) in patients with rheumatic disease receiving bDMARDs or tsDMARDs. We also aimed to evaluate vaccine-related adverse events and the rate of rheumatic disease flare after vaccination.

2. Subjects and methods

2.1. Study design and population

This cross-sectional, multi-center study was conducted at 10 rheumatology clinics in Turkey between May 1, 2021, and October 30, 2022 and data were analyzed on January 12, 2023. The study included patients aged ≥18 years who were receiving bDMARDs or tsDMARDs therapy for rheumatic diseases (such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis) and who had received at least two doses of COVID-19 vaccine (CoronaVac or BioNTech). Patients who had not received any vaccine or only one dose were excluded from the study (Figure 1).

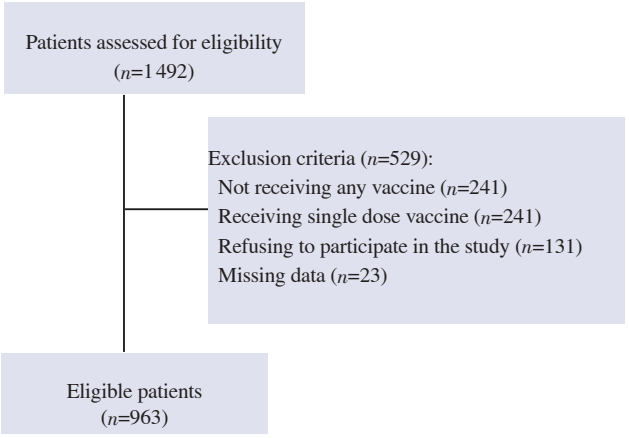

Figure 1. Flowchart of the study.

Data were collected from participants *via* face-to-face interviews or telephone calls. Recorded data included demographic characteristics, rheumatic disease diagnosis and duration, comorbid conditions, type of bDMARD or tsDMARD used, concurrent use of conventional synthetic DMARDs (csDMARDs) or glucocorticoids, and duration of therapy.

The study was approved by the ethics committee of Dokuz Eylül University (ethical approval number 2020/12-04, date 29.04.2021). All participants gave informed consent. The study was conducted in accordance with the Declaration of Helsinki 2013.

2.2. Outcomes

The effectiveness of vaccination was defined as the absence of

COVID-19 infection within 12 months after the first vaccine dose. If a participant had COVID-19 before the second vaccination dose, he or she was excluded from the final analysis. COVID-19 diagnosis was confirmed with a positive test of real-time polymerase chain reaction (RT-PCR). The severity of COVID-19 was divided into five categories: asymptomatic, symptomatic, need for hospitalization, need for ICU admission, and death. Adverse events were recorded if any of the following symptoms occurred within seven days after each vaccine dose: redness at the injection side, malaise, fever, headache, muscle or joint pain, allergic reactions, angioedema, nausea/vomiting, arthritis, and numbness. A flare of rheumatic disease was also recorded, defined as any condition that required a change in treatment as determined by a rheumatologist[22]. A flare was considered vaccine-related if it developed within six months after the first vaccine dose.

2.3. Statistical analysis

Continuous variables were presented as mean±standard deviation (SD) if the data were normally disturbed or median (interquartile range, IQR) if they were not normally disturbed. Categoric data were presented as *n* (%). Categoric data were compared with the *Chi*-Square test, and continuous data was compared with the Mann-Whitney *U* test. A *P*-value <0.05 was considered statistically significant.

3. Results

3.1. General characteristics of patients

A total of 963 participants were included in the final analysis, 424 (44%) participants were male, and the median age of 49 years (IQR, 39-60 years). Ankylosing spondylitis (AS) and rheumatoid arthritis (RA) were the most frequently reported rheumatic diseases (37.2% and 32.6%, respectively). The median duration of rheumatic disease among all patients was 11 years (IQR, 7-19 years). Adalimumab (19.2%) and infliximab (17.8%) were the most frequently used bDMARDs, followed by etanercept (13.4%). The median duration of bDMARDs use was 36 months (IQR, 15-60 months). A total of 366 (38%) patients received csDMARDs, and 237 (24.6%) patients concurrently received glucocorticoids. The most common comorbid conditions were hypertension (29.3%) and diabetes mellitus (14.8%) (Table 1).

A total of 634 (65.9%) patients were vaccinated with the inactivated vaccine, and 329 (34.1%) received the mRNA vaccine. Of these, 502 (52.1%) received a booster dose, with 370 (73.7%) receiving the mRNA vaccine.

Table 1. Demographic and clinical features of participants.

Characteristics	Participants (*n*=963)
Age, median (IQR), years	49 (39-60)
Sex male, *n* (%)	424 (44.0)
BMI, median (IQR), kg/m^2	27.0 (24.0-30.0)
Smoking status, *n* (%)*	
Never smoker	507 (52.6)
Current smoker	262 (27.2)
Former smoker	157 (16.3)
Unknown	37 (3.9)
Duration of smoking, median (IQR), years	12 (5-21)
Rheumatic disease, *n* (%)	
Ankylosing spondylitis	358 (37.2)
Rheumatoid arthritis	314 (32.6)
Psoriatic arthritis	72 (7.5)
nr-axSpA	60 (6.2)
Enteropathic arthritis	15 (1.6)
FMF	16 (1.7)
Behcet's disease	42 (4.4)
Systemic lupus erythematosus	10 (1.0)
Systemic sclerosis	12 (1.2)
Takayasu arteritis	14 (1.5)
Granulomatosis with polyangiitis	11 (1.1)
MPA	4 (0.4)
EGPA	1 (0.1)
Dermatomyositis/polymyositis	5 (0.5)
Adult onset Still disease	5 (0.5)
Primary Sjögren's Syndrome	5 (0.5)
uSpA	1 (0.1)
GCA	5 (0.5)
PMR	3 (0.3)
Undifferentiated connective tissue disease	1 (0.1)
Others	9 (0.9)
Duration of rheumatic disease, median (IQR), years	11 (7-19)
Biologic DMARDs, *n* (%)	
Adalimumab	185 (19.2)
Infliximab	171 (17.8)
Etanercept	129 (13.4)
Certolizumab	77 (8.0)
Golimumab	72 (7.5)
Rituximab	123 (12.8)
Abatacept	17 (1.8)
Tocilizumab	33 (3.4)
Secukinumab	49 (5.1)
Ustekunimab	5 (0.5)
Ixekizumab	2 (0.2)
Canakunimab	14 (1.5)
Anakinra	9 (0.9)
Other	17 (1.8)
Targeted-synthetic DMARDs, *n* (%)	
Tofacitinib	60 (6.4)
Duration of biologic DMARDs use, median (IQR), months	36 (15-60)
Conventional synthetic DMARDs, *n* (%)	366 (38.0)
Immunosuppressive agents, *n* (%)	
Azathioprine	40 (4.2)
Mycophenolate mofetil	19 (2.0)
Cyclosporine	6 (0.6)
Corticosteroids	237 (24.6)
Non-steroid anti-inflammatory drugs, *n* (%)	172 (17.9)
Colchicine, *n* (%)	48 (5.0)
Comorbid diseases, *n* (%)	
Hypertension	282 (29.3)

Table 1. Continued.

Characteristics	Participants (n=963)
Diabetes mellitus	143 (14.8)
Coronary artery disease	58 (6.0)
Congestive heart failure	11 (1.1)
Cerebrovascular disease	2 (0.2)
Asthma	46 (4.8)
Chronic obstructive pulmonary disease	13 (1.3)
Interstitial lung disease	44 (4.6)
Hematologic malignancy	2 (0.2)
Solid organ malignancy	4 (0.4)
Hypothyroidism	56 (5.8)
Psoriasis	41 (4.3)
COVID-19 vaccine, n (%)	
CoronaVac	634 (65.9)
BioNTech	329 (34.1)
Booster dose	502 (52.1)

BMI: Body Mass Index; COVID-19: Coronavirus disease-19; DMARDs: Disease-modifying anti-rheumatic drugs; EGPA: Eosinophilic granulomatosis with polyangiitis; FMF: Familial mediterranean fever; GCA: Giant cell arteritis; IQR: Interquartile range; MPA: Microscopic polyangiitis; nr-axSpA: Non-radiographic axial spondyloarthritis; PMR: Polymyalgia rheumatica; uSpA, Undifferentiated spondyloarthropathy. *Non-smoker: Someone who has not smoked more than 100 cigarettes in their lifetime and does not currently smoke; Active smoker: Somenoe who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes; Ex-smoker: Someone who has smoked more than 100 cigarettes in their lifetime but has not smoked in the last 28 days.

3.2. Adverse events after vaccination

One hundred ninety-two (19.9%) patients reported at least one adverse event after the first vaccination dose. The most common adverse events were redness at the injection site (81.3%) and malaise (57.8%), followed by headaches and muscle pain. After the second vaccination dose, 153 participants (15.9%) experienced at least one adverse event, with redness at the injection site and malaise again being the most frequently reported (Table 2). Participants who received mRNA vaccine had a higher rate of adverse events after both the first and second doses of vaccination compared to those who received inactivated vaccine [after the first dose: 29.2% (96/329) *vs.* 15.1% (96/634), P<0.001, and after the second dose: 28.0%, (88/329) *vs.* 10.4% (65/634), P<0.001]. The rate of adverse events was 26.7% (134/502) after the third dose of vaccination.

3.3. Flares after vaccination

A total of 42 patients (4.4%, 42/963) experienced a flare within six months after the first vaccination dose. Among these, 18 patients (42.9%, 18/42) experienced a flare within one month, and 15 patients (35.7%, 15/42) within three months of the first dose. Of the patients experiencing flares, 15 (35.7%, 15/42) had RA, and 11 (26.2%, 11/42) had AS. No significant difference was found between the mRNA and inactivated vaccines regarding flare incidence (3.6% *vs.* 4.7%, P=0.610) (Table 3).

3.4. COVID-19 after vaccination

A total of 79 participants (8.2%, 79/963) had COVID-19 after two vaccination doses. The median duration from the second dose of vaccination to diagnosis of COVID-19 was 118 days (IQR, 47-198 days). Most cases were symptomatic, but six patients needed hospitalization; three of them were admitted to the intensive care unit due to the severity of the disease. One participant died due to COVID-19. Seventeen patients (3.4%, 17/502) had COVID-19 after the third dose of the vaccine, and most of them did not require

Table 2. Adverse events after each dose of vaccination [n (%)].

Adverse events	After the first dose (n=963)	After the second dose (n=963)	After the third dose (n=502)
Total	192 (19.9)	153 (15.9)	134 (26.7)
Redness or pain at injection site	156 (81.3)	109 (71.2)	82 (61.2)
Malaise	111 (57.8)	101 (66.0)	56 (41.8)
Fever	51 (26.6)	37 (24.2)	36 (26.9)
Headache	73 (38.0)	48 (31.4)	27 (20.1)
Joint or muscle pain	73 (38.0)	61 (39.9)	15 (11.2)
Allergic reactions	5 (2.6)	2 (1.3)	3 (2.2)
Angioedema	0	0	4 (3.0)
Nausea/vomiting	27 (14.1)	14 (9.2)	2 (1.5)
Arthritis	8 (4.2)	4 (2.6)	3 (2.2)
Numbness	4 (2.1)	3 (2.0)	1 (0.7)

Table 3. Comparison of participants who have received two doses of vaccines.

Characteristics	Inactivated vaccine (n=634)	mRNA vaccine (n=329)	P value
Age, years, median (IQR)	51 (40-63)	45 (37-52)	<0.001
Duration of rheumatic disease, years, median (IQR)	12 (7-19)	11 (7-17)	0.514
Duration of biologic DMARDs use, months, median (IQR)	36 (17-67)	34 (12-60)	0.619
COVID-19 after vaccination, n (%)	57 (9.0)	22 (6.7)	0.194
Any adverse events after the first dose of vaccination, n (%)	96 (15.1)	96 (29.2)	<0.001
Any adverse events after the second dose of vaccination, n (%)	65 (10.4)	88 (28.0)	<0.001
Flare of rheumatic disease, n (%)	30 (4.7)	12 (3.6)	0.610

COVID-19: Coronavirus disease-19; DMARDs: Disease-modifying anti-rheumatic drugs; IQR: Interquartile range.

hospitalization; only one participant was hospitalized due to disease severity. The rate of COVID-19 was lower in participants who received a booster dose compared to those who did not receive a booster dose [3.4% (17/502) *vs.* 8.2% (79/963); $P<0.001$].

4. Discussion

Vaccination against SARS-CoV-2 has been effective in reducing hospitalization and mortality among healthy individuals. However, its effectiveness in specific populations, such as patients receiving bDMARDs or tsDMARDs for rheumatic diseases, remains unclear. This study showed that 8.2% of patients with rheumatic diseases on bDMARDs or tsDMARDs had COVID-19 after two doses of vaccination, and only 7.6% of these patients with COVID-19 needed hospitalization. Our results also suggested that patients who received the mRNA vaccine experienced a higher rate of adverse events than those who received the inactivated vaccine.

The reported COVID-19 rate in immunosuppressed patients after two doses of the vaccine against SARS-CoV-2 varied between 2.8% and 84.3%, possibly related to the type of vaccine and methodological differences in studies[16,23–25]. Both mRNA and inactivated vaccines have been shown to be effective in preventing COVID-19 infection, hospitalization, and mortality in phase 3 trials[9,10]. However, patients receiving immunosuppressive therapy were excluded from the phase 3 trials, so the effectiveness of vaccines was unclear in these patients. In real-world studies, the mRNA vaccine appears more effective than the inactivated vaccine in both general and rheumatic populations[16,23–25]. Immunogenicity was also found to be higher with the mRNA vaccine than with the inactivated vaccine among rheumatic disease patients on immunosuppressive therapy[26]. In an international multicenter study, Machado and colleagues reported a COVID-19 infection rate of 0.7% among fully vaccinated (with mRNA or vector vaccine) patients with inflammatory rheumatic diseases[24]. In contrast, Chen and colleagues found an infection rate of 84.1% in patients with rheumatic diseases, and vaccination did not reduce the infection rate[27]. Pehlivan *et al*. reported a higher COVID-19 rate among patients vaccinated with the inactivated vaccine compared to the mRNA vaccine (20.3% *vs.* 15.3%, $P=0.017$)[25]. In our study, 79 participants (8.2%) had COVID-19 after two doses. Although the infection rate was higher among those who received the inactivated vaccine than the mRNA vaccine, this difference was not statistically significant (9.1% *vs.* 6.6%, $P=0.194$). After the third dose, only 17 participants (3.4%) developed COVID-19, supporting the recommendation for a booster dose, especially for immunosuppressed patients, as vaccine effectiveness may wane over time[28,29].

The median time from the second vaccination dose to COVID-19 diagnosis among our patients was 118 days. Vaccine effectiveness is generally reported to decrease significantly after six months[28]. In patients receiving immunosuppressive or immunomodulatory treatment, the protective effect of the vaccine may last less than six months due to a reduced humoral response to SARS-CoV-2 vaccination[30–32]. Patel *et al*. found that multiple immunomodulatory therapies increase the risk of SARS-CoV-2 infection among fully vaccinated patients compared to antimalarial monotherapy[14]. In our study, all participants received bDMARDs or tsDMARDs, with no significant difference in post-vaccination COVID-19 rates between the two drug types.

Despite the low rate of serious adverse events, patients reported a higher incidence of mild adverse events, including local and systemic reactions. Phase 3 trials have shown that patients receiving the mRNA vaccine reported more adverse events than those given a placebo (27% *vs.* 12%), while those receiving the inactivated vaccine had slightly more adverse events than placebo recipients (18.9% *vs.* 16.9%)[9,10]. A meta-analysis also found that inactivated vaccines had the lowest risk ratio for adverse events, while mRNA vaccines had the highest[33]. Consistent with this, patients with rheumatic diseases who received the mRNA vaccine reported a higher rate of adverse events than those who received the inactivated vaccine. Esquivel-Valerio *et al*. reported that adverse event rates were higher with the mRNA vaccine in patients with autoimmune and inflammatory rheumatic diseases[34]. Similarly, Altan *et al.* found a higher adverse event rate in mRNA-vaccinated rheumatic patients compared to those receiving the inactivated vaccine (62.6% *vs.* 40.0%, $P<0.001$)[35]. In our study, adverse event rates following the first, second, and third vaccination doses were 19.9%, 15.9%, and 26.7%, respectively. Participants who received the mRNA vaccine as a booster reported more adverse events, which may explain the higher rate after the third dose. Although we had no comparison group, our adverse event rates were comparable to those in phase 3 trials and similar to those reported for rheumatic and non-rheumatic populations in previous studies[36,37].

A common concern regarding SARS-CoV-2 vaccination is the risk of rheumatic disease flare-ups. Previous studies have reported relatively low flare rates post-vaccination. Two multicenter international studies found flare rates of 4.4% and 4.9%, respectively, among patients primarily vaccinated with mRNA vaccines[22,24]. Li *et al*. also found that full vaccination with either the mRNA or inactivated vaccine was not associated with arthritis flare-ups in RA patients[38]. However, Fong and colleagues reported a higher flare rate of 21.9%[39]. The main reason for the difference in flare rates is due to the methodological differences of the studies. Differences in flare rates across studies may be due to variations in study methodology. In our study, the flare rate of 4.4% was consistent with previous findings, and no association was observed between flare rates and vaccine type. Rider *et al*. noted that patients with systemic lupus erythematosus, psoriatic arthritis, or polymyalgia rheumatica had a higher likelihood of reporting disease flares[22]. Different rheumatologic diseases may have different flare rates, and inflammatory arthritis may have a lower risk of flare than

systemic rheumatic diseases[40]. The low flare rate in our study may be attributed to most of the patients having inflammatory arthritis. Additionally, disease flares may be associated not only with vaccination but also with higher disease activity in the rheumatic population before vaccination.

Our study has several limitations. First, there was no comparison group of unvaccinated patients, so comparisons were limited to those between mRNA and inactivated vaccine recipients. Second, disease activity status was not assessed at the time of vaccination. Higher rheumatic disease activity during vaccination may reduce vaccine effectiveness, increase the risk of adverse events, or worsen disease activity, and this should be considered when interpreting our results.

In conclusion, our study demonstrated that both mRNA and inactivated vaccines against SARS-CoV-2 effectively prevented severe COVID-19 outcomes. The rate of disease flares among patients on bDMARDs or tsDMARDs for rheumatic diseases was low and acceptable. Although the mRNA vaccine was associated with more adverse events than the inactivated vaccine, most of these were local, and the rate of severe adverse events was low for both vaccines.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

The authors received no extramural funding for the study.

Data availability

The article's underlying data will be shared on reasonable request to the corresponding author.

Authors' contributions

TDY, FO, AT, AÇ, AMB, GŞ, NY and IS contributed to the conceptualization of the study; TDY, BO, CA, HC, DY, SH, ÖÖI, RPS, HA, BNC, TYİ, YE, SG, AK, NY contributed data curation; TDY, FO, AK, SG contributed to statistical analysis; TDY, FO, SG, ED, ŞE, SSK, SA, SY, YP, GYÇ contributed to preparing and writing the manuscript. All authors reviewed, provided critical review at each stage, and approved the final version of the manuscript. FO is the guarantor.

References

[1] World Health Organization. N*umber of COVID-19 deaths reported to WHO*. [Online]. Available from: https://data.who.int/dashboards/covid19/deaths. [Accessed on 9 January 2024].

[2] Ahmed S, Gasparyan AY, Zimba O. Comorbidities in rheumatic diseases need special consideration during the COVID-19 pandemic. *Rheumatol Int* 2021; **41**(2): 243-256.

[3] Ge E, Li Y, Wu S, Candido E, Wei X. Association of pre-existing comorbidities with mortality and disease severity among 167 500 individuals with COVID-19 in Canada: A population-based cohort study. *PLoS One* 2021; **16**(10): e0258154.

[4] Marques CDL, Kakehasi AM, Pinheiro MM, Mota LMH, Albuquerque CP, Silva CR, et al. High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: First results of ReumaCoV Brasil registry. *RMD Open* 2021; **7**(1): e001461.

[5] Conway R, Grimshaw AA, Konig MF, Putman M, Duarte-García A, Tseng LY, et al. SARS-CoV-2 infection and COVID-19 outcomes in rheumatic diseases: A systematic literature review and meta-analysis. *Arthritis Rheumatol* 2022; **74**(5): 766-775.

[6] Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: Results from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2021; **80**(7): 930-942.

[7] Sparks JA, Wallace ZS, Seet AM, Gianfrancesco MA, Izadi Z, Hyrich KL, et al. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 global rheumatology alliance physician registry. *Ann Rheum Dis* 2021; **80**(9): 1137-1146.

[8] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021; **384**(15): 1412-1423.

[9] Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. 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* 2021; **398**(10296): 213-222.

[10] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; **383**(27): 2603-2615.

[11] Yildirim S, Yilmaz C, Polat G, Baris S, Başyiğit İ, Kaya İ, et al. Clinical characteristics and outcomes of nosocomial COVID-19 in Turkey: A retrospective multicenter study. *Asian Pac J Trop Med* 2023; **16**(8): 347-353.

[12] Sandal A, Cifci AG, Arbak PM. COVID-19 vaccination and associated factors in Turkish healthcare workers practicing chest medicine. *Asian Pac J Trop Med* 2023; **16**(3): 110-118.

[13] Ammitzbøll C, Kragh Thomsen M, Andersen JB, Bartels LE, From Hermansen ML, Dahl JA, et al. COVID-19 vaccination in patients with rheumatic diseases leads to a high seroconversion rate and reduced self-imposed isolation and shielding behaviour. *Mod Rheumatol* 2023; **33**(4): 777-785.

[14] Patel NJ, Wang X, Fu X, Kawano Y, Cook C, Vanni KMM, et al. Factors associated with COVID-19 breakthrough infection among vaccinated patients with rheumatic diseases: A cohort study. *Semin Arthritis Rheum* 2023; **58**: 152108.

[15]Shen C, Risk M, Schiopu E, Hayek SS, Xie T, Holevinski L, et al. Efficacy of COVID-19 vaccines in patients taking immunosuppressants. *Ann Rheum Dis* 2022; **81**(6): 875-880.

[16]Zhou HR, Li GF, Wang XM, Zhou Z, Hu JF, Ye KY, et al. COVID-19 breakthrough infection after four doses of the vaccines: A case report. *One Health Bull* 2023; **3**: 7.

[17]Mehta P, Gasparyan AY, Zimba O, Kitas GD. Systemic lupus erythematosus in the light of the COVID-19 pandemic: Infection, vaccination, and impact on disease management. *Clin Rheumatol* 2022; **41**(9): 2893-2910.

[18]Zavala-Flores E, Salcedo-Matienzo J, Quiroz-Alva A, Berrocal-Kasay A. Side effects and flares risk after SARS-CoV-2 vaccination in patients with systemic lupus erythematosus. *Clin Rheumatol* 2022; **41**(5): 1349-1357.

[19]Braun-Moscovici Y, Kaplan M, Braun M, Markovits D, Giryes S, Toledano K, et al. Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2. *Ann Rheum Dis* 2021; **80**(10): 1317-1321.

[20]Xie Y, Liu Y, Liu Y. The Flare of rheumatic disease after SARS-CoV-2 vaccination: A review. *Front Immunol* 2022; **13**: 919979.

[21]T.C. *Sağlık Bakanlığı*. [Online]. Available from: https://covid19asi.saglik.gov.tr. [Accessed on 10 January 2024].

[22]Rider LG, Parks CG, Wilkerson J, Schiffenbauer AI, Kwok RK, Noroozi Farhadi P, et al. Baseline factors associated with self-reported disease flares following COVID-19 vaccination among adults with systemic rheumatic disease: Results from the COVID-19 global rheumatology alliance vaccine survey. *Rheumatology (Oxford)* 2022; **61**(SI2): SI143.

[23]Kahn R, Janusz CB, Castro MC, Da A, Matos R, Domingues C, et al. The effectiveness of COVID-19 vaccines in Latin America, 2021: A multicenter regional case-control study. *Lancet Reg Heal–Am* 2023; **20**: 100474.

[24]Machado PM, Lawson-Tovey S, Strangfeld A, Mateus EF, Hyrich KL, Gossec L, et al. 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* 2022; **81**(5): 695-709.

[25]Pehlivan Ö, Gezer HH. Single-center experience of COVID-19 vaccine in patients with inflammatory rheumatic disease: Real-life data. *J Surg Med* 2022; **6**(9): 792-797.

[26]Cosan F, Demirel OU, Yalcin D, Sonkaya MM, Uluisik IE, Cecen O, et al. Comparison of anti-spike IgG, anti-spike IgA levels and neutralizing antibody activity induced by CoronaVac and BNT162b2 vaccines in patients with inflammatory rheumatic diseases receiving immunosuppressive therapy. *BMC Rheumatol* 2023; **7**(1): 1-17.

[27]Chen C, Huang S, Geng L, Lai P, Dou H, Zhang H, et al. COVID-19 vaccination and infection status: A cross-sectional survey of patients with rheumatic diseases in China. *Rheumatol Int* 2024; **44**(4): 703-713.

[28]Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: Results of a systematic review and meta-regression. *Lancet* 2022; **399**(10328): 924-944.

[29]CDC. *COVID-19 vaccines for people who are moderately or severely immunocompromised.* [Online]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html. [Accessed on 28 January 2024].

[30]Ahmed S, Gupta L, Kuwana M, Pauling JD, Day J, Ravichandran N, et al. Correlates of breakthrough COVID-19 in vaccinated patients with systemic sclerosis: Survival analysis from a multicentre international patient-reported survey. *Rheumatol Int* 2024; **44**(1): 89-97.

[31]Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky D, et al. 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* 2021; **80**(10): 1330-1338.

[32]Friedman MA, Curtis JR, Winthrop KL. Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity in patients with inflammatory rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2021; **80**: 1255-1265.

[33]Kouhpayeh H, Ansari H. Adverse events following COVID-19 vaccination: A systematic review and meta-analysis. *Int Immunopharmacol* 2022; **109**: 108906.

[34]Esquivel-Valerio JA, Skinner-Taylor CM, Moreno-Arquieta IA, Cardenas-de la Garza JA, Garcia-Arellano G, Gonzalez-Garcia PL, et al. Adverse events of six COVID-19 vaccines in patients with autoimmune rheumatic diseases: A cross-sectional study. *Rheumatol Int* 2021; **41**(12): 2105-2108.

[35]Altan L, Mısırcı S, Yağcı İ, Karacaatlı M, Özkan FÜ, Güner A, et al. How do COVID-19 vaccines affect rheumatic diseases? *Arch Rheumatol* 2022; **38**(1): 75-81.

[36]Aboud FM, Hussein RS, Hassan RM. Safety and reported adverse effects of coronavirus disease-2019 (COVID-19) vaccines in patients with rheumatic diseases. *Egypt Rheumatol* 2023; **45**(2): 133.

[37]Boekel L, Kummer LY, van Dam KPJ, Hooijberg F, van Kempen Z, Vogelzang EH, et al. Adverse events after first COVID-19 vaccination in patients with autoimmune diseases. *Lancet Rheumatol* 2021; **3**(8): e542-e545.

[38]Li X, Tong X, Yeung WWY, Kuan P, Yum SHH, Chui CSL, et al. Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. *Ann Rheum Dis* 2022; **81**(4): 564-568.

[39]Fong W, Woon TH, Chew LC, Low A, Law A, Poh YJ, et al. Prevalence and factors associated with flares following COVID-19 mRNA vaccination in patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis: A national cohort study. *Adv Rheumatol* 2023; **63**(1): 1-9.

[40]Fan Y, Geng Y, Wang Y, Deng X, Li G, Zhao J, et al. Safety and disease flare of autoimmune inflammatory rheumatic diseases: A large real-world survey on inactivated COVID-19 vaccines. *Ann Rheum Dis* 2021; **81**(3): 443.

Publisher's note

The Publisher of the *Journal* remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Edited by Zhang Q, Lei Y, Pan Y