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ORIGINAL ARTICLE

Effects of anti-SARS-CoV-2 vaccination on safety and disease exacerbation in patients with Behçet syndrome in a monocentric cohort

Hakan Apaydin[1] | Abdulsamet Erden[2] | Serdar Can Güven[1] | Berkan Armağan[1] | Hatice Ecem Konak[1] | Bünyamin Polat[1] | Yağnur Afşin[3] | Merve Kaygisiz[3] | Ahmet Omma[4] | Orhan Kucuksahin[2]

[1]Clinical Rheumatology, Ankara City Hospital, Cankaya, Turkey

[2]Division of Rheumatology, Department of Internal Medicine, Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Türkiye

[3]Internal Medicine, Ankara City Hospital, Ankara, Türkiye

[4]Clinical Rheumatology, University of Health Sciences, Ankara, Türkiye

Correspondence
Hakan Apaydin, Division of Rheumatology, Department of Internal Medicine, Ankara City Hospital, Ankara 06100, Türkiye.
Email: drhakanapaydin@gmail.com

Abstract

Aim: Vaccination represents a cornerstone in mastering the coronavirus disease 2019 (COVID-19) pandemic. There is a paucity of data regarding the safety of COVID-19 vaccines in patients with rheumatic diseases such as Behçet syndrome (BS). The present study aimed to investigate the side-effects and post-vaccine disease exacerbation rates of COVID-19 vaccines in a BS cohort.

Methods: We retrospectively evaluated 450 BS patients followed in our clinic who met the criteria of the International Study Group. COVID-19 vaccination status, type of vaccine received (Pfizer-BioNTech vs CoronaVac), post-vaccine side-effects and exacerbations were evaluated by interviewing patients over the phone or face to face. Behçet's Disease Current Activity Form (BDCAF) scores were calculated for BS symptoms before and after vaccination.

Results: In all, 287 patients received at least one dose of the COVID-19 vaccine. Of the total number of COVID-19 vaccines (n = 639), 379 (59%) were Pfizer-BioNTech vaccines and 257 (41%) were CoronaVac vaccines. The number of side-effects after first, second, third and fourth vaccine doses were 151 (52.6%), 135 (49.4%), 29 (42.6%), and 3 (30%), respectively. BS exacerbation after first, second, third, and fourth vaccine doses were 151 (52.6%), 135 (49.4%), 16 (23.5%), and 3 (30%), respectively. Injection site pain/swelling was the most common side-effect at all vaccine doses followed by fatigue and arthralgia.

Conclusion: COVID-19 vaccines are well tolerated in patients with BS, and more side-effects develop after mRNA vaccines. Regardless of the vaccine type, exacerbations after the COVID-19 vaccine are common, predominantly mucocutaneous and articular involvement, and exacerbations in the form of other organ involvement are rare.

KEYWORDS
Behçet syndrome, coronavirus, COVID-19, inactive, mRNA, vaccination

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been a major global health concern since December 2019, affecting millions of people worldwide and causing death. During the COVID-19 pandemic, vaccination has become one of the cornerstones of the fight against this disease in the general population, as well as in patients with inflammatory rheumatic diseases, and highly effective vaccines have been developed.[1,2] During the pandemic process, both CoronaVac inactivated vaccine[2] and Pfizer-BioNTech mRNA vaccine[1] were used in primary vaccination in Türkiye. Booster doses have been put into practice because of the decrease of immunity over time.[3] The results of phase studies on the safety and efficacy of mRNA and inactivated vaccines have been reported, demonstrating a significant rate of effectiveness in preventing COVID-19 without unexpected safety findings.[1,2,4] Patients with chronic inflammatory diseases and those taking immunosuppressive medicines were excluded from SARS-CoV-2 vaccination clinical studies. Therefore, there is ambiguity about the efficacy and safety of vaccination in individuals with immunocompromised inflammatory rheumatic illness due to underlying immune dysfunction and concomitant immunosuppressive therapy.

Behçet syndrome (BS) is a multisystem vasculitis characterized by oral and genital ulcers, arthritis, nodular and papulopustular lesions, uveitis, arterial and venous thrombosis, and may include the central nervous system and gastrointestinal tract.[5] It has a distinct geographical distribution on the "Old Silk Road" including Mediterranean countries, the Middle East, and the Far East, and Türkiye has the highest prevalence worldwide with a rate of up to 420 per 100 000 adult population.[6] Disease activity, comorbidities, immunosuppressive medication, and other variables all contribute to an increased risk of morbidity and mortality from vaccine-preventable infections in patients with rheumatic disorders.[7]

There is a theoretical risk of exacerbation or worsening of inflammatory rheumatic disease following vaccination with COVID-19. The recent VAXICOV study found limited willingness of patients with inflammatory rheumatism to be vaccinated against SARS-CoV-2.[8] One of the most important reasons for vaccine hesitancy among individuals with inflammatory rheumatic disorders is concerns about adverse reactions and increased autoimmune disease activities. BS has a unique clinical heterogeneity and clinical conditions such as thrombosis,[9] uveitis,[10] and cerebral venous sinus thrombosis,[11] which can be seen in the course of the disease, have been reported after COVID-19 vaccines. There is limited knowledge about the safety and disease exacerbations associated with anti-SARS-CoV-2 vaccines in patients with BS,[12] and better information could benefit clinicians and patients in decision-making and vaccine hesitancy.

In this study, we aimed to evaluate the safety, post-vaccine BS exacerbation rate, and exacerbation characteristics of inactivated and mRNA anti-SARS-CoV-2 vaccines in BS patients by retrospectively examining our BS cohort.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was conducted in the Rheumatology Clinic of Ankara City Hospital as a cross-sectional, retrospective cohort study with the approval of the institutional ethics committee (IRB no. E2-22-1439) and was therefore carried out in accordance with the ethical standards laid out in the 1964 Declaration of Helsinki and its later amendments. The Ministry of Health granted official authorization to conduct this research.

2.2 | Patients

We retrospectively evaluated adult BS patients followed in our clinic using hospital records and composed a retrospective patient cohort who met the criteria of the International Study Group.[13] Between September 15 and November 30, 2021 patients were evaluated either during the visit or by telephone calls. BS patients vaccinated for COVID-19 were included in the study, and patients under the age of 18 years were excluded.

The primary outcome was the occurrence of side-effects, including a BS flare. For each patient, demographic data such as age, duration of disease, smoking history, comorbidities, and ongoing medications were collected from our hospital records at enrollment. Afterwards, all of the patients were reached via phone using information from our hospital's database. Side-effects during the vaccination period, post-vaccine disease flare findings, features of flare-up, type of vaccine received (Pfizer-BioNTech vs CoronaVac), continuation of BS treatment, post-vaccine treatment change, post-vaccine COVID-19 history and BS symptoms before and after COVID-19 vaccination were investigated upon verbal consent. BS patients were classified as group 1 if they had mucocutaneous-articular involvement and group 2 if they had ocular, vascular, neurological, or gastrointestinal involvement. The Turkish version of the Behçet's Disease Current Activity Form (BDCAF) was used to evaluate BS symptoms.[14] During the 4 weeks leading up to the day of assessment, the BDCAF evaluates the presence of symptoms in 12 clinical categories. Clinical symptoms include oral and genital ulcers, arthralgia, arthritis, erythema nodosum, skin pustules, nausea or vomiting or abdominal pain, diarrhea or hematochezia, headache, and symptoms related to the eye, nervous system, and major vessel involvement. The BDCAF has been fulfilled for both pre-COVID-19 and post-COVID-19 vaccination BS symptoms. If any new complaints were identified by the patient in the post-COVID-19 vaccination survey, we considered it a BS flare. In the post-COVID-19 vaccination evaluation, the presence of a symptom at least 1 month after the COVID-19 vaccination was considered significant for BS. HA, YS, MÇ, and HEK collected all data using a standardized case report form.

2.3 | Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 22 was used for statistical analysis (IBM Inc., Armonk, NY, USA). Visual

(histogram and probability graphics) and analytical methods were used to look at the normality of variables (Kolmogorov-Smirnov test). Descriptive statistics are presented as either median and interquartile range (IQR) or mean ± standard deviation, according to normality. Numbers and percentages were used to represent categorical variables. The Student *t* test or the Mann-Whitney *U* test were employed to compare continuous variables for normality. Pearson's χ^2 test and Fisher's final test were employed to assess categorical variables. Statistical significance was accepted as *P* values less than 0.05.

3 | RESULTS

A total of 450 BS patients were evaluated for eligibility. Eighteen (4%) of them did not want to participate in the study and 85 (18.8%) could not be reached. Sixty of the remaining 347 patients were not vaccinated.

Between January 13 and December 31, 2021, 287 patients had at least one dose of any COVID-19 vaccine. In all, 273 (95.1%) patients received a second dose, 68 (23.6%) patients received a third dose, and 10 (3.4%) patients received a fourth dose. According to vaccine groups, patients most frequently received two doses of mRNA vaccine (Pfizer-BioNTech) (n = 160); others received two doses of inactive vaccines (CoronaVac) (n = 46) and two doses of inactive vaccines plus one dose of mRNA vaccine (n = 33). According to the total number of vaccines, 379 (59%) of the patients received mRNA vaccine and 257 (41%) received inactivated vaccine. A flow chart of the study is shown in Figure 1.

The median age of patients was 42 years (IQR 34-50 years), 157 (54.7%) were male, the median disease duration was 120 months (IQR 1-480 months), and 91 (31.7%) were active smokers. Among these 287 BS patients, oral ulcer (283; 98.6%) was the most common manifestation in previous BS symptoms, followed by genital ulcer (225; 78.4%), papulopustular eruption (218; 76%), erythema nodosum (135; 47%), and uveitis (130; 45.3%). The percentages of patients treated with colchicine, azathioprine, and corticosteroids were 217 (75.6%), 94 (32.8%), and 53 (18.5%), respectively. In all, 112 (39%) of the patients had Mucocutaneous and articular involvement alone and 175 (61%) had other organ involvement. Demographics and clinical characteristics of the patients are shown in Table 1.

Side-effects were reported by 151 (52.6%) patients after the first dose, by 135 (49.4%) after the second vaccine dose, by 29 (42.6%) patients after the third vaccine dose, and by 3 (30%) patients after the fourth vaccine dose, a median of 1 day after COVID-19 vaccination. Among the 287 patients, a BS flare was reported by 151 (52.6%) after the first vaccine dose, 135 (49.4%) after the second vaccine dose, 16 (23.5%) after the third vaccine dose, and 3 (30%) after the fourth dose of vaccine. Injection site pain/swelling was the most common side-effect at all vaccine doses (105 [36.5%], 87 [31.8%], 20 [29.4%], and 3 [30%], respectively), followed by fatigue (57 [19.9%], 62 [22.7%], 13 [19.1%], and 3 [30%]) and arthralgia (42 [14.6%], 44 [16.1%], 10 [14.7%], and 2 [20%]). BS flare after COVID-19 vaccination typically appeared as musculoskeletal and mucocutaneous symptoms. The most common symptoms were arthralgia/arthritis (33 [11.4%], 39 [14.2%] 13 [19.1%], and 3 [30%] respectively), followed by oral ulcers, papulopustular eruption, and erythema nodosum. These flares led to a change in BS medication in three patients, and they did not cause hospitalization in any of the patients. Twenty-two (7.7%) patients discontinued the drug during vaccination, and colchicine (13; 59%), azathioprine (5; 22.7%), and infliximab (2; 9.1%) were discontinued most frequently. Eighty-nine (31%) patients used analgesics or antipyretics; 61 (68.5%) most commonly used paracetamol and 28 (31.5%) used nonsteroidal anti-inflammatory drugs. The type of side-effects and disease flares after the COVID-19 vaccination are shown in Table 2.

After the COVID-19 vaccine, BS exacerbation other than mucocutaneous and musculoskeletal involvements was seen in four patients, bilateral anterior uveitis in one patient, unilateral anterior uveitis in two patients, and bilateral posterior uveitis and deep vein thrombosis in one patient. Uveitis developed in one patient who had been in remission for a long time who did not receive treatment, but uveitis was also observed in a patient who did not have a uveitis attack for 1 year, and this patient was continuing his medical treatment. The other patient who developed uveitis was a patient who had frequent uveitis attacks and continued his medical treatment during vaccination. The other patient who developed uveitis and deep vein thrombosis continued his medical treatment during vaccination. The characteristics of patients with exacerbation in the form of organ involvement after COVID-19 vaccine are shown in Table 3.

Compared with side-effects by type of COVID vaccine after the first vaccine dose (104 [61.9%] vs 47 [39.5%], $P<0.001$) and after the second vaccine dose (101 [63.1%] vs 34 [30.1%], $P<0.001$), side-effects were statistically higher in the Pfizer-BioNTech group than in the CoronaVac group. Although side-effects were higher in the Pfizer-BioNTech group between the third doses, statistical significance was not found. There was no difference in BS exacerbation between Pfizer-BioNTech and CoronaVac after first vaccine dose (24 [14.3%] vs 13 [11.0%], $P = 0.417$), after second vaccine dose (31 [19.4%] vs 18 [15.9%], $P = 0.465$), and after the third dose of vaccine (11 [26.2%] vs 5 [20.0%], $P = 0.565$). Side-effects and BS flare according to COVID vaccines are shown in Table 4.

Post-COVID-19 vaccine side-effects were statistically higher in women than in men at the first (83 [63.8%] vs 68 [43.3%], $P = 0.001$) and second (69 [56.6%] vs 66 [43.7%], $P = 0.035$). Similarly, side-effects were seen more frequently in the first and second doses in the mucocutaneous and articular group than in the other organ involvement group. BS exacerbation did not differ between genders and organ involvement groups. BS flare at all doses after COVID-19 vaccine did not differ between genders and between organ involvement groups. Side-effects and disease flare according to gender and organ involvement after COVID-19 vaccine are shown Table 5.

We evaluated and compared BDCAF scores before and at least 1 month after the COVID-19 vaccine. We found an increase in BDCAF scores before and after vaccination in the two doses of CoronaVac (median2 [IQR 1-3] vs 2 [IQR 1-3], $P = 0.001$) and two doses of Pfizer-BioNTech groups (median 2 (IQR 1-3.5) vs 2 [IQR 1-5],

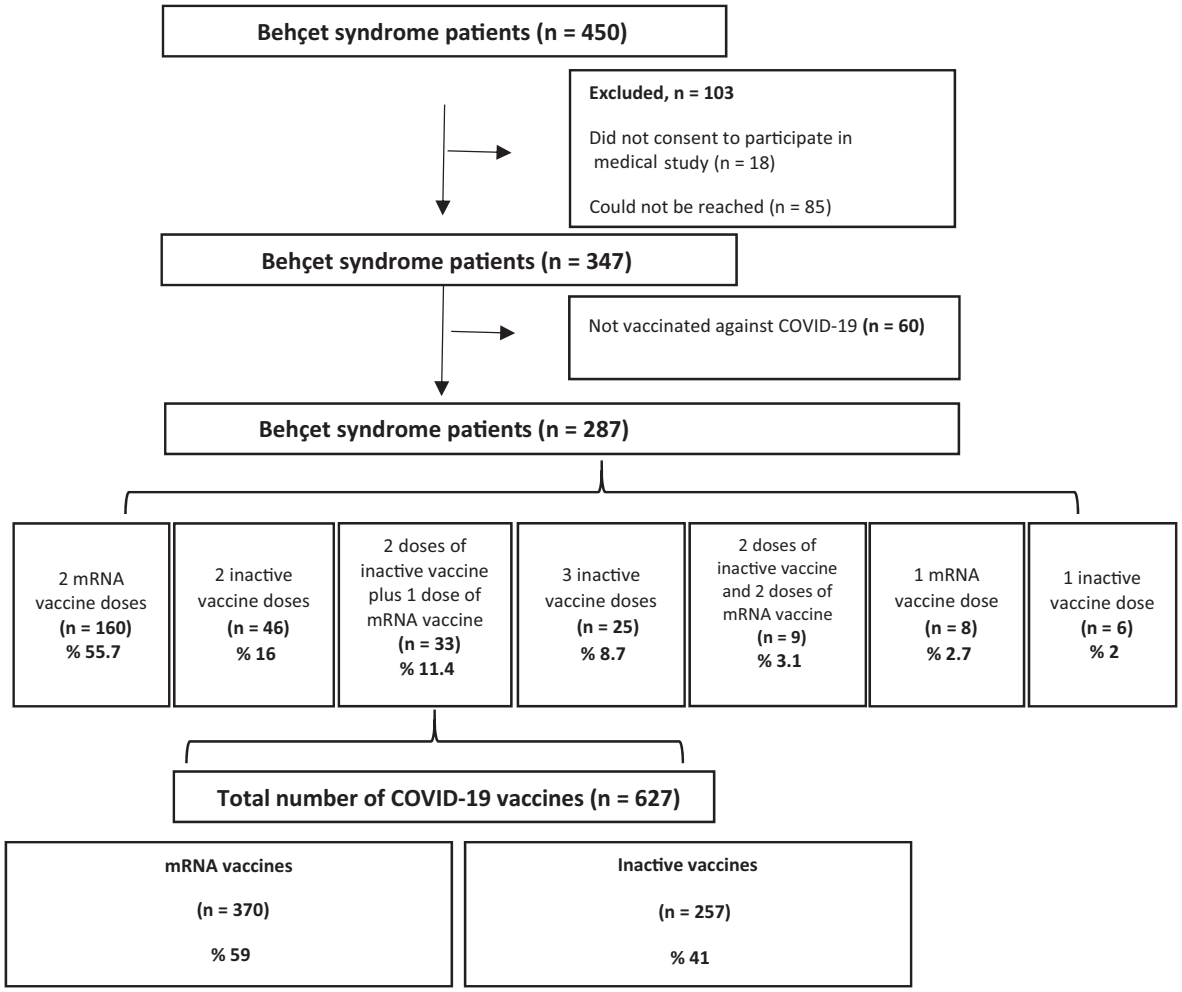

FIGURE 1 Flow chart of the study

$P < 0.001$). A comparison of disease activity scores before COVID-19 vaccination and after COVID-19 vaccination according to COVID-19 vaccine group among BS patients is shown the Supplementary material (Table S1).

4 | DISCUSSION

In this retrospective large cohort study, we studied tolerance and disease flaring after vaccination with the Pfizer-BioNTech (mRNA) and CoronaVac (inactive) COVID-19 vaccines in patients with BS. Our data demonstrated that patients frequently experienced adverse events after vaccination, but these were consistent with expected vaccine reactogenicity, and injection site pain/swelling, fatigue, and arthralgia were the most common events. Women, mucocutaneous-articular subtype, and the Pfizer-BioNTech group had more side-effects at the first and second doses. BS exacerbations were not infrequent, but exacerbations in the form of organ involvement other than mucocutaneous and articular were rare, and we found no difference in BS exacerbations between the inactive and mRNA vaccines.

Vaccinations have been used as an important tool in the fight against infectious diseases for the past two centuries, and they have been successful in improving public health and eradicating or reducing the spread of various diseases around the world.[15] However, adverse reactions may occur following vaccinations, ranging from local to systemic. The two-dose BNT162b2 regimen was found to be 95% effective against COVID-19, with mild to moderate pain at the injection site the most commonly reported local reaction (71% reported pain after first dose; 66% after second dose), with most frequently reported systemic events being fatigue and headache.[1] In the study evaluating the safety and immunogenicity of the inactivated SARS-CoV-2 CoronaVac vaccine in a healthy adult subgroup in Chile; the most frequently reported local side-effects were pain at the injection site, whereas headaches were the most common systemic side-effects. The majority of observed adverse reactions were mild and local.[2] The COVID-19 Global Rheumatology Vaccine Association evaluated 2860 adult patients with systemic rheumatic disease who received the COVID-19 vaccine, and the most frequently reported adverse events after vaccination were fatigue (33.4%), headache (27.7%), muscle/joint pains (22.8%), and fever/chills (19.9%). Among adults with the COVID-19 vaccine, patient-reported adverse events

TABLE 1 Demographics and clinical characteristics of patients with Behçet syndrome who were vaccinated for COVID-19 at baseline (n = 287)

	Patients
Age (years), median (IQR 25-75)	42 (34-50)
Female, n (%)	130 (45.3)
Male, n (%)	157 (54.7)
Active smokers, n (%)	91 (31.7)
Disease duration (months), median (min-max)	120 (1-480)
Comorbidities, n (%)	
Hypertension	63 (22)
Diabetes mellitus	24 (8.4)
Chronic kidney disease	8 (2.8)
Coronary artery disease	21 (7.3)
Chronic liver failure (cirrhosis)	1 (0.3)
COPD	25 (8.7)
Malignancy	9 (3.1)
Prior Behçet's syndrome manifestations, n (%)	
Oral ulcers	283 (98.6)
Genital ulcers	225 (78.4)
Papulopustular eruption	218 (76)
Erythema nodosum	135 (47)
Arthritis	94 (32.8)
Uveitis	130 (45.3)
Neurological	20 (7)
Gastrointestinal	10 (3.5)
Cardiac	5 (1.7)
Thrombosis	89 (31)
Aneurysm	11 (3.8)
Sacroileitis	24 (8.4)
Pathergy positivity	109/253 (43%)
Behçet syndrome subtype, n (%)	
Mucocutaneous and articular (group 1)	112 (39)
Other organ involvement (group 2)	175 (61)
Behçet syndrome treatments, n (%)	
Colchicine	217 (75.6)
Azathioprine	94 (32.8)
Corticosteroid	53 (18.5)
Cyclophosphamide	0
Interferon-α	5 (1.7)
Infliximab	11 (3.8)
Adalimumab	11 (3.8)
Benzathine penicillin	6 (2.1)
Sulfasalazin	14 (4.9)
Acetylsalicylic acid	52 (18.1)
Warfarin	7 (2.4)
Adherence to Behçet syndrome drugs during vaccination,[a] n (%)	265 (92.3)
Vaccine type, n (%)	
Pfizer-BioNTech	379 (59)
CoronaVac	257 (41)

Abbreviations: BS, Behçet syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; max, maximum; min, minimum.

[a]After each vaccination.

were similar to those reported in the general population.[16] The tolerance of the COVID-19 vaccine in 696 patients with systemic lupus erythematosus (SLE) was evaluated by the VACOLUP study. All patients received at least one dose of vaccine and 343 (49%) patients received a second dose; the most common vaccines were Pfizer-BioNTech (399 [57%] participants) followed by CoronaVac (156 [22%] participants). After the first vaccine dosage, 316 patients (45%) experienced side-effects, and 181/343 patients (53%) experienced side-effects after the second vaccine dose.[17] In a multicenter cross-sectional study in Hong Kong, 1367 patients with rheumatic disease were investigated for vaccination rates, reported adverse effects, and patient concerns for the COVID-19 vaccine. Adverse events were reported in 81.1% of patients who received the vaccine, the most common of which were pain or swelling at the injection site (66.3%), fatigue (57.1%), fever (19.9%), and headache (19.6%). Younger age and mRNA vaccinations were related to higher adverse outcomes in the multivariate logistic regression model.[18] It has been reported that women have a stronger immune response to vaccines than men and show more frequent and severe adverse events.[19,20] The most common reaction in BS patients in our cohort was pain/swelling at the injection site. Side-effects were more common in the first and second doses, and were less common after booster doses. Side-effects were more common in the Pfizer-BioNTech vaccine compared with the CoronaVac vaccine, and in women than in men. The COVID-19 vaccine provided a good safety profile in the majority of patients with BS, similar to those reported in the general population, and no serious adverse events were detected in the patients.

There is a potential risk for exacerbation of the patient's underlying inflammatory rheumatic disease following vaccination. Before the COVID-19 pandemic, research published in the UK Clinical Practice Research Database indicated no increased risk of flare in patients with autoimmune inflammatory rheumatic disease who received influenza vaccination.[21] In two prospective studies, disease activity remained stable in patients with systemic rheumatic disease following COVID-19 vaccination.[22,23] At tertiary centers, immune-mediated disease exacerbations or new disease onset within 28 days of SARS-CoV-2 vaccination were assessed. They included 27 cases, 17 flares, and 10 new-onset immune-mediated diseases. Twenty-three of the 27 received BNT-162b2 vaccine, two received mRNA-1273 and two received ChAdOx1 vaccines. Twenty-one (78%) of the 27 had at least one underlying

TABLE 2 Type of side-effects and flare after COVID-19 vaccination

Side-effects	First dose n = 287	Second dose n = 273	Third dose n = 68	Fourth dose n = 10
Side-effects after vaccination, n (%)	151 (52.6)	135 (49.4)	29 (42.6)	3 (30)
Injection site pain/swelling, n (%)	105 (36.5)	87 (31.8)	20 (29.4)	3 (30)
Arthralgia, n (%)	42 (14.6)	44 (16.1)	10 (14.7)	2 (20)
Fatigue, n (%)	57 (19.9)	62 (22.7)	13 (19.1)	3 (30)
Chest pain/discomfort, n (%)	11 (3.8)	6 (2.1)	1 (1.47)	0
Headache, n (%)	26 (9.1)	28 (10.2)	9 (13.2)	0
Dizziness, n (%)	10 (3.5)	7 (2.5)	1 (1.47)	0
Fever, n (%)	13 (4.5)	14 (5.2)	6 (8.82)	0
Nausea-vomiting, n (%)	11 (3.8)	5 (1.8)	5 (7.3)	0
Diarrhea, n (%)	1 (0.3)	0	0	0
Allergic reaction, n (%)	0	1 (0.3)	0	0
Timing of onset of side-effects after vaccination (days), median (IQR)	1 (1-2)	1 (1-2)	1 (1-1)	1 (1-1)
BS flare after vaccination	First dose n = 287	Second dose n = 273	Third dose n = 68	Fourth dose n = 10
BS flare after vaccination, n (%)	151 (52.6)	135 (49.4)	16 (23.5)	3 (30)
Oral ulcers, n (%)	12 (4.1)	18 (6.5)	6 (8.8)	1 (10)
Arthralgia or arthritis, n (%)	33 (11.4)	39 (14.2)	13 (19.1)	3 (30)
Genital ulcers, n (%)	4 (1.39)	7 (2.5)	1 (1.47)	0
Papulopustular eruption, n (%)	13 (4.5)	10 (3.6)	3 (4.4)	1 (10)
Erythema nodosum, n (%)	4 (1.39)	6 (2.1)	1 (1.47)	1 (10)
Thrombosis, n (%)	1 (0.34)	1 (0.36)	0	0
Uveitis, n (%)	2 (0.69)	2 (0.73)	1 (1.47)	0
Neurological, n (%)	0	0	0	0
Gastrointestinal, n (%)	0	0	0	0
Patient discontinued medication during the vaccination, n (%)				22 (7.7)
Colchicine, n (%)				13 (59)
Azathioprine, n (%)				5 (22.7)
Infliximab, n (%)				2 (9.1)
Adalimumab, n (%)				1 (4.5)
Methotrexate, n (%)				1 (4.5)
Use of analgesic or antipyretic medicine, n (%)				89 (31)
Paracetamol, n (%)				61 (68.5)
NSAIDs, n (%),				28 (31.5)
Consequences of BS flare[a]				
Change in BS treatment, n (%)				3/4 (75)
Medical consultation, n (%)				1/4 (25)
Admission to hospital, n (%)				0
COVID-19 after vaccination, n (%)				16/287 (5.6)
BDCAF score before vaccination, median(IQR), min-max				2 (1-3), 0-10
BDCAF score after vaccination, median(IQR), min-max				2 (1-4), 0-11

Abbreviations: BDCAF, Behçet's Disease Current Activity Form; BS, Behçet syndrome; COVID-19, coronavirus disease 2019; IQR, interquartile range; max, maximum; min, minimum; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a]Four patients had BS exacerbation.

autoimmune/rheumatic disease before vaccination. Four attacks occurred after the second dose in patients with exacerbation or activation, and one patient had attacks after both the first and second doses; 20/27 (75%) of cases were mild to moderate.[24] Post-vaccination SLE exacerbation occurred in 21 (3%) patients in the VACOLUP study, with musculoskeletal symptoms (joint, arthritis,

TABLE 3 Characteristics of patients with exacerbation in the form of organ involvement after COVID-19 vaccine

Patient number	Age, Gender Comorbidities	Prior BS manifestations	BS treatment	Adherence to BS drugs during vaccination	Vaccine	BS flare	Comment
1	36 years Male	-Oral and genital ulcers -Pan uveitis	No treatment	-	2 doses of Pfizer-BioNTech	Bilateral anterior uveitis at second dose	The patient, who has been in remission for a long time, develops uveitis 10 days after vaccination, topical treatment is applied.
2	68 years Female	-Oral ulcer -Anterior uveitis	-Azathiopyrin 100 mg/day, methylprednisolone 2 mg/day	Continued	2 doses of CoronaVac *plus* 1 doses of Pfizer-BioNTech	Unilateral anterior uveitis after third dose Pfizer- BioNTech	The patient who has not had a uveitis attack for 1 year, develops a uveitis attack 20 days after the vaccination. The dose of azathioprine is increased from 100 mg/d to 150 mg/d.
3	47 years Female Diabetes mellitus, Hypertension, COPD	-Oral and genital aphthae -Erythema nodosum -Pan uveitis -Deep vein thrombosis	Colchicine 1 mg/d, Azathioprine 100 mg/d	Continued	2 doses of Pfizer-BioNTech	-Oral aphthae, arthralgia/arthritis, bilateral posterior uveitis, deep vein thrombosis after first dose, -Erythema nodosum and deep vein thrombosis after second dose	Intravitreal steroid injection was performed for uveitis. The patient was started on interferon for acute deep vein thrombosis and uveitis, but an allergic reaction developed. The patient was started on infliximab 5 mg/kg at weeks 0, 2, 6, and then every 6 weeks.
4	24 years Male	Oral and genital aphthae -Erythema nodosum, -Arthritis -Uveitis	Colchicine 1,5 mg/d Azathioprine 200 mg/d	Continued	1 dose of CoronaVac	Oral aphthae, arthralgia/arthritis, erythema nodosum, anterior uveitis after the first dose	-A patient with frequent uveitis, -No change in treatment -Local treatment for uveitis.

Abbreviations: BS, Behçet syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019.

TABLE 4 Side-effects and BS flare according to COVID vaccines

Side-effects according to COVID-19 vaccines								
COVID vaccine, n/N	Side-effects after first dose of vaccine, n (%)	*P*	Side-effects after second dose of vaccine, n (%)	*P*	Side-effects after third dose of vaccine, n (%)	*P*	Side-effects after fourth dose of vaccine, n (%)	*P*
CoronaVac	47 (39.5)	<0.001	34 (30.1)	<0.001	9 (36)	0.353	None	--
Pfizer-BioNTech	104 (61.9)		101 (63.1)		20 (47.6)		3 (33.3)	
BS flare according to COVID-19 vaccines								
COVID vaccine, n/N	Flare after first dose of vaccine, n (%)	*P*	Flare after second dose of vaccine, n (%)	*P*	Flare after third dose of vaccine, n (%)	*P*	Flare after fourth dose of vaccine, n (%)	*P*
CoronaVac	13 (11.0)	0.417	18 (15.9)	0.465	5 (20.0)	0.565	None	--
Pfizer-BioNTech	24 (14.3)		31 (19.4)		11 (26.2)		3 (33.3)	

Abbreviations: BS, Behçet syndrome; COVID-19, coronavirus disease 2019; max, maximum; min, minimum; NSAIDs, non-steroidal anti-inflammatory drugs.

arthralgia, or myalgia) the most common exacerbations (19/21; 90%). Change in SLE treatment due to SLE exacerbation was observed in 15 of the 21 (71%) patients, medical consultation in all 21 (100%), and hospitalization in four (19%) patients.[17] Uveitis may develop after application of the COVID-19 vaccine. In a study evaluating uveitis and other ocular complications after COVID-19 vaccine, 42 eyes of 34 patients were included. Among the reported cases, there were two retinal vasculitis and one bilateral pan uveitis in new-onset Behçet's disease.[10] In our study, 151 (52.6%) of 287 patients reported BS exacerbation after the first vaccine dose, and 135 (47%) after the second vaccine dose. Mucocutaneous and articular manifestations such as arthralgia or arthritis, oral ulcers, papulopustular eruption and erythema nodosum accounted for the majority of exacerbations. Exacerbations in the form of organ involvement other than mucocutaneous and articular constituted 1.3% of the whole cohort (uveitis in four and thrombosis in one). Although changes were made in the BS treatment of three patients as a result of the BS flare, no patient required hospitalization. There was no difference in exacerbations between Pfizer-BioNTech and CoronaVac vaccines.

Behçet syndrome is unique among vasculitides because it mostly affects veins and probably causes inflammation of the vein wall itself.[5] According to Mehta et al., the pathophysiology of thrombosis in COVID-19 patients is comparable to that in BS patients.[25] In the background of thromboses in BS, inflammation-induced thrombosis, rather than a hypercoagulable condition, appears to play a prominent role. Direct viral effects, sepsis-induced hyperinflammation, high D-dimer levels, and a variety of other variables can all contribute to coagulopathy in COVID-19.[26] Immunosuppression is a significant key strategy for the therapy of vascular involvements in this situation.[27] We previously described COVID-19 outcomes and BS exacerbations due to COVID-19 in our BS cohort;[28] 32.2% of patients complained of exacerbation of at least one BD-related symptom, the most common being arthralgia/arthritis and oral ulcers. Thrombosis was seen in only 2 (10.5%) patients. In this study, thrombosis was seen in only one patient after COVID-19 vaccine, and this may indicate that COVID-19 vaccines do not increase the risk of thrombosis in BS patients relative to COVID-19 infection.

Patients with inflammatory rheumatism are more susceptible to viral infections than the general population.[29] There is a potential risk for exacerbation of the patient's underlying inflammatory rheumatic disease following vaccination. The American College of Rheumatology recommends that patients with rheumatic and musculoskeletal diseases be vaccinated against COVID-19.[29] BS is a disease characterized by exacerbations and spontaneous remissions.[30] Mucocutaneous and joint involvement reduces the quality of life and does not cause permanent damage.[30] On the other hand, major organ involvement causes morbidity or mortality in patients and requires immunosuppressive treatment.[31] Common exacerbations seen in this patient group after COVID-19 vaccine are mucocutaneous and articular manifestations and can also be seen in the natural course of the disease. Exacerbations in the form of organ

TABLE 5 Side-effects and disease flare according to gender and organ involvement after COVID-19 vaccine

	Female n (%)	Male n (%)	*P* value[a]	Mucocutaneous and articular involvement (Group 1) n (%)	Other organ involvement (Group 2) n (%)	*P* value[a]
Side-effects after first vaccine dose	83 (63.8)	68 (43.3)	**0.001***	74 (66.1)	77 (44)	**<0.001***
Side-effects after second vaccine dose	69 (56.6)	66 (43.7)	**0.035***	65 (60.2)	70 (42.4)	**0.004***
Side-effects after third vaccine dose	12 (48)	17 (39.5)	0.496*	6 (42.9)	23 (42.6)	0.986*
Side-effects after fourth vaccine dose	2 (66.7)	1 (14.3)	0.183**	1 (50)	2 (25)	1.000**
BS flare after first vaccine dose	22 (16.9)	15 (9.6)	0.067*	16 (14.4)	21 (12)	0.553*
BS flare after second vaccine dose	28 (23)	21 (13.9)	0.053*	22 (20.4)	27 (16.4)	0.399*
BS flare after third vaccine dose	5 (17.9)	11 (26.2)	0.416*	3 (18.8)	13 (24.1)	0.748**
BS flare after fourth vaccine dose	2 (66.7)	1 (16.7)	0.226**	1 (50)	2 (28.6)	1.000**

Abbreviations: BS, Behçet syndrome; COVID-19, coronavirus disease 2019.

[a]Statistical tests were: *Pearson χ^2; **Fisher's exact test.

involvement other than mucocutaneous and articular were rare after vaccination, and in the BS patient group, COVID-19 vaccination also outweighs its potential risks.

There are some strengths and limitations in this study. The major strength of our study is that it is the first large-scale study of the safety of COVID-19 vaccines in patients with BS and includes inactivated and mRNA vaccines and booster doses. The major limitation of this study is the lack of a control group. Another important limitation of our study is the self-reported and subjective nature of the results. We tried to reduce this by asking patients to report only medically confirmed exacerbations, and we confirmed this clinically and radiologically in patients with exacerbations with organ involvement other than mucocutaneous and articular. As a result of the heterogeneities of each vaccination patient group (due to cross-vaccination) it is difficult to isolate the vaccine side-effect. Another important limitation is that it is difficult to distinguish whether some symptoms, such as arthralgia and thrombosis, are associated with a BS exacerbation or the COVID-19 vaccine. To avoid this conflict as much as we can, we evaluated the COVID-19 post-vaccine BDCAF at least 1 month after the COVID-19 vaccine. Finally, the BDCAF questionnaire was completed via telephone interviews in patients with BS, which may lead to an over- or underestimation of BDCAF scores due to lack of physical examination in some patients.

In conclusion, our study demonstrates that the COVID-19 vaccines are well tolerated in patients with BS and more side-effects develop after mRNA vaccines. Regardless of the vaccine type, exacerbations after the COVID-19 vaccine are common, predominantly mucocutaneous and articular involvement, and exacerbations in the form of other organ involvement are rare. Therefore, these data may be crucial for increasing SARS-CoV-2 vaccine coverage in patients with BS.

AUTHOR CONTRIBUTIONS

All authors provided final approval of the manuscript and revised it critically. Concept and design were by AE and HA; AE, BA, HA, and SCG supervised the study. HA, AE, SCG, BA, HEK, BP, YA, MK, AO, and OK contributed to materials, data collection and/or processing, analysis and/or interpretation, literature review, writing and the critical review.

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ORCID

Hakan Apaydin https://orcid.org/0000-0001-7219-1457
Abdulsamet Erden https://orcid.org/0000-0002-8084-2018
Serdar Can Güven https://orcid.org/0000-0003-1965-9756
Berkan Armağan https://orcid.org/0000-0003-4409-059X
Hatice Ecem Konak https://orcid.org/0000-0002-9218-8965
Bünyamin Polat https://orcid.org/0000-0003-4972-8142
Yağnur Afşin https://orcid.org/0000-0003-3444-4892
Merve Kaygisiz https://orcid.org/0000-0001-7391-5541
Ahmet Omma https://orcid.org/0000-0003-2582-7445
Orhan Kucuksahin https://orcid.org/0000-0003-4530-2304

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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