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Safety of SARS-CoV-2 vaccination in patients with Behcet's syndrome and familial Mediterranean fever: a cross-sectional comparative study on the effects of M-RNA based and inactivated vaccine

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Abstract

Most of the published data relate to classical forms of rheumatic diseases (RD) and information on rare inflammatory disorders such as Behçet's syndrome (BS) and familial Mediterranean fever (FMF) is limited. We studied the frequency of side effects and disease flares after COVID-19 vaccination with either Pfizer/BioNTech or Sinovac/CoronaVac in 256 patients with BS, 247 with FMF, and 601 with RD. Telephone interviews were conducted using a questionnaire survey in a cross-sectional design in patients with BS, FMF, and RD followed by a single university hospital. Study participants were vaccinated either with CoronaVac (BS:109, FMF: 90, and RD: 343,) or BioNTech (BS: 147, FMF: 157 and RD: 258). The majority have received double dose (BS: 94.9%, FMF 92.3% and RD: 86.2%). BioNTech ensured a significantly better efficacy than CoronaVac against COVID-19 in all patient groups (BS: 1.4% vs 10.1%; FMF: 3.2% vs 12.2%, RD:2.7% vs 6.4%). Those with at least one adverse event (AE) were significantly more frequent among those vaccinated with BioNTech than those with CoronaVac (BS: 86.4% vs 45%; FMF: 83.4% vs 53.3%; and RD: 83.3% vs 45.5%). The majority of AEs were mild to moderate and transient and this was true for either vaccine. There were also AEs that required medical attention in all study groups following CoronaVac (BS: 5.5%, FMF: 3.3%, and RD:2.9%) or BioNTech (BS: 5.4%, FMF: 1.9%, and RD: 4.7%). The main causes for medical assistance were disease flare and cardiovascular events. Patients with BS (16.0%) and FMF (17.4%) were found to flare significantly more frequently when compared to those with RD (6.0%) ($p < 0.001$). This was true for either vaccine. BS patients reported mainly skin-mucosa lesions; there were however, 11 (4.3%) who developed major organ attack such as uveitis, thrombosis or stroke. Flare in FMF patients were associated mainly with acute serositis with or without fever. Arthralgia/arthritis or inflammatory back pain were observed mainly in the RD group. Our study demonstrates that BS and FMF patients vaccinated with either CoronaVac or BioNTech demonstrated similar AE profile and frequency compared to RD patients. AEs that required physician consultation or hospitalization occurred in all study groups after either CoronaVac or BioNTech. Increased frequency of flares in BS and FMF compared to that seen in RD might reflect defects in innate immunity and deserves further investigation. Caution should be required when monitoring these patients after vaccination.

Keywords COVID-19 · Vaccination · Side effects · Flares · Behçet's syndrome · Familial Mediterranean fever

Introduction

Since it first emerged in December 2019, the COVID-19 pandemic has affected at least 445 million people and resulted in a death toll surpassing 5.9 million worldwide [1]. There have been 14,352,997 confirmed cases and 95,549 deaths in Turkey, as of 8 March 2022 [2]. The clinical manifestations of SARS-Cov-2 infection may vary, ranging from being asymptomatic to respiratory failure with acute respiratory

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distress syndrome [3]. A high tendency for venous thrombosis and pulmonary embolism is also included in the clinical spectrum and contributes to the increased mortality rate [3]. Besides the considerably high morbidity and mortality burden, the COVID-19 pandemic had severe consequences on the global economy, environment, public health and social life [4].

Multiple potential vaccines against COVID-19 have been developed swiftly [5] and as shown in several phase 3 clinical trials, they demonstrated considerable efficacy without an unusual safety signal in healthy individuals [6–9]. Local and systemic adverse effects such as pain at injection site, fatigue, headache, myalgia, arthralgia and fever were observed however these effects were mostly mild to moderate and transient resolving within a few days after vaccination. Consequently, large scale administration of the vaccines was launched as of December 2020. Thereafter, some rare adverse events (AEs) such as Guillain–Barre syndrome, myocarditis and unusual thrombotic events, which may be clinically significant appeared [10–12].

As the mass vaccination is still ongoing, more information is being gathered about the efficacy and safety of these vaccines. It has been found that immunocompromised patients often fail to show an adequate response to a primary series of COVID-19 vaccine, as reflected by lower protective immune response rates compared with healthy individuals [13, 14]. Therefore, very recently, WHO recommended an additional dose for all COVID-19 vaccines in immunocompromised persons [15]

Whether patients with rheumatic diseases (RD) would have different side effects or would experience exacerbations following vaccination were other issues of concern. Our previous study has revealed that the acceptance rate of vaccination against COVID-19 among patients with RD was indeed low [16]. Only 29.2% were willing to be vaccinated, 19.0% were unwilling and 51.8% were undecided [16]. Several observational studies reported that the incidence and profile of adverse events of these vaccines in this patient population have been similar to the general population and severe AEs have been rarely observed [17–25]. On the other hand, post-vaccination flares in several patients with RD as well as new-onset RD in previously healthy individuals have been documented in a number of case series and registries [26–30]. It has to be noted that, most of the published data relate with classical forms of RD, and there is limited information with rare inflammatory disorders such as Behçet's syndrome (BS) and familial Mediterranean fever (FMF). BS, a complex inflammatory disorder of unknown etiology, is characterized by recurrent skin mucosa lesions and uveitis, but may also involve joints, vascular, gastrointestinal, and central nervous systems. FMF is an autoinflammatory hereditary disease characterized by recurrent attacks of fever and serositis. Both BS and FMF are among the most prevalent RD in Turkey, whereas considered to be rare in most parts of the world.

In this study, we aimed to evaluate vaccine reactivity and disease flare following vaccination with either Sinovac/CoronaVac or Pfizer/BioNTech among BS and FMF patients compared with patients with various diagnosis of RD. Our secondary objective was to compare two vaccines with regard to safety issues. As an exploratory outcome, we also compared the incidence of cases diagnosed with COVID-19 following vaccination.

Patients and methods

This was a cross-sectional observational study. We studied 1500 patients who were seen consecutively between January 1, 2021 and March 31, 2021 at the rheumatology outpatient clinic of Cerrahpasa Medical Faculty of Istanbul University-C. Only those patients who received at least one single shot of either CoronaVac or BioNTech against COVID-19 were included in the study. We tried to contact all of these patients consecutively by telephone and attempted to make interviews with the eligible ones. To be able to assess side effects and disease flares properly we planned to evaluate study participants after at least 4 weeks of the last dose of vaccination. A total of 396 (26.4%) patients were excluded because either a. they were unable to be reached, b. they have not been vaccinated, and c. they declined to participate in the study.

Telephone survey

During telephone interviews we used a standardized questionnaire which included questions about socio-demographic variables (age, gender, educational status), disease duration, currently used immunosuppressive drugs, previous diagnosis with a comorbid disease (such as cardiovascular disease, chronic lung disease, hypertension, diabetes mellitus, or else), information about vaccination (type, dose, date), COVID-19 diagnosis before or after vaccination, side effects due to vaccination and exacerbations of the inherent rheumatic disease that occurred after vaccination. The list of the side effects was structured according to the information obtained from the previously reported COVID-19 vaccine clinical trials [6, 8, 9]. It included local reactions, arm pain, headache, fever, allergic reaction, back pain or myalgia, joint pain, coughing, loss of appetite, nausea/vomiting, diarrhea, fatigue/weakness, lymph node swelling, thromboembolic event/myocardial infarction/stroke/transient ischemic attack, outpatient visit/emergency room admission/hospitalization, or any other miscellaneous complaints. The questionnaire also sought whether patients have temporarily discontinued taking drugs or decreased the dose

of their immunosuppressives. Further information on clinical characteristics were collected from patients' charts, when required.

We first tested the questionnaire on 14 patients to check its usability and to see whether there are unnecessary or complicated questions. After these pre-test evaluations, we were able to proceed with the survey. We started to make telephone calls by June 1, 2021. We ended data collection at November 10, 2021. The questionnaire survey took in average 5–10 min to complete.

Adverse events following immunization were based as defined by the WHO [31] 'any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. It may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease'. Disease flares were identified as attack if confirmed by one of us or by the physician who follow the patient or by the patient's description and/or requiring intensification of medical treatment. In this study, we considered only those AEs and disease exacerbation that developed within the 4 weeks after the last dose of the vaccine (either first or second dose or both). We did not analyze the side effects or flares associated with the third dose of vaccination because of the low number of patients in each group (BS: $n=6$, FMF: $n=11$ and RD: $n=58$). All AEs and disease flares that developed after vaccination were evaluated separately for those who were vaccinated either with CoronaVac or BioNTech.

Vaccination program in Turkey

The vaccination campaign in Turkey started first with healthcare workers and then continued with the elderly on January 14, 2021. As of April 2, 2021, the country entered the second stage of campaign beginning immunizations for immunocompromised individuals as well as individuals aged 60 and above and other prioritized groups. CoronaVac was the first available vaccine in Turkey for the first 14 weeks, until 2 April, when BioNTech vaccine was started to be administered. After that date, both types of vaccines were made available by online selection option. Second dose of either vaccine was done 28 days after the first inoculation. In Turkey, as a rule, the first two doses had to be the same vaccine such as CoronaVac-CoronaVac or BioNTech- BioNTech. By July 1st, "booster" vaccines, or third doses were started to be given to healthcare workers and elderly and to other prioritized groups. Booster vaccines were scheduled 6 months after the second dose. Through the whole vaccination rollout, vaccine administration was kept optional and volunteers were asked to sign a consent form before the inoculation. We, in our university hospital, recommended complete vaccination with either inactivated or mRNA-based vaccine to all our patients according to the latest ACR guidelines [32].

Statistical analysis

Descriptive data are presented as mean and standard deviations (SD) for continuous variable and frequencies and percentages (%) for categorical variables. Categorical data were compared using Pearson's Chi-square test and Fisher exact test. Continuous variables were evaluated for normality distribution using Shapiro–Wilk test. Kruskall Wallis test was used to examine differences between groups for continuous variables. Age and gender adjusted univariate logistic regression models were fit to examine whether BS or FMF patients had increased risk for having AEs or disease flares compared to patients with RD. Next, we wanted to find parameters that could be associated independently with having AE or disease flare when all data were pooled. Eight probable variables (type of vaccine, group, being < 40 years of age, gender, education, having any comorbidity, using immunosuppressive treatment, previous diagnosis with COVID-19) that could induce AEs or disease flare were defined. We used first, univariate analysis to investigate whether these variables were associated with the occurrence of any AEs or disease flares (no vs yes). Those variables which were found statistically significant were included in the multivariate logistic regression analysis with Enter method. Odds ratio (OR) and their 95% confidence intervals (CI) were presented. All significant tests were two-tailed, and values of $p<0.05$ were considered statistically significant. All statistical analyzes were performed by SPSS software version 21 (Chicago, IL).

Ethical statement

This study was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpaşa Medical Faculty (12/10/2020-134022) and by the Ministry of Health (2020-08-18T15_54_13). All of the participants were informed about the objectives of the study and oral consent was obtained at the beginning of each telephone interview.

Results

Description of patient groups

We studied three groups of patients:

Patients with BS ($n=256$; 159 M/97 F)

All patients fulfilled international study group criteria for BS [33]. Nineteen (11 M/8 F) had solo skin-mucosa involvement while the remaining 237 (92.6%) had one or more organ involvement such as eye ($n=137$, 53.5%), vascular ($n=82$, 32.0%), central nervous system ($n=22$, 8.6%), joint

($n=114$, 44.5%) or gastrointestinal involvement ($n=11$, 4.3%).

Patients with FMF ($n=247$; 101 M/146 F)

All patients fulfilled Tel-Hashomer criteria [34]. Information about MEFV mutations was available in 239 patients (96.8%). Of these, 196 (82.0%) had exon 10 mutations on at least 1 allele, 32 (13.4%) had exon 2 mutations on at least 1 allele and 11 (4.6%) had no defined mutation.

Patients with RD (other than BS and FMF) ($n=601$; 172 M/429 F)

The group included patients with rheumatoid arthritis (RA) ($n=150$), systemic lupus erythematosus (SLE) ($n=88$), primary Sjögren syndrome (pSS) ($n=36$), systemic sclerosis (SSc) ($n=43$), mixed connective tissue disease ($n=5$), dermatomyositis ($n=3$); ankylosing spondylitis (AS) ($n=160$), psoriatic arthritis (PsA) ($n=28$), Takayasu arteritis (TAK) ($n=71$), giant cell arteritis (GCA) ($n=6$) and ANCA associated vasculitis ($n=6$), retroperitoneal fibrosis ($n=3$), primary CNS vasculitis ($n=2$).

Demographic and clinical characteristics (Table 1)

While patients with FMF were the youngest those with RD were the oldest (Table 1). BS patients were more likely to be male, in contrast to the remaining groups. About third in BS and FMF groups had at least one comorbid disease, while this was more than half in the RD group. The rate of COVID-19 prior to vaccination was similar between patients with BS, FMF and RD. A total of 215 (84.0%) patients with BS, 244 (98.8%) with FMF and 556 (92.5%) with RD were using one or more immunosuppressive/immunomodulator drug, while the remaining were off treatment for at least 1 year. BS patients were using mostly colchicine, conventional DMARDs, and anti-TNF agents; whereas FMF patients, colchicine and anti-IL 1 agents. On the other hand, conventional DMARDs, glucocorticoids, anti-TNF agents and hydroxychloroquine

Table 1 Demographic and clinical characteristics of patient groups

	Behçet's syndrome, $n=256$	Familial Mediterranean fever, $n=247$	Rheumatic diseases, $n=601$
Females, *n* (%)*	97 (37.9)	146 (59.1)	429 (71.4)
Age, mean ± SD, years*	43.21 ± 10.13	40.03 ± 10.33	49.33 ± 12.13
Disease duration, mean ± SD, years*	16.62 ± 8.78	17.10 ± 10.23	10.32 ± 7.65
Education (high-school or higher), *n* (%)*	133 (52.0)	145 (58.7)	305 (50.7)
Comorbid disease (at least one), *n* (%)*	79 (30.9)	73 (29.6)	328 (54.6)
History of COVID-19 infection prior to vaccination, *n* (%)	41 (16.0)	43 (17.4)	92 (15.3)
Drugs, *n* (%)			
Currently using any immunosuppressive drug or glucocorticoid*	215 (84.0)	244 (98.8)	556 (92.5)
Biological agents*	57 (22.3)	63 (25.5)	263 (43.8)
Anti-TNF*	56 (21.9)	8 (3.2)	182 (30.3)
Anti-CD 20*	0	0	47 (7.8)
Anti-IL 1*	0	53 (21.5)	1(0.2)
Other biologicals*	1 (0.4)	2 (1.2)	33 (5.5)
Conventional DMARDs*	115 (44.9)	4 (1.6)	263 (43.8)
Glucocorticoids*	36 (14.1)	2 (0.8)	227 (37.8)
Colchicine*	125 (48.8)	233 (94.3)	16 (2.7)
Hydroxychloroquine*	0	0	173 (28.8)
Off treatment, *n* (%)*	41 (16.0)	3 (1.2)	45 (7.5)
Temporarily stopped treatment or made dose reduction, *n* (%)*	9 (3.5)	11 (4.5)	73 (12.1)

There were significant differences between the study groups with regard to gender ratio, mean age, mean disease duration, educational level, the frequency of having comorbid diseases and immunosuppressive treatment regimens

DMARD disease modifying anti-rheumatic drugs, *IL* interleukin, *TNF* tumor necrosis factor

Significance level between the study groups: *$p<0.001$

were mostly prescribed drugs in the RD group. At the time of vaccination, 3.5%, 4.5% and 12.1% in BS, FMF and RD, respectively, temporarily stopped their immunosuppressives or made some dose reductions.

Vaccine types and doses (Table 2)

As shown in Table 2, 109 patients with BS, 90 with FMF, and 343 with RD were vaccinated with CoronaVac, whereas 147 patients with BS, 157 with FMF, and 258 with RD were vaccinated with BioNTech. BioNTech was the most preferred vaccine among patients with BS and FMF, whereas CoronaVac was mostly used among patients with RD. A great majority in our study population (BS: 94.9%, FMF: 92.3% and RD: 86.2%) had received double doses of vaccines while the remaining (BS: 5.1%, FMF: 7.7% and RD: 13.8%) had only one shot. Additionally, a small percentage received the booster dose (BS: 2.3%, FMF: 4.4% and RD: 9.7%).

BS, FMF and RD groups were balanced with regard to post-vaccine COVID-19 infection for either CoronaVac (BS: 10.1%, FMF: 12.2% and RD: 6.4%) or BioNTech (BS: 1.4%, FMF: 3.2% and RD: 2.7%). Among BS patients, the rate of post-vaccine COVID-19 was significantly lower among those who chose BioNTech (1.4%) compared to CoronaVac (10.1%), ($p < 0.01$). This was also true for patients with FMF (3.2%, vs 12.2%, $p < 0.01$) and RD (2.7% vs 6.4%, $p = 0.036$).

AEs after CoronaVac (Tables 3, 4)

A total of 49 (45.0%) patients with BS, 48 (53.3%) patients with FMF, and 156 (45.5%) with RD had at least one AE after CoronaVac ($p = 0.381$) (Table 3). The most common AE was arm pain followed by fatigue/weakness, headache and back pain/myalgia. The majority of the AEs were mild/moderate and transient. The frequency of side effects appeared to be statistically similar between the study groups. Similarly, age and gender adjusted logistic regression analysis revealed that patients with BS and FMF had no increased risk of having side effect compared to patients with RD (Table 4).

A total of six (5.5%) patients with BS, three (3.3%) patients with FMF, and ten (2.9%) patients with RD reported AEs that required medical attendance such as outpatient visit, emergency unit admittance or hospitalization. These were due to deep vein thrombosis (BS: $n = 2$), uveitis (BS: $n = 3$), severe headache associated with parenchymal CNS attack (BS: $n = 1$), acute peritonitis attack (FMF: $n = 1$), acute myocardial infarction that required coronary angiography (FMF: $n = 1$), exacerbation of pre-existing heart failure (FMF: $n = 1$), acute ischemic stroke (RA: $n = 1$), arthritis (RA $n = 2$), vertigo (SLE $n = 1$, RA $n = 1$), exacerbations of digital ulcers (SSc: $n = 1$), severe COVID-19 infection that required 17 days of hospitalization (SSc: $n = 1$), gastrointestinal bleeding (pSS: $n = 1$; primary CNS vasculitis: $n = 1$) and Bell's palsy (GCA: $n = 1$).

AEs after BioNTech (Tables 3, 4)

As shown in Table 3, the frequency of individuals with at least one AE after vaccination with BioNTech was found to be similar between the study groups (BS: 86.4%, FMF: 83.4%, and RD: 83.3%; $p = 0.689$). This was also confirmed in the age and gender adjusted univariate logistic regression analysis (Table 4). The most common AEs were arm pain, fatigue/weakness, headache, back pain/myalgia and joint pain (Table 3). The majority of the AEs were mild/moderate and transient. As shown in the age and gender adjusted univariate logistic regression analysis, patients with BS were found to be more likely to have fatigue/weakness (OR 1.832; 95% CI 1.161–2.891, $p = 0.009$) and headache (OR 4.394, 95% CI 2.553–7.562, $p < 0.001$), compared to patients with

Table 2 Information about vaccination in the study groups

	Behçet's syndrome, $n = 256$	Familial Mediterranean fever, $n = 247$	Rheumatic diseases, $n = 601$	p
Vaccine type, n (%)				< 0.001
CoronaVac	109 (42.6)	90 (36.4)	343 (57.1)	
BioNTech	147 (57.4)	157 (63.6)	258 (42.9)	
Vaccine dose, n (%)				< 0.001
Single shot	13 (5.1)	19 (7.7)	83 (13.8)	
Double shots	243 (94.9)	228 (92.3)	518 (86.2)	
Days passed since last dose, mean ± SD, years	87.10 ± 43.82	80.22 ± 49.75	77.38 ± 44.74	< 0.001
Post-vaccine COVID-19, n (%)				
CoronaVac	11 (10.1)	11 (12.2)	22 (6.4)	0.140
BioNTech	2 (1.4)	5 (3.2)	7 (2.7)	0.566

Table 3 Side effects and flares after vaccination with either CoronaVac or BioNTech

	CoronaVac				BioNTech			
	BS, $n=109$	FMF, $n=90$	RD, $n=343$	p	BS, $n=147$	FMF, $n=157$	RD, $n=258$	p
Any side effect, *n* (%)	49 (45.0)	48 (53.3)	156 (45.5)	0.381	127 (86.4)	131 (83.4)	215 (83.3)	0.689
Arm pain, *n* (%)	29 (26.6)	29 (32.2)	95 (27.7)	0.638	106 (72.1)	119 (75.8)	185 (71.7)	0.638
Fatigue/weakness *n* (%)	14 (12.8)	12 (13.3)	49 (14.3)	0.920	55 (37.4)	53 (33.8)	71 (27.5)	0.101
Headache, *n* (%)	11 (10.1)	10 (11.1)	29 (8.5)	0.697	49 (33.3)	25 (15.9)	39 (15.1)	<0.001
Back pain or myalgia, *n* (%)	3 (2.8)	3 (3.3)	13 (3.8)	0.872	21 (14.3)	22 (14.0)	30 (11.6)	0.675
Joint pain, *n* (%)	3 (2.8)	3 (3.3)	12 (3.5)	0.931	15 (10.2)	25 (15.9)	19 (7.4)	0.022
Fever, *n* (%)	7 (6.4)	5 (5.6)	11 (3.2)	0.278	27 (18.4)	31 (19.7)	35 (13.6)	0.204
Nausea/vomiting, *n* (%)	6 (5.5)	3 (3.3)	11 (3.2)	0.531	12 (8.2)	11 (7.0)	23 (8.9)	0.789
Diarrhea, *n* (%)	2 (1.8)	2 (2.2)	3 (0.9)	0.514	8 (5.4)	8 (5.1)	9 (3.5)	0.590
Loss of appetite, *n* (%)	0	1 (1.1)	3 (0.9)	0.586	4 (2.7)	12 (7.6)	20 (7.8)	0.105
Cough, *n* (%)	0	0	2 (0.6)	0.559	4 (2.7)	3 (1.9)	3 (1.2)	0.516
Allergic reaction, *n* (%)	2 (1.8)	0	4 (1.2)	0.462	5 (3.4)	2 (1.3)	0	0.012
Local reaction (swelling or redness), *n* (%)	2 (1.8)	0	9 (2.6)	0.287	8 (5.4)	10 (6.4)	20 (7.8)	0.655
Lymph node swelling, *n* (%)	0	0	2 (0.6)	0.559	2 (1.4)	5 (3.2)	4 (1.6)	0.421
Somnolence, *n* (%)	0	0	2 (0.6)	0.559	5 (3.4)	0	2 (0.8)	0.018
Vertigo, *n* (%)	0	1 (1.1)	6 (1.7)	0.366	1 (0.7)	1 (0.6)	3 (1.2)	0.817
Any cardiovascular complaints[a], *n* (%)	3 (2.8)	1 (1.1)	6 (1.7)	0.677	1 (0.7)	4 (2.5)	7 (2.7)	0.363
Miscellaneous complaints[b, c], *n* (%)	1 (0.9)	2 (2.2)	5 (1.5)	0.749	7 (4.8)	2 (1.3)	9 (3.5)	0.212
AE requiring medical attendance, *n* (%)	6 (5.5)	3 (3.3)	10 (2.9)	0.439	8 (5.4)	3 (1.9)	12 (4.7)	0.248
Any thromboembolic/cardiovascular AE, *n* (%)	2 (1.8)	2 (2.2)	1 (0.3)	0.126	4 (2.7)	3 (1.9)	3 (1.2)	0.516
Diseases flares, *n* (%)	12 (11.0)	22 (24.4)	18 (5.2)	<0.001	29 (19.7)	21 (13.4)	18 (7.0)	0.001

BS Behçet's syndrome, *FMF* Familial Mediterranean fever, *RD* rheumatic diseases, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *AS* ankylosing spondylitis, *TAK* Takayasu arteritis

[a]Dyspnea, chest pain, palpitations, hypertension

[b]Miscellaneous complaints after vaccination with CoronaVac are defined as cyanotic changes in hands and toes (RA: $n=1$), onset of eczema (RA: $n=1$), allergic rhinitis (RA: $n=1$), paresthesia (SLE: $n=1$), uneasiness (AS: $n=1$), dryness in the mouth (BS: $n=1$), attention deficit (FMF: $n=1$) and flu like symptoms (FMF: $n=1$)

[c]Miscellaneous complaints after vaccination with BioNTech are defined as abdominal pain (RA: $n=1$, SLE: $n=1$), flu like symptoms (BS: $n=1$, FMF: $n=1$, RA: $n=1$), paresthesia (BS: $n=1$, RA: $n=1$), cyanotic changes in hands and foot (FMF: $n=1$, TAK: $n=1$), blurry vision (SLE: $n=1$), pain and burning sensation in the eye (SLE: $n=1$), anosmia (BS: $n=1$, AS: $n=1$), temporary amnesia (BS: $n=1$), tinnitus (BS: $n=1$), dysuria (BS: $n=1$), temporary sensation loss (BS: $n=1$), herpes labialis (TAK, $n=1$)

RD (Table 4). Patients with FMF were more likely to have joint pain compared to patients with RD (OR 2.954, 95% CI 1.506–5.793, $p=0.002$). Both BS (OR 1.922, 95% CI 1.071–3.449, $p=0.029$) and FMF patients (OR 1.923, 95% CI 1.093–3.383) were found to have increased risk for fever compared to patients with RD. Besides that, no particular trend was observed across the study groups.

A total of 8 (5.4%) patients with BS, 3 (1.9%) patients with FMF, and 12 (4.7%) patients with RD reported adverse events that required medical help. These were due to acute ischemic stroke that required 22 days of hospitalization (BS: $n=1$), lower extremity deep vein thrombosis (BS $n=3$), uveitis (BS $n=2$), peritonitis with arthritis (BS $n=1$), epididymitis (BS $n=1$), dyspnea and hypertension (FMF: $n=1$), nausea, vomiting, abdominal pain and diarrhea (FMF: $n=1$), hazy vision (FMF: $n=1$), myocardial infarction (AS: $n=1$ and TAK: $n=1$), stroke (TAK: $n=1$), severe COVID-19 like symptoms (SLE $n=1$ and SSc $n=1$), arthritis (RA: $n=2$), inflammatory back pain (AS: $n=1$), exacerbation of Raynaud phenomenon (SSc $n=1$), severe vomiting (AS: $n=1$), emergence of small vessel vasculitis (AS: $n=1$), vertigo and dizziness (TAK: $n=1$).

Among all patients, BioNTech was found to cause significantly more side effects compared to CoronaVac. These were especially true for local reaction, arm pain, headache, fever, back pain/myalgia, joint pain, fatigue/weakness, cough, loss of appetite, diarrhea, nausea/vomiting, and lymph node swelling.

Table 4 Age and gender adjusted univariate logistic regression analysis for side effects and disease flares (patients with rheumatic diseases were considered as the reference category)

	CoronoVac		BioNTech	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Any side effect				
Behçet's syndrome	1.014 (0.630–1.634)	0.953	1.357 (0.741–2.488	0.323
Familial Mediterranean fever	1.057 (0.634–1.764)	0.831	0.831 (0.471–1.466)	0.522
Arm pain				
Behçet's syndrome	0.948 (0.561–1.60)	0.841	1.012 (0.626–1.635)	0.962
Familial Mediterranean fever	0.960 (0.558–1.653)	0.884	0.986 (0.608–1.600)	0.956
Fatigue/weakness				
Behçet's syndrome	0.897 (0.454–1.769)	0.753	1.832 (1.161–2.891)	0.009
Familial Mediterranean fever	0.684 (0.331–1.414)	0.306	1.459 (0.928–2.293)	1.459
Headache				
Behçet's syndrome	1.487 (0.684–3.232)	0.317	4.394 (2.553–7.562)	<0.001
Familial Mediterranean fever	1.309 (0.582–2.946)	0.515	1.215 (0.681–2.168)	0.509
Back pain or myalgia				
Behçet's syndrome	0.818 (0.216–3.106)	0.768	1.749 (0.923–3.313)	0.087
Familial Mediterranean fever	0.835 (0.218–3.208)	0.793	1.600 (0.855–2.995)	0.141
Joint pain				
Behçet's syndrome	0.556 (0.145–2.135)	0.393	1.784 (0.846–3.760)	0.128
Familial Mediterranean fever	0.552 (0.143–2.136)	0.390	2.954 (1.506–5.793)	0.002
Fever				
Behçet's syndrome	2.702 (0.956–7.637)	0.061	1.922 (1.071–3.449)	0.029
Familial Mediterranean fever	1.939 (0.610–6.166)	0.262	1.923 (1.093–3.383)	0.023
Nausea/vomiting				
Behçet's syndrome	1.653 (0.556–4.912)	0.366	1.375 (0.632–2.993)	0.422
Familial Mediterranean fever	0.878 (0.225–3.431)	0.852	0.974 (0.443–2.140)	0.947
Diarrhea				
Behçet's syndrome	2.314 (0.320–14.233)	0.434	2.055 (0.736–5.739)	0.169
Familial Mediterranean fever	2.032 (0.297–13.885)	0.470	1.698 (0.611–4.721)	0.310
Loss of appetite				
Behçet's syndrome	NA	NA	0.557 (0.180–1.728)	0.311
Familial Mediterranean fever			1.296 (0.584–2.878)	0.524
Cough				
Behçet's syndrome	NA	NA	2.400 (0.493–11.695)	0.279
Familial Mediterranean fever			1.744 (0.324–9.383)	0.517
Allergic reaction				
Behçet's syndrome	NA	NA	NA	NA
Familial Mediterranean fever				
Local reaction				
Behçet's syndrome	NA	NA	0.958 (0.393–2.331)	0.924
Familial Mediterranean fever			0.997 (0.436–2.282)	0.955
Lymph node swelling				
Behçet's syndrome	NA	NA	1.611 (0.282–9.792)	0.575
Familial Mediterranean fever			2.859 (0.695–11.764)	0.146
Vertigo				
Behçet's syndrome	NA	NA	0.696 (0.067–7.256)	0.762
Familial Mediterranean fever			0.452 (0.043–4.741)	0.508
Any cardiovascular complaints				
Behçet's syndrome	1.642 (0.358–7.527)	0.523	0.300 (0.035–2.570)	0.272
Familial Mediterranean fever	0.722 (0.079–6.641)	0.774	0.976 (0.263–3.626)	0.971
Miscellaneous complaints, *n* (%)				
Behçet's syndrome	0.814 (0.088–7.518)	0.856	2.550 (0.855–7.608)	0.093
Familial Mediterranean fever	1.489 (0.254–8.748)	0.659	0.489 (0.100–2.402)	0.379

Table 4 (continued)

	CoronoVac		BioNTech	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
AEs requiring medical attendance				
Behçet's syndrome	2.110 (0.694–6.418)	0.188	1.369 (0.514–3.650)	0.530
Familial Mediterranean fever	1.160 (0.291–4.622)	0.834	0.490 (0.131–1.832)	0.289
Thromboembolic/cardiovascular events				
Behçet's syndrome	6.758 (0.539–84.654)	0.138	2.198 (0.451–10.705)	0.330
Familial Mediterranean fever	7.810 (0.602–101.252)	0.116	1.836 (0.341–9.897)	0.480
Disease flares				
Behçet's syndrome	3.428 (0.790–14.872)	0.100	9.286 (2.399–35.946)	0.001
Familial Mediterranean fever	7.830 (2.252–27.223)	0.001	4.673 (1.258–17.362)	0.021

NA: not applicable due to zero or low number of values

Disease flares and their clinical description (Tables 3, 4, 5)

As shown in Table 3, disease flares after vaccination were significantly more frequent among BS and FMF patients compared to patients with RD among those vaccinated either with CoronaVac (BS: 11.0%, FMF: 24.4% and RD: 5.2%, $p<0.001$) or BioNTech (BS: 19.7%, FMF: 13.4% and RD: 7.0%, $p=0.001$). These were also confirmed in the age and gender adjusted logistic regression analysis (Table 4). The frequency of those with flare was similar among those who temporarily stopped taking drugs compared to those who continued to use (data not shown). Flares of the underlying disease was the cause of AEs that required medical help in 57.1% (24/42) in all patient groups when CoronaVac (BS: $n=6$, FMF: $n=1$ and RD: $n=3$) and BioNTech (BS: $n=7$, FMF $n=1$, RD: $n=6$) were combined.

Table 5 enlists clinical description of the flares in patient groups. BS patients reported mainly skin-mucosa lesions such as oral ulcers ($n=24$; 9.4%), papulo-pustular lesions ($n=11$; 4.3%), erythema nodosum ($n=5$; 1.9%) and genital ulcers ($n=3$; 1.1%). There were also patients who reported

Table 5 Clinical description of the flares among patients with Behçet's syndrome, familial Mediterranean fever and rheumatic diseases after vaccination with CoronaVac and BioNTech

CoronaVac		
Behçet's syndrome, $n=12$ (11.0%)	Familial Mediterranean fever, $n=22$ (24.4%)	Rheumatic diseases, $n=18$ (5.2%)
Oral ulcers ($n=5$) Erythema nodosum ($n=3$) Papulopustular lesion ($n=1$) Uveitis ($n=3$) Upper extremity deep vein thrombosis ($n=1$) Lower extremity deep vein thrombosis ($n=1$) CNS parenchymal attack ($n=1$)	Fever, peritonitis with or without diarrhea ($n=13$) Peritonitis and pleuritis ($n=3$) Pleuritis alone ($n=2$) Fever attack with increased acute phase reactants ($n=4$) Pain or swelling in the joints ($n=3$)	Pain or swelling in the joints (RA: $n=6$, AS: $n=3$, SSc: $n=1$, GCA: $n=1$) Inflammatory back pain and stiffness (AS: $n=4$) Psoriasis (PsA: $n=1$) Digital ulcer (SSc: $n=1$) Shoulder pain and stiffness (GCA-PMR: $n=1$)
BioNTech		
Behçet's syndrome, $n=29$ (19.7%)	Familial Mediterranean fever, $n=21$ (13.4%)	Rheumatic diseases, $n=18$ (7.0%)
Oral ulcers ($n=19$) Genital ulcers ($n=3$) Erythema nodosum ($n=2$) Uveitis ($n=2$) Papulopustular lesion ($n=10$) Lower extremity deep vein thrombosis ($n=3$) Epididymitis ($n=1$) Bouts of hemoptysis ($n=1$) Pain or swelling in the joints ($n=7$) Peritonitis attack due to concomitantly present FMF ($n=1$)	Fever, peritonitis with or without diarrhea ($n=8$) Peritonitis and pleuritis ($n=5$) Pleuritis alone ($n=2$) Fever attack with increased acute phase reactants ($n=6$) Pain or swelling in the joints ($n=7$) Development of hidradenitis suppurativa lesions ($n=1$)	Pain or swelling in the joints (RA: $n=5$, SSc: $n=1$, pSA: $n=3$) Myastenia gravis ($n=1$) Raynaud and digital ulcers (SSc: $n=1$) Inflammatory back pain (AS: $n=6$, pSA: $n=1$) Emergence of small vessel vasculitis (AS: $n=1$) Stroke (TAK: $n=1$) Myocardial ischemia (TAK: $n=1$)

RA rheumatoid arthritis, *BS* Behçet's syndrome, *PsA* psoriasis, *FMF* familial Mediterranean fever, *CNS* central nervous system, *GCA* giant cell arteritis, *PMR* polymyalgia rheumatica, *pSA* psoriatic arthritis, *SSc* systemic sclerosis, *TAK* Takayasu arteritis

joint symptoms ($n=7$; 2.7%), uveitis ($n=5$; 1.9%), deep vein thrombosis ($n=5$; 1.9%) epididymitis ($n=1$) and parenchymal CNS attack ($n=1$). Acute peritonitis and arthritis developed in one patient who had been diagnosed with both BS and FMF. The patient who developed CNS attack had been diagnosed with BS 20 years ago due to recurrent skin-mucosa lesions, uveitis, arthritis and CNS parenchymal disease. She was quiescent for BS for about 15 years, however was using azathioprine 150 mg/day. After 6 days of the second dose of CoronaVac, she developed multiple erythema nodosum lesions and severe persistent headache. She was hospitalized for 24 days. Her cranial MRI disclosed acute brain stem lesion (Fig. 1).

FMF patients reported mainly peritonitis ($n=29$, 11.7%), pleuritis ($n=12$, 4.9%), fever attack alone ($n=10$, 4.0%) and arthritis ($n=10$, 4.0%). Each patient described the attack as typical for their disease. Hidradenitis suppurativa lesions along with peritonitis attack developed in one patient who had both diseases. The flare rate was similar between those with exon 10 mutations (17.9%), exon 2 mutations (18.8%) and no definite mutations (18.2%), $p=0.992$). On the other hand, those who were using anti-IL 1 were found to be more likely to experience FMF flare than those who were not (34.0% vs 12.9%, $p<0.001$). It was noted that flares were significantly more frequent among those vaccinated with CoronaVac rather than BioNTech (Tables 3, 4).

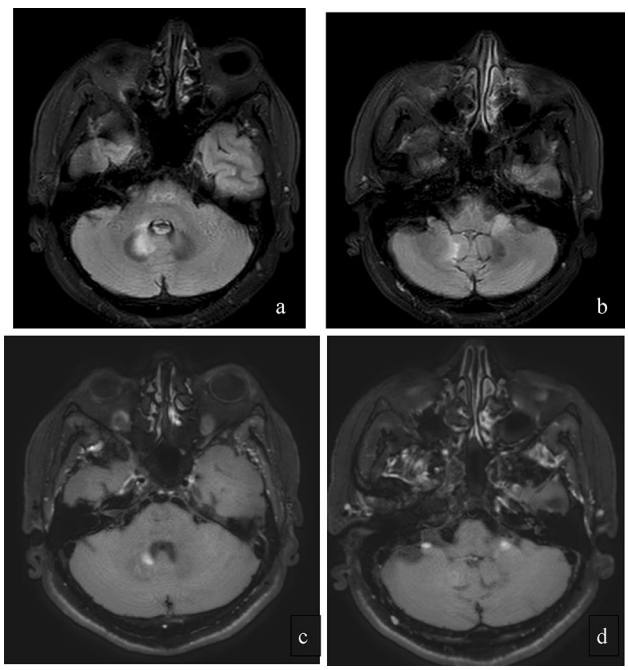


Fig. 1 **a**, **b** Cranial MRI images showing T2-FLAIR hyperintense lesions on both right (extending from superior cerebellar peduncle to middle superior cerebellar peduncle) and left middle cerebellar peduncle. **c**, **d** Diffuse contrast enhancement can be seen in the images taken after IV contrast infusion

Patients with RD reported mainly pain or swelling in the joints ($n=20$, 3.3%) and inflammatory back pain ($n=11$, 1.8%). Myastenia gravis exacerbated in one patient with RA. Raynaud and digital ulcers flared in two patients with SSc. Psoriasis erupted in one PsA patient previously in remission. One patient, previously in remission for GCA and PMR developed shoulder pain and stiffness similar to that she had experienced at the onset of the disease. One patient with TAK with previous stroke history underwent another stroke. Another patient with TAK who had previously coronary artery involvement, underwent an acute myocardial infarction that required coronary angiography and stent insertion.

One patient with AS who was switched to secukinumab recently developed constitutional symptoms, high acute phase response, multiple digital necrosis (Fig. 2) and proteinuria after 1 week of the second dose of BioNTech. He was hospitalized for 2 weeks and was found to have Ig A nephritis in the renal biopsy. He was treated with pulses of methyl prednisolone and monthly cyclophosphamide.

Variables associated with AE and disease flare (multiple regression analysis)

Using BioNTech (OR 6.22, CI 95%: 4.62–8.39; $p<0.001$), being female (OR 2.07, CI 95% 1.53–2.80; $p<0.001$), and being < 40 years of age (OR 2.54, CI 95% 1.82–3.56; $p<0.001$) were found to be independently associated with having any AE when all groups were pooled for multiple regression analysis. On the other hand, independent



Fig. 2 Digital necrotic lesions on the tip of the fingers

correlates for disease flare were experiencing any AE (OR 2.60, CI 95% 1.53–4.43; $p < 0.001$) and being diagnosed as BS (compared to RD) (OR 3.14, CI 95% 1.92–5.63; $p < 0.001$) or FMF (compared to RD) (OR 3.21, CI 95% 1.95–5.30; $p < 0.001$). Being female or young (< 40 years of age) or using BioNTech were not found to be associated with being more prone to have disease flares.

The AEs and flares occurred either after the first dose or the second or after both shots with similar frequency across the study groups without any statistical difference (data not shown). This was also true for both CoronaVac and BioNTech.

Discussion

In this study, BS and FMF patients vaccinated with either CoronaVac or BioNTech demonstrated almost similar AE profile and frequency compared to RD patients. BioNTech caused significantly more AEs than CoronaVac, however, ensured a significantly better efficacy against COVID-19. Most of the AEs were mild to moderate and of short duration. On the other hand, there have been AEs that required medical attendance in all study groups, after either CoronaVac or BioNTech. BS (3.14 times) and FMF patients (3.21 times) were more likely to have disease flares compared to patients with RD irrespective of age, gender and type of vaccine.

While most of the exacerbations in BS were manifested as skin-mucosa lesions, there were also deep vein thrombosis, uveitis and parenchymal CNS lesion. Case reports and surveillance reports indicating new onset BS cases or flares in quiescent disease after vaccination are in line with our observations [29, 30, 35, 36]. One retrospective study reported uveitis and several other ocular complications including scleritis, retinal vasculitis and retinal vein occlusions in 34 patients after COVID-19 vaccinations [30]. Authors described a new onset BS with panuveitis, retinal vasculitis, papillary oedema, and deep vein thrombosis [30]. The exact mechanism underlying this phenomenon is unknown. Infectious agents such as herpes simplex virus or bacteria belonging to Streptococcus species have long been proposed as triggering factors in BS development [37]. Skin hypersensitivity and the induction of systemic symptoms in response to streptococcal antigens, as well as significant inflammatory reactions to polysaccharide pneumococcal vaccine in BS are well known [38–41]. Moreover, we observed very recently that 36 of 214 (16.8%) patients with BS experienced a flare during COVID-19 infection [42].

FMF patients similar to those with BS experienced significantly more flares than RD patients. Interestingly, this was more common after CoronaVac than BioNTech. Exacerbations were not found to be associated with carrying exon 10 mutations or not. However, those who were using IL-1 were more inclined to have post-vaccine flare than those who were not, suggesting a relation between disease severity and exacerbation. In line with our findings, a very recent study done among young adults with diverse RD found that 15 of 123 patients with FMF had typical peritonitis attack after mRNA vaccine [43]. Another recent survey done in 175 patients with autoinflammatory diseases reported that single dose of COVID-19 vaccine was generally well tolerated with no serious outcome and about 20% AEs were consistent with a flare of the underlying disease [44].

We found that those who were experiencing any AE were found to be more prone for getting disease flare. This information may help us in being more prudent and cautious in the follow-up of these patients. Although the flare rate was high in BS and FMF, a great majority consisted of mild and self-remitting exacerbations such as recurrent skin-mucosa lesions in BS and peritonitis in FMF. Hence, most attacks were quite easy to manage and recovered without leaving any sequalae.

We observed post vaccination disease flare among patients with RD as well (6.0%). Although their numbers were lower than that observed in BS (16.0%) and FMF (17.4%), some exacerbations such as ischemic cardiovascular events in patients with large vessel vasculitis and a new onset IgA vasculitis in a patient with AS who was treated with secukinumab were considerably significant. While the latter phenomenon could be also associated with recently started secukinumab use as previously reported [45], the role of the vaccine in exacerbating inflammation could not be ignored. The low rate of disease flares in RD was consistent with other publications [17–25]. It has been also suggested that the underlying risk of flare may differ among RD [17].

Exact mechanisms behind post-vaccine flare of underlying inflammatory disease are not clear. Several steps in the immune system mechanisms, including molecular mimicry or reaction to adjuvants that are used to boost immune reactivity may be responsible [29]. The aberrant innate immune system activation which is thought to play role in the pathogenesis of both BS and FMF [46] might perhaps explain why these patients are more prone to exacerbate after immunization.

The profile and the frequency of AEs observed among patients with BS and FMF were not much different from that observed among patients with diverse RD. This was especially true for those vaccinated with CoronaVac. After BioNTech, however, a few AEs such as headache, fatigue/weakness and fever appeared to occur more frequently in BS and FMF when compared to RD. This could be possibly related with the much younger age of the BS and FMF patients compared to RD patients. It was also reassuring that the majority of AEs were mild to moderate and transient. On the other hand, the rate of AEs that necessitated

medical assistance (3.8% of all patients) was found slightly higher in the current study than previously reported [17–24]. Despite the dominance of BioNTech on the mild to moderate AEs, the AEs requiring medical help were similarly distributed between CoronaVac (patients: 3.5%) and BioNTech (patients: 4.3%). While several studies found no serious AEs at all, one 'physician-reported registry' including 5121 participants with inflammatory and non-inflammatory RD, reported that 2.9% of all patients had AEs of special interest [17]. It has to be noted that, in our study, disease flares were responsible of the 57.1% of the serious AEs. In the remaining patients, we observed clinically significant AEs such as Bell's palsy, acute myocardial infarction, acute ischemic stroke, lymphadenopathy and gastrointestinal bleeding [47–52]. These adverse reactions should be taken into caution with their background rates to assess the causality [53].

As found in the multiple logistic regression analysis, being young and female along with using BioNTech rather than CoronaVac were independently associated with having AEs. This was documented in several randomized controlled studies and in real world data [6, 8, 54–56]. In line with our findings, as reported in several studies, vaccines that use mRNA technology were found to be more effective in preventing symptomatic COVID-19 cases and were associated with more adverse events compared to viral vector, protein subunit and inactive vaccines [57].

We observed that the temporary discontinuation of the immunosuppressive drugs before vaccination was low, in line with the published literature [15]. This shows our patients' compliance with our warnings and suggestions and also is reassuring for preventing further possible exacerbation. The current attitude was quite different than what we had observed at the onset of the pandemic [58]. Among 750 patients with RD 123 (16.4%) had decreased or skipped their drugs while 45 (6.0%) had completely stopped taking them [58].

This study has several limitations including the cross-sectional questionnaire-based design, and descriptive statistical analysis. As our survey was voluntary, selection bias could not be ruled out and the information obtained might not be generalized. Self-reports of the study participants could be subject to recall bias. Most of the side effects reported have not been confirmed by a physician. There is a possibility that particularly mild effects might not have been reported. We did not assess the disease activity of the patients at the time of the study entry. We were not able to evaluate the disease activity during the pre-vaccination period either. Self-remitting attacks are common and the main characteristic in both BS and FMF and some of the RD as well. Therefore, it is difficult to make causal inferences particularly for the post-vaccine exacerbations. Patients were not matched by age and gender. Furthermore, the questionnaire we used was not validated nor approved by an authority.

The study has also strengths. We were able to compare two vaccines in terms of efficacy, safety and flare of the underlying disease. Study groups had large number of participants. Most importantly, we made telephone interviews which has comparable quality with face-to-face interviews. The interviews were made by physicians which enabled us to get efficient and accurate information. Finally, the period between the last vaccine dose and the interview date was long enough to be able to see long-term adverse events.

Conclusions

The AEs after the BioNTech and CoronaVac vaccines that were identified in patients with BS and FMF were not different than that observed among patients with RD. BioNTech was more effective than CoronaVac in preventing infection, however was associated with more side effects. It was reassuring to see that the majority of the AEs were mild to moderate and transient. AEs that required medical assistance was not frequent, which was similarly comforting. Yet, some of the AEs such as Bell's palsy, stroke and myocardial infarction were clinically significant. Exacerbations were mostly mild and self-remitting and particularly common among BS and FMF patients. Increased frequency of flares in BS and FMF might reflect defects in innate immunity and deserves further investigation. Our results should be interpreted with caution and causality cannot be demonstrated due to the inherent inflammatory potential of the underlying diseases. Finally, it would be prudent to monitor these patients for a period of time after receiving their vaccine doses.

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Data availability statement The data that support the findings of this study are available on request from the corresponding author [ES]. The data are not publicly available due to [restrictions, their containing information that could compromise the privacy of research participants].

Declarations

Conflict of interest Ayse Ozdede, Sabriye Guner, Guzin Ozcifci, Berna Yurttas, Zeynep Toker Dincer, Zeynep Atli, Ugur Uygunoglu, Eser Durmaz, Didar Ucar, Sabahattin Saip, and Vedat Hamuryudan declare that they have no conflict of interest. Serdal Ugurlu has received honoraria, consulting or speaker fees from Novartis, Pfizer, Lilly and

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