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Original article

Safety of the BNT162b2 mRNA COVID-19 vaccine in patients with familial Mediterranean fever

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Abstract

Objectives. Evidence suggests a possible association between the COVID-19 vaccine and autoimmune disease flares or new onset of various autoinflammatory manifestations, such as pericarditis and myocarditis. The objective of this study was to assess the safety of an mRNA-based BNT162b2 anti-COVID-19 vaccine in individuals with FMF, a prototypic autoinflammatory disease.

Methods. Patients participating in this study fulfilled the criteria for diagnosis of FMF, were older than 18 years and received at least one dose of the vaccine. Data on baseline characteristics, features of FMF, post-vaccination side effects, and disease flares were acquired using electronic medical files and telephone interviews.

Results. A total of 273 FMF patients were recruited for the study. >95% were vaccinated with two doses of the vaccine. The rates of local reactions following the first and second vaccine doses were 65.5% and 60%, respectively, and 26% and 50.4%, respectively, for systemic adverse events. These rates are lower than those reported for the general population from real-world and clinical trial settings. Postvaccination FMF activity remained stable in most patients. None of the patients reported an attack of pericarditis or myocarditis, considered the most serious vaccine-associated adverse events. Patients with a more active FMF disease and patients harboring the M694V mutation had a significantly higher rate of post-vaccination systemic side effects and attacks.

Conclusion. The BNT162b2 mRNA COVID-19 vaccine is safe in patients with FMF. Our results support the administration of this vaccine to FMF patients according to guidelines applicable to the general population.

Key words: FMF, COVID-19, vaccine, mRNA

CLINICAL SCIENCE

Rheumatology key messages

- The BNT162b2 mRNA COVID-19 vaccine is safe for FMF patients.
- The rate of side-effects is lower compared to data from the general population.
- Postvaccination disease activity remained stable in most patients.

Introduction

FMF is the most common hereditary autoinflammatory disease, affecting an estimated population of 150000 individuals worldwide [1], mostly located in the Mediterranean basin. The pathogenesis of FMF is associated with mutations in the Mediterranean fever (MEFV) gene leading to a mutant pyrin protein. These mutations activate certain innate immune sensors, such as Toll-like receptors (TLRs) [2–4], culminating in the activation of the inflammasome complex, overproduction of interleukin (IL)-1β, and spontaneous bursts of systemic inflammation. These autoinflammatory attacks manifest mainly

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by fever, serositis (i.e. pericarditis, etc.) and elevation of acute phase reactants [5].

The ongoing coronavirus disease 2019 (COVID-19) pandemic is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, there is not a consistently applied and accepted treatment for individuals infected with the virus, and vaccination is the most effective tool to prevent infections and control the pandemic. Most anti-COVID-19 vaccines are based on a relatively new mRNA technology composed of nucleic acids and liposomes that activate innate immune receptors (including TLRs), potentially triggering autoinflammation [6, 7]. Indeed, continuous vaccine monitoring data suggest a possible association between anti-COVID 19 vaccinations and flares or new onset of various immune and autoinflammatory manifestations including fever, myocarditis and pericarditis, which are also part of the spectrum of FMF attacks [8–11].

Naturally, these autoinflammatory-like side effects raise concerns regarding the safety of mRNA-based vaccines in individuals with autoinflammatory diseases, where the vaccine might trigger attacks or result in an increased rate of side effects. Additionally, patients with systemic rheumatic diseases often hesitate to be vaccinated against COVID-19 because of the fear of side effects including disease flares [12, 13]. The objective of this study was to assess the safety of mRNA-based anti-COVID-19 vaccines in individuals with FMF, a prototypic autoinflammatory disease.

Methods

Study design and population

By the end of March 2021, more than half of Israel's population (~5 million people) were vaccinated with two doses of the mRNA-based BNT162b2 vaccine (Pfizer–BioNTech), administered 3 weeks apart [14]. For the present retrospective study, individuals with FMF were selected randomly from a cohort of patients followed regularly at the Israeli National Center for FMF at the Sheba Medical Center, Tel-HaShomer. A total of 1,136 electronic files of patients with a presumed diagnosis of FMF were screened. In total, 478 patients fulfilled the clinical criteria for the diagnosis of FMF, were 18 years of age or older, had records of consistent yearly medical follow-up, and no record of additional rheumatic diseases. Of these, 273 patients with at least one dose of the anti-COVID-19 vaccine consented to participate in the study and provided written informed consent. The study was approved by the IRB of the Sheba Medical Center.

Baseline characteristics of the participants, including sex, age, age at FMF diagnosis and type of MEFV mutation were retrieved from the electronic medical records. All participants underwent a telephone interview to acquire the data on FMF parameters, postvaccination disease flares and side effects occurring within 1 month of vaccination. In addition to unsolicited self-reported adverse events, participants were asked about the occurrence of specific post-vaccination adverse events, such as the need for medical attention due to flares and changes in disease management.

Study variables

Compliance with colchicine treatment was defined as very high (skipping up to 1 day of treatment per month), high (skipping up to 2 days of treatment per month) and partial (skipping 3 or more days of treatment per month). Post-vaccination FMF flares were differentiated from vaccine side effects by the timing of the symptoms (i.e. fever occurring within 3 days of the vaccine was regarded as a side effect and not as an FMF attack) and by the patient's identification of symptoms as related to an FMF attack or other causes.

Statistical analysis

Results are presented as mean (± S.D.) and proportions, as appropriate. Differences between proportions were evaluated using the z-test or χ^2 depending on the sample size. All *P*-values are two-sided with a statistical significance set at $P < 0.05$.

Results

Of the 273 individuals included in the study, >95% were vaccinated with two doses of the mRNA-based BNT162b2 vaccine, and 4.7% ($N = 13$) were vaccinated with only one vaccine dose. Participants with only one dose had contracted SARS-CoV-2 infection before the administration of the first vaccine and were following the Israeli Ministry of Health guidelines for people who had been infected with COVID-19 to receive only one dose.

The baseline characteristics of the patients are shown in Table 1. The mean age of the participants was 41 ± 15.5 years and >93% were regularly treated with colchicine. ~8% of the patients were colchicine-resistant and were treated with an IL-1 blocking agent (canakinumab) in addition to colchicine.

The rates of different mutations in the MEFV gene are shown in Table 2. Most patients carried the M694V mutation in one or two copies of their gene, which is the most prevalent mutation in the original cohort of patients. ~7% of the patients had no identified mutation, probably due to the limited genetic testing used in Israel which assesses only 5–14 of the most common mutations. ~13% of the patients did not undergo genetic testing, mostly due to a lack of compliance, but nonetheless had an unequivocal clinical diagnosis of FMF.

Local reactions

Local reactions within seven days of the first and second vaccine doses are shown in Table 3. Pain at the injection site was the most common reaction, reported by >60% of the patients, followed by swelling and erythema. The rates of local reactions were comparable

Table 1 Baseline characteristics of study participants

	n (%)
Total number of patients	273
Age (years) (S.D.)	41 (15.5)
Female	149 (54.5)
Patients vaccinated with 2 doses	260 (95.2)
Patients vaccinated with 1 dose	13 (4.8)
Colchicine treatment	255 (93)
Low dose (0.5–1 mg/day)	101 (39.6)
Moderate dose (1.5–2 mg/day)	117 (45.8)
High dose (>2 mg/day)	37 (14.6)
Mean colchicine dose (mg/day) (± S.D.)	1.48 ± 0.77
Patients treated with colchicine + canakinumab	23 (8)
Compliance with colchicine therapy	
Very high	166 (65.1)
High	52 (20.4)
Partial	37 (14.5)
Number of FMF attacks during the year before the vaccination	
0	124 (45.4)
1–6	90 (33)
≥7	59 (21.6)
Number of FMF attacks during the month before the vaccination	
0	206 (75.5)
1	31 (11.3)
≥2	36 (13.2)

Table 2 Distribution of mutations in the FMF gene

Genotypes	Number of patients *n* (%)
M694V homozygous	78 (28.6)
M694V heterozygous	60 (22)
M694V compound heterozygous	49 (18)
Other mutations	30 (11)
No mutations	20 (7.3)
Unknown mutation	36 (13.1)

Table 3 Local reactions within 7 days of vaccination

Symptom	First dose (*n* = 273)	Second dose (*n* = 260)	*P*-value
	n (%)	*n* (%)	
Any local reaction	179 (65.5)	156 (60)	0.18
Pain at injection site	179 (65.5)	156 (60)	0.18
Swelling	15 (5.49)	15 (5.77)	0.89
Erythema	8 (2.93)	7 (2.69)	0.86
Itching	1 (0.37)	2 (0.77)	N/A
Hematoma	3 (1.1)	2 (0.77)	N/A

between the first and second vaccine doses. Most reactions were mild to moderate in severity.

Systemic adverse effects

Systemic adverse events occurring within 7 days of receiving the vaccination were significantly more common after the second dose than after the first dose (50.4% *vs* 26%, respectively, $P < 0.05$), with fatigue (38% *vs* 18%, $P < 0.05$), muscle pain (27% *vs* 12%, $P < 0.05$) and fever (17% *vs* 8%, $P < 0.05$) being the most common events (Table 4). All reactions generally resolved within 2 days of onset. No cases of pericarditis or myocarditis were reported.

FMF attacks

Altogether, 68 patients reported an FMF attack in the first month post-vaccination. There was no significant difference in the rate of attacks following the first and second doses of vaccination (19% *vs* 19.2%, respectively). Thirty-four patients (12%) experienced attacks after both doses of the vaccine. Most patients (65%) reported more than one site of attack following vaccination. The rates of the different subtypes of FMF attacks are listed in Table 5. The most frequent sites of attacks were the abdomen and joints, which are generally the most common sites of FMF attacks. Fever usually accompanied abdominal and pleuritic attacks, but there were no attacks of fever alone. No pericarditis attacks were reported. Among the patients who experienced attacks, eight sought medical evaluation in the emergency department. Of these, six were hospitalized. Seven patients required an increase in their regular colchicine dose following the post-vaccination attack.

Subgroup analysis

We assessed the rate of adverse events (local and systemic) and post-vaccination attacks according to treatment with colchicine alone, treatment with colchicine + canakinumab, dosage of colchicine, MEFV genotype and the number of attacks during the year and the month prior to the vaccine. As we did not have data on disease activity scores, we used the yearly attack rate as a surrogate parameter. We used the attack rate in the month before vaccination to assess the correlation between disease activity prior to vaccination with post-vaccination activity and safety outcomes. The results are listed in Table 6. The incidence of post-vaccination attacks was significantly higher in patients treated with canakinumab and colchicine than in those treated with colchicine alone, patients treated with higher doses of colchicine compared with patients treated with lower doses, and in patients who had a higher rate of attacks in the month and the year prior to vaccination compared with patients with a low rate of attacks.

The rate of local and systemic side effects post-vaccination was higher in patients carrying the M694V mutation (in one or two copies of their gene) compared

Table 4 Systemic adverse events within 7 days of vaccination

Symptom	First dose ($n = 273$)	Second dose ($n = 260$)	*P*-value
	n (%)	*n* (%)	
Any systemic symptom	71 (26)	131 (50.4)	**<0.05**
Fatigue	50 (18)	100 (38)	**<0.05**
Myalgia	32 (12)	70 (27)	**<0.05**
Fever	22 (8)	44 (17)	**<0.05**
Chills	17 (6)	24 (9)	0.19
Headache	26 (9)	40 (15)	**<0.05**
Arthralgia	10 (4)	16 (6)	0.18
Vomiting	10 (4)	9 (3)	0.9
Diarrhea	3 (1)	4 (2)	N/A
Abdominal pain	7 (3)	11 (4)	0.28
Chest pain	4 (2)	6 (2)	N/A

Bold type signify that there is statistical significance as opposed to the non bold rows.

Table 5 Subtypes of FMF attacks within 1 month of vaccination

Type of attack	($n = 68$)
	n (%)
Abdomen	43 (63.24)
Joints	46 (67.65)
Pleurisy	15 (22.06)
Erysipelas-like erythema	3 (4.41)
Pericarditis	0 0
Fever	0 0

with patients with other mutations or patients with no mutations. In patients who had the most active disease (seven or more attacks per year), the rate of systemic adverse events was significantly higher than that in patients without attacks.

Discussion

This study aimed to assess the safety of an mRNA-based BNT162b2 anti-COVID-19 vaccine in individuals with FMF, a prototypic autoinflammatory disease. Overall, our results show that the vaccine is safe for FMF patients. Data on the safety of COVID-19 vaccine in patients with autoimmune inflammatory diseases have been published [15–17] but contain a mix of autoimmune diseases rather than focusing solely on FMF or another autoinflammatory disease. To the best of our knowledge, this is the first report on the safety of the COVID-19 vaccine in FMF patients.

The reported rates of local reactions following the first and second vaccine doses in our study cohort (65.5% and 60%, respectively) and systemic adverse events (26% and 50.4%, respectively) were lower than those reported for the general population in real-world and clinical trial settings [18–19]. In the Center for Disease Control (CDC) surveillance system, the rate of local reactions following the first and second BNT162b2 vaccines were 65% and 68.6% and 48% and 64.2%, respectively, for systemic side effects [18]. The lower rate of side effects reported in our study may be attributed to the use of different populations, study designs and data acquisition methods.

It is worth noting that almost all patients in the present study were treated with colchicine regularly at the time of vaccination. This raises the question of whether colchicine, which is an inhibitor of the innate immune system through various sites of action, has a general effect of reducing the rate of post-vaccination side effects. To date, no data on the effect of colchicine on vaccine reaction have been reported, and further studies are needed to assess its association with side effects in the general population after vaccines for COVID-19 and other diseases.

The rate of local reactions in the study cohort was similar between the first and second doses of the vaccine, while the rate of systemic adverse events increased significantly after the second dose. These findings are in line with the data reported in the general population, showing an increase in the rate of systemic but not local side effects after the second COVID-19 vaccine dose [18].

None of the patients in our study reported pericarditis or myocarditis events, which are part of the autoinflammatory manifestations of FMF and are considered among the most serious COVID-19 vaccine-associated adverse events. In the general population, the reported incidence of post-COVID-19 vaccine pericarditis or myocarditis is very low (2.13 per 100 000 persons for myocarditis) [20–22], therefore a much larger cohort of FMF patients is needed to assess the susceptibility of FMF patients to this adverse event.

The rate of FMF attacks in the month post-vaccination was ∼19% after each dose. Although we

Table 6 Adverse events according to subgroup

Subgroup	Local adverse events *n* (%)	*P*-value	Systemic adverse events *n* (%)	*P-value*	Attack after vaccine *n* (%)	*P-value*
Treatment for FMF						
Colchicine ($n=232$)	172 (74)		137 (59)		55 (24)	
Colchicine + canakinumab ($n=23$)	19 (82)	0.37[a]	17 (73)	0.16[a]	12 (52)	**≤0.05**[a]
Dose of colchicine						
Low ($n=101$)	75 (74)		59 (58)		15 (15)	
Moderate ($n=117$)	86 (73)	0.90[b]	67 (57)	0.86[b]	37 (32)	**≤0.05**[b]
High ($n=37$)	30 (81)	0.40[b]	28 (76)	0.06[b]	15 (41)	**≤0.05**[b]
MEFV genotype						
M694V carrier ($n=187$)	146 (78)		121 (65)		50 (27)	
Other mutations ($n=30$)	14 (47)	**≤0.05**[c]	13 (43)	**≤0.05**[c]	7 (23)	0.69[c]
No mutations ($n=20$)	11 (55)	**≤0.05**[c]	9 (45)	0.08[c]	2 (10)	0.1[c]
Unknown mutation ($n=36$)	32 (89)	N/A	22 (61)	N/A	9 (25)	N/A
Number of FMF attacks during the year before the vaccination						
0 ($n=124$)	89 (72)		66 (53)		8 (6)	
1–6 ($n=90$)	68 (76)	0.53[d]	58 (64)	0.1[d]	19 (21)	**≤0.05**[d]
≥7 ($n=59$)	46 (78)	0.37[d]	41 (70)	**≤0.05**[d]	41 (70)	**≤0.0001**[d]
Number of FMF attacks during the month before the vaccination						
0 ($n=206$)	149 (72)		118 (57)		21 (10)	
1 ($n=31$)	26 (84)	0.17[d]	21 (68)	0.27[d]	18 (58)	**≤0.0001**[d]
≥2 ($n=36$)	28 (78)	0.49[d]	26 (72)	0.09[d]	29 (81)	**≤0.0001**[d]

[a]Compared with colchicine alone. [b]Compared with low dose colchicine. [c]Compared with carriage of the M694V mutation (homozygous, heterozygous and compound heterozygous combined). [d]Compared with 0 attacks. N/A: not applicable. The bold signify that there is statistical significance as opposed to the non bold rows.

cannot determine with certainty whether the attacks were sporadic or triggered by the vaccine, post-vaccination disease activity remained stable in most patients, as the rate of attacks in the month prior to the vaccination (25%) was higher than that after vaccination.

Patients with a more active disease had a significantly higher rate of systemic side effects and post-vaccination attacks than those with a less active one. Similarly, patients harboring the M694V mutation in at least one copy of their MEFV gene had a higher rate of local and systemic side effects compared with patients with other mutations or no mutations. This corresponds with the known correlation between the M694V mutation and disease severity and activity [23]. Patients with a more active disease might have more priming of their innate immune system, rendering it more responsive to an mRNA-based vaccine. It is not known whether this correlation between FMF disease activity or M694V genotype and post-vaccination side effects is unique to mRNA or COVID-19 vaccines, or universal to all vaccines in FMF patients. We believe that these findings should lead to further studies on the side effects of vaccines in FMF patients.

Patients treated with colchicine and canakinumab had a significantly higher rate of attacks following vaccination compared with patients treated with colchicine alone. This is probably because treatment with IL-1 blockade is associated with high disease activity, as it is indicated for patients with the most severe and active disease, and not because of the effect of IL-1 blockade itself. There was no significant correlation between the dose of colchicine and the vaccine side effects, although there was a trend towards a higher rate of side effects in patients who were treated with higher doses of colchicine. Again, this is probably the result of the correlation between the level of disease activity and the rate of side effects, and not the effect of colchicine itself.

The limitations of our study include its retrospective nature and the relatively small number of patients, rendering it underpowered to assess the rate of rare side effects such as pericarditis and myocarditis, which are of interest when considering potential COVID-19 vaccine side effects. However, because FMF is a rare disease, the present study includes the largest cohort of COVID-19 vaccinated FMF patients published to date. Another limitation is that respondents with adverse events might have been more likely to give consent to participate in the study and answer the questionnaire, resulting in selection bias. Furthermore, the study site is a tertiary center and therefore, the study cohort is biased towards patients with a more active and severe disease, reflected in the relatively high frequency of the M694V mutation, which might skew the rate of reported side effects and post-vaccine attacks. Despite this, the frequency of disease flares requiring medication changes remained low in the study population. Finally, we could not assess whether colchicine had any protective effect on the individual regarding side effects as there were not enough patients who were not taking colchicine to compare results.

In conclusion, our results show that the BNT162b2 mRNA COVID-19 vaccine is safe for FMF patients. These results may support the administration of the vaccine to FMF patients according to local guidelines applicable to the general population.

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Data availability statement

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

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