Safety profile and low risk of disease relapse after BNT162b2 mRNA SARS-COV-2 vaccination in patients with rare rheumatic diseases.

Fornaro M, Venerito V, Iannone F*, Cacciapaglia F

Rheumatology Unit, Department of Emergency and Organ Transplantations, Bari, Italy

Marco Fornaro,	MD, Lecturer	marco3987@hotmail.it
Vincenzo Venerito	MD, Lecturer	vincenzo.venerito@uniba.it
Florenzo Iannone	MD, PhD, Full Professor of Rheumatology	florenzo.iannone@uniba.it
Fabio Cacciapaglia	MD, PhD, Lecturer	fabio.cacciapaglia79@gmail.com

*Corresponding author: Florenzo Iannone, Department of Emergency and Organ Transplantation – Rheumatology Unit, Piazza G Cesare, 11 70124 Bari, Italy. Email florenzo.iannone@uniba.it

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Vaccination today represents the first defence against the effects of the Coronavirus disease 2019, mainly in rheumatic patients, where an increased risk for hospitalization and death has been reported (1,2). The previous studies on the safety and tolerability of BNT162b2 mRNA-SARS-CoV-2 (3) vaccine in patients affected with rheumatic diseases(RDs) included predominantly patients with inflammatory arthritis (4-6). This study was focused on patients affected with rare RDs and systemic lupus erythematosus (SLE) to assess the safety of the BNT162b2 mRNA SARS-CoV-2 vaccine and possible disease flares after vaccination.

We performed an observational study including patients affected with rare RDs and SLE vaccinated at the Rheumatology Unit of Bari with BNT162b2 mRNA-SARS-CoV-2 vaccine during a vaccination campaign launched in April 2021. All clinical and demographic data of the overall population are reported in Table 1, while more specific data on the individual diseases are reported in Supplementary materials(Supplementary tables 1-6). The patient global assessment of disease activity (PGA) was measured on a 0 to 10 visual analogue scale (VAS) before the first dose (baseline), at the time of the second vaccine dose, and 4 weeks apart. Rheumatic-specific drugs were managed according to the current recommendations by the American college of rheumatology (7). After the first and second shots, a paper survey was distributed to all patients. All patients could contact our centre by phone or email, and patients reporting a worsening of the disease were promptly seen in the outpatient clinic.

Among 452 patients with rare RDs and SLE followed in our outpatient clinics, 287 (63.5%) agreed to be vaccinated during our vaccination campaign and were included in the study. After the first dose of the BNT162b2 mRNA-SARS-CoV-2 vaccine, 152 (53%) patients reported at least one adverse event(AE). Data regarding AEs are shown in detail in Table 2. The number of AEs increased after the second vaccine dose administration, being reported by 176 (64.7%) patients. Among the AEs, a condition of flu-like syndrome was significantly increased after the second vaccine dose. We observed a growth of prevalent patients who suffered from arthralgias or myalgias, fatigue, and fever. No major AEs, such as major cardiovascular events, thrombosis, or anaphylaxis reactions were

observed. All AEs were self-limiting and no patients needed hospitalization. Excluding injection site pain, multiple regression analysis showed that female gender (HR = 2.34, 95% CI:1.51-4.76), a high/moderate disease activity according to PhGA (HR = 2.89, 95% CI:1.24-6.74), and advanced age (HR = 0.95, 95% CI:0.93-0.97) were statistically significant predictors for AE.

No differences in VAS-PGA of disease activity during the vaccination period were observed. The median (IQR) PGA was 4 (2.0-5.5) at baseline and remained 4 (2.0-6.0) before and 4 weeks after the second vaccine dose, respectively. Although 7 patients reported worsening of PGA after the first dose of vaccine, this was negligible (≤2) with no clear signs of clinical reactivation of the disease. Afterward, all patients were evaluated during a routine follow-up visit after a mean of 7.1 ± 2.8 weeks after the second vaccine dose. Only six (2.1%) patients referred a worsening of disease activity during the follow-up visit. Two SLE patients complained of a relapse of arthralgias, and the other 2 SLE patients reported a cutaneous flare. One SSc patient referred an increase in the frequency of Raynaud's phenomenon, while one patient with Behçet's syndrome reported an erythema nodosum relapse. These patients did not show significant evidence of worsening of the disease at clinical assessment.

SLE patients showed no worsening of SLEDAI-2K at follow-up visit after vaccination [baseline SLEDAI-2K median (IQR): 2 (0-4) vs follow-up SLEDAI-2K median (IQR): 2 (0-2), p=0.6]. Behçet's Disease Current Activity Form (BDCAF) remained stable in Beçhet patients [baseline BDCAF median (IQR): 1 (0-1) vs follow-up BDCAF median (IQR): 1 (0-1), p=0.1]. Finally, also in patients affected with idiopathic inflammatory myopathies we did not find an increase of creatine phosphokinase (CPK) [baseline CPK median (IQR): 96 (65-166) UI/L vs follow-up CPK median (IQR): 125 (69-275), p=0.6] or a worsening of manual muscle test-8(MMT-8) [baseline MMT-8 median (IQR): 80 (75-80) UI/L vs follow-up CPK median (IQR): 80 (75-80), p=0.5].

In conclusion, our study supports the safety of BNT162b2 mRNA-SARS-CoV-2 vaccine in patients with rare RDs and SLE, in whom we highlighted mild AEs and no disease relapse.

Declarations:

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Table 1. Population vaccinated with BNT162b2 mRNA SARS-CoV-2 vaccine during the vaccination campaign carried out at the Rheumatology Unit of Bari.

Variables	Populations n.287
Age, mean (SD)	53±14
Female, n. (%)	239 (83.3)
Number of comorbidities, mean (SD)	2.4±2
Patient's VAS of disease activity, mean (SD)	3.8±2.5
Physician disease activity	
High, n. (%)	1 (0.3)
Moderate, n. (%)	50 (17.4)
Low, n. (%)	161 (56.1)
Remission, n. (%)	75 (26.1)
SSc, n. (%)	90 (31.4)
SLE and primary ApS, n. (%)	68 (23.7)
Idiopathic inflammatory myositis, n. (%)	47 (16.4)
Behcet, n. (%)	39 (13.6)
Vasculitis, n. (%)	27 (9.4)
MCTD, n. (%)	9 (3.1)
UCTD, n (%)	7 (2.4)
Glucocorticoid, n. (%)	143 (49.8)
At least one csDMARD, n. (%)	209 (72.8)
Hydroxychloroquine, n. (%)	84 (29.3)
Methotrexate, n. (%)	55 (19.2)
Mycophenolate mofetil, n. (%)	45 (15.7)
Azathioprine, n. (%)	44 (15.3)

Colchicine, n. (%)	10 (3.5)
Cyclophosphamide, n. (%)	7 (2.4)
Leflunomide, n. (%)	6 (2.1)
Salazopyrin, n. (%)	4 (1.4)
Immunoglobulins ev, n. (%)	2 (0.7)
Cyclosporine, n. (%)	1 (0.3)
Tacrolimus, n. (%)	1 (0.3)
b- and tsDMARD, n. (%)	72 (25.1)
TNF inhibitors, n. (%)	26 (9.1)
Rituximab, n. (%)	16 (5.6)
Tocilizumab, n. (%)	8 (2.8)
Belimumab, n. (%)	8 (2.8)
Benralizumab, n. (%)	5 (1.7)
Apremilast, n. (%)	3 (1)
Abatacept, n. (%)	2 (0.7)
Anakinra, n. (%)	2 (0.7)
Ustekinumab, n. (%)	2 (0.7)

Abbreviations: ApS= antiphospholipid syndrome; cs-, b- and tsDMARD= conventional systemic and biologic disease modified anti-rheumatic drug; ev= endovenous; SLE= systemic lupus erythematosus; SD=standard deviation; SSc= systemic sclerosis; U- and M-CTD= undifferentiated and mixed connective tissue disease; VAS= visual analogue scale.

Table 2. Adverse events recorded after the first and the second dose of BNT162b2 mRNA SARS-CoV-2 vaccine

Variables, n. (%)	First dose of BNT162b2 mRNA SARS-CoV-2 vaccine Population at first dose, n. 287	Second dose of BNT162b2 mRNA SARS-CoV-2 vaccine Population at second dose n. 272
Patients with at least one AE, n. (%)	152 (53)	176 (64.7) *
Injection site pain, n. (%)	124 (43.2)	127 (46.7)
Headache , n. (%)	45 (15.7)	55 (20.2)
Arthralgias or myalgias, n. (%)	29 (10.1)	76 (27.9) ***
Fatigue, n. (%)	12 (4.2)	46 (16.9) ***
Fever, n. (%)	11 (3.8)	48 (17.6) ***
Allergic reaction, n. (%)	5 (1.7)	9 (3.3)
Gastrointestinal disorders, n. (%)	6 (2.1)	9 (3.3)
Other AEs, n. (%)	10 (3.5)	11 (4)

Data are expressed as number and percentage. Abbreviations: AE= adverse event.

*p<0.05, **p<0.01, ***p<0.001 vs first dose of BNT162b2