Reactogenicity, safety and disease flares following BNT162b2 mRNA COVID-19 vaccine in patients with chronic immune-inflammatory arthritis treated with biological and targeted synthetic disease-modifying anti-rheumatic drugs

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Abstract

Objective

The safety of COVID-19 vaccination in rheumatic patients treated with biological (b) and targeted synthetic (ts) disease-modifying anti-rheumatic drugs (DMARDs) remains poorly explored.

Methods

Reactogenicity, safety and disease flares following each of the two doses of the BNT162b2 mRNA vaccine was evaluated in 186 patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis treated with b/tsDMARDs, who discontinued anti-rheumatic treatments around vaccination. A group of 53 healthy controls was used for comparison.

Results

The frequency and severity of systemic events was similar to that reported in the general population, and no particular safety concerns emerged. The use of methotrexate reduced systemic reactogenicity (adjORs [95% CI] 0.49 [0.25–0.94] and 0.63 [0.32–0.99] after each vaccine dose), whilst no specific effects of different b/tsDMARDs were seen. Flares around vaccination were reported by 24.5% of the patients. Factors associated with flares were active disease (adjORs [95% CI] 2.8 [1.01–8.09] and 1.86 [0.99–6.03] after each vaccine dose) and use of JAKi (adjORs [95% CI] 3.96 [1.39–11.27] and 3.10 [0.99–7.85]). The percentage of cases requiring change or increase in DMARD therapy due to persistent worsening of disease activity at follow-up visits was low (3.2%).

Conclusion

The safety of mRNA COVID-19 vaccination in arthritis patients on treatment with b/tsDMARDs is reassuring. In a regimen of peri-vaccine drug interruption, transient flares of the disease more commonly occur in association with active arthritis and use of shorter half-life drugs. Most flares do not require treatment escalation or change.

Key words

COVID-19, vaccine, rheumatic, arthritis, methotrexate, biological drugs, JAK inhibitors, safety, flare

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Introduction

Patients with rheumatic diseases on immunomodulatory treatment are at higher risk of viral infections (1), including infection by SARS-CoV-2 (2, 3), and are prioritised to receive COVID-19 vaccination. Based on evidence derived from studies on other non-live vaccines, the overall safety and efficacy profile of the new mRNA COVID-19 vaccines in rheumatic patients is expected to be reassuring (4). Both SARS-CoV-2 infection and the new technology of mRNA vaccines however have complex and bidirectional relationships with immune-mediated inflammatory diseases and their immunomodulatory treatments. Several anti-rheumatic drugs may indeed variably influence the course of COVID-19 (5-11) and response to vaccines (12-16). Equally important, both SARS-CoV-2 infection and vaccines may trigger autoimmunity and drive inflammation through molecular mimicry and potent type I interferon responses (17-21).

Safety concerns fuel vaccine hesitancy among rheumatic patients receiving immunomodulatory drugs (22-25). Apart from scarcity of experience regarding the new COVID-19 vaccines in general, reasons for refusing or doubting vaccination include fear of possible flares of the disease (22, 23, 25). At present, guidance for optimal use of the COVID-19 vaccines in rheumatic patients mostly relies on expert opinion (4), and only few studies have reported on safety issues thus far, with no particular warnings arising (14, 21, 26, 27). However, rheumatic patients exhibit high variability with respect to their underlying health condition, disease severity and treatments, all of which may differently affect the outcomes of COVID-19 vaccination. In particular, the impact of biological (b) and targeted synthetic (ts) disease-modifying anti-rheumatic drugs (DMARDs) remains under intense scrutiny. Here we present data analysis on the reactogenicity, safety and disease flares following the completion of two doses of the BNT162b2 mRNA COVID-19 vaccine in a large mono-centric cohort of patients with chronic immune-inflammatory arthritis, specifically rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA), all treated with b/tsDMARDs.

Methods

Study population

The study population consisted of patients diagnosed with RA, PsA and SpA, fulfilling respectively the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) (28), ClASsification criteria for Psoriatic ARthritis (CASPAR) (29) and Assessment in SpondyloArthritis international Society (ASAS) (30) classification criteria, all on treatment with b/tsDMARDs and regularly followed at the Division of Rheumatology of the IRCCS Policlinico San Matteo University Hospital of Pavia, Italy. Demographic and clinical variables were retrieved from the electronical records of the last available rheumatologic assessment (median [IQR] 14 [9-22] days before vaccination). A group of 53 healthy controls (HC) (all healthcare workers) receiving the same vaccine was used for comparison. The study was conducted according to the declaration of Helsinki: all patients signed a written informed consent before the inclusion and the study protocol was approved by the local ethics committee.

Vaccination protocol

Both patients and HC were administered the two-dose regimen BNT162b2 mRNA vaccine, 30μg per dose, by intramuscular injection 3 weeks apart. In arthritis patients, the vaccine was personally administered by the treating rheumatologists. Upon pre-vaccine phone consultation, patients were advised to discontinue both the b/tsDMARD and concomitant methotrexate around vaccination, although adherence to this guideline was left voluntary. In particular, the following suggestions were made: (i) for all the bDMARDs and methotrexate, withholding of therapy in the 7 days before and 7 days after each vaccine dose; (ii) for tsDMARDs, withholding of therapy from the day before until day 7 after each dose. For glucocorticoids and conventional synthetic (cs) DMARDs other than methotrexate,

no modifications were advised. Such recommendations were agreed internally before the publication of guidance statements by international scientific societies (4) on the basis of a cautionary and restrictive adaptation of the recommendations for other vaccines in rheumatic patients (31).

Survey

In both patients and HC, solicited, specific local reactions and systemic adverse events, as well as unsolicited adverse reactions, were collected in accordance with the original protocol of the phase 2/3 trial of BNT162b2 (32) by face-to-face interviews 21 days after the first dose and 14 days after the second dose. Briefly, redness, swelling and pain at the injection site, as well as fever, fatigue, headache, chills, vomiting, diarrhoea, muscle, and joint pain were rated by the participants as absent, mild, moderate, or severe. Fever was defined as a temperature ≥38°C. Other adverse events and COVID-19 infection confirmed by nucleic acid amplification-based tests were also recorded.

At the same time as the face-to-face interviews, flares of the disease associated to vaccine administration were investigated subjectively by asking the patients whether they had experienced changes in arthritis disease activity following each vaccine dose (33, 34). Duration of flares and eventual therapy (analgesics, non-steroidal anti-inflammatory drugs, glucocorticoids) were recorded. Patient global assessment (PGA) of disease activity and pain severity (on 0–100 visual analogue scales, VAS) were also assessed 21 days after the first dose and 14 days after the second dose, and compared with pre-vaccination scores. Clinically significant worsening was defined as a relative change in PGA or pain ≥20% from baseline (35).

Following completion of the vaccination cycle, all patients continued their routine rheumatological follow-up, with bimonthly comprehensive clinical evaluations. Disease activity was regularly assessed through validated composite measures, namely the Disease Activity Score on 28 joints (DAS28) for RA (36), the Disease Activity index for Psoriatic Arthritis (DAPSA) (37), and the Ankylosing Spondylitis Disease Activity Score with C-reactive protein levels (ASDAS-CRP) for SpA (38). Flares were defined as worsening of disease activity that lead to a change of therapy (39), specifically increase in the dose of csDMARDs, csDMARDs initiation and/or change of the b/tsDMARD. For the purpose of this study, only flares documented at the first or second rheumatological access were considered potentially related to vaccination.

Statistical analysis

Baseline demographics and clinical characteristics were evaluated with descriptive statistics. Categorical variables were expressed as number (percentage), and continuous variables with mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. Changes in subjective and objective measures of diseases activity from baseline were evaluated through paired samples t-test. Predictors of local and systemic reactogenicity as well as disease flares after each vaccine dose were analysed by unadjusted and adjusted linear regression analysis, generating odds ratios (OR) with 95% confidence intervals (95% CI). Variables with a p-value ≤0.1 in univariate analysis were included. Statistical analyses were performed using MedCalc® v. 12.7.0.0, and the level of significance was set at 0.05.

Results

Demographic and clinical characteristics of the study population

Out of 188 b/tsDMARD-treated patients receiving the BNT162b2 vaccine during the study period, 186 agreed to participate to the safety survey after the first dose, 94.6% of whom (n=176) also returned for face-to-face interviews 14 days after the second dose. None of the ten patients lost to follow-up reported serious adverse events upon phone contacts. All the 186 patients continued their routine rheumatological follow-up and underwent regular clinical evaluations after a median (IQR) of 42 (29–54.5) and 96.5 (85–109.5) days upon completion of the vaccination cycle.

Baseline demographic and clinical characteristics are summarised in Table I. Most patients had RA (66.7%), followed by PsA (17.7%) and SpA (15.6%). Mean (SD) age was 56.3 (13.8) years, and 44.1% of the patients was aged ≤55 years. The cohort was

Table I. Demographic and clinical characteristics of the study population.

	n=186 pts
Age, mean (SD), yrs	56.3 (13.8)
Females, n. (%)	127 (68.3)
BMI, mean (SD)	26.4 (5.4)
Smoking, n. (%)	32 (17.2)
Hypertension, n. (%)	71 (38.2)
Obesity, n. (%)	43 (23.1)
CCI, mean (SD)	0.6 (0.9)
≥1 comorbidity*, n. (%)	65 (64.9)
Previous COVID-19#, n. (%)	10 (5.4)
Diagnosis, n. (%):	
RA	124 (66.7)
PsA,	33 (17.7)
SpA	29 (15.6)
Disease duration, mean (SD), yrs	13.2 (8.1)
Active disease§, n. (%)	51 (27.4)
Glucocorticoids, n. (%)	72 (38.7)
Prednisone dose, mean (SD), mg/die	3.8 (1.6)
HCQ, n. (%)	45 (24.2)
csDMARDs, n. (%)	108 (58.1)
MTX	87 (46.8)
SSZ	15 (8.1)
LFN	8 (4.3)
CYA	3 (1.6)
MTX dose, mean (SD), mg/week	14.4 (5.4)
b/tsDMARDs, n. (%)	186 (100)
TNFi	64 (34.4)
IL-6Ri	15 (8.1)
IL-17/IL-23i	22 (11.8)
CTLA4Ig	50 (26.9)
JAKi	30 (16.7)
PDE4i	5 (2.7)

*among those listed in the Charlson Comorbidity Index

#based on patient-reported history of swab-confirmed SARS-CoV-2 infection

§above the threshold of low disease activity according to the appropriate composite index: DAS28 >3·2; DAPSA >14; ASDAS-PCR >2·1.

DAS28: Disease Activity Score on 28 joints; DAPSA: Disease Activity in Psoriatic Arthritis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score calculated with C-reactive protein. b/ts: biologic/targeted synthetic; BMI: Body Mass Index; CCI: Charlson Comorbidity Index; cs: conventional synthetic; CTLA4Ig: cytotoxic T-lymphocyte associated protein-4 Immunoglobulin; CYA: cyclosporine; DMARD: disease-modifying anti-rheumatic drug; HCQ: hydroxychloroquine; IL-6Ri: interleukin-6 receptor inhibitor; IL-17/IL-23i: interleukin-17/interleukin-23 inhibitor; JAKi: Janus Kinase inhibitor; LFN: leflunomide; MTX: methotrexate; PDE4i: phosphodiesterase-4 inhibitor; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SpA: spondyloarthritis; SSZ: sulphasalazine; TNFi: tumour necrosis factor inhibitor.

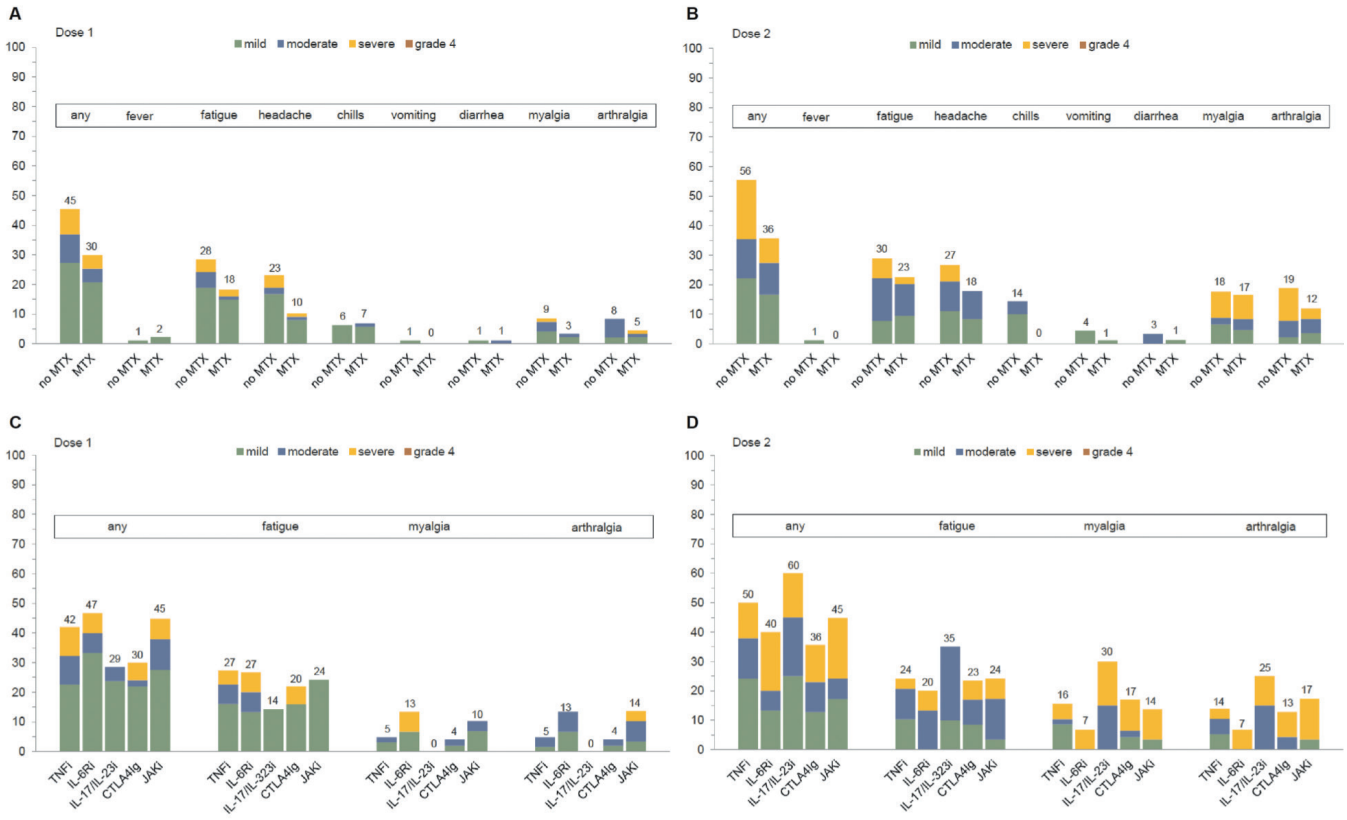

Fig. 1. Systemic reactogenicity following each dose of the BNT162b2 mRNA COVID-19 vaccine in relation with the use of different medications.
A-**D**: Frequency and severity of systemic events after the first (**A**, **C**) and the second dose (**B**, **D**) of BNT162b2 in arthritis patients stratified for the use of methotrexate (**A**, **B**) and different classes of biological or targeted disease-modifying anti-rheumatic drugs (**C**, **D**). Histograms report frequencies of the event of interest, expressed as percent of patients. The different colours refer to the severity of the event, graded as mild (green), moderate (blue), severe (yellow) or requiring hospitalisation (grade 4, red).
MTX: methotrexate; TNFi: tumour necrosis factor inhibitor; IL-6Ri: interleukin-6 receptor inhibitor; IL-17/IL-23i: interleukin-17/interleukin-23 inhibitor; CTLA4Ig: cytotoxic T-lymphocyte associated protein-4 immunoglobulin; JAKi: Janus kinase inhibitor.

mainly composed of patients on treatment with tumour necrosis factor inhibitors (TNFi) (34.4%) or cytotoxic T-lymphocyte antigen 4-immunoglobulin (CTLA-4Ig) (26.9%), followed by Janus Kinase inhibitors (JAKi) (16.7%). Seventy-two patients (38.7%) were concomitantly receiving low-dose glucocorticoids, with a mean (SD) prednisone dose of 3.8 (1.6) mg/day, and in 94.4% of the cases not exceeding 5 mg/day. The b/tsDMARD was given in combination with a csDMARD (mostly methotrexate) in 58.1% of the patients. Arthritis was on average well controlled, with 72.6% of the patients being in low disease activity according to the appropriate composite index. Of the total population, 77.4% adhered to our recommendation of b/tsDMARDs withholding around the first dose, a proportion that increased to 84.1% around the second dose. Adherence to methotrexate withholding was instead lower (46% and 60% at the first and second dose, respectively).

HC were aged ≤55 years in 94.3% of the cases (mean [SD] age 45.1 [11.4] years), and 50.9% were females. None was or had been suffering from immune-mediated inflammatory diseases, nor was on treatment with immunomodulatory drugs.

Reactogenicity

Overall, local reactions were reported by 72% of the patients after the first dose and 67% after the second dose. Local reactions resolved within a median of two days and were mostly mild-to-moderate, with <5% reporting severe pain. At multivariable analysis, local reactogenicity was diminished in relation to longer disease duration (adjOR [95% CI] 0.95 [0.91–0.99], p=0.02), with a trend also for use of csDMARDs (adjOR [95% CI] 0.60 [0.28–1.18], p=0.13).

Systemic events were slightly more frequent (45.5% *vs*. 37.1%, p=0.13) and severe (14.2% *vs*. 6.5%, p=0.03) after the second dose. The most common events were fatigue (23.7% and 26.1% after the first and second dose, respectively) and headache (17.2% and 22.2%). Musculoskeletal symptoms globally occurred in 8.6% and 20.5% of the cases after each of the two doses. In most of the patients (~55%), management of systemic events did not require any medication. Systemic events were only slightly more common in subjects aged ≤55, who in any case showed a trend for reduced reactogenicity compared to HC (51.9% *vs*. 58.6% after the second dose). Concomitant therapy with methotrexate was associated with significantly reduced rates of systemic events (Fig. 1 A-B and Table II), whilst prednisone doses >2.5 mg/day reduced reactogenicity only after the first vaccine dose (Table II). Adherence to methotrexate withholding around vac-

Table II. Demographic and clinical factors associated with systemic reactogenicity of each of the two doses of the BNT162b2 mRNA COVID-19 vaccine. Univariable and multivariable analysis.

	Dose 1			Dose 2		
	OR	95% CI	*p*	OR	95% CI	*p*
Univariable analysis						
Age >55	0.93	0.51 to 1.71	0.82	0.62	0.34 to 1.14	0.12
Female gender	1.68	0.86 to 3.29	0.13	1.15	0.61 to 2.17	0.67
BMI >30	0.87	0.40 to 1.89	0.72	0.69	0.31 to 1.51	0.35
Smoking	0.92	0.41 to 2.09	0.85	0.76	0.33 to 1.76	0.53
≥1 comorbidity*	0.53	0.27 to 1.04	0.06	0.63	0.33 to 1.21	0.16
Previous COVID-19[#]	0.40	0.08 to 1.95	0.22	0.50	0.12 to 1.99	0.32
Systemic reactogenicity after D1	--	--	--	3.53	1.84 to 6.77	**<0.001**
Diagnosis						
RA	Reference			Reference		
PsA	0.88	0.39 to 2.00	0.79	1.64	0.73 to 3.67	0.23
SpA	1.19	0.52 to 2.72	0.68	4.09	1.66 to 10.08	**0.002**
Disease duration	0.98	0.94 to 1.02	0.26	0.96	0.93 to 1.00	0.07
Active disease[§]	1.40	0.69 to 2.82	0.35	1.38	0.68 to 2.76	0.37
Glucocorticoids	1.06	0.57 to 1.97	0.85	1.22	0.66 to 2.26	0.52
Prednisone dose >2.5 mg/d	0.45	0.19 to 1.06	0.07	0.86	0.40 to 1.85	0.70
HCQ	0.90	0.45 to 1.82	0.77	0.59	0.29 to 1.21	0.15
csDMARD	0.51	0.28 to 0.94	**0.03**	0.45	0.24 to 0.83	**0.01**
MTX	0.49	0.26 to 0.90	**0.02**	0.46	0.25 to 0.86	**0.01**
SSZ	1.48	0.48 to 4.60	0.50	0.51	0.15 to 1.72	0.28
LFN	1.72	0.42 to 7.11	0.45	0.71	0.16 to 3.07	0.65
b/tsDMARD						
TNFi	Reference			Reference		
IL-6Ri	1.21	0.39 to 3.76	0.74	0.67	0.21 to 2.11	0.49
IL-17/IL-23i	0.43	0.14 to 1.33	0.14	1.22	0.44 to 3.39	0.16
CTLA-4Ig	0.59	0.27 to 1.30	0.19	0.57	0.26 to 1.24	0.16
JAKi	1.13	0.46 to 2.74	0.80	0.81	0.33 to 1.99	0.65
PDE4i	0.92	0.14 to 5.92	0.93	1.50	0.23 to 9.65	0.67
Adherence to MTX witholding	1.01	0.33 to 2.84	0.76	1.04	0.45 to 1.96	0.45
Adherence to b/tsDMARD witholding	0.98	0.54 to 3.93	0.47	0.95	0.34 to 2.56	0.71
Multivariable analysis						
Systemic reactogenicity after D1	n.i.			3.06	1.52 to 6.16	**0.002**
Age >55	n.i.			--	--	--
Female gender	2.11	1.02 to 4.36	**0.04**	n.i.		
≥1 comorbidity	0.58	0.29 to 1.16	0.12	--	--	--
Diagnosis SpA	n.i.			3.25	1.25 to 8.46	**0.02**
Disease duration	n.i.			0·96	0.92 to 1.01	0.09
Prednisone dose >2.5 mg/d	0.43	0.18 to 1.04	0.06	n.i.		
HCQ	n.i.			--	--	--
MTX	0.49	0.25 to 0.94	**0.03**	0.63	0.32 to 0.99	**0.04**
CTLA-4Ig	--	--	--	--	--	--
IL-17/IL-23i	--	--	--	n.i.		

*among those listed in the Charlson Comorbidity Index; [#]based on patient-reported history of swab-confirmed SARS-CoV-2 infection; [§]above the threshold of low disease activity according to the appropriate composite index: DAS28 >3·2; DAPSA >14; ASDAS-PCR >2·1.
DAS28: Disease Activity Score on 28 joints; DAPSA: Disease Activity in Psoriatic Arthritis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score calculated with C-reactive protein; b/ts: biologic/targeted synthetic; BMI: Body Mass Index; CCI: Charlson Comorbidity Index; cs: conventional synthetic; CTLA4Ig: cytotoxic T-lymphocyte associated protein-4 immunoglobulin; DMARD: disease-modifying anti-rheumatic drug; HCQ: hydroxychloroquine; IL-6Ri: interleukin-6 receptor inhibitor; IL-17/IL-23i: interleukin-17/interleukin-23 inhibitor; JAKi: Janus Kinase inhibitor; LFN: leflunomide; MTX: methotrexate; PDE4i: phosphodiesterase-4 inhibitor; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SpA: spondyloarthritis; SSZ: sulphasalazine; TNFi: tumour necrosis factor inhibitor.

cination did not modify the odds of systemic events (Table II). Also, the use of different classes of b/tsDMARDs did not significantly impact on reactogenicity. The lower frequency of any systemic event reported by patients on treatment with CTLA-4Ig (Fig. 1 C-D) was not independent of other covariates, including use of methotrexate (Table II).

Safety

None of the HC reported either SARS-CoV-2 infection or adverse events following vaccination. In contrast, two patients developed RT-PCR-confirmed COVID-19 after the first dose, and two additional patients after the second dose. Of them, two were on TNFi, one on IL-17i, and one on CTLA-4Ig; two were receiving concomitant methotrexate, and all were on glucocorticoids (two with prednisone 2.5 mg/day, two with 7.5 mg/day). In all cases, COVID-19 was mildly symptomatic (fever <38°C, malaise), and resolved within 14 days. Five patients reported labial herpes simplex, and two superficial thrombophlebitis (one with IL-17i, one with CTLA-4Ig).

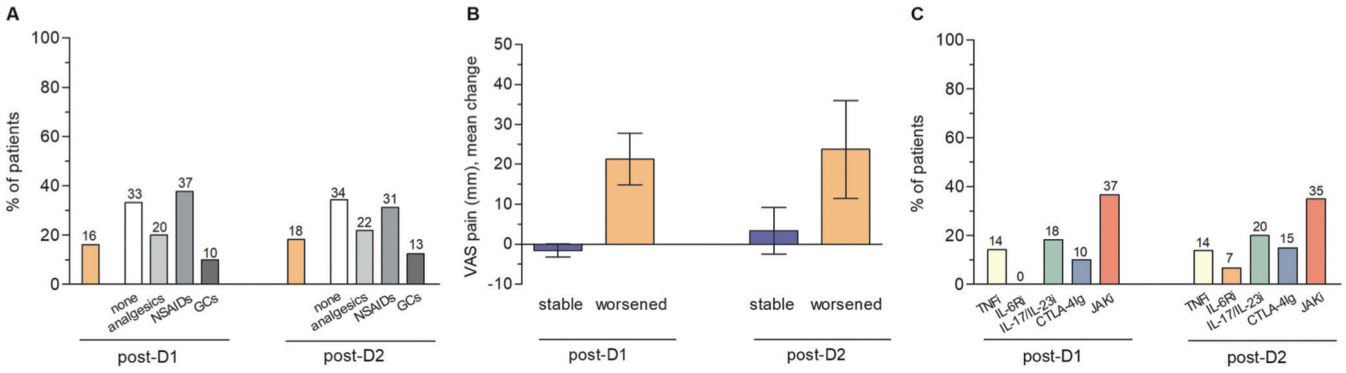

Fig. 2. Disease flares following each dose of the BNT162b2 mRNA COVID-19 vaccine.
A: Frequency of self-reported disease worsening and use of medication after each of the two vaccine doses. **B**: Changes in the visual analogue scale (VAS) for pain in patients experiencing self-reported flare after each of the two vaccine doses compared with patients reporting disease stability.
C: Frequency of self-reported disease worsening after each of the two vaccine doses stratified for the use of different classes of biological or targeted disease modifying anti-rheumatic drugs. Histograms in **A** and **C** report frequencies of the event of interest, expressed as percentage of patients. Bars in **B** represent mean (standard deviation) change values. D1: first vaccine dose; D2: second vaccine dose; NSAIDs: non-steroidal anti-inflammatory drugs; GCs: glucocorticoids; VAS: visual analogue scale (0-100); TNFi: tumour necrosis factor inhibitor; IL-6Ri: interleukin-6 receptor inhibitor; IL-17/IL-23i: interleukin-17/interleukin-23 inhibitor; CTLA4Ig: cytotoxic T-lymphocyte associated protein-4 immunoglobulin; JAKi: Janus Kinase inhibitor.

Arthritis flares

Arthritis was judged stable by the majority of the patients, with 16.1% reporting worsening after the first dose, and 17% after the second dose (Fig. 2A). In more detail, 7.4% of the 176 patients completing the survey flared only after the first dose, 9.7% only after the second dose, and 7.4% after both doses (24.5% of the patients in total). In patients who flared, the PGA increased of +42.5% and +54.4% after each vaccine dose ($p<0.001$), compared to stability in patients not reporting disease worsening (-4.9% and +12.8%). VAS pain increased of a mean (SD) of 21.2 (17.6) and 23.8 (31.7) mm (Fig. 2B). Self-reported flares coincided with clinically significant worsening of the PGA in 72.4% and 79.3% of the cases after each of the two doses, and in clinically significant increase in pain in 58.6% and 72.4%, respectively. Despite being mild-to-moderate in most patients, flares lasted for >14 days in 29.6% of the cases after the first dose, and in 53.1% after the second dose. Nearly 70% of the patients who flared required symptomatic therapy, including 10-13% managed with glucocorticoids (Fig. 2A). Active disease at the time of vaccination was associated with significantly increased risk after each vaccine dose (adjusted ORs [95% CI] 2.8 [1.01–8.09] and 1.86 [0.99–6.03] respectively, Table III). Furthermore, subjective flares were more common among patients on treatment with JAKi (37% after the first dose, 35% after the second dose, Fig. 2C), irrespective of pre-vaccine disease activity, concomitant use of csDMARDs, adherence to withholding of treatment, and systemic reactogenicity to vaccination, including musculoskeletal events (Table III).

Objective assessments of disease activity after a median (IQR) of 42 (29-54.5) and 96.5 (85-109.5) days after completion of the vaccination cycle demonstrated overall stable DAS28, DAPSA and ASDAS-CRP scores (mean [95% CI] changes of 0.17 [-0.23–0.57], 1.03 [-3.02–5.08] and 0.14 [-0.35–0.63], respectively, at the first assessment; 0.23 [-0.33–0.60], 1.12 [-2.05–6.13] and 0.12 [-0.29–0.61] at the second assessment; $p>0.5$ for all). Increased disease activity requiring change of DMARD treatment globally occurred in 6 patients (3.2%), 4 of whom at the second visit after vaccination. Five had RA, and 1 PsA. Of the patients with RA, 2 were on treatment with JAKi after multiple failures; in the remaining 3 patients, disease activity had been adequately controlled with TNFi (n=2) or CTLA4-Ig (n=1) for >6 months before vaccination (secondary failures). In bivariate logistic regression models, treatment change tended to be associated with active arthritis (OR 4.3 [95% CI 0.7 to 27.3] but not with class of b/tsDMARD at the time of vaccination.

Discussion

Our data reassure on the overall tolerability and safety of COVID-19 mRNA vaccines administered on the background of several classes of b/tsDMARDs with different impact on the immune system. Most of the systemic effects were indeed comparable in frequency and severity to those reported in the general population (40) and also seen in our study. However, our cohort consisted of patients with chronic immune-inflammatory arthritis mostly in good disease control. Whether more systemic rheumatic diseases and/or more active disease activity states impact on reactogenicity needs to be further evaluated. Relevantly, b/tsDMARD-treated patients concomitantly receiving methotrexate experienced reduced reactogenicity to vaccination. In phase 2/3 trials of the BNT162b2 mRNA vaccine, systemic reactions were less common and milder in older adults, who also experienced slightly reduced protection against SARS-CoV-2 (32). The reduced reactogenicity seen in association with methotrexate may thus reflect an impairment in immunogenicity which is starting to be reported for this drug (12, 13).

As COVID-19 vaccination has progressed, rare immunologic adverse events (Bell's palsy, Guillain-Barré syndrome, anti-RNA antibodies, immune thrombocytopenic purpura, anaphylaxis) possibly linked to mRNA vaccines have been reported (40). Immunological reactions may be of particular concern in patients with immune-mediated inflammatory diseases, in whom underly-

Table III. Demographic and clinical factors associated with arthritis flares after of each of the two doses of the BNT162b2 mRNA COVID-19 vaccine. Univariable and multivariable analysis.

	Dose 1			Dose 2		
	OR	95% CI	*p*	OR	95% CI	*p*
Univariable analysis						
Age >55	0.97	0.44 to 2.16	0.94	0.89	0.40 to 1.96	0.77
Female gender	0.85	0.37 to 1.97	0.71	1.20	0.51 to 2.83	0.67
BMI >30	0.12	0.02 to 0.90	**0.04**	0.40	0.11 to 1.45	0.16
Smoking	1.81	0.69 to 4.78	0.23	0.52	0.15 to 1.87	0.32
≥1 comorbidity*	1.00	0.43 to 2.34	0.99	0.63	0.26 to 1.53	0.31
Previous COVID-19[#]	0.57	0.07 to 4.66	0.60	0.52	0.06 to 4.24	0.54
Systemic reactogenicity	1.94	0.87 to 4.33	0.10	3.36	1.44 to 7.85	**0.005**
Flare after D1	--	--	--	6.99	2.82 to 17.35	**<0.001**
Diagnosis						
RA	Reference			Reference		
PsA	0.97	0.33 to 2.83	0.96	1.66	0.62 to 4.43	0.31
SpA	0.81	0.25 to 2.58	0.72	1.18	0.40 to 3.52	0.76
Disease duration	1.01	0.96 to 1.06	0.78	0.99	0.94 to 1.04	0.63
Active disease[§]	2.76	1.17 to 6.51	**0.02**	2.48	1.05 to 5.83	**0.04**
Glucocorticoids	1.43	0.64 to 3.20	0.38	1.11	0.50 to 2.48	0.80
Prednisone dose >2.5 mg/d	1.16	0.43 to 3.10	0.77	0.83	0.29 to 2.36	0.72
HCQ	0.76	0.29 to 1.99	0.57	0.95	0.37 to 2.40	0.91
csDMARD	0.52	0.23 to 1.15	0.11	0.53	0.24 to 1.16	0.11
MTX	0.63	0.28 to 1.42	0.26	0.67	0.30 to 1.48	0.32
SSZ	1.64	0.42 to 6.36	0.48	0.38	0.05 to 3.03	0.36
LFN	0.74	0.09 to 6.25	0.78	--	--	--
b/tsDMARD						
TNFi	Reference			Reference		
IL-6Ri	0.16	0.09 to 4.77	0.94	0.67	0.21 to 2.11	0.49
IL-17/IL-23i	1.48	0.40 to 5.42	0.56	1.22	0.44 to 3.39	0.70
CTLA-4Ig	0.65	0.20 to 2.09	0.47	0.57	0.26 to 1.24	0.16
JAKi	3.60	1.28 to 10.09	**0.01**	6.37	1.35 to 10.79	**0.01**
Adherence to MTX witholding	0.99	0.87 to 1.89	0.45	1.03	0.86 to 2.98	0.33
Adherence to b/tsDMARD witholding	1.74	0.62 to 3.57	0.28	2.03	0.75 to 4.84	0.23
Multivariable analysis						
Systemic reactogenicity	--	--	--	5.77	1.68 to 19.92	**0.006**
Flare after D1	n.i.			24.72	5.21 to 17.18	**<0.001**
BMI >30	0.13	0.02 to 1.04	0.05	--	--	--
Active disease	2.82	1.01 to 8.09	**0.04**	1.86	0.99 to 6.03	0.05
csDMARDs	0.41	0.15 to 1.10	0.08	--	--	--
JAKi	3.96	1.39 to 11.27	**0.01**	3.10	0.99 to 7.85	0.05

*among those listed in the Charlson Comorbidity Index

[#]based on patient-reported history of swab-confirmed SARS-CoV-2 infection

[§]above the threshold of low disease activity according to the appropriate composite index: DAS28 >3·2; DAPSA >14; ASDAS-PCR >2·1. DAS28: Disease Activity Score on 28 joints; DAPSA: Disease Activity in Psoriatic Arthritis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score calculated with C-reactive protein.

b/ts: biologic/targeted synthetic; BMI: Body Mass Index; CCI: Charlson Comorbidity Index; cs: conventional synthetic; CTLA4Ig: cytotoxic T-lymphocyte associated protein-4 immunoglobulin; DMARD: disease-modifying anti-rheumatic drug; HCQ: hydroxychloroquine; IL-6Ri: interleukin-6 receptor inhibitor; IL-17/IL-23i: interleukin-17/interleukin-23 inhibitor; JAKi: Janus kinase inhibitor; LFN: leflunomide; MTX: methotrexate; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SpA: spondyloarthritis; SSZ: sulphasalazine; TNFi: tumour necrosis factor inhibitor.

ing dysregulation of the immune system and concurrent use of immunosuppressive therapies coexist. In our cohort, adverse events such as venous thrombosis were rare and more likely associated with the general state of inflammation and immune-suppression typical of RA (41). Similarly, reactivations of herpetic infections, as also reported by others (42), might be intrinsic to rheumatic diseases and their medications rather than to interference of mRNA vaccines with the interferon pathway. We acknowledge that small observational studies are unable to detect rare events. However, at present, no particular warnings on COVID-19 vaccines seem to emerge for patients with immune-mediated inflammatory diseases on various classes of immunomodulatory agents (43).

Virus-derived antigens, including SARS-CoV-2, may trigger or worsen immune-mediated rheumatic diseases both in course of natural infection and, although less commonly, after vaccination (17-20). The new technology of mRNA vaccines is under intense investigation because of the possible inflammatory responses elicited by toll-like receptor stimulation (20). The impact of COVID-19 vaccination on arthritis flares found in our study was overall reassuring. Even though ~25% of the

patients reported a transient worsening of disease activity, most required no or temporary symptomatic therapies to be managed. Although objective measures of disease activity could not be obtained in the immediate post-vaccination period, these patient-reported flares were either transitory or predominantly subjective, as the disease remained mostly stable at subsequent follow-up visits, with no significant need of DMARDs changes. The relatively high rate of self-perceived worsening found in this study however deserves some further considerations. A number of factors other than vaccine-induced immune mechanisms may affect risk of disease flares in arthritis patients, including disease activity, type of medications and treatment interruptions at the time of vaccination (4). Based on a cautionary adaptation of the recommendations for vaccination in rheumatic diseases (31), peri-vaccine drug suspension was advised to our patients. This might have accounted for the slightly higher rates of flares found here in comparison with other studies in which arthritis medications were not interrupted (21, 26, 27, 43). Absence of a control group not withdrawing therapy around vaccination hampers drawing definitive conclusions on the possible pro-inflammatory effect of mRNA vaccines. However, the increased risk of subjective disease worsening seen in association with shorter half-life drugs, such as JAKi, underscores the importance of balancing recommendations on drug management on the basis of careful benefit-risk analyses. Due to theoretical interference with immunogenicity to mRNA vaccines through inhibition of interferon signaling, current guidelines explicitly recommend JAKi withholding for one week after each vaccine dose (4). Experience with COVID-19 vaccines is however very limited, and interruption of JAKi in the context of other immunisations, such as pneumococcal and influenza, does not apparently increase efficacy in the face of significant worsening of the disease (44). Until definitive data on the impact of different classes of b/tsDMARDs on COVID-19 vaccine immunogenicity become available, drug suspension should therefore be advised with caution, particularly in patients with insufficient disease control.

In summary, mRNA COVID-19 vaccines appear overall safe and well-tolerated in arthritis patients receiving b/tsDMARDs alone or in combination with methotrexate and low-dose glucocorticoids. Although subjective relapses of the disease are not infrequent in a regimen of peri-vaccine drug withholding, most of them are transient and manageable with symptomatic therapies, with no significant impact on disease reactivation. These data help reassuring hesitant patients and guiding rheumatology health care providers on the use of COVID-19 vaccines during the pandemic.

Key messages

- *Reactogenicity*
  In patients with chronic immune-inflammatory arthritis receiving b/tsDMARDs, local and systemic reactions to BNT162b2 mRNA COVID-19 vaccine were slightly reduced compared to those observed in the general population. Methotrexate, but not b/tsDMARDs, significantly reduced the rates of systemic events.
- *Safety*
  BNT162b2 mRNA COVID-19 vaccine adverse events were rare, and no special safety warnings emerged.
- *Disease flare*
  Although subjective relapses of the disease in the peri-vaccination period occurred frequently in a regimen of DMARD withdrawal, most of them were transient and could be managed with symptomatic therapy. Patient-reported flares more commonly occurred in association with active arthritis and use of shorter half-life drugs, such as JAKi.

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