Systemic rheumatic disease flares after SARS-CoV-2 vaccination among rheumatology outpatients in New York City

Vaccination against SARS-CoV-2 is crucial for patients with systemic rheumatic diseases (SRDs), who may be at increased risk of severe outcomes post-COVID-19.[1] However, as patients with SRDs were not included in the mRNA vaccine trials (ie, Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273)), no data exist regarding whether these vaccines might trigger SRD flares. Sparse data suggest that other vaccines may be associated with SRD flares,[2 3] possibly from molecular mimicry triggering immune activation or non-specific adjuvant effects. As SRD flares are associated with disease deterioration, increased flares could have serious clinical implications.[4]

We report the interim results of a web-based survey evaluating SRD flare incidence post-SARS-CoV-2 vaccine. The survey was e-mailed 5 March 2021 to 3545 outpatients with SRDs seen at a large rheumatology division in New York City. ICD-10 algorithms were used to identify SRDs (online supplemental material). A self-reported disease flare was defined as 'a sudden worsening of your rheumatology condition or arthritis' within 2 weeks of the vaccine.

As of 12 April 2021, out of 1483 respondents (41.8% response rate), 1101 patients (74.2%) with SRDs reported receiving at least one dose of a SARS-CoV-2 vaccine and provided flare data (mean age: 60.8 years (14.2 years); 80.6% female; 86.0% White and 5.7% Hispanic/Latinx ethnicity). Five hundred and ninety seven patients (54.2%) received Pfizer vaccine, 483 (43.9%) received Moderna vaccine, 16 (1.5%) received Janssen vaccine and 3 (0.3%) received AstraZeneca vaccine. A total of 202 SRD flares were reported by 165 patients (14.9%). History of suspected/confirmed COVID-19 occurred in 7.9% with SRD flare and 6.7% without SRD flare. Mean age of patients reporting an SRD flare was 59.6 years (13.9 years) versus 61.0 years (14.2 years) in the non-flare group; the majority of both groups were female (89.7% vs 80.0%), White (88.5% vs 85.6%) and non-Hispanic/Latinx (95.2% vs 92.2%). 15.9% of patients receiving Moderna vaccine and 14.2% receiving Pfizer vaccine reported SRD flares.

Of the patients receiving either Pfizer or Moderna vaccines, 654 (59.4%) had received both doses. Of these patients, 113 (17.0%) flared, 26 (23.0%) flared only after the first dose, 48 (42.5%) flared only after the second dose and 37 (32.7%) flared after both doses. Flares after the first and second dose of Pfizer vaccine were 10.3% vs 10.9%, and flares after the first and second dose of Moderna vaccine were 9.6% vs 16.3%, respectively.

Both the flare and non-flare groups used medications for prevention and treatment of vaccine side effects (table 1). Most SRD flares were characterised as moderate to severe (57.3% after first vs 62.4% after second dose), and as qualitatively 'typical' SRD flares (70.9% after first dose vs 68.2% after second dose). Flares were predominantly reported as joint pain, joint swelling, muscle aches and fatigue (table 1). While 27.7% of flares started 1 day after vaccination, 61.4% began after 2–7 days and 10.9% occurred more than 7 days later (table 1). Most SRD flares resolved within 7 days of onset, but 26.2% lasted for 8–21 days and 8.9% for >21 days.

Interim data from our cohort demonstrate that >85% of patients did not report an SRD flare post-SARS-CoV-2

Table 1 Vaccine and flare characteristics in outpatients with systemic rheumatic diseases, stratified by flare status post-COVID-19 vaccination

	First dose vaccine N=1101		Second dose vaccine* N=626	
	Flare N=117 (10.4%)	No Flare N=984 (87.5%)	Flare N=85 (13.6%)	No Flare N=541 (86.4%)
Vaccine manufacturer, N%				
Pfizer	67 (57.3%)	530 (53.9%)	35 (41.2%)	285 (52.7%)
Moderna	47 (40.2%)	436 (44.3%)	50 (58.8%)	256 (47.3%)
Janssen	3 (2.6%)	13 (1.3%)	N/A	N/A
AstraZeneca	0 (0%)	3 (0.3%)	0 (0%)	0 (0%)
Other†	0	1 (0.1%)	0	0
Missing	0	1 (0.1%)	0	0
Medications taken for prevention of COVID-19 vaccine side effects (prior to vaccine) (N, %)‡				
No medications	104 (88.9%)	911 (92.6%)	73 (85.9%)	502 (92.8%)
Benadryl	7 (6.0%)	20 (2.0%)	2 (2.4%)	13 (2.4%)
Corticosteroids	2 (1.7%)	7 (0.7%)	3 (3.5%)	4 (0.7%)
Acetaminophen	4 (3.4%)	29 (3.0%)	7 (8.2%)	24 (4.4%)
NSAIDs/CoX-2 inhibitors	4 (3.4%)	22 (2.2%)	1 (1.2%)	11 (2.0%)
Medications taken for treatment of COVID-19 vaccine side effects (after vaccine) (N, %)‡				
No medications	64 (54.7%)	748 (76.0%)	26 (30.6%)	310 (57.3%)
EpiPen	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)
Benadryl	7 (6.0%)	10 (1.0%)	4 (4.7%)	13 (2.4%)
Corticosteroids	6 (5.1%)	3 (0.3%)	4 (4.7%)	5 (0.9%)
Acetaminophen	29 (24.8%)	152 (15.5%)	36 (42.4%)	166 (30.7%)
NSAIDs/CoX-2 inhibitors	25 (21.4%)	82 (8.3%)	31 (36.5%)	76 (14.1%)
Flare severity (N, %)				
Mild	50 (42.7%)		32 (37.7%)	
Moderate	49 (41.9%)		44 (51.8%)	
Severe	18 (15.4%)		9 (10.6%)	
Flare described as 'typical' (N, %)				
Yes	83 (70.9%)		58 (68.2%)	
No	18 (15.4%)		16 (18.8%)	
Not sure	16 (13.7%)		11 (12.9%)	
Flare symptoms (N, %)‡				
Fever	6 (5.1%)		9 (10.6%)	
Joint pain	98 (83.8%)		74 (87.1%)	
Joint swelling	56 (47.9%)		38 (44.7%)	
Skin rash	14 (12.0%)		10 (11.8%)	
Fatigue	62 (53.0%)		57 (67.1%)	
Muscle aches	57 (48.7%)		48 (56.5%)	
Other§	16 (13.7%)		11 (12.9%)	
Number of days after vaccine when flare started (N, %)				
1 day	30 (25.6%)		26 (30.6%)	
2–3 days	39 (33.3%)		26 (30.6%)	
4–7 days	35 (29.9%)		24 (28.2%)	
>7 days	13 (11.1%)		9 (10.6%)	
Length of flare (N, %)				
1 day	7 (6.0%)		2 (2.4%)	
2–4 days	23 (19.7%)		40 (47.1%)	
5–7 days	41 (35.0%)		16 (18.8%)	
8–21 days	28 (23.9%)		25 (29.4%)	
>21 days	18 (15.4%)		0 (0%)	
Missing	0		2 (2.4%)	

Flare defined as self-reported 'sudden worsening of rheumatology condition or arthritis' within 2 weeks of COVID-19 vaccination.
*654 patients reported receiving 2/2 vaccine doses, but 28 of these patients did not respond to second dose flare questions.
†One participant reported receiving Sinovac vaccine from China.
‡Rows not mutually exclusive.
§Other flare symptoms indicated by patients at first COVID-19 vaccine dose: paresthesias, swelling in face or feet, 'brain fog', muscle spasms, psoriasis rash, migraines. Other symptoms at second vaccine dose: paresthesias, swelling in face or feet, and muscle spasms.
CoX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammtory drugs.

vaccination. This information is reassuring and can help inform vaccine decision-making for patients with SRDs. Although we did not collect laboratory studies, most SRD flares were described as 'typical', suggesting these symptoms are not vaccine's adverse effects being misreported as disease flares. However, when patients did flare, the majority of flares were reported as moderate to severe, with some lasting >3 weeks. Therefore, it will be important to follow these patients prospectively, as well as to perform analyses which incorporate potential confounders to identify predictors of SRD flares post-vaccination. Whether vaccine manufacturer is an independent predictor of SRD flare remains to be determined.

Medha Barbhaiya ,[1,2] **Jonah M. Levine**,[3] **Vivian P. Bykerk** ,[1,4] **Deanna Jannat-Khah**,[1,4] **Lisa A. Mandl**[1,2]

[1]Division of Rheumatology, Hospital for Special Surgery, New York, New York, USA
[2]Department of Medicine and Department of Population Health Sciences, Weill Cornell Medicine, New York, New York, USA
[3]Hospital for Special Surgery, New York, New York, USA
[4]Department of Medicine, Weill Cornell Medical College, New York, New York, USA

Correspondence to Dr Medha Barbhaiya, Division of Rheumatology, Hospital for Special Surgery, New York, NY 10021-4898, USA; barbhaiyam@hss.edu

Handling editor Josef S Smolen

Contributors All authors have made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data; were involved in drafting the work or revising it critically for important intellectual content; provided final approval of the version published; and were in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding MB is currently supported by the Rheumatology Research Foundation Investigator Award and the Barbara Volcker Centre for Women and Rheumatic Diseases at Hospital for Special Surgery. LAM received grant support from Regeneron Pharmaceuticals, and is an associate editor at Annals of Internal Medicine.

Disclaimer The funders had no role in study design, data collection, analysis, decision to publish or preparation of the manuscript.

Competing interests MB is currently supported by the Rheumatology Research Foundation Investigator Award and the Barbara Volcker Center for Women and Rheumatic Diseases at Hospital for Special Surgery. LAM received grant support from Regeneron Pharmaceuticals, and is an associate editor at *Annals of Internal Medicine*. The funders had no role in study design, data collection, analysis, decision to publish or preparation of the manuscript.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220732).

To cite Barbhaiya M, Levine JM, Bykerk VP, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2021-220732

Received 6 May 2021
Accepted 10 June 2021

Ann Rheum Dis 2021;**0**:1–2. doi:10.1136/annrheumdis-2021-220732

ORCID iDs
Medha Barbhaiya http://orcid.org/0000-0002-6670-7696
Vivian P. Bykerk http://orcid.org/0000-0002-1219-3845

REFERENCES

1 D'Silva KM, Jorge A, Cohen A, *et al*. COVID-19 outcomes in patients with systemic autoimmune rheumatic diseases (SARDs) compared to the general population: a US multi-center comparative cohort study. *Arthritis Rheumatol* 2020.
2 Mok CC, Chan KH, Ho LY, *et al*. Safety and immune response of a live-attenuated herpes zoster vaccine in patients with systemic lupus erythematosus: a randomised placebo-controlled trial. *Ann Rheum Dis* 2019;78:1663–8.
3 Ray P, Black S, Shinefield H, *et al*. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15-59 years of age. *Vaccine* 2011;29:6592–7.
4 Bechman K, Tweehuysen L, Garrood T, *et al*. Flares in rheumatoid arthritis patients with low disease activity: predictability and association with worse clinical outcomes. *J Rheumatol* 2018;45:1515–21.

Supplementary Material

Additional Methods:

Our entire survey was piloted among 12 non-physicians, 6 rheumatologists, and 3 other physicians who provided valuable feedback regarding the clarity of questions and length, covering a range of ages from 19 years to mid-80s. Patients with incomplete questionnaires contributed data from questions which they answered; missing data is reported for individual covariates. This study was approved by the Hospital for Special Surgery Institutional Review Board. ICD-10 codes were used to identify patients with SRDs (Supplementary Table 1). We evaluated demographic baseline characteristics of survey respondents to non-respondents (Supplementary Table 2).

Supplementary Table 1. ICD-10 Algorithms Used to Identify Patients with Systemic Rheumatic Diseases (SRDs)

SRD	ICD-10 Codes*
Rheumatoid arthritis	M05.x, M06.x
Polyarthritis-multiple sites, Type not Specified	M13.xx
Palindromic rheumatism	M12.3x
Behcets	M35.2
Systemic lupus erythematosus	M32.x
Systemic sclerosis	M34.x
Ankylosing spondylitis/sacroiliitis	M45.x
Inflammatory Spondyloarthropathy	M46.9x, M46.80, M46.82, M46.84, M46.86, M46.87, M46.88
Sjogren's/Sicca syndrome	M35.0x
Psoriatic arthritis	L40.5x
Juvenile Arthritis	M08.x
Mixed connective tissue disease	M35.8, M36.8
Undifferentiated Connective Tissue Disease	M35.9
Myositis	M33.x, G72.41, M36.0
Vasculitides	M30.x, M31.x, I77.6
Sarcoidosis	D86.x
Overlap syndrome	M35.1
Relapsing Polychondritis	M94.1
Diffuse eosinophilic fasciitis	M35.4
IgG4-related disease	M35.5
Autoinflammatory Syndromes	M04.x
Enteropathic arthritis-multiple sites, Inflammatory Arthritis Associated with IBD	M07.69, M07.6
Primary Antiphospholipid Syndrome	D68.61, D68.62, D68.3
Polymyalgia Rheumatica	M35.3

**Algorithms required two codes within the same row ≥ 7 days apart*

Additional Results:

Respondents to our survey were slightly older (58.7 [14.2] versus 57.2 [16.5] years) and were more likely to be white (84.2% versus 78.3%) (Supplementary Table 2). Although the difference in age was statistically significant likely due to our large sample size, this difference was very small and not likely to be clinically meaningful. Given that fewer non-White patients responded, our survey may not be generalizable to non-White patients.

Supplementary Table 2. Demographic Characteristics of Survey Respondents with an SRD to Non-Respondents with an SRD

	Respondents N=1483	Non- Respondents N=2062	P-value**
Age in years, mean (SD)	58.7 (14.2)	57.2 (16.5)	<0.01
BMI, mean (SD)	26.8 (8.2)	26.6 (6.3)	0.41
Female	1213 (81.8)	1652 (80.1)	0.24
Race			<0.01
• White	1248 (84.2)	1614 (78.3)	
• Non-white*	192 (12.9)	387 (18.8)	
• Missing	43 (2.9)	61 (3)	
Ethnicity			0.71
• Hispanic/Latinx	115 (7.8)	167 (8.1)	
• Not Hispanic/ Latinx	1338 (90.2)	1846 (89.5)	
• Missing	30 (2)	49 (2.4)	

*Includes: American Indian/Alaskan Native/ Native Hawaiian/Other, Asian/ Indian Subcontinent, Black race
**T-tests were used for continuous variables, Fisher's Exact tests were used for categorical variables. Missing values are reported but were not included in p-value calculations.