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Association of COVID-19 Vaccinations with Flares of Systemic Rheumatic Disease: A Case-Crossover Study

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Abstract

Objectives: To determine the association of COVID-19 vaccination with flares of systemic rheumatic disease (SRD).

Methods: Adults with autoimmune or autoinflammatory conditions ("systemic rheumatic disease") in a single-center COVID-19 Rheumatology Registry were invited to enroll in a study of flares. COVID-19 vaccine information from 3/5/21-9/6/22 was obtained from chart review and self-report.

Participants self-reported periods of SRD flare and periods without SRD flare. "Hazard periods" were defined as time before self-report of flare, and "control periods" as time before self-report of no flare. The association between flare and COVID-19 vaccination was evaluated during hazard and control periods through univariate conditional logistic regression stratified by participant, using lookback windows of 2, 7 and 14 days.

Results: 434 subjects (mean age 59 years [°13], 84.1% female, 81.8% White, 64.5% inflammatory arthritis, 27.0% connective tissue diseases) contributed both hazard and control periods and were included in analysis. A total of 1316 COVID-19 vaccinations were identified (58.5% Pfizer-BioNTech, 39.5% Moderna, 1.4% Johnson & Johnson);96.1% of participants received ≥1 dose and 93.1% ≥2 doses. There was no association between COVID-19 vaccination and flares in the subsequent 2, 7 or 14 days (OR 1.46 [95% CI, 0.86-2.46], OR 1.09 [95% CI, 0.76-1.55], OR 0.85 [95% CI, 0.64-1.13] respectively). Analyses stratified on sex, age, SRD subtype and vaccine manufacturer similarly showed no association between vaccination and flare.

Conclusion: COVID-19 vaccination was not associated with flares in this cohort of participants with SRD. These data are reassuring and can inform shared decision-making on COVID-19 immunization.

Graphical Abstract

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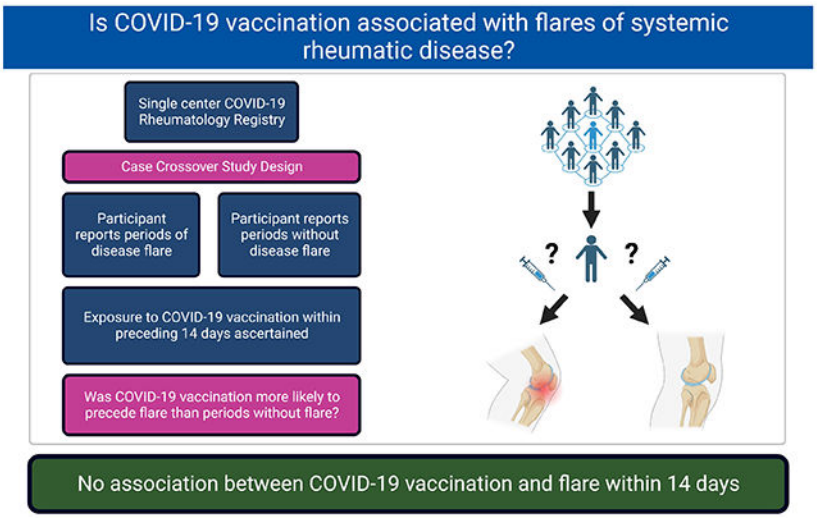

INTRODUCTION

COVID-19 has caused over 770 million infections and 6.9 million deaths worldwide since the first cases were reported in December 2019 (1). The dissemination of effective COVID-19 vaccines has markedly diminished the virus's impact on the general public. However, as those with systemic rheumatic disease (SRD) were largely excluded from vaccine clinical trials, potential disease-specific risks of immunization in this population are less clear (2, 3).

Accumulating real-world evidence has demonstrated the safety (4) and immunogenicity (5, 6, 7, 8) of COVID-19 vaccines in vulnerable SRD populations. The American College of Rheumatology's (ACR) COVID-19 vaccination clinical guidance summary recommends patients with SRD be prioritized for immunization (9). However, individuals with SRD often refuse routine immunizations due to fears of triggering disease flares (10, 11). Vaccine-induced flare has biologic plausibility with theoretical mechanisms including molecular mimicry (12) or inflammatory cytokine production (13). Because SRD flares increase risks of disability and end-organ damage (14), mitigating triggers is an important component of disease management.

Data suggest 4-27% of individuals may flare following COVID-19 vaccination (4, 15, 16, 17, 18, 19, 20, 21), but there is no clear evidence demonstrating a causal link between immunization and flare. Studies attempting to investigate this association are limited by lack of comparator groups, recall bias and information bias (16, 18, 19, 21, 22). Patients with SRD can benefit from vaccination: data suggest this group may be at increased risk of hospitalization, mechanical ventilation and death from COVID-19 (23, 24), and a recent population-based study found the risk of severe COVID-19 infection has persisted since the emergence of the Omicron variant (25). As vaccination coverage expands among individuals with SRD and approaches rates in the general population (25), an accurate estimation of flare risk following immunization is important for informing both public health guidance and individual patient care.

Rheumatologists play a central role in assessing patients' vaccination status and directing shared decision-making on vaccine uptake, and offering evidence-based recommendations is key to patient-centered care. To address this knowledge gap, we designed a study to determine the association between COVID-19 vaccination and SRD flares.

METHODS

Participants

Patients ≥18 years evaluated at least once by a rheumatologist at Hospital for Special Surgery (HSS) from 4/1/2018-4/21/2020 were invited to join the HSS COVID-19 Rheumatology Registry. Based in New York City, HSS is an academic referral center for musculoskeletal and rheumatic diseases. Participant demographic data were collected through self-report, with missing values abstracted from the electronic health record (EHR) as available. Data were collected and maintained on the REDCap platform, a secure software tool developed for clinical research data management (26).

Subjects enrolled in the Registry were eligible for this study if they met International Classification of Diseases (ICD)-10 definitions for an SRD diagnosis, which required the same ICD-10 code on 2 visits ≥14 days apart (Supplemental Table 1). Subjects with ICD-10-identified rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and psoriatic arthritis (PsA) had diagnoses validated by chart review using classification criteria (27, 28, 29, 30). Diagnoses were grouped into composite categories for analyses: 1. inflammatory arthritis (radiographic and non-radiographic axial spondyloarthritis [AxSpA], enteropathic arthritis, juvenile idiopathic arthritis, palindromic rheumatism, polymyalgia rheumatica [PMR], polyarthritis, PsA, RA and spondyloarthropathy), 2. connective tissue disease (secondary antiphospholipid syndrome [APS], eosinophilic fasciitis, mixed connective tissue disease [MCTD], myositis, overlap connective tissue disease, Sjogren's/sicca, SLE, SSc and undifferentiated connective tissue disease [UCTD]) and 3. all other SRD diagnoses (any vasculitis, autoinflammatory syndromes, primary APS, Behcet's, IgG4-related disease, relapsing polychondritis and sarcoidosis). If an individual had ICD-10-identified diagnoses across multiple composite categories, the participant's treating rheumatologist was consulted and the chart reviewed to determine the primary SRD diagnosis. Participants who did not have a primary SRD diagnosis after adjudication were analyzed in a fourth category, ">1 SRD subtype."

HSS COVID-19 Rheumatology Registry enrollees completed comprehensive web-based questionnaires on demographics and medical history, and were invited to opt into a study evaluating SRD flares. Participants were aware the investigators were studying flare, but they were not informed of the hypothesis that flares may be associated with COVID-19 vaccination. Subjects enrolling in the flare study received an electronic link to a shorter, flare-focused survey that could be accessed each time their disease flared. Participants were also sent the survey link in monthly reminder e-mails to access the flare-focused survey during flares.

Exposure Classification

The exposure of interest was COVID-19 vaccination. We obtained COVID-19 vaccination information by reviewing each participant's immunization tab of our institution's EHR, which includes records from the New York City Immunization Registry, Surescripts™ pharmacy network and clinical data inputted by staff. We also extracted vaccine information from survey data when available. Participants self-reported dates and manufacturers of COVID-19 immunizations as part of over 90 items on the comprehensive Registry questionnaires. To mask the specific interest in the relationship between flare and COVID-19 vaccination on the shorter flare-focused surveys, participants who reported an SRD flare were queried about a range of recent exposures, including COVID-19 vaccinations, non-COVID-19 vaccinations, infections, medication adjustments, fatigue and stress levels. Subjects who indicated their SRD was not flaring on the flare-focused survey did not self-report exposures. Information on CDC categories of local and systemic vaccine side-effects (31, 32) was collected when subjects self-reported COVID-19 vaccinations.

EHR and self-reported vaccination data were checked against each other prior to analyses. If dates were discordant or unavailable from both sources and within 14-day hazard or control periods, the study team requested participants upload their COVID-19 immunization card to the EHR as the gold standard. A random subset of 76 immunization cards was checked against EHR and self-report data; EHR dates were more often concordant with immunization cards than self-reported vaccination dates (77.6% vs. 63.2% agreement). The median days of difference between immunization card and EHR vaccine dates was 0 (range −350 to 352); the median days of difference between immunization card and self-report dates was 0 (range −365 to 352). EHR-based vaccine data was thus preferentially used over self-report vaccine information when the two were discrepant.

Outcome Classification

The outcome of interest was SRD flare. Participants were asked on comprehensive Registry questionnaires and flare-focused surveys whether their SRD was currently flaring, and if so, to report the flare's onset date, symptoms and severity (mild/moderate/severe). Participants were also asked on flare-focused surveys to indicate whether their current symptoms were consistent with their "typical" SRD flares.

Subjects self-identifying as having SLE (33), RA (34) or SSc (35) were prompted to complete a validated disease-specific disease activity instrument (SLAQ, RA-FQ and ScleroID). The lupus flare instrument was modified to reflect disease activity over the past week (original SLAQ survey: past 3 months) to standardize with the other instruments. The original ScleroID contains a single item regarding social and physical limitations; in this study, physical and social limitations were queried separately, and a composite average was used for scoring. Subjects reporting other SRD diagnoses completed a generic instrument adapted from the validated RA-FQ (34).

"Hazard periods" were defined as time prior to self-reported SRD flare. Control periods" were identified by the submission date of either the Registry questionnaires or flare-focused surveys in which patients indicated they were not currently having an active SRD flare.

Participants could contribute hazard and control periods from comprehensive Registry questionnaires and/or flare-focused surveys. Flares submitted >62 days after the reported onset date were excluded to minimize recall bias. To be included in analysis, a participant had to have an ICD-10-identified SRD and submit ≥1 hazard and ≥1 control period (i.e. report at least 1 flare and 1 non-flare period); the first hazard period could occur before the first control period, or vice versa.

Statistical Methods

In the case-crossover design, subjects contribute “hazard periods” when they experience the outcome of interest and “control periods” when they do not. Within each subject, the occurrence of an exposure is compared during hazard and control periods; if an exposure is associated with the outcome of interest, it will be more likely to occur during hazard periods than during control periods (Figure 1) (36, 37). Because participants serve as their own controls, the case-crossover methodology accounts for time-invariant covariates within each subject. To 1) minimize time-varying confounding and 2) use biologically-plausible windows for vaccines to induce flare through both innate and adaptive immune activation, we performed our primary analysis with 3 exposure periods: 2, 7 and 14 days.

Primary Analysis

We used a univariate conditional logistic regression model, stratified by participant with a log likelihood equivalent Cox proportional hazards, to evaluate for an association between flare and vaccination in the 2, 7 and 14 days preceding flare onset. These co-primary exposure windows were chosen to account for the phases of immune system activation following vaccination, as theoretical models of vaccine-induced flare involve both arms of the immune system. The innate immune response is primarily activated in the 48 hours following immunization, after which time adaptive immunity mounts and subsequently amplifies (38, 39). We did not extend the exposure window back further due to the risk of confounding and recall bias. Because vaccinations were detected by more than one method, we performed a sensitivity analysis determining the association of vaccination and flare using only vaccine doses with concordant EHR/self-report data or data verified by immunization card review.

Secondary Analyses

We performed univariate subgroup analyses exploring the association between vaccination and flare stratified on sex (F/M), age group (18-44, 45-64, 65+), SRD category (inflammatory arthritis/connective tissue disease), dose number (1, 2, 3+) and manufacturer (Pfizer-BioNTech, Moderna); we included only those subgroups with adequate numbers to model associations. The primary and secondary case-crossover analyses detail unadjusted 95% confidence intervals (CI). We did not adjust for any covariates in this model, as each participant was analyzed as a unique stratum and thus self-controlled for time-invariant demographic variables over the course of the study period (age, sex, race/ethnicity, medical comorbidities etc.). No multiple comparison adjustments were performed, maximizing our power to detect sub-groups with potentially harmful associations with vaccination.

We performed exploratory descriptive analyses of CDC vaccine symptoms and flare occurrence with Chi square testing. We also evaluated the association between flare severity (mild/moderate/severe) and the flare's temporal relation to vaccination via an ordinal logistic regression model applied to the entire study population. In this additional secondary analysis, our independent variable of interest was timing of flare onset following vaccination (0-2, 3-7, 8-14 days), as compared to the referent group of flares with no recent prior vaccination exposure. Covariates included binary sex(F/M), ethnicity (Hispanic/non-Hispanic), age group (18-44, 45-64, 65+), SRD category (inflammatory arthritis/connective tissue disease/other/≥1), CDC comorbidity count (none/1/2+) and BMI (<24.9, 25-29.9, 30+).

The HSS Institutional Review Board approved this study.

RESULTS

Data were collected between 3/5/2021 (the first comprehensive Registry questionnaire distribution following authorization of COVID-19 vaccines) and 9/6/2022 (the final day that monovalent COVID-19 mRNA vaccines were authorized for use in New York State). 1128 Registry participants with ICD-10-identified SRD opted into this study. After exclusion of subjects who reported only hazard periods or only control periods, 434 participants (38.5%) were eligible for analysis (Supplemental Figure 1).

Participant and vaccine characteristics

At the time of Registry enrollment, study subjects' mean age was 59 years (±13), 84.1% were female, 81.8% were White, 6.7% were Hispanic or Latino; 59.0% had commercial insurance and 35.3% had a non-Medicaid Medicare plan. ICD-10 codes and clinical adjudication identified 64.5% of participants with primary inflammatory arthritis and 27.0% with connective tissue diseases; 5.3% had another SRD and 3.2% >1 SRD subtype (Table 1). 86.3%, 88.2%, 74.6% and 64.0% subjects with ICD-10-identified SLE, SSc, RA and PsA met classification criteria. When they entered the Registry, 355 (81.8%) participants self-reported using immunosuppression and/or immunomodulatory medications. 157 (36.2%) were taking an antimalarial, 177 (40.8%) were taking a conventional synthetic DMARD (csDMARD), 181 (41.7%) reported biologic use and 39 (9.0%) were taking a small molecule. 160 (36.9%) subjects reported corticosteroid use (Table 2).

During the study period, 997 disease flares and 1176 non-flare control periods were reported, with a mean of 2.3 (±2.04) flares and 2.7 (±1.94) control periods per subject. At time of flare self-report, 35.0% flares had a duration ≤2 days, 63.6% were ≤7 days and 76.8% were ≤14 days; 8.1% flares had a duration >1 but ≤2 months (Supplemental Table 2). 11.0% flares were preceded by infection in the week before onset.

96.1% of participants received at least 1 dose of a COVID-19 vaccine and 93.1% received at least 2 doses. In total, 1316 COVID-19 vaccine doses were ascertained: EHR review identified 1182 vaccinations, while 890 doses were self-reported. 770 (58.5%) vaccinations were Pfizer-BioNTech, 520 (39.5%) were Moderna, 19 (1.4%) were Johnson & Johnson; 7 (0.5%) were missing manufacturer information. 664/1316 (50.5%) doses had either

concordant EHR/self-report dates or dates provided directly from immunization cards. 288 doses fell in the 14-day hazard and control periods of which 225 had both EHR/self-report data available; 198/225 (88.0%) dates for this subgroup were concordant and 14 were subsequently validated by immunization card confirmation. This subset was used in the sensitivity analysis.

Primary analysis

Using 2-, 7- and 14-day lookback windows there were 44, 91 and 135 vaccine exposures during hazard periods, with flare occurring after 3.3%, 6.9% and 10.3% of vaccinations, respectively. There were 31, 77 and 153 vaccine exposures during control periods during the 2-, 7-, and 14-day exposure windows. There was no association between flare and COVID-19 vaccination with 2-day (OR 1.46 [95% CI 0.86-2.46]), 7-day (OR 1.09 [95% CI 0.76-1.55]) or 14-day (OR 0.85 [95% CI 0.64-1.13]) lookback windows. Sensitivity analyses on the subset of vaccinations with concordant EHR/self-report or immunization card-confirmed dates similarly showed no association between flare and vaccination (2-day OR 1.49 [95% CI, 0.84-2.66]; 7-day OR 1.13 [95% CI, 0.76-1.68]; 14-day OR 0.86 [95% CI, 0.63-1.18]) (Table 3).

Secondary analyses

Subgroup analyses stratified by age, sex, SRD category and vaccine manufacturer showed no association between flare and recent COVID-19 immunization using any lookback period. On 14-day lookback, there were significantly fewer flares after the second dose of COVID-19 vaccination (OR 0.62 [95% CI, 0.41-0.94]) (Table 4).

Information on whether flares were “typical” was available for 813/997 (81.5%) flares, of which 664/813 (81.7%) were typical. Flare severity was available for 996 flares; 356 (35.7%) were rated mild, 515 (51.7%) moderate and 125 (12.6%) severe. Secondary analysis of flare severity predictors found that flares preceded by vaccination in the prior 3-7 days were more likely to be rated in a higher severity category than those flares without a vaccine exposure in the hazard period (adjusted OR 1.92 [95% CI, 1.05-3.51]). Using the same model, subjects with connective tissue diseases were more likely to report milder flares than participants with inflammatory arthritis (adjusted OR 0.55 [95% CI, 0.40-0.74]). Multi-variable regression also found that male participants reported more severe flares than female participants (adjusted OR 1.53 [95% CI, 1.08-2.17]). Increased flare severity was not associated with age, ethnicity, BMI or number of CDC high-risk comorbid conditions for severe COVID-19 (Table 5).

Disease-specific flare instrument scores were similar to global severity rankings. For respondents with ICD-algorithm-identified RA, the mean flare severity score on the RA-FQ was 29 (±10; range 0-50; higher=more severe), for those with SLE, the mean score on the SLAQ was 14 (±5; range 3-26; higher=more severe) and for those with SSc, the mean ScleroID score was 4.6 (±1.6; range 1.3-8.3; higher=more severe). The mean score on the general arthritis instrument, adapted from the RA-FQ, was 26 (±11; range 3-50).

Peri-vaccination medication use and side-effects

Information on peri-vaccination analgesic or anti-inflammatory use, local and systemic side-effects (31, 32) and allergic reactions was submitted by 374/434 (86.2%) subjects who self-reported vaccine doses; this information was unavailable for those vaccine doses detected exclusively through EHR or immunization card review. Participants reported no acetaminophen or NSAID use prior to 812/897 (90.5%) doses and no such supportive therapy after 547/897 (61.0%) doses. Data on peri-vaccination SRD medication management was available for 895 self-reported vaccine doses: rheumatologic medications were taken without adjustment 64.6-75.8% of the time, depending on vaccine dose number.

Of the 374 participants with side-effect data, 86.1% reported at least one local, system or allergic side-effect following at least one vaccination dose. 468/896 (52.2%) and 491/896 (54.8%) self-reported doses were complicated by local and systemic side-effects, respectively. Injection site pain, fatigue and headache were the most common post-vaccination side-effects, reported following 377 (42.1%), 352 (39.3%) and 258 (28.8%) of doses, respectively. Subjects reported allergic side-effects for 115 (12.8%) doses. 14 (1.6%) vaccine doses resulted in an adverse event requiring an urgent care visit, emergency room evaluation or hospitalization, most commonly after doses 1 or 2. There was no association between reporting a vaccine side-effect and reporting an SRD flare within 14 days (any vaccine side-effect: OR 1.51 [95% CI, 0.93-2.52]; systemic side-effect: OR 1.41 [95% CI, 0.92-2.18]). There was no significant difference between Pfizer-BioNTech and Moderna in report of systemic side-effects or mean number of side-effects in the 2 days post-vaccination (systemic side-effect: OR 0.93 [95% CI, 0.17-5.54]; mean difference in side-effects 0.15 [95% CI, −3.52-3.82]).

DISCUSSION

This case-crossover study of participants with a range of SRD found no association between flare and COVID-19 vaccination in the preceding 2, 7 or 14 days. Additionally, we found no such association when stratifying by SRD subtype, age group, sex or vaccine manufacturer. Over 90% of subjects in our cohort received at least 2 doses of vaccines with low incidence of serious adverse events, confirming existing research on the reassuring safety profile of COVID-19 vaccines in this population (40).

The results of this investigation help clarify the still-debated relationship between COVID-19 vaccination and flares of rheumatic diseases, which has shown mixed results to-date. A self-controlled case series of subjects with SRD in the United Kingdom found a negative correlation between first vaccination dose and subsequent flare requiring primary care consultation and corticosteroid prescription; this effect was seen most strongly in patients with inflammatory arthritis. No association was found between flare and subsequent vaccination doses (22). A retrospective cohort study of patients with RA and reactive arthritis in Hong Kong similarly detected no association between two doses of mRNA and inactivated viral vector vaccines with subsequent arthritis-related hospitalizations or subspecialist outpatient visits (41). However, both studies used proxy measures for flares. Given the reliance on healthcare encounter or prescriptions for outcome ascertainment, these analyses were unlikely to detect milder flares that did not rise to the level of requiring

healthcare evaluation but may nevertheless be important for patients' quality of life and long-term health.

Several studies using patient-reported flare have published post-vaccination flare rates. A large, international case series of patients with SRD who received COVID-19 vaccination found that 4.4% of subjects flared as determined by physician report (4). Another international study conducted April-August 2021 queried patients with SRD about flares in the 2 months following vaccination and found that 4.9% of participants experienced flare requiring change in treatment (20). One prospective study of individuals with self-identified SRD who received mRNA vaccination from 12/2020-4/2021 found that 11% of patients reported a disease flare requiring treatment (19); our group surveyed Registry participants 12/2020-4/2021 on whether their disease flared in the 14 days following vaccination and found that 17% vaccine recipients reported it had (42). A multinational, cross-sectional study of 3543 patients using electronic surveys found flare rates ranging from 9.5-26.7% depending on the flare metric used (21). Our finding of flare following 135 (10.3%) doses of vaccines over the 18-month study period is in line with the flare rates reported in the recent literature. However, our case-crossover design critically includes a comparator group, demonstrating that although some participants flared within 14 days of vaccination, they were statistically no more likely to do so relative to vaccine-unexposed periods. This finding challenges the assumption that there is a causal link between SRD flare and COVID-19 vaccine.

Vaccine side-effects and SRD flares share overlapping features, and differentiating side-effect from flare is important. Patients with SRD have been shown to be reliable assessors of their disease status (43, 44, 45, 46). When asked, participants judged their flares to be consistent with typical flares 81.5% of the time. It is possible that some participants misclassified post-vaccine adverse events as disease flares. However, this would have led to flare over-detection, making it more likely to find a harmful association between COVID-19 vaccination and flares. Conversely, some subjects may have misclassified flare as vaccine side-effect, which would have resulted in under-ascertainment of our outcome. To further distinguish flare from vaccine side-effects, we tested the association of self-reported vaccine side-effects with flare, and found none therein.

Knowledge of whether specific SRD subpopulations are at higher risk for postvaccine flare can inform individual decision-making on vaccine uptake. The literature offers conflicting evidence in this regard. Certain investigations have found correlations between post-vaccine flare and particular SRDs, with greater risk associated with inflammatory arthritides in some studies and connective tissue diseases in others, though there is substantial heterogeneity of results (4, 16, 20, 21). Still others suggest an association between flare risk and use of particular immunosuppressive regimens—such as JAK inhibitors, combination csDMARD therapy and steroid use—though there is significant variability across studies (4, 15, 16, 17, 19). We performed several secondary analyses to evaluate associations of particular covariates with flare and flare severity; we found no increased risk of disease flare following vaccination when stratified by composite disease type, age group, sex or vaccine manufacturer. We did not analyze this association by individual SRDs as this was not planned *a priori* and we preferred to avoid multiple comparisons. We found a negative

association between vaccination and flare after the second dose of vaccine; this may represent confounding by indication, as those who flared after their first dose may have been less likely to obtain a second.

Participants deemed their flares mild-moderate 87.4% of the time. When flares occurred, they tended to be rated as more severe by men and when the onset was 3-7 days after vaccination. Since the adaptive immune response begins amplifying 3-7 days after vaccination (47), this immunologically primed window may lead to more severe flares. However we did not see continued increased flare severity as the humoral response and cellular response continue to mount in the 7 and 14 days post-vaccine. Whether these post-hoc analyses represent chance findings or true signals is unclear.

This study has limitations. The single-center setting and relative racial, ethnic and socioeconomic homogeneity of the study population may restrict generalizability of our findings. By design, 100% of the participants in our study flared at least once during the 18-month study period, which may represent selection bias in favor of a more flare-prone patient population. However, flares are common: literature suggests the expected background flare rate is 30-50% annually for individuals with well-controlled RA and 20-35% over 1-2 years for those with SLE (48, 49, 50, 51). Although we asked subjects to self-report all flares in real-time, it is possible that flares were under-reported.

While we collected vaccination data through multiple sources, we nevertheless may have failed to detect all immunizations in the cohort. However, it is unlikely that vaccine data would be systematically missing in the EHR based on flare status; additionally, 93.1% of our participants received at least 2 COVID-19 vaccinations, reducing concern for information bias. It is possible we had incorrect vaccine dates, as immunization cards were not available for all participants, and in instances of disputed dates, immunization card information was only concordant with self-report and EHR data 63.2% and 77.6% of the time, respectively. Most dates were minimally different and it is unlikely there was systematic misclassification of vaccine timing; further, our sensitivity analysis was similar to our primary analysis for all 3 lookback periods.

We did not have data on disease severity at time of vaccination, which may be a risk factor for SRD flare (4, 15, 16, 17, 18, 19). Our institution's COVID-19 Registry leveraged the power of remote data collection at a time when in-person visits for both routine clinical care and research purposes were severely limited, particularly in the pre-Omicron era of the pandemic. When enrolling in the Registry, 81.8% of participants were on immunosuppression and/or immunomodulatory medications and 36.9% reported corticosteroid use, suggesting a cohort-wide degree of baseline disease activity. We were unable to adjust for time variance of immunosuppression/immunomodulation regimens as these data were not ascertained; this is a potential limitation of our analysis.

To our knowledge, this is the first case-crossover study evaluating the association of SRD flare and COVID-19 vaccination. The case-crossover design is ideal for studying outcomes triggered by transient exposures with short windows of time-to-effect and brief washout periods (36). In this study, subjects were unaware of the interest in associations between

COVID-19 vaccination and flare, minimizing vaccine-specific recall bias, a significant limitation of most studies evaluating the relationship between vaccinations and SRD flares. The narrow hazard period prior to outcome assessment further reduces information bias, and the within-subject analysis both mitigates confounding by time-invariant variables and maximizes statistical power (37, 52). We confirmed immunization dates and manufacturers, and analyzed 3 lookback periods to ensure we did not miss an association between COVID-19 vaccine and SRD flare.

In conclusion, our data do not support the association of COVID-19 vaccination with SRD flares. These results are reassuring and can inform shared decision-making with patients contemplating COVID-19 vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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SIGNIFICANCE AND INNOVATIONS

- Although fear of disease has been shown to contribute to COVID-19 vaccine hesitancy in patients with systemic rheumatic disease (SRD), accurately differentiating post-vaccine flares from routine vaccine side-effects is challenging.
- Use of a case-crossover design minimizes recall bias.
- This study shows no association between recent COVID-19 vaccination and increased risk of SRD flare.
- This research provides important data to inform vaccine decision-making with direct implications for the care of patients with SRD.

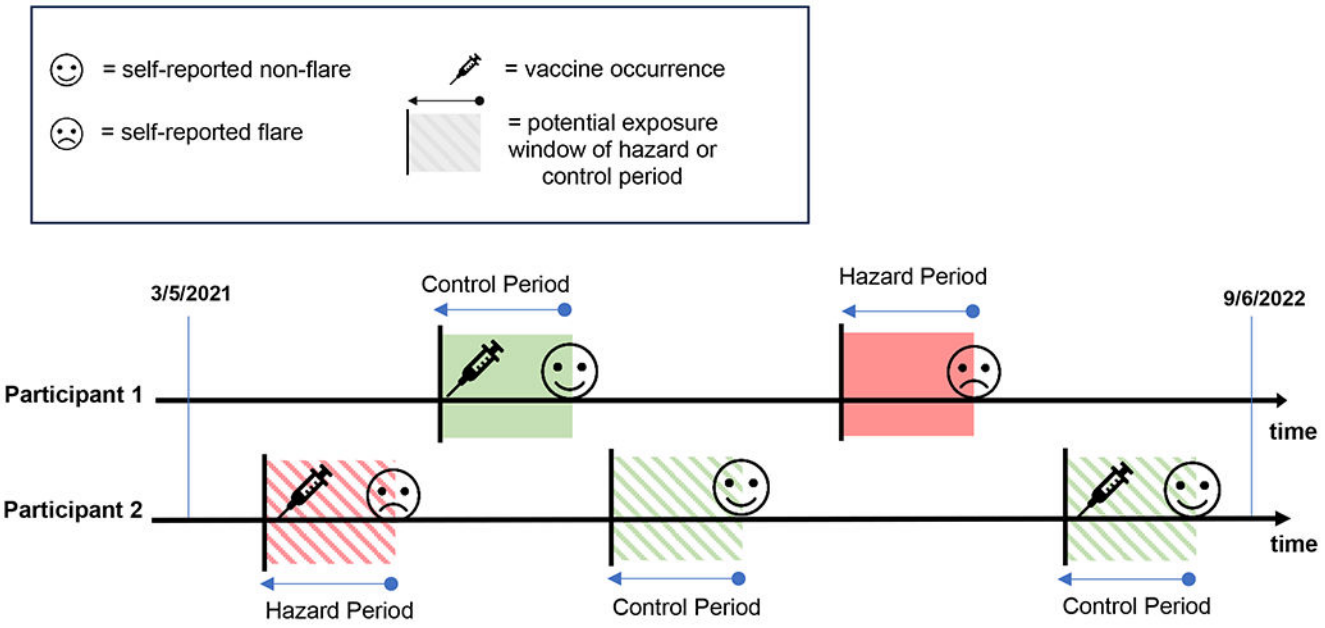

Figure 1.

Case-Crossover Design The below graphic depicts the case-crossover design employed in this study. Time is represented by the horizontal black lines and moves left to right; the time axes for two theoretical participants (Participants 1 and 2) are represented over the course of the study period (bounded on right and left by vertical lines). Participants report on the activity of their systemic rheumatic disease throughout the study period (smiling face = no disease flare; frowning face = disease flare). Depending on the status of disease at the time of survey submission, a subject either contributes data as a case—i.e., while experiencing a flare—or crosses over to serve as his/her own matched control—i.e., while not experiencing a flare. Hazard periods (red blocks) encompass the windows of time immediately prior to the onset of flares. Control periods (green blocks) are derived from the windows preceding self-reported non-flares. The occurrence of the exposure of interest —i.e., vaccination (syringe)—is evaluated during hazard and control periods within the same subject (exposure windows shaded completely for Participant 1 and with diagonal lines for Participant 2). Each participant represents his/her own unique stratum for analysis, and multiple control periods and hazard periods within the same participant can be compared.

Table 1.

Study Participant Demographics at Time of Registry Enrollment (N=434)

Demographic Variable	Value
Age in years, mean (SD)	59 (13)
Sex, N (%)	
Female	365 (84.1)
Male	67 (15.4)
Prefer not to answer/other	2 (0.5)
Race, N (%)	
White	355 (81.8)
Black or African American	18 (4.1)
Asian or Indian Subcontinent	10 (2.3)
Multiracial	31 (7.1)
Other	7 (1.6)
Prefer not to answer	13 (3.0)
Ethnicity, N (%)	
Not Hispanic or Latino	403 (92.9)
Hispanic or Latino	29 (6.7)
Prefer not to answer/unknown	2 (0.5)
Smoking Status, N (%)	
Current smoker	4 (0.9)
Former smoker	150 (34.6)
Never smoker	280 (64.5)
Body Mass Index (kg/m^2), N (%)	
<18	7 (1.6)
18-24.9	169 (38.9)
25-29.9	112 (25.8)
30-34.9	82 (18.9)
35–39.9	39 (9.0)
≥ 40	21 (4.8)
Unknown/missing	4 (0.9)
Educational, N (%)	
High school graduate or equivalent	12 (2.8)
Some college	58 (13.4)
College graduate	105 (24.2)
Some post-college courses	46 (10.6)
Masters, professional or doctorate degree	188 (43.3)
Unknown/missing	25 (5.8)
Insurance, N (%)	

Demographic Variable	Value
Commercial only	256 (59.0)
Medicare * (excluding Medicaid)	153 (35.3)
Medicaid **	11 (2.5)
Self-pay/uninsured	12 (2.8)
Unknown/missing	2 (0.5)

* alone or in combination with another non-Medicaid plan

** alone or in combination with other insurance

Table 2.

Medical History and Medications (N=434)

Variable	Value
SRD Categories, N (%)	
Inflammatory arthritis *	280 (64.5)
Connective tissue disease **	117 (27.0)
More than one category	14 (3.2)
Other ***	23 (5.3)
CDC-Defined High Risk Medical Comorbidities, N (%)	
Asthma	112 (25.8)
Cancer	71 (16.4)
Cerebrovascular disease	14 (3.2)
Chronic Kidney disease	19 (4.4)
Chronic lung disease	20 (4.6)
Chronic liver diseases	16 (3.7)
Diabetes	25 (5.8)
Heart conditions	40 (9.2)
Solid organ or blood stem cell transplantation	1 (0.2)
Mental health disorders	26 (6.0)
Unknown/missing	21 (4.8)
Multimorbidity – comorbidities/participant, N (%)	
No comorbidities	206 (47.5)
1 comorbidity	140 (32.2)
2 comorbidities	63 (14.5)
3 comorbidities	22 (5.1)
4 comorbidities	3 (0.7)
Immunosuppression at time of registry enrollment, N (%)	
None	62 (14.3)
Any antimalarial #	157 (36.2)
Any conventional synthetic DMARD (csDMARD) ǂ	177 (40.8)
Any biologic ¥	181 (41.7)
Any cyclophosphamide	2 (0.5)
Any targeted small molecule §	39 (9.0)
Any IVIG	11 (2.5)
Unknown/missing	17 (3.9)
Combination antimalarial/csDMARD + csDMARD, N (%)	79 (18.2)
Combination antimalarial/csDMARD + biologic or small molecule, N (%)	68 (15.7)
Steroid use at time of registry enrollment, N (%)	160 (36.9)

* AxSpA, enteropathic arthritis, juvenile idiopathic arthritis, palindromic rheumatism, polymyalgia rheumatica, polyarthritis, PsA, RA and spondyloarthropathy.

** Secondary antiphospholipid syndrome (APS), eosinophilic fasciitis, mixed connective tissue disease, myositis, overlap connective tissue disease, Sjogren's/sicca, SLE, SSc and undifferentiated connective tissue disease

*** Any vasculitis, autoinflammatory syndromes, primary APS, Behcet's, IgG4-related disease, relapsing polychondritis and sarcoidosis

Chloroquine or hydroxychloroquine

‡ Azathioprine, cyclosporine, leflunomide, methotrexate, mycophenolate, sulfasalazine, tacrolimus

¥ Abatacept, belimumab, IL-1i, IL-6i, IL-17i, IL-12/23i, TNFi, rituximab

§ Apremilast, JAKi

Table 3.

Case-Crossover Analysis: Association of COVID-19 Vaccination with SRD Flares

COVID-19 Vaccination	Hazard Periods, N	Control Periods, N	OR (95% CI)
2-day lookback			
Yes	44	31	1.46 (0.86, 2.46)
No	953	1145	
7-day lookback			
Yes	91	77	1.09 (0.76, 1.55)
No	906	1099	
14-day lookback			
Yes	135	153	0.85 (0.64, 1.13)
No	862	1023	
Sensitivity Analysis			
2-day lookback			
Yes	40	23	1.49 (0.84, 2.66)
No	957	1153	
7-day lookback			
Yes	77	58	1.13 (0.76, 1.68)
No	920	1118	
14-day lookback			
Yes	111	116	0.86 (0.63, 1.18)
No	886	1060	

Table 4.

Case-Crossover Analysis: Stratified Subgroup Analyses

Category	Exposure window	OR	95% CI
Sex			
Females	2-day	1.46	0.86, 2.46
	7-day	0.89	0.64, 1.25
	14-day	0.85	0.64, 1.13
Males	2-day	1.16	0.69, 1.93
	7-day	1.09	0.76, 1.55
	14-day	0.78	0.60, 1.01
Age (years)			
18-44	2-day	1.46	0.86, 2.46
	7-day	1.04	0.48, 2.22
	14-day	0.85	0.64, 1.13
45-64	2-day	1.66	0.58, 4.74
	7-day	1.09	0.76, 1.55
	14-day	0.76	0.41, 1.38
65+	2-day	1.46	0.86, 2.46
	7-day	0.56	0.23, 1.35
	14-day	0.85	0.64, 1.13
SRD Type			
Connective Tissue Disease	2-day	1.36	0.37, 4.96
	7-day	1.09	0.76, 1.55
	14-day	0.5	0.25, 1.00
Inflammatory Arthritis	2-day	1.46	0.86, 2.46
	7-day	1.54	0.96, 2.46
	14-day	0.85	0.64, 1.13
Vaccine Dose			
Dose 1	2-day	1.59	0.66, 3.83
	7-day	1.2	0.66, 2.16
	14-day	0.82	0.52, 1.29
Dose 2	2-day	1.02	0.46, 2.24
	7-day	0.78	0.46, 1.34
	14-day	0.62	0.41, 0.94
Dose 3+	2-day	2.36	0.78, 7.17
	7-day	1.47	0.73, 2.97
	14-day	1.55	0.90, 2.65
Vaccine Brand			
Pfizer	2-day	1.07	0.53, 2.17
	7-day	0.94	0.58, 1.52

Category	Exposure window	OR	95% CI
	14-day	0.79	0.53, 1.15
Moderna	2-day	2.61	0.98, 6.97
	7-day	1.56	0.82, 2.97
	14-day	1.07	0.67, 1.71

Table 5.

Multivariable Logistic Regression of Self-Reported Flare Severity*

Characteristic	OR	95% CI
COVID-19 Vaccine Timing Prior to Flare		
No vaccination within 14 days (ref.)	—	—
0-2 days prior	1.54	0.84, 2.84
3-7 days prior	1.92	1.05, 3.51
8-14 days prior	1.25	0.68, 2.30
Sex		
Female (ref.)	—	—
Male	1.53	1.08, 2.17
Age		
18-44 years (ref.)	—	—
45-64 years	1.13	0.78, 1.64
65+years	1.42	0.96, 2.09
SRD category		
Inflammatory arthritis (ref.)	—	—
Connective Tissue Disease	0.55	0.40, 0.74
Multiple SRD	1.41	0.75, 2.65
Other	1.07	0.57, 2.00
High-risk comorbidity		
None (ref.)	—	—
1	0.84	0.63, 1.12
2+	0.97	0.70, 1.36
BMI		
<24.9 (ref.)	—	—
25-29.9	0.78	0.57, 1.07
30+	1.15	0.85, 1.57
Ethnicity		
Hispanic (ref.)	—	—
Non-Hispanic	0.9	0.56, 1.46

*Multivariable logistic regression included all variables listed in the table, as well as a binary category for presence of self-reported White race.

Flare severity: 3 level variable - mild, moderate, severe.