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ORIGINAL RESEARCH

Rheumatoid Arthritis Flare-ups Following Immunization with Sinopharm Inactivated Virus-based COVID-19 Vaccine

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Abstract: **Introduction:** This study aimed to investigate the incidence of rheumatoid arthritis (RA) flare-ups following immunization with the Sinopharm COVID-19 inactivated virus-based vaccine. **Methods:** We conducted a retrospective observational study at the Rheumatology Clinic of Imam Hossein Hospital, incorporating 200 RA patients in remission undergoing non-biologic Disease-Modifying Antirheumatic Drugs (DMARDs) treatments. A rheumatologist confirmed a flare-up based on patients complain of arthralgia and joint stiffness and complete examination of joints over a three-month period following vaccination. **Results:** Twelve percent of all included patients experienced symptom recurrence. The average age of patients with flare-ups was significantly higher, but no gender-based differences were observed ($p<0.001$ and $p=0.071$, respectively). The second vaccine dose resulted in a higher number of symptom flares compared to the first dose (9.30% vs. 3.0%, $p < 0.001$). No significant differences were observed between patients experiencing flare-ups after the first dose and the second dose in terms of the number of involved joints ($p=0.321$) and the time gap from vaccination to symptom recurrence ($p=0.526$). No patients required hospitalization, and prednisolone dosage adjustments effectively managed symptoms. **Conclusion:** The occurrence of flare-ups was relatively low after the Sinopharm COVID-19 vaccination in RA patients undergoing treatment with DMARDs during remission. The majority of these flares were mild and no hospitalizations were required.

Keywords: Rheumatoid arthritis, COVID-19, Sinopharm, Flare-ups

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1. Introduction

The COVID-19 pandemic came to an end following the large-scale global immunization, with the majority of the currently affected patients expressing less severe symptoms (1). Given the heightened vulnerability to COVID-19 due to the underlying autoimmune disorders, the American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) strongly recommend prior immunization in RA patients with approved COVID-19 vaccines (2,3).

The potentiality of the vaccine antigen/adjuvants to affect immunomodulation and the imitating manifestations of vaccination side effects gave rise to concerns regarding the safety and implications of immunization in RA patients undergoing treatment; the recurrence of fever, fatigue, joint inflammation, stiffness, and reduced range of motion, observed both after vaccination and in exacerbated RA, led researchers to evaluate the possible association of disease aggravation or flare-ups with COVID-19 vaccinations (4–6).

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A better understanding of the long-term impacts of vaccination in vulnerable populations plays a crucial role in informed decision-making in the post-pandemic era, safeguarding the well-being of individuals with autoimmune inflammatory rheumatic diseases. While existing research has predominantly focused on mRNA and adenoviral vectors, less information is available on inactivated virus-based vaccines, which are widely used in densely populated and developing countries (7). Therefore, we sought to shed light on the safety and efficacy of Sinopharm COVID-19 vaccination for patients with RA by thoroughly examining the potential risk factors of subsequent disease exacerbation and adverse outcomes.

2. Methods

2.1. Study design and ethics approval

We conducted this retrospective cohort study by convenience sampling of patient records at the Rheumatology Clinic of Imam Hossein Hospital from April 2021 to May 2022. The patients were followed for a duration of three months after the final vaccine dose.

The ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved this study (IR.SBMU.MSP.REC.1401.100) and the authors complied with the Declaration of Helsinki.

2.2. Patient selection

The inclusion criteria encompassed patients with a rheumatologist-confirmed diagnosis of RA who were on DMARDs therapies in the remission phase of the disease within the last 3 months and had received at least one dose of the Sinopharm inactivated virus-based COVID-19 vaccine. The exclusion criteria were as follows:

1. Recent COVID-19 infection: patients who had experienced a confirmed COVID-19 infection within the last 6 months.
2. Concomitant rheumatological diseases: individuals with other concurrent rheumatological conditions such as systemic lupus erythematosus or psoriatic arthritis.
3. High therapeutic regimes: patients undergoing high therapeutic regimes, including biologic and targeted synthetic DMARDs.
4. Other vaccination: individuals who had received mRNA or adenoviral COVID-19 vaccines.
5. Insufficient data, including no visits to the clinic during the 3-months follow-up period.

2.3. Data collection

Demographic data, including age, gender, and vaccine-related data as well as data related to RA flares and outcomes, were collected from patients' medical record. During follow-up period, the occurrence of RA flares was monitored and recorded to observe any potential changes in disease activity.

Table 1: Baseline clinical characteristics

	Total patients (n=200)
Female, n (%)	196 (98.00)
Age [median (IQR)], years	43.5 (32.5 – 57)
Treatment	
Hydroxychloroquine	200 (100)
Methotrexate	200 (100)
Prednisolone	200 (100)
Patients with symptom flare n (%)	24 (12.00)
Vaccine	
Patients received one dose n (%)	200 (100)
Patients received two doses n (%)	194 (97.00)

2.4. Outcome measurement

Precise assessment of RA patients was carried out during a 3-month follow-up period from the last dose of vaccination. A rheumatologist confirmed a flare-up based on patients complain of arthralgia and joint stiffness and complete examination of joints over a three-month period following vaccination and was recorded as number of tender and swollen joints. Precise assessment of RA patients was carried out during a 3-month follow-up period.

2.5. Statistical analysis

Statistical analyses were performed using the STATA 14.0 software. The normality of continuous variables was assessed using Q-Q plots. Quantitative variables were described with a median and interquartile range (IQR). Categorical variables were recorded as the frequency and percentage (%). If the quantitative variables did not exhibit a normal distribution, the comparison of means was conducted using the Mann-Whitney U test. To explore the differences in the distribution of categorical variables, Fisher's exact test was applied. All statistical analyses were conducted as two-tailed tests with a significance level set at less than 0.05.

3. Results

3.1. Participants and baseline characteristics

A total of 200 patients in the remission phase of rheumatoid arthritis (RA) were included in the study, with a predominantly female representation (98%) and a median age of 43.5 years (IQR: 32.5 – 57). All patients were under regular DMARDs therapy and received at least one dose of the Sinopharm inactivated COVID-19 vaccine. Among the 200 patients, 24 (12%) experienced a flare of RA symptoms during the follow-up period (Table 1).

Table 2: Clinical Characteristics of Patients with or without Flare-up after Vaccination

	Flare-up (n= 24)	No-flare-up (n= 176)	P value
Age [median (IQR)], years	54.5 (48.5 – 61)	41 (31 – 55.5)	<0.001
Female, n (%)	22 (11.22)	174 (88.78)	0.071
Vaccine			
Patients received one dose n (%)	6 (3.00)	194 (97.00)	<0.001
Patients received two doses n (%)	18 (9.30)	176 (90.70)	

Table 3: Clinical Characteristics of Patients Experiencing Flare-ups after One or Two Doses of Vaccination

	Flare-up after one dose (n= 6)	Flare-up after two doses (n= 18)	Total Flare-up (n= 24)	P value
Involved joints count	2.5 (2 – 4)	3 (2 – 4)	3 (2 – 4)	0.321
Timing of onset of flare after vaccination(days)	3 (2 – 5)	3 (2 – 3)	3 (2 – 3.5)	0.526
Hospitalization (Yes)	0 (0.0)	0 (0.0)	0 (0.0)	-

Data presented as median and interquartile range (Q1-Q3) and n (%).

3.2. Clinical characteristics of patients in the follow-up period

The statistical analysis revealed that individuals who experienced a recurrence of RA symptoms were significantly older compared to those who did not experience flares (p<0.001). Additionally, the study found no significant difference in symptom flares between male and female patients (p=0.071). Six patients (3%) experienced the flare-up of RA symptoms after their first dose, and 18 (9.30%) experienced it after the second dose of the vaccine. The number of participants who showed symptoms after the second dose is significantly higher than the ones who received the first dose (p < 0.001) (Table 2).

Patients experiencing symptom recurrence had a median of 3 [IQR: 2 – 4)] affected joints. There was no significant difference between the group that experienced flare symptoms after the first dose and the second dose (median: 2.5 [IQR: 2 – 4] vs. 3 [IQR: 2 – 4], p=0.321). The median time from vaccination to flare onset was 3 days [IQR: 2 – 3.5]. However, no statistically significant difference was observed between the first dose group and the second dose group in the timing of onset (median: 3 [IQR: 2 – 5] vs. 3 [IQR: 2 – 3], p=0.526). In response to the symptom flares, the prednisolone dosage was adjusted. Importantly, none of the patients required hospitalization after the recurrence of symptoms (Table 3).

4. Discussion

This study aimed to assess the incidence of RA flare-ups in patients who received the Sinopharm inactivated virus-based COVID-19 vaccine. A total of 200 RA patients in remission, undergoing DMARDs therapies were included in the study. Flare-ups were evaluated through patient self-reports of joint tenderness and swelling during a 3-month follow-up period after vaccination and confirmed by the attending rheumatologist. Results revealed that symptom recurrence is relatively unprobeable, but the average age of those with flare-ups is significantly higher. No gender-based differences were observed in symptom recurrence. Additionally, the second vaccine dose resulted in a higher number of symptom flares compared to the first dose. No patients required hospitalization, and prednisolone dosage adjustments effectively managed symptoms.

Previous literature estimates the overall rate of flare-ups in patients with rheumatoid disease to be at about 7%, to 9% after immunization with different COVID-19 vaccines (8–11). Our study also reported a comparable incidence of flare-ups, with 12% of patients experiencing symptoms post-vaccination. Importantly, the flare-up definition varies among different articles; Geng's study defined flare as the disease activity scores, based on the 28-joint count (DAS28) >3.2 with ΔDAS28 ≥0.6 (8). Variations in flare-up definitions, vaccine types, and patients' baseline characteristics could contribute to the observed differences in the flare-up prevalence. Nevertheless, the findings of the previous cohort studies indicated that there was no notable difference in the risk of flare-ups between patients who received vaccinations and those who did not (12–14).

Numerous other risk factors have been reported to increase the likelihood of flare-ups in RA patients after vaccination. These factors include old age, female gender, a history of allergies, a previous history of infection with SARS-CoV-2, being currently infected, stressful situations, and poor adherence to treatments (9,15). In accordance with the current evidence, we discovered that individuals who experienced symptom flare-ups were notably older. However, we did not find any differences in symptom recurrence based on gender. Immunocompromised patients, such as those with RA or

those receiving immunosuppressive treatments, require protocolized two-dose vaccination schedules to enhance immune responses to COVID-19. Studies have consistently shown that immunosuppression leads to suboptimal immune responses to the first dose of the COVID-19 vaccine, emphasizing the need for boosters (16,17). However, several studies have reported a higher risk of symptom flares after the second vaccine dose (18,19). These findings align with ours, where we observed a 3% rate of flare-up after the first dose compared to 9% after the second dose. One possible explanation is that the second dose of the COVID-19 vaccine may trigger a stronger immune response, which could potentially lead to increased inflammation and disease activity in susceptible individuals.

It is important to note that inactivated vaccines, such as Sinopharm, are less commonly used in comparison to mRNA vaccines like Pfizer, but studies examining the impact of different vaccine types on flare rates have shown that there is no significant difference between mRNA and inactivated vaccines (9,20). Therefore, further extensive research is required to draw more conclusive results in this area, demonstrating a better overview for choosing the best option for patients in this setting.

The majority of RA flares observed after COVID-19 vaccination were previously reported to manifest as joint pain, stiffness, and swelling shortly after vaccination, and persisting for a week (10). Barbhaiya et al. reported that only a small proportion (10.9%) of flares occurred beyond seven days after vaccination and Pinte et al. found no significant differences in the duration of flare-ups between the vaccinated and non-vaccinated groups (13,21). We also found that the average time of onset for flare-ups was 2.8 days, which aligns with the findings of previous studies.

At last, we found no increased need for hospitalization due to the observed flare-ups. The majority of these flares were previously reported to be of mild to moderate intensity, with only a small portion experiencing severe flares (11).

This study has certain limitations. Firstly, the sample size is relatively small. Secondly, we lack a group of unvaccinated individuals to compare disease activity. Additionally, we did not have access to the number of previous flare-ups during last year in our patients.

Furthermore, our study only focused on RA patients in remission, which aligns with current expert recommendations for COVID-19 vaccination in patients with RA. This narrow focus may restrict the generalizability of the study findings to patients with active RA.

5. Conclusion

The occurrence of symptom flares in RA patients who received the Sinopharm COVID-19 vaccine while adhering to DMARDs therapies and during the remission phase of the disease was relatively low. The majority of these flares were mild and effectively managed with prednisolone dosage adjustments, and no hospitalizations were required. However, it was observed that receiving the second dose of the vaccine was associated with a higher risk of symptom recurrence. These findings provide valuable insights into the safety of vaccination in RA patients and emphasize the significance of close monitoring in the following period.

6. Declarations

6.1. Acknowledgement

None.

6.2. Conflict of interest

The authors declare no conflict of Interest.

6.3. Funding and supports

The authors received no specific funding for this work.

6.4. Informed consent

The patients have provided written consent for publication.

6.5. Ethical statement

The ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved this study (IR.SBMU.MSP.REC.1401.100) and the authors complied with the Declaration of Helsinki.

6.6. Author contributions

Study design: PD, AR, FF, SHA
Data gathering: SHA, PD
Analysis: NT
Interpretation of the findings: All authors
Drafting: AA, NT
Critically revised: All authors

6.7. Availability of supporting data

The data is available to the corresponding author and will be made available to third party upon request.

6.8. Using artificial intelligence chatbots statement

The authors did not use artificial intelligence chat bots to write the manuscript.

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