RHEUMATOLOGY RESEARCH JOURNAL

Vol. 8, No. 3, July 2023,
Webpage: http://rheumres.org
Email: rheumres@gmail.com
ISSN:2476-5856
doi: 10.32592/RR.2023.8.3.121

Original Article **Open Access**

COVID-19 vaccination in patients with rheumatic diseases: A cross-sectional study in Iran

Dena Mohamadzadeh[1], Shirin Assar[*1], Mehran Pournazari[1], Parviz Soufivand[1], Mojdeh Bonyadi[1]

[1]Clinical Research Development Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran.

The severe acute respiratory syndrome coronavirus 2 (SARS CoV2), also known as coronavirus disease 2019 (COVID-19), originated in Wuhan, China, and has since become an ongoing pandemic. COVID-19 vaccination has been underway since December 2020. The most common vaccination side effects are pain at the injection site, fever, myalgia, and malaise. The study aimed to investigate any potential complications of COVID-19 vaccination in rheumatic patients. This cross-sectional study was conducted in KUMS-associated rheumatology clinics to identify patients with rheumatic diseases who have received COVID-19 vaccines. The following data were obtained from participants: age, sex, type of vaccine, type of rheumatic disease, medications, side effects, and complications after vaccine injection. Participants were divided into two groups: patients who developed complications and those who did not after vaccine injection. The variables mentioned above were compared between our groups. We identified 297 patients with rheumatic diseases (mean age = 49.17 ± 13.79, 81.5% female) who received at least one dose of the COVID-19 vaccine. Among these, 131 (44.66%) reported at least one type of complication following a vaccine injection. The most common side effects were myalgia, fever and chills, headache, injection site pain, and malaise, which were self-limited. Younger patients developed more complications. In contrast, patients taking more than 5mg of prednisolone on a daily basis had fewer complications. Most vaccine complications in rheumatic patients are self-limiting and similar to healthy individuals. More complications are associated with being younger. Using more than 5mg of prednisolone daily could be a preventive measure.

Keywords: Rheumatic diseases; COVID-19; SARS CoV2; Vaccine; Side effects

Introduction

Patients with autoimmune inflammatory rheumatic diseases (AIRDs) have a higher risk of developing infectious diseases. The nature of the AIRDs and the immunosuppressive agents used to treat them predispose these patients to infections [1]. Infections are well-known triggering factors for autoimmune diseases, and previous research has shown a link between infections and autoimmune disease flare [2]. Therefore, vaccination against infectious agents may assist in preventing AIRD relapses. For patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), the American College of Rheumatology (ACR) recommends yearly influenza and pneumococcus vaccinations. The efficacy and safety of influenza and other vaccines have been

*Corresponding author: Shirin Assar, Associate Professor of Rheumatology, Clinical Research Development Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran. E-mail: sh758us@yahoo.com.Phone: +989128332358
Received: 27 October 2022; **Accepted:** 08 June 2023

previously demonstrated.

Vaccination against the novel coronavirus disease (COVID-19) has begun since December 2020. This vaccine's efficacy and side effects in patients with rheumatic diseases have yet to be thoroughly studied. The present study aimed to investigate the side effects of COVID-19 vaccination in patients with AIRD and to identify potential risk factors for vaccine side effects in this population.

Materials and Methods

We conducted this cross-sectional study in Kermanshah, Iran, from June 22nd to September 22nd, 2021. We interviewed patients with rheumatic diseases attending Kermanshah University of Medical Sciences (KUMS) rheumatology clinics to determine who had received COVID-19 vaccines. There were 297 patients included.

The sampling used was convenience sampling. Inclusion criteria were meeting the American College of Rheumatology (ACR) classification or European League Against Rheumatism criteria (EULAR) for at least one type of rheumatologic disease (including the 2010 ACR/EULAR criteria for RA, 2019 ACR/EULAR criteria for SLE, 2016 ACR/EULAR criteria for Sjogren's syndrome, 2009 ASAS criteria for seronegative spondyloarthritis (SpA), 2017 ACR/EULAR criteria for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), and 2013 ACR/EULAR criteria for systemic sclerosis (SSc) and Bohan and Peter 1975 criteria for inflammatory myopathies) [3-9], and receiving at least one dose of the COVID-19 available vaccines.

The following information was gathered from the patients, including age, sex, type of rheumatic disease (RA, SpA, SLE, SSc, vasculitis, Sjogren's syndrome, inflammatory myositis, sarcoidosis), anti-rheumatic disease medications (glucocorticoids, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), biologic (bDMARDs) or targeted synthetic DMARDs (tsDMARDs), type of COVID-19 vaccine, whether they had complications after vaccine injection and type of complications (injection site pain, fever, chills, myalgia, malaise, headache, skin rashes, deterioration of the rheumaic disease, vertigo, nausea, sore throat, chest pain, dyspnea), whether they discontinued immunosuppressive and immunomodulatory drugs.

Patients were divided into two groups: those who experienced complications after receiving the COVID-19 vaccine and those who did not. The two group's demographic and clinical characteristics were compared to identify the potential risk factors for developing complications after COVID-19 vaccination in rheumatologic patients.

Statistical analysis

The IBM SPSS version 25 was used to analyze the data. Variables were reported as frequency, percentage, mean, and standard deviation [SD]. An Independent T-test was used to compare the two groups' quantitative variables (age). The chi-squared test and Fisher exact test were used to compare the categorical variables (gender, type of disease, type of drug, type of vaccine) and to calculate P-values for qualitative variables. A P-value of less than 0.05 was considered statistical significance.

Results

We identified 297 rheumatic patients who had received at least one dose of the COVID-19 vaccine. There were 242 (81.5%) female patients. The patients' mean age was 49.17, with a standard deviation 13.79. The most commonly injected type of vaccine among the patients (86.87%) was the Sinopharm BIBP COVID-19 vaccine (BIBP-CorV), followed by Oxford/ AstraZeneca (ChAdOx1-S [recombinant] vaccine) (7.74%). RA was the most common type of disease among sample patients (42.42%), followed by SPA (21.88%), SLE (20.54%), and SSc (5.72%). Prednisolone was used by 81.81% of the participants. Most (64.30%) were taking ≤ 5 mg/d. Methotrexate was the most commonly used csDMARD by 143 patients (48.15%), followed by hydroxychloroquine (31.31%) and sulfasalazine (27.27%). Adalimumab was the most frequently used biologic DMARD (10.77%).

After receiving a vaccine injection, 131 patients (44.10%) reported at least one type of complication. Myalgia was the most commonly reported complication (51 (17.17%)). The second most common complication was fever and chills, which were reported by 47 patients (15.82%), followed by headache (12.12%) and injection site pain (11.78%). Only eight patients (2.69%) reported a deterioration of their rheumatic disease following the vaccine injection. Table 2 reports details the age, sex, frequency of disease types and medication types,

Table 1: Frequency of different complications after COVID-19 vaccination in the study population.

Vaccine complications	Number (percent)
Myalgia (%)	51 (17.17)
Fever and chills (%)	47 (15.82)
Headache (%)	36 (12.12)
Injection site pain (%)	35 (11.78)
Malaise (%)	14 (4.71)
Vertigo (%)	8 (2.69)
Deterioration of rheumatic disease (%)	8 (2.69)
Nausea (%)	5 (1.68)
Sore throat (%)	3 (1.01)
Skin rash (%)	2 (0.67)
Chest pain (%)	2 (0.67)
Dyspnea (%)	2 (0.67)
Cardiovascular (%)	0

and type of injected COVID-19 vaccine in the study population and patients who developed and did not develop complications after COVID-19 vaccination. The two groups (with and without vaccine complications) were compared on various demographic and clinical variables. Patients who developed vaccine complications were younger (46.63 ± 13.84 vs 51.18 ± 13.45, P = 0.005). The patient's gender and type of rheumatic disease or type of vaccine were not associated with developing vaccine complications. We discovered that patients taking prednisolone in doses greater than 5 mg daily had fewer complications (16 (12.21) vs 36 (21.68), P = 0.02). However, the observed differences between prednisolone ≤ 5 mg/d and other rheumatic drugs were not statistically significant. Furthermore, temporary discontinuation of immunosuppressive agents following vaccine injection was not associated with vaccine complications (18 (13.74) vs 21 (12.65), P = 0.78).

Discussion

The severe acute respiratory syndrome coronavirus 2 (SARS CoV2), also known as COVID-19, originated in Wuhan, China, and has since become an ongoing pandemic. COVID-19 vaccination has been underway since December 2020. In the general population, the most common adverse events (AE) of vaccination are pain at the injection site, fever, nausea, myalgia, and malaise. In this cross-sectional survey, we studied 297 rheumatic patients who had received five different COVID-19 vaccines. The most common AEs were similar to those seen in the general population. Only eight patients reported rheumatic disease deterioration after vaccine injection, with none requiring hospitalization.

In theory, there is a risk of relapse or exacerbation of disease in rheumatic patients following COVID-19 vaccination. Vaccines containing COVID-19 virus antigens can induce autoimmunity via mechanisms such as molecular mimicry, bystander activation, epitope spreading, and polyclonal activation [10]. Vaccine adjuvants, in addition to antigens, can also induce autoimmunity through various mechanisms [11] . Current evidence does not support an increased risk of post-vaccination flare-up

Table 2. Demographic and clinical characteristics of patients with and without vaccine complications

Variables	Total population (Number = 297)	Patients with vaccine complication (Number = 131)	Without vaccine complication (Number = 166)	P-value
Age, (mean ± SD)	49.17 ± 13.79	46.63 ± 13.84	51.18 ± 13.45	**0.005**
Sex				
Female (%)	242 (81.5)	111 (84.73)	131 (78.91)	0.20
Male (%)	55 (18.5)	20 (15.26)	35 (21.08)	
Type of disease				
RA (%)	126 (42.42)	56 (42.75)	70 (42.17)	0.92
SLE (%)	61 (20.54)	24 (18.32)	37 (22.29)	0.40
SPA (%)	65 (21.88)	31 (23.66)	34 (20.48)	0.51
SSc (%)	17 (5.72)	6 (4.58)	11 (6.62)	0.45
Vasculitis (%)	13 (4.38)	9 (6.87)	4 (2.41)	0.06
Sjogren's syndrome	6 (2.02)	2 (1.52)	4 (2.41)	0.69
Inflammatory myopathies (%)	4 (1.34)	1 (0.76)	3 (1.81)	0.63
Sarcoidosis (%)	1 (0.33)	0	1 (0.60)	> 0.99
Other (%)	4 (1.34)	2 (1.52)	2 (1.20)	> 0.99
Medications				
Prednisolone (%)	243 (81.81)	107 (81.68)	136 (81.93)	0.95
≤ 5 mg/d (%)	191 (64.30)	91 (69.46)	100 (60.24)	0.09
> 5 mg/d (%)	52 (17.51)	16 (12.21)	36 (21.68)	**0.02**
Hydroxychloroquine (%)	93 (31.31)	39 (29.77)	54 (32.53)	0.61
Methotrexate (%)	143 (48.15)	61 (46.56)	82 (49.39)	0.62
Sulfasalazine (%)	81 (27.27)	40 (30.53)	41 (24.70)	0.26
Leflunomide (%)	64 (21.55)	33 (25.19)	31 (18. 67)	0.17
Azathioprine (%)	54 (18.18)	18 (13.74)	36 (21.68)	0.65
Mycophenolate Mofetil	22 (7.41)	8 (6.10)	14 (8.43)	0.44
Calcineurin inhibitor	10 (3.36)	7 (5.34)	3 (1.81)	0.11
Cyclosporine (%)	7 (2.35)	5 (3.82)	2 (1.20)	0.24
Tacrolimus (%)	3 (1.01)	2 (1.52)	1 (0.60)	0.58
TNF inhibitors	48 (16.16)	24 (18.32)	24 (14.45)	0.36
Adalimumab (%)	32 (10.77)	18 (13.74)	14 (8.43)	0.14
Etanercept (%)	13 (4.37)	5 (3.82)	8 (4.82)	0.77
Infliximab (%)	3 (1.01)	1 (0.76)	2 (1.20)	> 0.99
Type of vaccine				
Sinopharm	258 (86.87)	110 (83.97)	148 (89.15)	0.18
AstraZeneca	23 (7.74)	14 (10.69)	9 (5.42)	0.09
Sputnik	1 (0.34)	0 (0.0)	1 (0.60)	> 0.99
Barekat	14 (4.71)	6 (4.58)	8 (4.82)	0.92
Bharat	1 (0.34)	1 (0.76)	0 (0.0)	0.44
Immunosuppressive discontinuation	39 (13.13)	18 (13.74)	21 (12.65)	0.78

RA, rheumatois arthritis; SLE, systemic lupus erythematosus; SpA, seronegative spondyloarthritis; SSC, systemic sclerosis

flare-ups in rheumatic patients receiving COVID-19 vaccines, which is consistent with our study. Xue Li et al. [12] studied 5493 RA patients and concluded that mRNA or inactivated virus COVID-19 vaccines are not associated with arthritis flares. Furer et al. [13] studied 710 rheumatic patients and 124 healthy individuals as a control group. The COVID-19 vaccine had an acceptable safety profile and no significant disease flare in their study of rheumatic patients. A recent Brazilian clinical trial from [14] studied 910 autoimmune rheumatic patients and showed the safety and acceptable short-term immune-genicity of the CoronaVac inactivated vaccine. Cherian et al. [15] studied 724 patients with rheumatic and musculoskeletal diseases who had at least one dose of ChAdOx1 or BBV152. Of these, 61.61% had AEs after vaccination that were all self-limiting and did require hospitalization. Esquivel-Valerio et al. [16] studied 225 AIRD patients for AE associated with 6 different COVID-19 vaccines (ChadOX1 nCoV-19 (AZD1222), Ad5-nCoV2, Ad26.COV2 S, mRNA-1273, BNT162b2, and CoronaVac). Localized pain is the most commonly reported AE, and no serious AE requires medical intervention. The obtained results confirmed the safety of the studied vaccines. Janssen and Pfizer-BioNTech were responsible for the most of the observed AE. Although the Sinopharm vaccine was received in most patients in this survey, only one received Bharat, one received the Sputnik vaccine, 25 received AstraZeneca, and 14 received Barekat, so compression and conclusions about these vaccines may be misleading.

Vaccine hesitancy appears to be a challenging issue. Gaur et al. [17] conducted an interview-based survey on 280 AIRD patients to investigate their vaccination perception. 46% of the patients refused to get vaccinated. A lack of education was a risk factor. Concerns about vaccine-related adverse effects have been identified as one of the primary causes of vaccine hesitancy. Our study, as well as the majority of the previous ones, found that most post-vaccination adverse events in AIRD patients are mild and self-limiting. Making these findings known to patients helps to reduce vaccine hesitancy in this population.

In our survey, vaccine type was not associated with AEs, in contrast to Al Khames Aga et al.'s study, which found that the AstraZeneca vaccine was associated with a higher risk and a longer duration of post-vaccination signs and symptoms than with the Pfizer and Sinopharm [18]. After vaccination, none of the sample patients experienced cardiovascular complications such as clot formation, stroke, or ischemia.

We found that temporarily discontinuing immunosuppressive agents following vaccine administration was not associated with vaccine complications. In contrast to the American College of Rheumatology, which advised holding methotrexate, JAK inhibitors, abatacept, mycophenolate mofetil, and rituximab in controlled disease patients [19], EULAR did not recommend stopping or adjusting the schedule of any of these drugs (except rituximab) when SARS-CoV-2 immunization is administered [20]. More research is needed to determine whether or not transient discontinuation of anti-rheumatic medications is necessary.

In our survey, patients who received more than 5 milligrams of prednisolone per day had a lower risk of post-vaccine complications, which could be due to the more potent anti-inflammatory effects of prednisolone at higher dosages.

Although the age difference between the two groups of patients (with and without post-vaccine complications) was only four years, we discovered that the younger patients had more difficulties.

The study's strengths include many participants and various types of diseases. The main limitation of this study was the unavailability of some COVID-19 vaccines in our country (Pfizer-BNT162b2 mRNA and Moderna mRNA-1273). Still, the sample size was sufficient for the other vaccine types studied, and the results for these vaccines were reassuring. The second limitation was a lack of investigation into the impact of specific comor-biddities like hypertension, diabetes mellitus, and smoking on the adverse effects of vaccination. Another limitation is the cross-

sectional design, which is based on collecting data through interviewing and physical examinations so we may have missed possible cases of post-vaccination death.

Acknowledgment

Not applicable.

Conflict of interest

None.

Funding

No funds.

References

1. Mehta B, Pedro S, Ozen G, Kalil A, Wolfe F, Mikuls T, Michaud K. Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. ***RMD Open*** 2019; 5(1):e000935. doi: 10.1136/rmdopen-2019-000935.
2. Jung J-Y, Suh C-H. Infection in s ystemic lupus erythematosus, similarities, and Rheumatology/European league against rheumatism collaborative initiative. ***Arthritis Rheum*** 2010; v62(9):2569-81. doi: 10.1002/art.27584.
3. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd. *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. ***Ann Rheum Dis*** 2010; 69(9):1580-8. doi: 10.1136/ard.2010.138461.
4. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. ***Arthritis & rheumatology***2019;71(9):1400-12. doi: 10. 1002/ art.40930
5. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM. *et al*. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. ***Ann Rheum Dis*** 2017; 76(1):9-16. doi: 10.1136/annrheumdis-2016-210571.
6. Rudwaleit M, Van Der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J. et al. The development of Assessment of Spondylo Arthritis international Society classification criteria for axial spondyl-arthritis (part II): validation and final selection. ***Ann Rheum Dis*** 2009; 68(6): 777-83. doi: 10.1136/ard.2009.108233.
7. Pimentel-Quiroz VR, Sánchez-Torres A, Reátegui-Sokolova C, Gamboa-Cárdenas RV, Sánchez-Schwartz C, Medina-Chinchón M, et al. Performance of the 2017 American College of Rheumatology/European League against rheumatism provisional classification criteria for antineutrophil cytoplasmic Antibody–Associated vasculitis in a Peruvian tertiary care center. ***JCR: Journal of Clinical Rheumatology*** 2022; 28(2):e397-e400. doi: 10.1097/RHU.0000000000001741
8. Khanna D, Christopher P, Maureen D, Fransen J. Classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. ***Ann Rheum Dis*** 2013; 72(11): 1747–55. doi: 10.1136/annrheumdis-2013-204424.
9. Bohan A, Peter JB. Polymyositis and Dermatomyositis: (First of Two Parts). ***N Engl J Med*** 1975; 292(7):344-47. doi: 10. 1056/NEJM197502132920706
10. Agmon-Levin N, Paz Z, Israeli E, Shoenfeld Y. Vaccines and autoimmunity. ***Nature Reviews Rheumatology*** 2009; 5(11):648-52. doi.org/ 10.1038 /nrrheum. 2009.196.
11. Guimarães LE, Baker B, Perricone C, hoenfeld Y. Vaccines, adjuvants and auto-immunity. Pharmacol Res 2015; 100:190-209. doi: 10.1016/j.phrs.2015.08. 003.
12. Li X, Tong X, Yeung WWY, Kuan P, Yum SHH, Chui CSL. et al. Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. ***Ann Rheum Dis*** 2022; 81(4):564-68. doi: 10.1136/annrheumdis-2021-221571.

13. Furer V, Eviatar T, Zisman D, Peleg OH, Paran D, Levartovsky D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis 2021; 80(10):1330-38. doi: 10.1136/annrheumdis- 2021-220647.
14. Medeiros-Ribeiro AC, Aikawa NE, Saad CGS, Yuki EFN, Pedrosa T, Fusco SRG. et al. Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial. ***Nat Med*** 2021; 27(10):1744-51. doi: 10.1038/s41591-021-01469-5.
15. Cherian S, Paul A, Ahmed S, Alias B, Manoj M, Santhosh AK. et al. Safety of the ChAdOx1 nCoV-19 and the BBV152 vaccines in 724 patients with rheumatic diseases: a post-vaccination cross-sectional survey. ***Rheumatol Int*** 2021; 41(8):1441-45. doi: 10.1007/s00296-021-04917-0.
16. Esquivel-Valerio JA, Skinner-Taylor CM, Moreno-Arquieta IA, Cardenas-de la Garza JA, Garcia-Arellano G, Gonzalez-Garcia PL. et al. Adverse events of six COVID-19 vaccines in patients with autoimmune rheumatic diseases: a cross-sectional study. ***Rheumatol Int*** 2021; 41(12):2105-08. doi: 10.1007/ s00296-021-05017-9.
17. Gaur P, Agrawat H, Shukla A. COVID-19 vaccine hesitancy in patients with systemic autoimmune rheumatic disease: an interview-based survey. ***Rheumatol Int*** 2021; 41(9):1601-05. doi: 10.1007/s00296-021-04938-9.
18. Al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT. et al. Safety of COVID-19 vaccines. ***J Med Virol*** 2021; 93(12):6588-94. doi: 10. 1002/jmv.27214.
19. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR. et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 3. ***Arthritis Rheumatol*** 2021; 73(10):e60-e75. doi: 10.1002/ art. 41928.
20. Bijlsma JW. EULAR December 2020 view points on SARS-CoV-2 vaccination in patients with RMDs. ***Ann Rheum Dis*** 2021; 80(4):411-12. doi: 10.1136/annrheumdis-2020-219773.