Original Article

Journal of Iranian Medical Council, Volume 8, Issue no. 1
http://dx.doi.org/10.18502/jimc.v8i1.17059

The Flare-up of Rheumatic Autoimmune Diseases Following COVID-19 Vaccination

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Received: 13 Jan 2024
Accepted: 20 Apr 2024

Citation to this article
Sahebari M, Otani F, Rezaieyazdi Z, Salari M, Mirfeizi Z, Khodashahi R, *et al.* The Flare-up of Rheumatic Autoimmune Diseases following COVID-19 Vaccination. *J Iran Med Counc.* 2025;8(1):38-49.

Abstract

Background: Individuals with Autoimmune Rheumatic Disease (AIRD) are vulnerability to severe SARS-CoV-2 outcomes and vaccination. The present study aimed to determine the incidence of AIRDs flares following COVID-19 vaccination and its risk factors.

Methods: The study was retrospective cross-sectional focused on patients with AIRD who experienced a flare-up at least during 30 days after receiving the COVID-19 vaccine. These patients were seen at Rheumatology Clinics at Imam Reza and Ghaem Hospitals, affiliated with Mashhad University of Medical Sciences, as well as private clinics in Mashhad, Iran, over a period of 1 years.

Results: The rate of recurrence following COVID-19 vaccination was estimated to be 3.16%. Rheumatoid arthritis (18.9%), systemic lupus erythematosus (12.9%), and cutaneous vasculitis (10.6%) were the most frequent AIRDs among patients who experienced a flare-up following COVID-19 vaccination. More than 85% of patients who were vaccinated with AstraZeneca experienced a flare-up after the first dose of vaccination. In the majority of patients, the flare-up occurred after the first dosage of COVID-19 vaccination.

Conclusion: In Mashhad, Iran, the incidence of flare-ups in autoimmune and inflammatory rheumatic diseases following COVID-19 vaccination is estimated to be a mere 3%. Despite their rarity, flare-ups in autoimmune and inflammatory rheumatic diseases post-COVID-19 vaccination can still pose a public health issue, potentially undermining public confidence in vaccinations.

Keywords: COVID-19 vaccines, Iran, Rheumatology, Rheumatic diseases, Vaccination

Introduction

Normally, creating a safe and effective vaccine takes 10-15 years on average, but in a rapidly evolving pandemic, this long process could cost more lives than it saves. During the COVID-19 pandemic, due to the emergency situation, there was not enough time to fully evaluate the safety and effectiveness of the COVID-19 vaccine (1). In this regard, vaccines were created quickly through worldwide cooperation and extraordinary efforts (2,3). This accelerated development has allowed for the creation of vaccines much faster than the traditional timeline, which has not only been a testament to the advancements in science and technology, but also a reflection of the global urgency to against the pandemic (4,5).

Based on randomized clinical trials, the authorized COVID-19 vaccines and those awaiting approval have demonstrated excellent effectiveness, safety, and tolerability (6-9). Reports of Autoimmune Rheumatic Disease (AIRD) flares following vaccination with other vaccines, such as influenza and herpes zoster, have been relatively rare (10,11). However, due to the emergency situation of the COVID-19 pandemic, several steps in the path to prevention have been accelerated, increasing uncertainties about the long-term efficacy and safety of vaccines. There are concerns about the risk of AIRD flares following COVID-19 vaccination. Based on the results of one study, systemic side effects were reported by 13.5% and 22% of individuals after the first dose of BNT162b2. Additionally, 33.7% of individuals experienced systemic side effects after the first dose of ChAdOx1 nCoV-19. Furthermore, local side effects were reported in more than half of the people after the initial doses of both BNT162b2 and ChAdOx1 nCoV-19 (12). The findings from another study indicated that frailty is associated with post-vaccination infection in adults over 60 years old, particularly those living in highly deprived areas (13).

Probably, individuals with AIRDs are vulnerable to severe SARS-CoV-2 outcomes and vaccination. However, some evidence suggests that the COVID-19 vaccine is safe for patients with autoimmune rheumatic diseases and has a low rate of severe adverse effects (14,15). Based on one study, the vaccination rate in rheumatic patients was 30.2%, which is lower than in the general population (16). Reports on the willingness of vaccinations in rheumatic patients vary. A study found that COVID-19 vaccination had similar odds ratios among different autoimmune diseases and the nonrheumatic group (17). In contrast, other studies found that vaccination is not associated with an increased risk of side effects in any particular disease. Vaccine hesitancy remains one of the most challenging public health issues worldwide (18,19). However, vaccination remains the most effective preventive method for halting the transmission chain. Fear of side effects was one of the main reasons for declining COVID-19 vaccination (20).

On the other hand, some reports indicate that after receiving the COVID-19 vaccine, up to one-third of SLE patients experienced a flare, although the majority of cases were mild (21,22). This may decrease the willingness to be vaccinated among these individuals. There are several potential risk factors for AIDR flare-ups that should be taken into account in the context of post-vaccination flare-ups. Firstly, comorbidities and demographic factors, which are also risk factors for the onset of AIDRs or are linked to disease activity, may be associated with flare-ups following vaccination. Apart from baseline characteristics, the discontinuation of immunosuppressive treatments could lead to disease flare-ups. This has been noted in studies involving patients who temporarily stopped taking methotrexate after receiving influenza and pneumococcal vaccines (23). The varying immune responses elicited by different vaccines could potentially contribute to disease flare-ups. There have been isolated instances of autoimmune side effects, such as Guillain-Barre syndrome following the Janssen/Johnson & Johnson vaccine, and immune thrombocytopenia after the Oxford-AstraZeneca vaccine (24).

Considering that until now, there have not been enough studies on the flare-up of AIDRs in patients after COVID-19 vaccination, and also the vital value of such information for these patients, this study aimed to determine the incidence of AIRDs flares following inactivated whole virus vaccines (Sinopharm and Barecatco) and viral vector vaccines (AstraZeneca and Sputnik V) vaccination in Mashhad, Iran.

Methods and Materials

The study was retrospective and cross-sectional

in nature. It focused on patients with rheumatic autoimmune diseases who experienced a flare-up after receiving the COVID-19 vaccine. These patients were seen at Rheumatology Clinics at Imam Reza and Ghaem Hospitals, affiliated with Mashhad University of Medical Sciences, as well as private clinics in Mashhad, Iran, over a period of 1 year.

Inclusion and exclusion criteria

The study includes individuals with a rheumatic autoimmune disease who experienced a flare after receiving the COVID-19 vaccine, with a maximum of one month having passed since their vaccination, and those who experienced primary symptoms were entered in this study. Those with incomplete medical records, more than one month since their vaccination, or who did not receive the COVID-19 vaccine were excluded from the study.

Study design

After obtaining approval from the Ethics Committee of Mashhad University of Medical Sciences and Health Services, researchers collected information from the archives of Rheumatology Clinics at Imam Reza Hospital, Ghaem Hospital, and the Rheumatology Professors Clinic. They collected data on patients who experienced flare-ups after receiving the COVID-19 vaccine, without imposing any age or gender restrictions.

In cases where medical records were incomplete, researchers attempted to gather the missing information through phone calls. If the information could not be completed, the patient was excluded from the study. In this study, a flare-up has been defined as the worsening of any symptom related to a disease, which could significantly impact daily tasks. These symptoms varied depending on the type of autoimmune diseases. For instance, in Rheumatoid Arthritis (RA), flare-ups may manifest as intense joint pain and stiffness, while in Systemic Lupus Erythematosus (SLE), patients may experience pain, inflammation, and rashes. The confirmation of flare-ups in each patient was conducted by a rheumatologist, considering both laboratory tests and clinical examination.

The researchers designed a questionnaire that includes the required demographic and clinical information to collect data. They gathered demographic and social information about the patients, including age, sex, education level, occupation, and smoking habits. They also collected clinical information, such as underlying diseases, type of autoimmune rheumatic disease, medication used, history of COVID-19 infection, severity of COVID-19 infection (mild, moderate or severe), time between COVID-19 vaccination and onset of flare-up, type of COVID-19 vaccine (Sinopharm, Kovaxin, Barkat, Strazenka or Sputnik V), number of vaccine doses received, whether a booster dose was given or not, clinical and laboratory manifestations of rheumatic disease, the immunosuppressive drugs, the type of medication stopped before receiving the vaccine, the side effects of immunosuppressive drug discontinuation (excessive pain in the joints, dryness and limited movement in joints, excessive inflammation of the joints,…), the duration of stopping the immunosuppressive drug, side effects caused by receiving the vaccine (fever, chills, pain, dizziness, fatigue, muscle pain and sore arms). All this information was recorded in a checklist. The frequency of flare-up after COVID-19 vaccination was then estimated and the variables were compared. Each patient was followed up for 1 month after the injection of each vaccine, and necessary measures were taken if there were any problems.

Treatment approaches varied for each patient. The treatment program and administered drug were provided based on the severity of the disease, test results, clinical examination, and the patient's circumstances.

Statistical analysis

For statistical analysis, the researchers used SPSS 24 (IBM Corp., Armonk, NY, USA). Dates were described using Mean±SD and frequencies. Chi-square and Fisher tests were used to assess categorical variables. The percentage incidence of each autoimmune rheumatic disease has been calculated by dividing the frequency of each disease by the total frequency of autoimmune rheumatic diseases reported following COVID-19 vaccination. A p-value lower than 0.05 was considered significant.

Ethical consideration

This study was derived from a thesis with the ethical

code IR.MUMS.REC.1400.214 to obtain a degree in rheumatology specialization. Data were coded and entered into a checklist to maintain confidentiality.

Results

In general, 4172 patients with different types of AIRDs were referred for COVID-19 vaccination during a one-year period in Mashhad, Iran. Among them, 132 cases experienced a relapse after vaccination. The incidence of recurrence following COVID-19 vaccination was estimated to be 3.16%.

The mean age of patients was 37.68±11.34 years, ranging between 19 to 59. The majority of patients were older than 30 years (72.7%) and were female (85.3%). Moreover, 26.5% of patients had underlying diseases.

Table 1 presents the demographic and clinical information of patients with flare-ups following COVID-19 vaccination. RA was the most frequent AIRD among patients who experienced a flare-up following COVID-19 vaccination (n=25; 18.9%). The other common AIRDs included SLE (n=17, 12.9%), cutaneous vasculitis (n=14; 10.6%), undifferentiated inflammatory arthritis (n=13, 9.8%), psoriatic arthritis (n=9, 6.8%), reactive arthritis (n=9, 6.8%), and Sjögren syndrome (n=7, 5.3%). Table 2 presents the frequencies of flare-ups in patients with autoimmune rheumatic diseases following COVID-19 vaccination. The majority of patients had a history of infection with SARS-CoV-2 (65.9%). The mean time interval between COVID-19 remission and vaccination was 63.94±44.2 days, ranging between 30 to 153 days. The majority of patients were vaccinated with Sinopharm (67.4%) and experienced a relapse after the first dosage of COVID-19 vaccination (71.2%).

There was a significant relationship between the type of vaccine and the number of COVID-19 vaccination injections (χ^2=12.13; p=0.007), so that more than 80% of patients who were vaccinated with AstraZeneca and CoBarecat experienced a flare-up after the first dose of vaccination; while 61.7% of patients who were vaccinated with Sinopharm had a flare-up after the first dose of vaccination. Table 3 presents the comparison between the type of vaccination, the number of received COVID-19 vaccination doses, and adverse effects immediately after vaccination. The flare-up occurred in less than 15 days for the majority of patients (n=80; 60.6%). The mean time interval between COVID-19 vaccination and flare-up was 13.43±8.68 days, ranging between 5 to 30 days.

In the first doses of COVID-19 vaccination, the majority of patients did not discontinue AIRDs medications at the time of vaccination. It was discontinued between one to two weeks before and after vaccination in 75% of patients, and it was discontinued one to two weeks only after vaccination in 25% of patients. In the second doses of COVID-19 vaccination, the AIRDs medication was discontinued between one to two weeks before and after vaccination in 68% of patients, and it was discontinued one to two weeks only after vaccination in 27% of patients. In 5% of patients, no medication was discontinued.

Discussion

In this study, the incidence of flare-ups in 4172 patients AIRDs who were recommended for COVID-19 vaccination over a period of one year were assessed. Our results showed that only 3.16% of patients experienced flare-ups of AIRDs. The common AIRDs included RA, SLE, cutaneous vasculitis, undifferentiated inflammatory arthritis, psoriatic arthritis, reactive arthritis, and Sjögren syndrome. The majority of flare-ups occurred within 15 days and after the first dose of the COVID-19 vaccine. The likelihood of a flare-up was higher in patients who received the AstraZeneca and CoBarecat vaccines compared to other types of COVID-19 vaccines.

In general, previous studies have estimated the rate of AIRDs flares following COVID-19 vaccination to be between 1.5-15% (15,25-29). In three large international studies, the rate of flares following COVID-19 vaccination was 4.3% out of 5619, 1.5% out of 4498, and 2.4% out of 696 patients with rheumatic diseases (15,27,30). These findings are similar to the present results, where the rate of flares following COVID-19 vaccination was estimated to be 3.1%. In another large study conducted in China, 3.5% of patients reported a disease flare that required a change in treatment (26).

In a study conducted on patients with autoimmune and inflammatory rheumatic diseases who received six different types of COVID-19 vaccines, only localized pain, fatigue, headache, and muscle ache were reported after receiving the COVID-19 vaccine,

Table 1. The demographic and clinical information of patients with flare-up following COVID-19 vaccination

Variables		No	%
(years)	<30	36	27.3
	≥30	96	72.7
Gender	Male	21	15.9
	Female	111	84.1
Education level	Illiterate	12	9.1
	Primary	40	30.3
	High school	66	50.0
	Academic	14	10.6
Occupational status	Unemployed	69	52.3
	Free employed	47	35.6
	Employee	16	12.1
Substance use	No	116	87.9
	Yes	16	12.1
Hypertension	No	101	76.5
	Yes	31	23.5
Hyperlipidemia	No	112	84.8
	Yes	20	15.2
Hypothyroidism	No	124	93.9
	Yes	8	6.1
Diabetes	No	114	86.4
	Yes	18	13.6
Underlying disease	No	97	73.5
	Yes	35	26.5
Type of vaccine (The first time)	AstraZeneca	28	21.2
	Sinopharm	89	67.4
	CoBarecat	13	9.8
	Sputnik V	2	1.5
Dose of COVID-19 vaccine in which the AIRDs* was relapsed	First dose	94	71.2
	Second dose	38	28.8
Hospitalized	No	75	86.2
	Yes	12	13.8
Prior COVID-19 infection	Yes	45	34.1
	No	78	65.9
Number of times infected with COVID	Never	45	34.1
	Once	74	56.1
	Two	11	8.3
	Three	2	1.5
Severity Of COVID-19 infection (first time)	Mild	57	65.5
	Moderate	28	32.2
	Severe	2	2.3
Severity Of COVID-19 infection (second time)	Mild	4	30.8
	Moderate	5	38.5
	Severe	4	30.8
Severity of COVID-19 infection (third time)	Mild	0	0
	Moderate	1	33.3
	Severe	2	66.7
Adverse effects of vaccine	No	54	40.9
	Yes	78	59.1
Type of adverse effects	Fever	14	10.6
	Malaise+Fever	20	15.2
	Headache	8	6.1
	Myalgia+Fever+ Headache	6	4.5
	Fever+Headache	2	1.5
	Malaise+ Headache	4	3.0
	Local Pain/ Redness/Swelling	15	11.3
	Local Pain/ Redness/Swelling +Hair Loss	1	0.8
	Myalgia	5	3.8
	Generalized Itching	5	3.8

* Autoimmune Rheumatic Diseases.

and no recurrence was reported in any of the patients (31). However, some studies have reported a higher rate of disease flares necessitating treatment changes (25,28,32). A study conducted on a large population revealed that nearly 1 in 10 individuals with AIRDs experience flare-ups after receiving the COVID-19 vaccine (33). The observed variations could be attributed to differences in the characteristics of the study groups, exposure to vaccines, and the definitions of flare used in different studies.

While COVID-19 vaccination could potentially trigger a flare-up in AIRDs, it appears that the severity of the disease activity is not overly high. These flare-ups are generally mild to moderate in severity (34). In many studies, transient flares have been reported in several cases after receiving the COVID-19 vaccine (25,28,32,35). In this study, flare-ups were managed by modifying treatments or resuming the use of immunosuppressive drugs. A study conducted in China revealed that 10.5% of patients with AIRDs experienced flare-ups after receiving the inactivated

Table 2. The frequency of flare-up in patients with autoimmune rheumatic diseases following COVID-19 vaccination

Autoimmune rheumatic disease	Subscale	No	%	Men of time between vaccination and onset of flare-up	Total	Percentage incidence
Seronegative spondyloarthropathy	Psoriatic arthritis	9	6.8	15.4(7-30)	26(19.7%)	0.62
	Reactive arthritis	9	6.8	12.3(5-20)		
	Peripheral spondyloartropaty	4	3	15.5(2-25)		
	Ankylosing spondylitis	4	3.0	11.2(7-18)		
Vasculitis	ANCA associated vasculitis	5	3.8	12.6(1-30)	29(22%)	0.69
	Behçet's Disease	5	3.8	17.8(5-30)		
	Takayasu arthritis	5	3.8	15.6(6-21)		
	Cutaneous vasculitis	14	10.6	13.2(2-30)		
Inflammatory myopathies	Dermatomyositis	3	2.3	8.6(7-12)	6(4.5%)	0.14
	IBM myositis	3	2.3	6.6(5-10)		
Systemic lupus erythematosus		17	12.9	14.7(0-30)	17(12.9%)	0.4
Rheumatoid arthritis		25	18.9	13.8(0-30)	25(18.9%)	0.59
Sarcoidosis		2	1.5	16(15-17)	2(1.5%)	0.04
Antiphospholipid syndrome		5	3.8	16.2(5-30)	5(3.8%)	0.11
Sjögren syndrome		7	5.3	10.8(5-21)	7(5.3%)	0.16
Isolated uveitis		2	1.5	25(20-30)	2(1.5%)	0.04
Undifferentiated inflammatory arthritis		13	9.8	9.2(0-19)	13(9.8%)	0.31

Table 3. The comparison between type of vaccination with dose of vaccine in which the AIRDs has been relapsed and adverse effect immediately after vaccination

Type of vaccine		Dose of COVID-19 vaccine in which the AIRDs* was relapsed		Adverse effect immediately after vaccination	
		Fist dose	Second dose	No	Yes
AstraZeneca	No	25	3	6	22
	%	89.3	10.7	21.4	78.6
Sinopharm	No	58	31	44	45
	%	65.2	34.8	49.4	50.6
Sputnik V	No	0	2	1	1
	%	0.0	100.0	50	50
CoBarecat	No	11	2	3	10
	%	84.6	15.4	23.1	76.9
χ^2		12.13		8.85	
p-value		0.007		0.037	

COVID-19 vaccine (26). Despite this somewhat alarming rate of disease recurrence, it's important to note that there were no instances of fatal flare-ups, suggesting that the inactivated COVID-19 vaccines were generally well-tolerated among the AIRD population.

According to the present study, RA, SLE, and cutaneous vasculitis are among the most frequently reported flares following COVID-19 vaccination. This aligns with the findings of a study by Rider *et al*, which indicated that the likelihood of a flare-up after COVID-19 vaccination is higher among patients with RA and SLE. Moreover, a relapse of Sjögren's syndrome was reported in 6% of patients, a figure that aligns closely with the present study, which found a rate of 5.3% (30).

However, when considering individual categories of AIRDs, a higher rate of disease flare was observed in patients with SLE compared to those with RA, as reported by Rider *et al* and Fan *et al* (26,30). While study by Vacolup *et al* reported that a flare following COVID-19 vaccination occurred in only 3% of SLE patients (15).

Theoretically, it's plausible that mRNA and adenoviral vector vaccines could trigger Toll-like receptors, intracellular sensors, and the production of Type I interferon. This could potentially influence the disease activity of AIRDs such as SLE (36). Apparently, SLE is one of the AIRDs with a high risk of flare-up following COVID-19 vaccination. However, the infrequent occurrence of disease flare and its variation based on diagnosis type suggest that genetic factors and other predisposing elements could also play a significant role (26,30). In the current study, it was impossible to calculate the flare-up rate for each autoimmune disease separately. Due to the lack of sufficient information on this topic, it is recommended that further studies be conducted.

Similar to this study, other studies have shown that disease flares occur predominantly among female and older patients (26,30). Boekel *et al* demonstrated that female gender and older age were associated with moderate or severe side effects post-COVID-19 vaccination (29). Similarly, the study conducted by Rider *et al* found that flare rates were higher in females (30). It should be noted that AIRDs are more common among middle-aged women.

Previous research has shown that experiencing a flare within 6 or 12 months before receiving the COVID-19 vaccine, and a previous history of SARS-CoV-2 infection were associated with AIRDs flares (15,25). However, we found no association between flare-ups and a previous history of SARS-CoV-2 infection. The difference may be due to the interval time between remission from COVID-19 infection and vaccination. The observed link between flare-ups following COVID-19 vaccines in patients who have previously had serious reactions to other non-COVID-19 vaccines is noteworthy. This suggests that a specific immune profile may make patients more susceptible to flare-ups after receiving COVID-19 and potentially other vaccines.

It was particularly noted that individuals with comorbidities (especially autoimmune diseases), mental health disorders, were especially susceptible to flare-ups of AIDRs (33). In a study conducted by Watad *et al*, it was found that 75% of individuals who experienced a flare-up had a pre-existing autoimmune/rheumatic disease before vaccination, and 80% responded to corticosteroid therapy. The average time between vaccination and the onset of immune-mediated diseases was estimated to be 4 days (34). It was found that 26% of patients who experienced a flare-up had an underlying disease. In this study, the average time interval between COVID-19 vaccination and a flare-up was 13 days.

It should be noted that patients who received the Moderna vaccine were especially susceptible to flare-ups of AIDRs (33). Another study showed that the majority (85%) of flare-ups occurred in individuals who were vaccinated with the BNT-162b2 vaccine (34). Due to the limited availability of the Moderna vaccine in Iran, we focused our research on inactivated whole virus vaccines (Sinopharm and Barecatco) and viral vector vaccines (AstraZeneca and Sputnik V). Our findings showed that more than 89% of patients who were vaccinated with AstraZeneca experienced a flare-up after the first dose of vaccination. The link between flare-ups and the AstraZeneca vaccine, a replication-deficient simian adenovirus vector containing the full-length coding sequence of the SARS-CoV-2 spike protein, compared to other vaccines, calls for further investigation. Boekel *et al* demonstrated that the AstraZeneca vaccine was

associated with moderate or severe side effects post-COVID-19 vaccination (29). Moreover, the AstraZeneca vaccine has been associated with other autoimmune side effects, including the risk of blood clotting events and autoimmune-induced low platelet count. Therefore, its potential association with flares in AIDRs could be considered reasonable (24).

There is substantial evidence indicating that immunosuppressants, particularly Mycophenolate mofetil, significantly hampers the immune response to various vaccines, including Moderna and Pfizer-BioNTech (21,37,38). It is also speculated that glucocorticoids may cause a dose-dependent reduction in antibody titres (37,39). This problem can be mitigated by administering a booster dose to achieve sufficient antibody titres (25). According to a study by Jagtap *et al*, it was found that the administration of corticosteroids and mycophenolate mofetil, was linked to a decrease in post-vaccination flare-ups. The use of immunosuppressants can reduce seroconversion rates, making the vaccine less immunogenic (33). In the present study, the majority of patients stopped taking AIRDs medications one to two weeks before and after vaccination.

In this study, 22.6% of patients received heterologous vaccination. The evidence obtained from the study by Jagtap *et al* demonstrated that heterologous vaccination did not increase the risk of flare-ups compared to homologous vaccination. However, a decrease in flare rates with subsequent vaccine doses has been reported (33). This could be attributed to either a reduction in vaccination rates among those who experienced a flare-up after the first dose, or a decreased risk of COVID infection-associated flare-ups in those who were more thoroughly vaccinated (37). Similarly, the present study showed that the majority of flare-ups occurred after the first dose of the COVID-19 vaccine.

It is not clear whether the COVID-19 vaccination triggered a flare of the disease in asymptomatic positive rheumatoid disease patients or directly led to the formation of the diseases. According to the concept of molecular mimicry, the immune system can potentially be activated due to similarities between viral peptides and the body's own peptides. The American College of Rheumatology guidelines suggest that COVID-19 vaccination could potentially risk a flare-up of an autoimmune disease, a view that is moderately agreed upon, although it remains theoretical. While there have been instances where vaccines, including those for tetanus, rubella, hepatitis B, and influenza, have been linked to the onset of RA, there is no definitive evidence to support these claims. Furthermore, no such correlation has been consistently observed in extensive, controlled research studies (7,40).

It should be noted that the use of some immunosuppressive agents has been discontinued before vaccination against SARS-CoV-2 (7). Therefore, it is not clear whether COVID-19 vaccination provokes flares of underlying rheumatic disease or directly leads to the disease. The causal effect of COVID-19 vaccination on the provocation of flares of rheumatic conditions is also unclear (41). The question whether the COVID-19 vaccination triggered a flare of rheumatoid diseases without performing a Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA) test before vaccination cannot be answered definitely. Despite these limitations, the present study data provided an interesting overview of the spectrum of diseases possibly associated with either SARS-CoV-2 infection or the COVID-19 vaccine.

Advantages and limitations

This study is the first comprehensive series description to estimate the incidence of flare-ups in AIRDs following COVID-19 vaccination in Iran, which is a significant strength of this study. Another major strength of this study is the confirmation of disease flares and subsequent changes to treatment by a medical professional, ensuring that it was indeed a true flare. However, many mild flares are managed at home without medical intervention, suggesting that the actual incidence rate could be higher than our estimates. Moreover, flare-ups could also occur due to the discontinuation of treatment before vaccination, considering the potential interaction between the vaccine and immunosuppressive medications. Therefore, the flare-ups might simply represent a coincidental relationship, and as such, we cannot infer any pathophysiological explanation from our data or that of others. In the current research, there was not access to certain information. This

includes the level of disease activity when the vaccine was administered, the severity of the disease flare, the history of previous flares, and any additional immunomodulatory medications that were being taken, including their dosage and timing in relation to the vaccination. Moreover, the impact of additional doses on the flare-up of autoimmune diseases was not evaluated. This is a crucial area for future research, especially since patients who have flare-ups might be hesitant to get further recommended doses. Furthermore, the flare-up rate for each autoimmune disease separately could not be calculated. The present study findings can serve as a warning to physicians about the potential for flare-ups following vaccination, enabling timely intervention and prevention of irreversible organ damage. However, the benefits of COVID-19 vaccination in managing the global pandemic are indisputable, so vaccinations should not be avoided. More research is required to identify individuals who may be at risk and to understand the autoimmune mechanisms activated by COVID-19 vaccines.

Conclusion

In Mashhad, Iran, the incidence of flare-ups in autoimmune and inflammatory rheumatic diseases following COVID-19 vaccination is estimated to be a mere 3.1%. These diseases include conditions such as RA, SLE, cutaneous vasculitis, undifferentiated inflammatory arthritis, psoriatic arthritis, reactive arthritis, and Sjögren syndrome. Despite their rarity, flare-ups in autoimmune and inflammatory rheumatic diseases post-COVID-19 vaccination can still pose a public health issue, potentially undermining public confidence in vaccinations. At present, a cause-effect relationship cannot be definitively established, but it has been observed that flare-ups in autoimmune and inflammatory rheumatic diseases may occur within a short period following the administration of COVID-19 vaccines. Therefore, we hypothesize that COVID-19 vaccination may act as a trigger for some rheumatic diseases.

Acknowledgement

We thank everyone who helped us in this study

Conflict of Interest

There was no conflict of interest in this manuscript.

References

1. Wagner CE, Saad-Roy CM, Grenfell BT. Modelling vaccination strategies for COVID-19. Nat Rev Immunol 2022;22(3):139-41.

2. Narducci DM, Diamond AB, Bernhardt DT, Roberts WO. COVID vaccination in athletes and updated interim guidance on the preparticipation physical examination during the SARS-CoV-2 Pandemic. Clin J Sport Med 2022;32(1):e1-e6.

3. Harris P, Moss D. Managing through the Covid second wave: Public affairs and the challenge of Covid vaccination. J Public Aff 2021 Feb;21(1):e2642.

4. Li Y-D, Chi W-Y, Su J-H, Ferrall L, Hung C-F, Wu T-C. Coronavirus vaccine development: from SARS and MERS to COVID-19. J Biomed Sci 2020;27(1):104.

5. Cuschieri S, Agius S, Souness J, Brincat A, Grech V. The fastest national COVID vaccination in Europe-Malta's strategies. Health Sci Rev (Oxf) 2021;1:100001.

6. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383(27):2603-15.

7. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384(5):403-16.

8. Ramasamy MN, Minassian AM, Ewer KJ ,Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2020; 396(10267):1979-93.

9. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21(2):181-92.

10. Stevens E, Weinblatt ME, Massarotti E, Griffin F, Emani S, Desai S. Safety of the zoster vaccine recombinant adjuvanted in rheumatoid arthritis and other systemic rheumatic disease patients: a single center's experience with 400 patients. ACR Open Rheumatol 2020;2(6):357-61.

11. Nakafero G, Grainge MJ, Myles PR, Mallen CD, Zhang W, Doherty M, et al. Association between inactivated influenza vaccine and primary care consultations for autoimmune rheumatic disease flares: a self-controlled case series study using data from the Clinical Practice Research Datalink. Ann Rheum Dis 2019;78(8):1122-6.

12. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis 2021;21(7):939-49.

13. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al .Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect Dis 2022;22(1):43-55.

14. Bartels LE, Ammitzbøll C, Andersen JB, Vils SR, Mistegaard CE, Johannsen AD, et al. Local and systemic reactogenicity of COVID-19 vaccine BNT162b2 in patients with systemic lupus erythematosus and rheumatoid arthritis. Rheumatol Int 2021;41(11):1925-31.

15. Felten R, Kawka L, Dubois M, Ugarte-Gil MF, Fuentes-Silva Y, Piga M, et al. Tolerance of COVID-19 vaccination in patients with systemic lupus erythematosus: the international VACOLUP study. Lancet Rheumatol 2021;3(9):e613-e5.

16. Aboud FM, Hussein RS ,Hassan RM. Safety and reported adverse effects of coronavirus disease-2019 (COVID-19) vaccines in patients with rheumatic diseases. Egypt Rheumatol 2023;45(2):133-7.

17. Boekel L, Hooijberg F, van Kempen ZL, Vogelzang EH, Tas SW, Killestein J, et al. Perspective of patients with autoimmune diseases on COVID-19 vaccination. Lancet Rheumatol 2021;3(4):e241-e3.

18. 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):1601-5.

19. Yurttas B, Poyraz BC, Sut N, Ozdede A, Oztas M, Uğurlu S, et al. Willingness to get the COVID-19 vaccine among patients with rheumatic diseases, healthcare workers and general population in Turkey: a web-based survey. Rheumatol Int 2021;41(6):1105-14.

20. Akiyama S, Hamdeh S, Micic D, Sakuraba A. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. Ann Rheum Dis 2021;80(3):384-91.

21. Zavala-Flores E, Salcedo-Matienzo J, Quiroz-Alva A, Berrocal-Kasay A. Side effects and flares risk after SARS-CoV-2 vaccination in patients with systemic lupus erythematosus. Clin Rheumatol 2022:1349-57.

22. Sattui SE, Liew JW, Kennedy K, Sirotich E, Putman M, Moni TT, et al. Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. RMD open 2021;7(3):e001814.

23. Park JK, Lee MA, Lee EY, Song YW, Choi Y, Winthrop KL, Lee EB. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. Ann

Rheum Dis 2017 Sep 1;76(9):1559-65.

24. Klok FA, Pai M, Huisman MV, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. Lancet Haematol 2022;9(1):e73-e80.

25. Connolly CM, Ruddy JA, Boyarsky BJ, Barbur I, Werbel WA, Geetha D, et al. Disease flare and reactogenicity in patients with rheumatic and musculoskeletal diseases following two-dose SARS–CoV-2 messenger RNA vaccination. Arthritis Rheumatol 2022;74(1):28-32.

26. Fan Y, Geng Y, Wang Y, Deng X, Li G, Zhao J, et al. Safety and disease flare of autoimmune inflammatory rheumatic diseases: a large real-world survey on inactivated COVID-19 vaccines. Ann Rheum Dis 2022;81(3):443-5.

27. Machado PM, Lawson-Tovey S, Strangfeld A, Mateus EF, Hyrich KL, Gossec L, et al. Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry. Ann Rheum Dis 2022;81(5):695-709./

28. Barbhaiya M, Levine JM, Bykerk VP, Jannat-Khah D, Mandl LA. Systemic rheumatic disease flares after SARS-CoV-2 vaccination among rheumatology outpatients in New York City. Ann Rheum Dis 2021;80(10):1352-4.

29. Boekel L, Kummer LY, van Dam KP, Hooijberg F, van Kempen Z, Vogelzang EH, et al. Adverse events after first COVID-19 vaccination in patients with autoimmune diseases. Lancet Rheumatol 2021;3(8):e542-e5.

30. Rider LG, Parks CG, Wilkerson J, Schiffenbauer AI, Kwok RK, Noroozi Farhadi P, et al. Baseline factors associated with self-reported disease flares following COVID-19 vaccination among adults with systemic rheumatic disease: results from the COVID-19 global rheumatology alliance vaccine survey. Rheumatology (Oxford) 2022;61(SI2):SI143-SI50.

31. 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 Dec;41(12):2105-8.

32. Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021;80(7):930-42.

33. Jagtap K, Naveen R, Day J, Sen P, Vaidya B, Nune A, et al. Flares in autoimmune rheumatic diseases in the post-COVID-19 vaccination period—a cross-sequential study based on COVAD surveys. Rheumatology (Oxford) 2023 Dec 1;62(12):3838-48.

34. Watad A, De Marco G, Mahajna H, Druyan A, Eltity M, Hijazi N, et al. Immune-mediated disease flares or new-onset disease in 27 subjects following mRNA/DNA SARS-CoV-2 vaccination. Vaccines 2021;9(5):435.

35. Baimukhamedov C, Makhmudov S, Botabekova A. Seropositive rheumatoid arthritis after vaccination against SARS-CoV-2 infection. Int J Rheum Dis 2021;24(11):1440-1.

36. Teijaro JR, Farber DL. COVID-19 vaccines: modes of immune activation and future challenges. Nat Rev Immunol 2021;21(4):195-7.

37. Paik JJ, Sparks JA, Kim AH. Immunogenicity, breakthrough infection, and underlying disease flare after SARS-CoV-2 vaccination among individuals with systemic autoimmune rheumatic diseases. Curr Opin Pharmacol 2022;65:102243.

38. Furer V, Eviatar T, Zisman D, Peleg H, 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):1330-8.

39. Fazal ZZ, Sen P, Joshi M, Ravichandran N, Lilleker JB, Agarwal V, et al. COVAD survey 2 long-term outcomes:

unmet need and protocol. Rheumatol Int 2022 Dec;42(12):2151-8.

40. Ray P, Black S, Shinefield H, Dillon A, Carpenter D, Lewis E, 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(38):6592-7.

41. Terracina KA, Tan FK. Flare of rheumatoid arthritis after COVID-19 vaccination. Lancet Rheumatol 2021;3(7):e469-e70.