Journal of Iranian Medical Council, Volume 7, Issue no. 4
http://dx.doi.org/10.18502/jimc.v7i4.16626

Original Article

Efficacy Evaluation of COVID-19 Vaccines in Patients with Autoimmune Rheumatic Diseases in Mashhad, Iran

Zahra Rezaieyazdi[1†], Farzaneh Sookhtanloo[1†], Masoumeh Salari[1], Rozita Khodashahi[2,3,4], Maryam Sahebari[1], Zahra Mirfeizi[1], Muhammed Joghatayi[2] and Mandana Khodashahi[1*]

1. Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
2. Clinical Research Development Unit, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3. Transplant Research Center, Montaserieh Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
4. Department of Infectious Diseases and Tropical Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
5. Montaserieh Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
† The first and the second authors have had equal contribution to this manuscript

Abstract

Background: Autoimmune Rheumatic Diseases (ARDs) patients are at high risk of COVID-19 re-infection even after vaccination. However, since the majority of studies in the related literature are focused on the efficacy of messenger RNA in rheumatic patients, the present study aimed to assess the efficiency of the inactivated whole virus vaccines and viral vector COVID-19 vaccines in rheumatic diseases in Mashhad, Iran.

Methods: This prospective cross-sectional study was conducted on ARDs patients who were referred to private clinics and rheumatologic clinics of Ghaem and Imam Reza Hospitals, Mashhad, Iran, during 2021-22. Anti-neutralizing antibodies have been considered to check antibodies of Sinopharm and Barkat vaccines, and an anti-spike antibody was considered to check Sputnik V and AstraZeneca vaccine antibodies. Humoral immunity was investigated using the anti-spike Enzyme-linked immunosorbent assay and anti-neutralizing antibodies.

Results: The obtained results showed that humoral immunity after COVID-19 vaccination was observed in 73.9% of the patients with ARDs. However, humoral immunity was lower in ARDs patients who took tacrolimus and higher in patients with a history of COVID-19 infection (χ^2=5.84, p=0.01). The infection after the second COVID-19 vaccination was lower in patients with humoral immunity (χ^2=5.69, p=0.01).

Conclusion: This study demonstrated that a homologous second dose of an inactivated whole viral vector SARS-CoV-2 vaccine was safe and provided a remarkable antibody response in ARDs patients.

Keywords: Autoimmune rheumatic diseases, COVID-19, Humoral immunity, Vaccination

*** Corresponding author**

Mandana Khodashahi, MD
Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: +98 51 3801 2753
Email: khodashahimn@mums.ac.ir, mkhodashahi53@gmail.com

Received: 29 Nov 2023
Accepted: 24 Jan 2024

Citation to this article
Rezaieyazdi Z, Sookhtanloo F, Salari M, Khodashahi R, Sahebari M, Mirfeizi Z, *et al*. Efficacy Evaluation of COVID-19 Vaccines in Patients with Autoimmune Rheumatic Diseases in Mashhad, Iran. *J Iran Med Counc.* 2024;7(4):645-56.

Introduction

The outbreak of the SARS-CoV-2 virus, the causative agent of a type of acute respiratory syndrome with a viral agent from the beta coronavirus family, was a crisis phenomenon in the world and affected all aspects of the lives of billions of people in recent years (1). Vaccines are one of the most important global strategies for controlling the SARS-CoV-2 pandemic, especially in high-risk groups (2,3).

Humoral immunity is a type of acquired immune response caused by the activity of antibodies in the extracellular fluids (4-6). In most forms of vaccination, the antigen of a pathogen or weakened pathogens is injected into the body and the immune system is stimulated to produce antibodies. There are five main categories of SARS-CoV-2 vaccines. These include inactivated whole virus vaccines, viral vector vaccines, live attenuated whole virus vaccines, messenger RNA (mRNA) and DNA-based vaccines, and recombinant protein vaccines (7). Many vaccines interact with the surface proteins of viruses directly or indirectly (8).

Many patients with Autoimmune Rheumatic Diseases (ARDs) are treated with immunosuppressive drugs. The mortality risk of these patients is higher compared to the general population if they are affected by the SARS-CoV-2 virus. Therefore, the efficacy and safety of emerging COVID-19 vaccines are very important in the rheumatology population, as a high-risk group of patients (9,10). Few trials have assessed the best-selected COVID-19 vaccine in patients with immune system deficiency treated with immunosuppressive drugs (11).

It appears that vaccines are currently safe to be used in the rheumatology population, except for live attenuated vaccines that seem to induce an adequate immune response (12). However, the effect of the COVID-19 vaccine on patients with ARDs should be monitored, especially if they are under treatment with immunosuppressive drugs (13,14). Soy *et al* showed a weaker immune response after COVID-19 vaccination in rheumatic patients who used immunosuppressive drugs and concluded that these patients were at risk of infection with COVID-19 even after vaccinations (15). Patients with ARDs may experience a slow reaction or a rapid decrease in antibody titer after the COVID-19 vaccine. However, there is currently no reason to exclude ARDs patients under treatment from getting vaccinated (16).

Some studies have shown an increase in the antibody level after vaccination of ARDs patients, at the threshold level of creating immunity against the COVID-19 vaccine, which is less than that in healthy people. To increase the rate of the immune response, it seems that the right time of vaccination should be considered in the case of patients treated with immunosuppressive drugs (16). ARDs patients are at risk of COVID-19 re-infection, even after vaccination (17). In some studies, inactivated whole-virus COVID-19 vaccines have been considered effective vaccines with mild, predictable, and non-life-threatening side effects in transplant patients (18,19). However, no studies have been conducted on the effect of the vaccine type in patients with ARDs.

Regarding the lack of studies on the effectiveness of COVID-19 vaccines for ARDs patients in Iran, and considering the fact that studies conducted in other countries are mainly focused on some specific types of vaccines, including mRNA, the present study aimed to evaluate the effectiveness of inactivated whole virus vaccines and viral vector COVID-19 vaccines for ARDs patients in Mashhad, Iran.

Materials and Methods

This prospective cross-sectional study was conducted on patients with ARDs who were referred to private clinics and the rheumatology center of Ghaem and Imam Reza Hospitals, Mashhad, Iran, during 2021-2022.

Inclusion and exclusion criteria

The rheumatic patients who received two doses of the COVID-19 vaccine were entered into this study. However, the patients who only received one dose of the COVID-19 vaccine, non-cooperative patients (during the follow-up), and those with insufficient information in the follow-up were excluded from the study.

Study design

Eligible COVID-19-vaccinated ARDs patients with were entered into the study, without restrictions for age and gender. The sample size was estimated based on previous studies (20). To increase the study power,

the number of samples was increased to 88.

Initially, the demographic characteristic data and clinical information were gathered and recorded in a checklist. These included the type of rheumatic disease, type of immunosuppressive drugs used, discontinuation of immunosuppressive drugs, co-morbidity, and the history of COVID-19 infection. The patients were referred for COVID-19 vaccination by a recommendation letter from a rheumatologist, taking into account the consumption of immunosuppressive drugs. If necessary, the drugs were discontinued under the supervision of a rheumatologist and considering the 2021 American College of Rheumatology (ACR) guidelines for COVID-19 vaccination (21). Patients who received two doses of vaccine were referred to the laboratory (at the beginning of the 3rd week after administration of the second dose) to take a venous blood sample (5 *ml*) and check the level of humoral immunity.

The majority of patients were vaccinated with inactivated whole virus vaccines. Anti-neutralizing antibodies were adopted to check Sinopharm and Barkat vaccine antibodies and anti-spike antibodies were used to check Astrazeneca vaccine antibodies. Humoral immunity was investigated using the anti-spike enzyme-linked immunosorbent assay (ELISA) and anti-neutralizing antibodies.

Statistical analysis

The data were entered into the SPSS 24 (IBM Corp., Armonk, NY, USA). Mean and frequency indices were used to describe the descriptive data. The Kolmogorov-Smirnov and Chi-square tests were used to evaluate the normality of the data and assess the categorical variables, respectively. The interval variables were evaluated using the t-test and its non-parametric equivalent. p-values lower than 0.05 ($p<0.05$) were considered significant.

Ethical considerations

The study protocol was approved by the Ethical Committee of Mashhad University of Medical Sciences, Mashhad, Iran (Ethics code: IR.MUMS.MEDICAL.REC.1401.319). The present study was extracted from a thesis to receive the specialist degree in rheumatology (Code:4000620). All the data were coded and recorded in a checklist anonymously to maintain confidentiality. Informed written consent was obtained from all the patients.

Results

A total of 88 ARDs patients with a mean±SD age of 44.07±11.06 years (age range of 20-76 years) were entered into this study. The majority of patients (n=76, 86.4%) were female. The mean±SD duration of rheumatic disease was 7.03±6.66 years (ranging from 6 mounts to 32 years). Table 1 presents the demographic and clinical information of patients with ARDs. In total, 39.8% of the patients had underlying diseases including diabetes mellitus, hypertension, and hyperlipidemia. Moreover, 3.4% (n=2) were suffering from anxiety, deep vein thrombosis, and irritable bowel syndrome. Asthma, benign prostatic hyperplasia, fatty liver, brain aneurysm, and minor thalassemia were reported in only 2.3% of the patients. Table 2 presents the frequency of medications used in patients with ARDs.

Table 1. Demographic and clinical information of patients with autoimmune rheumatic diseases

Variables		No	%
Social history	No	79	89.8
	Yes	9	10.1
Underlying disease	No	53	60.2
	Yes	35	39.8
Hypertension	No	77	87.5
	Yes	11	12.5
Dyslipidemia	No	80	90.9
	Yes	8	9.1
Hypothyroidism	No	73	83
	Yes	15	17
Diabetes	No	86	97.7
	Yes	2	2.3
Psoriasis	No	83	94.3
	Yes	5	5.7
Immune thrombocytopenia	No	85	96.6
	Yes	3	3.4
Mitral valve insufficiency	No	85	96.6
	Yes	3	3.4

Contd. table 1.

Ischemic heart disease	No	86	97.7
	Yes	2	2.3
Rheumatoid disease severity	Mild	11	12.5
	Moderate	20	22.7
	Severe	36	40.9
	Hospitalization	21	23.9
Education level	Illiterate	3	3.4
	Elementary to Cycle	28	31.8
	Diploma	30	34.1
	Academic	27	30.7
Occupational status	Housewife	60	68.2
	Retired	6	6.8
	Self-employed	11	12.5
	Employee or teacher	8	9.1
	Student	3	3.4
Rheumatologic diagnosis	Rheumatoid Arthritis (RA)	42	47.7
	Systemic Lupus Erythematosus (SLE)	12	13.6
	Behcet's Disease (BD)	7	8
	Ankylosing Spondylitis (AS)	5	5.7
	Psoriatic arthritis (PsA)	4	4.5
	Wegener'S Disease (WD)	3	3.4
	Sjogren's Syndrome (SS)+SLE	3	3.4
	Scleroderma	2	2.3
	Granulomatosis (GM)	2	2.3
	Churg-Strauss Syndrome (CSS)	2	2.3
	SS+APS	1	1.1
	RA+SLE	1	1.1
	RA+SS	1	1.1
	BD+AS	1	1.1
	RA+ PsA	1	1.1
	SLE+RA+ARF	1	1.1

Out of 88 participations, 47.7% were previously infected with COVID-19, and COVID-19 recurrence was reported in 23.9% of these patients after vaccination. The mean±SD time interval between COVID-19 vaccination and COVID-19 re-infection was 64±44.82 days (ranging from 5 to 180 days). Adverse effects after vaccination were reported in 47.7% of the patients. Local pain, swelling, and redness were the most commonly reported adverse effects in the patients (n=17, 19.3%). Headache, fever, malaise, myalgia, and dizziness were observed in 17.1% (n=15), 11.3% (n=10), 10.2% (n=9), 4.5% (n=4), and 2.3% (n=2) of the patients, respectively. Hair loss and nausea were observed in only 1.15% (n=1) of the patients. Table 3 indicates the patients' clinical information related to COVID-19.

In general, the mean±SD level of humoral immunity after COVID-19 vaccination in patients with ARDs was 82.9±68.64 (ranging from 0.4 to 180). Humoral immunity after COVID-19 vaccination was observed in 73.9% (n=65) of ARDs patients.

The rate of humoral immunity was not different in patients of various ages (t=-1.65, p=0.101) and was not associated with the duration of rheumatic disease (Z<0.01, p>0.99). The association between the use of rheumatic drugs and humoral immunity is presented in table 4. Based on the obtained results, the use of rheumatic drugs (*e.g.*, corticosteroids, cytotoxics, biologic disease-modifying antirheumatic drugs [DMARDs], traditional DMARDs), except for tacrolimus (χ^2=5.78, p=0.01), was not associated with the humoral immunity in the rheumatic patients.

Table 5 shows the association between humoral immunity and other variables. Based on the results, gender (χ^2=64, p=0.42), type of rheumatic disease (χ^2=17.82, p=0.27), the presence of underlying diseases (χ^2=0.32, p=0.56), patients' social history (χ^2=0.8, p=0.77), type of vaccination (χ^2=5.01, p=0.17), and rheumatoid disease severity (χ^2=0.1.9, p=0.59) were not related to humoral immunity. Humoral immunity was higher in patients with a history of COVID-19 infection (χ^2=5.84, p=0.01). The rate of relapse after COVID-19 vaccination was not significantly different in patients with and without humoral immunity, meaning that vaccination did not prevent COVID-19 re-infection after the first dose (p=0.98). However, COVID-19 infection after

Table 2. Frequency of medications used in patients with autoimmune rheumatic diseases

Variables		No	%	Variables		No	%
Methotrexate	Yes	59	67	Prednisolone	Yes	65	73.9
	No	29	33		No	23	26.1
Hydroxychloroquine	Yes	24	27.3	Infliximab	Yes	5	5.7
	No	64	72.7		No	83	94.3
Rituximab	Yes	3	3.4	Adalimumab	Yes	11	12.5
	No	85	96.6		No	77	87.5
Sulfasalazine	Yes	10	11.4	Colchicine	Yes	6	6.8
	No	78	88.6		No	82	93.2
Penicillamine	Yes	1	1.1	Acetylsalicylic acid	Yes	11	12.5
	No	87	98.9		No	77	87.5
Denosumab	Yes	1	1.1	Etanercept	Yes	6	6.8
	No	87	98.9		No	82	93.2
Non-steroidal anti-inflammatory drugs	Yes	10	11.4	Mycophenolate	Yes	13	14.8
	No	78	88.6		No	75	85.2
Azathioprine	Yes	10	11.4	Tacrolimus	Yes	2	2.3
	No	78	88.6		No	86	97.7
Cyclosporine	Yes	1	1.1	Cyclophosphamide	Yes	1	1.1
	No	87	98.9		No	87	98.9

Table 3. The patients' clinical information related to COVID-19

Variables		No	%	Variables		No	%
Pervious COVID-19 infection	Yes	42	47.7	COVID-19 recurrence after vaccination	Yes	21	23.9
	No	46	52.3		No	67	76.1
Number of COVID-19 infections	0	46	52.3	Adverse effects of vaccine	No	46	52.3
	1	36	40.9		Yes	42	47.7
	2	5	5.7	Medication cessation before vaccination	Yes	68	77.3
	3	1	1.1		No	20	22.7
Severity of COVID-19 infection (first time)	No symptoms	3	7.1	Type of vaccine	Sinopharm	73	83.0
	Mild	22	52.4		AstraZeneca	8	9.1
	Moderate	8	19.0		Sputnik V	1	1.1
	Hospitalization	8	19.0		Barecatco	6	6.8
Severity of COVID-19 infection (second times)	No symptoms	1	16.7	Infection after the first vaccination	Yes	19	21.6
	Mild	1	16.7		No	69	78.4
	Moderate	1	16.7	Infection after the second vaccination	Yes	2	2.3
	Hospitalization	1	16.7		No	85	96.6
Severity of COVID-19 infection (third times)	No symptoms	1	100	-	-	-	-
	Mild	0	0	-	-	-	-
	Moderate	0	0	-	-	-	-
	Hospitalization	0	0	-	-	-	-

Table 4. The association between the use of rheumatic drugs and humoral immunity

Variables		No humoral immunity		Humoral immunity		χ^2	p-value
		No	%	No	%		
Methotrexate	Yes	14	60.9	45	69.2	0.53	0.463
	No	9	39.1	20	30.8		
Prednisolone	Yes	18	78.3	47	72.3	0.31	0.577
	No	5	21.7	18	27.7		
Hydroxychloroquine	Yes	9	39.1	15	23.1	2.207	0.137
	No	14	60.9	50	76.9		
Infliximab	Yes	1	4.3	4	6.2	0.103	0.748
	No	22	95.7	61	93.8		
Rituximab	Yes	2	8.7	1	1.5	2.64	0.104
	No	21	91.3	64	98.5		
Adalimumab	Yes	2	8.7	9	13.8	0.41	0.521
	No	21	91.3	56	86.2		
Sulfasalazine	Yes	1	4.3	9	13.8	1.52	0.217
	No	22	95.7	56	86.2		
Colchicine	Yes	1	4.3	5	7.7	0.29	0.584
	No	22	95.7	60	92.3		
Penicillamine	Yes	0	0	1	1.5	0.35	0.550
	No	23	100	64	98.5		
Acetylsalicylic acid	Yes	2	8.7	9	13.8	0.41	0.521
	No	21	91.3	56	86.2		
Denosumab	Yes	1	4.3	0	0	2.85	0.091
	No	22	95.7	65	100		
Etanercept	Yes	1	4.3	5	7.7	0.29	0.584
	No	22	95.7	60	92.3		
Non-steroidal anti-inflammatory drugs	Yes	2	8.7	8	12.3	0.22	0.639
	No	21	91.3	57	87.7		
Mycophenolate	Yes	6	26.1	7	10.8	3.16	0.075
	No	17	73.9	58	89.2		
Azathioprine	Yes	5	21.7	5	7.7	3.32	0.068
	No	18	78.3	60	92.3		
Tacrolimus	Yes	2	8.7	0	0	5.78	0.016
	No	21	91.3	65	100		
Cyclosporine	Yes	1	4.3	0	0	2.85	0.091
	No	22	95.7	65	100		
Cyclophosphamide	Yes	0	0	1	1.5	0.35	0.550
	No	23	100	64	98.9		

Table 5. The association between humoral immunity and other variables

Variables		No humoral immunity		Humoral immunity		χ^2	p-value
		No	%	No	%		
Gender	Male	2	8.7	10	15.4	0.64	0.422
	Female	21	91.3	55	84.6		
Social History	No	21	91.3	58	89.2	0.8	0.778
	Yes	2	8.7	7	10.8		
Underlying disease	Yes	15	65.2	38	58.5	0.32	0.564
	No	8	34.8	27	41.5		
Type of vaccination	Sinopharm	20	87	53	81.5	5.01	0.171
	AstraZeneca	0	0	8	12.3		
	Sputnik V	0	0	1	1.5		
	Barecatco	3	13	3	4.6		
Rheumatoid disease severity	Mild	3	13	8	12.3	1.9	0.592
	Moderate	3	13	17	26.2		
	Severe	10	43.5	26	40		
	Hospitalization	7	30.4	14	21.5		
Pervious COVID-19 infection	Yes	6	26.1	36	55.4	5.84	0.016
	No	17	73.9	29	44.6		
Relapse after vaccination	Yes	8	38.1	13	61.9	2.04	0.153
	No	15	22.4	52	77.6		
Infection after which dose	No	17	25	51	75	6.16	0.046
	First dose	4	66.7	2	33.3		
	Second dose	2	14.3	12	85.7		
Infection after first vaccination	Yes	5	26.3	14	73.7	<0.01	0.981
	No	18	26.1	51	73.9		
Infection after second vaccination	No	21	24.7	64	75.3	5.69	0.017
	Yes	2	100	0	0		

the second vaccination was higher in patients without humoral immunity, indicating that humoral immunity could not prevent COVID-19 re-infection after the second dose ($\chi2=5.69$, $p=0.01$). Table 6 presents humoral responses in patients, based on the type of rheumatic diseases.

Table 6. Humoral response based on the type of rheumatic diseases

Rheumatic diseases		No Humoral immunity		Humoral immunity		χ^2	p-value
		No	%	No	%		
Rheumatoid arthritis	No	15	34.9	28	65.1	3.33	0.068
	Yes	23	17.8	37	82.2		
Systemic Lupus Erythematosus (SLE)	No	17	23.6	55	76.4	1.308	0.253
	Yes	6	37.5	10	76.4		
Behcet's disease	No	20	25	60	75	0.58	0.443
	Yes	3	37.5	5	62.5		
Ankylosing spondylitis	No	23	28	59	72	2.27	0.131
	Yes	0	0	6	100		
Sjogren's syndrome	No	20	24.1	63	75.9	3.14	0.076
	Yes	3	60	2	40		
Psoriatic arthritis	No	22	26.5	61	73.5	0.103	0.748
	Yes	1	20	4	80		
Wegener disease	No	21	24.7	64	75.3	2.64	0.104
	Yes	2	66.7	1	33.3		

Discussion

This is the first study to provide evidence of humoral immunity of two doses of inactivated whole virus and viral vector SARS-CoV-2 vaccines in patients with ARD in Iran. According to the results, humoral immunity after COVID-19 vaccination was found in 73.9% of ARDs patients. This immunity was lower in rheumatic patients who took tacrolimus, which could be attributed to their age, duration of rheumatic disease, gender, type of rheumatic disease, the presence of underlying diseases, patients' social history, type of vaccine, and rheumatoid disease severity. Humoral immunity was higher in patients with a history of COVID-19 infection. Humoral immunity could not prevent COVID-19 re-infection after the first dose; however, it could decrease COVID-19 re-infection after the second COVID-19 vaccination.

It seems that patients with rheumatic diseases may benefit from an additional heterologous dose to achieve their full potential of immunogenicity by inactivated whole virus vaccines such as the Sinovac-CoronaVac vaccine (22,23). Based on the study conducted by Hagen *et al*, each DNA-based vaccine (BNT162b2) can remarkably increase neutralizing capacity for patients with slow-responding ARD. They showed that these patients could benefit from up to three partly dose-intensified booster vaccinations, even with low or no peripheral B cells. The different outcomes seem to support the hypothesis that even individual differences play an important role in humoral response (24). Most patients with ARD included in this study were positive for humoral immunity. It should be noted that the second SARS-CoV-2 vaccination resulted in a significant increase in overall antibody response.

Humoral response rates in immunocompromised patients with rheumatic diseases have been reported to be between 49 and 100% in various studies (25-28), which may be explained by differences in the study design, type of vaccines, and consumed medications. In some studies, the seropositivity rate was reported to be 94% in patients who did not receive RTX, abatacept, or Mycophenolate Mofetil (MMF) (26), while the humoral response has been lower in studies

focusing on RTX therapy (49-59.3%) (27,28).

In one study performed by Krasselt *et al*, the seropositivity rate after COVID-19 vaccination was estimated to be 78.5% in patients with inflammatory rheumatic diseases who consumed different anti-rheumatic drugs (29). Although they found a significant vaccination response in subjects with and without immunosuppressive therapy, no such relationship was found between the use of immunosuppressive drugs and humoral immunity except for tacrolimus in the current study. Moreover, no difference was found in humoral immunity in terms of the vaccine type. It should also be noted that there were limitations in choosing vaccines due to their unavailability in Iran. Therefore, only inactivated whole virus vaccines (Sinopharm and Barecatco) and viral vector vaccines (AstraZeneca and Sputnik V) were used in the present study due to their availability.

In the present study, no significant difference was reported between patients with and without humoral immunity among rheumatic patients who received Methotrexate (MTX) and MMF. However, the results may have been affected by the small sample size, which causes to cast doubts on the apparent immunogenicity increase. Moreover, the detrimental effect of immunosuppressive therapy on antibody production has been previously demonstrated in patients with ARD (2, 30-32).

Some studies showed that prednisone (in doses ≥7.5 *mg*/day) and rituximab had a negative impact on immune response (31-33).

It has been suggested that rituximab treatment and low B cell counts are the two main suppressors of humoral response to vaccination (34-37). Krasselt *et al* reported that humoral immunity was prevented by the use of rituximab, abatacept, glucocorticoids, mycophenolate-mofetil, and even TNFi (29), while other studies showed no negative impact of TNFi on the humoral response (25). The decreased humoral response has been reported after one vaccination due to the consumption of TNFi in combination with MTX (38). In general, it seems that combination therapy (*e.g.*, MTX+TNFi) is more immunosuppressive compared to monotherapy. However, the difference in humoral response after vaccination was not reported in the present study. Similar to our study, the results of another study demonstrated that humoral immunity was not weakened in psoriasis patients under MTX monotherapy who were vaccinated for COVID-19 (39). It is noteworthy that the majority of aforementioned studies have investigated vaccination with the mRNA vaccines (BNT162b2), while the present study was focused on the inactivated whole virus and viral vector vaccines.

A high humoral response has been reported in patients treated with AZA, MTX monotherapy, and JAK inhibitors. These results may indicate that there is no need to withhold immunosuppressive medication therapy prior to vaccination. However, suspending immunosuppressive medication therapy should be considered when MTX is used in combination with other DMARDs (29). Due to the relationship between humoral response rate and the time since the last application of immunosuppressive agents, it is recommended that the interval be lengthened in rheumatic patients if clinically feasible.

The results of the present study showed no significant difference between the types of rheumatic diseases and humoral response. However, since some patients had two or more rheumatic diseases simultaneously and it was not possible to separate them, this result cannot be considered definite. Based on one study, Systemic Lupus Erythematosus (SLE) patients tended to have higher rates of positive antibody responses compared to patients with Sjogren's syndrome and Rheumatoid Arthritis (RA) (29). The separate assessment of the patients with rheumatic diseases indicated that 82.2% of the RA patients had humoral immunity, while the humoral response was observed in 76.4% of SLE patients and in only 40% of the patients with Sjogren's syndrome. Considering the small number of studies that have either rejected or confirmed these findings, further studies in this regard can yield more definite results.

Advantages and limitations

This was the first study to provide evidence of humoral immunity of two doses of inactivated whole virus and viral vector SARS-CoV-2 vaccines in patients with ARDs. The results of this study can provide useful information on the effect of vaccine type on rheumatic patients. The small size and cross-sectional observational nature of this study are its main limitations, which prevent us from generalizing

the findings to other populations. Failure to follow up and evaluate the patients after receiving the third dose of vaccine can be considered another limitation of this study. Moreover, the cellular immunity was not assessed in the current study. The results of other studies showed that rituximab taking could not remarkably compromise T cell response, which provided a further argument for vaccinations despite B cell depletion (40,42). Therefore, it is suggested that future studies assess the longitudinal determination of anti-S IgG antibody levels for measuring individual courses of decreasing antibody responses.

Conclusion

The obtained results in this study demonstrated that a homologous second dose of an inactivated whole viral vector SARS-CoV-2 vaccine was safe and provided a remarkable antibody response in patients with ARDs.

Funding

Mashhad University of Medical Sciences (Code: 4000620).

Conflict of Interest

The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

References

1. 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.

2. Bagcchi S. The world's largest COVID-19 vaccination campaign. Lancet Infect Dis 2021;21(3):323.

3. Hosseinzadeh A, Sahab-Negah S, Nili S, Aliyari R, Goli S, Fereidouni M, *et al*. COVID-19 cases, hospitalizations and deaths after vaccination: a cohort event monitoring study, Islamic Republic of Iran. Bull World Health Organ 2022;100(8):474.

4. Yazdanpanah F, Hamblin MR, Rezaei N. The immune system and COVID-19: Friend or foe? Life Sci 2020;256:117900.

5. Dodd RH, Pickles K, Nickel B, Cvejic E, Ayre J, Batcup C, *et al*. Concerns and motivations about COVID-19 vaccination. Lancet Infect Dis 2021;21(2):161-3.

6. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. Nutrients 2020;12(1):236.

7. Mullard A. COVID-19 vaccines buoy hope. Nat Rev Drug Discov 2021;20(1):8-9.

8. Borriello A, Master D, Pellegrini A, Rose JM. Preferences for a COVID-19 vaccine in Australia. Vaccine 2021;39(3):473-9.

9. Bhardwaj A, Sapra L, Saini C, Azam Z, Mishra PK, Verma B, *et al*. COVID-19: immunology, immunopathogenesis and potential therapies. Int Rev Immunol 2022;41(2):171-206.

10. Khodashahi R, Naderi HR, Sedaghat A, Allahyari A, Sarjamee S, Eshaghi S, *et al*. Intravenous immunoglobulin for treatment of patients with COVID-19: a case-control study. Arch Clin Infect Dis 2021;16(1).

11. Byravan S, Fardanesh A, Tahir H, Moorthy A. Emerging COVID-19 vaccines: a rheumatology perspective. Int J Rheum Dis 2021;24(2):144.

12. Nakafero G, Grainge MJ, Myles PR, Mallen CD, Zhang W, Doherty M, *et al*. Effectiveness of inactivated influenza

vaccine in autoimmune rheumatic diseases treated with disease-modifying anti-rheumatic drugs. Rheumatology (Oxford) 2020;59(12):3666-75.

13. Melmed GY, Rubin DT, McGovern DP. Winter is coming! Clinical, immunologic, and practical considerations for vaccinating patients with inflammatory bowel disease during the coronavirus disease-2019 pandemic. Gastroenterology 2021;160(3):639-44.

14. El Ouali S, Rubin DT, Cohen BL, Regueiro MD, Rieder F. Optimal inflammatory bowel disease management during the global coronavirus disease 2019 pandemic. Curr Opin Gastroenterol 2021;37(4):313-9.

15. Soy M, Keser G, Atagunduz P, Mutlu MY, Gunduz A, Koybaşi G, *et al*. A practical approach for vaccinations including COVID-19 in autoimmune/autoinflammatory rheumatic diseases: a non-systematic review. Clin Rheumatol 2021;40(9):3533-45.

16. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, *et al*. Reply to commentary on the ACR "COVID-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal diseases". Arthritis Rheumatol (Hoboken, NJ) 2021;73(9).

17. Sahebari M, Heidari H, Nabavi S, Khodashahi M, Rezaieyazdi Z, Dadgarmoghaddam M, *et al*. A double-blind placebo-controlled randomized trial of oral saffron in the treatment of rheumatoid arthritis. Avicenna J Phytomed 2021;11(4):332.

18. Ghasemi A, Khodashahi R, Aliakbarian M, Khaleghi E, Razmkhah B, Vahdatinia M, *et al*. Efficacy of Sinopharm vaccine among stem cell transplant recipient during two peaks of Delta and Omicron variants of COVID-19. Curr Drug Saf 2023;18(4):540-546.

19. Ghasemi A, Khodashahi R, Aliakbarian M, Khaleghi E, Razmkhah B, Vahdatinia M, *et al*. Efficacy of Sinopharm vaccine among stem cell transplant recipient during two peaks of Delta and Omicron variants of COVID-19. Curr Drug Saf 2023;18(4):540-6.

20. Rezaei Z, Eshraghi A, Noori A. Survey of variety of rheumatic disease in patients who referred to the rheumatology clinic of Ghaem hospital in Mashhad. JGUM 2007;16(62):48-57.

21. 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 4. Arthritis Rheumatol 2022;74(5):e21-e36.

22. Alejo JL, Mitchell J, Chiang TPY, Abedon AT, Boyarsky BJ, Avery RK, *et al*. Antibody response to a fourth dose of a SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. Transplantation 2021;105(12):e280.

23. Kamar N, Abravanel F, Marion O, Romieu-Mourez R, Couat C, Del Bello A, *et al*. Assessment of 4 doses of SARS-CoV-2 messenger RNA–based vaccine in recipients of a solid organ transplant. JAMA Netw Open 2021;4(11):e2136030-e.

24. Ten Hagen A, Hermann S, Habermann E, Frommert LM, Arumahandi de Silva AN, Scholz V, *et al*. Improvement of humoral immunity by repeated dose-intensified COVID-19 vaccinations in primary non- to low-responders and B cell deficient rheumatic disease patients. J Autoimmun 2023;135:102996.

25. 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.

26. Simon D, Tascilar K, Fagni F, Krönke G, Kleyer A, Meder C, *et al*. SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. Ann Rheum Dis 2021;80(10):1312-6.

27. Prendecki M, Clarke C, Edwards H, McIntyre S, Mortimer P, Gleeson S, et al. Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. Ann Rheum Dis 2021;80(10):1322-9.

28. Moor MB, Suter-Riniker F, Horn MP, Aeberli D, Amsler J, Möller B, *et al*. Humoral and cellular responses to

mRNA vaccines against SARS-CoV-2 in patients with a history of CD20 B-cell-depleting therapy (RituxiVac): an investigator-initiated, single-centre, open-label study. Lancet Rheumatol 2021;3(11):e789-e97.

29. Krasselt M, Wagner U, Nguyen P, Pietsch C, Boldt A, Baerwald C, *et al*. Humoral and cellular response to COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases under real-life conditions. Rheumatology (Oxford, England) 2022 Jun 28;61(SI2):SI180-SI188.

30. Araujo CSR, Medeiros-Ribeiro AC, Saad CG, Bonfiglioli KR, Domiciano DS, Shimabuco AY, *et al*. Two-Week methotrexate discontinuation in patients with rheumatoid arthritis vaccinated with inactivated SARS-CoV-2 vaccine: a randomised clinical trial. Ann Rheum Dis 2022;81(6):889-97.

31. Medeiros-Ribeiro AC, Aikawa NE, Saad CG, Yuki EF, Pedrosa T, Fusco SR, *et al*. Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial. Nat Med 1744-51:(10)27;2021.

32. Yuki EF, Borba EF, Pasoto SG, Seguro LP, Lopes M, Saad CG, et al. Impact of distinct therapies on antibody response to SARS-CoV-2 vaccine in systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2022;74(4):562-71.

33. Aikawa NE, Kupa LdVK, Medeiros-Ribeiro AC, Saad CGS, Yuki EFN, Pasoto SG, et al. Increment of immunogenicity after third dose of a homologous inactivated SARS-CoV-2 vaccine in a large population of patients with autoimmune rheumatic diseases. Ann Rheum Dis 2022;81(7):1036-43.

34. Stefanski AL, Rincon-Arevalo H, Schrezenmeier E, Karberg K, Szelinski F, Ritter J, *et al*. B Cell Numbers predict humoral and cellular response upon SARS–CoV-2 vaccination among patients treated with Rituximab. Arthritis Rheumatology 2022;74(6):934-47.

35. Mrak D, Tobudic S, Koblischke M, Graninger M, Radner H, Sieghart D, *et al*. SARS-CoV-2 vaccination in rituximab-treated patients: B cells promote humoral immune responses in the presence of T-cell-mediated immunity. Ann Rheum Dis 2021;80(10):1345-50.

36. Bitoun S, Avouac J, Henry J, Ghossan R, Al Tabaa O, Belkhir R, *et al*. Very low rate of humoral response after a third COVID-19 vaccine dose in patients with autoimmune diseases treated with rituximab and non-responders to two doses. RMD Open 2022;8(1):e002308.

37. Bonelli M, Mrak D, Tobudic S, Sieghart D, Koblischke M, Mandl P, *et al*. Additional heterologous versus homologous booster vaccination in immunosuppressed patients without SARS-CoV-2 antibody seroconversion after primary mRNA vaccination: a randomised controlled trial. Ann Rheum Dis 2022;81(5):687-94.

38. Boekel L, Steenhuis M, Hooijberg F, Besten YR, van Kempen ZL, Kummer LY, *et al.* Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: a substudy of data from two prospective cohort studies. Lancet Rheumatol 2021;3(11):e778-e88.

39. Mahil SK, Bechman K, Raharja A, Domingo-Vila C, Baudry D, Brown MA, *et al*. Humoral and cellular immunogenicity to a second dose of COVID-19 vaccine BNT162b2 in people receiving methotrexate or targeted immunosuppression: a longitudinal cohort study. Lancet Rheumatol 2022;4(1):e42-e52.

40. Shrotri M, Navaratnam AM, Nguyen V, Byrne T, Geismar C, Fragaszy E, *et al*. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet 2021;398(10298):385-7.

41. Simon D, Tascilar K, Schmidt K, Manger B, Weckwerth L, Sokolova M, *et al.* Humoral and cellular immune responses to SARS–CoV-2 infection and vaccination in autoimmune disease patients with B cell depletion. Arthritis Rheumatol 2022;74(1):33-7.

42. Bitoun S, Henry J, Desjardins D, Vauloup-Fellous C, Dib N, Belkhir R, *et al.* Rituximab impairs B cell response but not T cell response to COVID-19 vaccine in autoimmune diseases. Arthritis Rheumatol 2022;74(6):927-33.