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Research article

Comparative Study of Immunogenicity and reactogenicity of ChAdOx1 vaccine in patients with autoimmune inflammatory rheumatic diseases and healthy controls

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Abstract

The data are limited on vaccine responses in patients with autoimmune inflammatory rheumatic disease (AIRD), especially for the adenoviral vector ChAdOx1 vaccine. This single-center prospective cohort study evaluated the immunogenicity and safety of ChAdOx1 vaccine in patients with AIRD at Chulabhorn Hospital, Thailand. Thirty-five patients with AIRDs were enrolled between June 9 and July 1, 2021. The immune response and reactogenicity data of 70 healthcare workers (age- and sex-frequency matched) were used as a control group. All participants were vaccinated with two doses of ChAdOx1 vaccine with a 3-month interval. Antibodies against the receptor-binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein were assessed prevaccination, 3 months after the first dose, and 1 month after the second dose. Disease activity and reactogenicity were assessed before and 7 days after both vaccinations.

The geometric mean concentration of SARS-CoV-2 antibodies at 3 months after the first vaccination was significantly lower in patients than that in healthy controls (21.82 vs 66.01 BAU/mL, $P = 0.002$), although there was an insignificant decrease in antibody response in patients with AIRDs compared with that in healthy controls at 1 month after the second vaccination (647.05 vs 814.08 BAU/mL, $P = 0.484$). Vaccines were mostly well tolerated with mild adverse reactions, and no patients experienced a disease flare. The antibody responses of patients with AIRDs did not significantly differ from those of healthy controls but did tend to be lower. Most vaccinations were well-tolerated without postvaccination disease flares.

Keywords: COVID-19, SARS-CoV-2 vaccine, Immunogenicity, Reactogenicity, Autoimmune inflammatory rheumatic diseases (AIRDs)

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to threaten the health of patients worldwide. The risk factors for severe complications or death include older age and comorbidities such as diabetes or preexisting respiratory or cardiovascular disease.[1]

Autoimmune inflammatory rheumatic diseases (AIRDs) are a group of autoimmune diseases affecting the systemic organs, especially musculoskeletal organs. Each disease is characterized by a distinct type of

immune dysfunction, with a unique inflammatory response and cytokine profile[2]. The prevalence of coronavirus disease 2019 (COVID-19) among patients with AIRDs was reported to be increased compared with that in the general population[3,4]. Underlying autoimmune disease and treatment-induced immunosuppression may increase the risk of severe manifestation and complications of COVID-19 in patients with AIRDs[5,6]. The most important factors associated with a higher risk of hospitalization and death in these individuals were found to be older age and moderate to high disease activity as well as high glucocorticoid dosages (equivalent to prednisolone ≥10 mg)[7,8]. Patients treated with biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) were associated with a reduced risk of severe COVID-19 infection, whereas conventional DMARDs did not influence infection severity[4].

Developing suitable vaccines is critical in reducing COVID-19 mortality and morbidity. Patients with AIRDs and/or those taking immunosuppressive drugs were excluded from the phase III trials for COVID-19 vaccines because their immune systems are either suppressed or dysregulated, which could affect vaccine efficacy and safety. The issues of both safety and efficacy of vaccination in patients with AIRDs have been questioned, especially the viral vector vaccines[9].

Previous studies on COVID-19 vaccine immunogenicity in patients with AIRDs have suggested the presence of slightly reduced humoral responses but have been limited by small numbers of patients,[10] and most studies evaluated immunogenicity following messenger RNA vaccination of patients with AIRDs[11–13].

The adenovirus-vectored ChAdOx1 nCov-19 (ChAdOX1) vaccine was the first to become available during the pandemic in Thailand. In this study, we aim to provide data comparing the immunogenicity and reactogenicity of an adenovirus-vectored vaccine (i.e., ChAdOx1) in patients with AIRDs and immunosuppressive treatment with healthy controls in monocentric cohort.

Patients and Methods

Study design and participants

Healthy individuals were recruited from healthcare workers of the Chulabhorn Hospital, and patients with AIRDs were recruited from the Rheumatology Outpatient Department in Chulabhorn Hospital. Thirty-five adults with AIRDs and 70 age- and sex-frequency matched healthy adults (control group) who had no underlying disease were enrolled to this study. Participants were administered ChAdOx1 vaccines at an interval of 12 weeks between the two doses. Enrollment and vaccination occurred between June 9, 2021 and July 1, 2021.

Patients with AIRDs were included according to criteria: age ≥18 years, negative blood antibody test for COVID-19, no previous history of a severe form of vaccine allergy, no fever or history of fever in the past 14 days, no history of respiratory tract infection in the past 14 days, urine pregnancy test negative (women with pregnancy potential), and signed written informed consent; patients presenting any of the following criteria were not eligible for enrollment into the study: previous vaccination with COVID-19 before enrolment, any vaccination within 14 days before enrolment, pregnant, breast-feeding women, and those with active autoimmune disease within 6 months before enrolment.

The study protocol, consent form, and case records form were reviewed and approved by the Chulabhorn Ethics Committee (reference number: 056/2564). Written informed consent was obtained from all participants before enrollment. In addition, this study was registered at thaiclinicaltrials.org (TCTR20211228003) and was conducted in compliance with the International Conference for Harmonization Good Clinical Practice Guideline.

Procedure

Demographic information, current medication, disease activity, and relevant blood samples were collected at baseline.

Two 0.5-mL doses of the ChAdOx1 vaccine (AZD1222) were administered intramuscularly. Participants were observed in the clinic for 30 min after the vaccination procedure.

Antibodies (total) against the receptor-binding

domain (RBD) of the SARS-CoV-2 spike protein were measured using a US Food and Drug Administration approved method (Roche Elecsys, Roche Diagnostics International). Antibody testing was normally performed on day 0 before first vaccination (at baseline), 3 months after the first vaccination, and 1 month after the second dose of ChAdOx1 vaccine.

Monitoring for disease activity was performed at baseline (before first vaccination), 7 days after the first vaccination, on the day of the second vaccination, and 7 days after the second vaccination and use standard instruments to assess disease activity, e.g. Disease activity score 28 ESR (DAS28 ESR) rheumatoid arthritis, Axial Spondyloarthritis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for ankylosing spondylitis and other axial spondyloarthritis, Disease Activity in Psoriatic Arthritis (DAPSA) and DAS28 ESR for psoriatic arthritis, Clinical EULAR Sjögren's Syndrome Disease Activity Index (ClinESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) for Sjögren's syndrome and modified-SLE disease activity index 2000 (mSLEDAI-2K) for SLE that classified to remission, minimal or low disease activity, moderate disease activity and severe or high disease activity. Patients Global Assessment (PGA) and physician Global Assessment (PhGA) was performed for all patients with AIRDs.

Safety

After 30 minutes of observation to monitor the immediate adverse event, participants could go home. On days 1 and 7post-vaccinations, participants were queried regarding reactogenicities via a questionnaire sent by a short message service. The severity of adverse events was graded by participants (mild vs. moderate vs. severe severity). Severity was defined as (i) mild: not interfering with daily activity or a local reaction <5cm, (ii) moderate: some interference with daily activity or a local reaction of ≥5.1 cm to <10 cm, (iii) severe: significant interference with daily activity or a local reaction ≥10 cm.

Outcome

The primary outcome was humoral immunity, assessed by the geometric mean concentration (GMC) of anti-RBD antibodies against SARS-CoV-2 at 1 month after the second ChAdOx1 vaccination in all participants; GMC was compared between the groups using the geometric mean ratio (GMR).

The secondary outcomes were the GMC of anti-RBD antibodies against SARS-CoV-2 at 3 months after the first dose of ChAdOx1 vaccine, seroconversion rate in patients with AIRDs, reactogenicity after immunization in patients with AIRDs and documented inflammatory disease in patients with AIRDs at the time point of vaccination and 7 days after ChAdOx1 vaccination.

The meaning of seroconversion is the development of specific antibodies in the blood serum as a result of vaccination. Before vaccination, antibody is absent and then after vaccination antibody is present and detectable by standard techniques.

Statistical analysis

Baseline characteristics were reported as medians and interquartile ranges (IQRs). The anti-SARS-CoV-2 spike RBD antibody concentration was summarized as the GMC and 95% confidence interval (CI). The GMC was compared between the groups using a multiple linear regression model. The seroconversion rate was compared between the groups using a multilevel mixed-effects logistic regression model. Disease activity scores before and after vaccination were compared using dependent t-test and Wilcoxon rank sum test. Reactogenicity was measured using the Chi-square test and Fisher's exact test. Data were statistically analyzed using STATA/SE version 16. A P value <0.05 indicated statistical significance.

Results

Demographic and clinical characteristics

The median age of patients with AIRDs was 61 years while that of healthy controls with no comorbidities was 61.5 years; 85.7% of each cohort was female. No participant had previously had SARS-CoV-2-infection before vaccination.

Patients with AIRDs had the following disease diagnoses: rheumatoid arthritis (RA) (n = 17, 48.57%),

Sjögren's syndrome (n = 5, 14.29%), systemic lupus erythematosus (SLE) (n = 3, 8.57%), psoriatic arthritis (n = 2, 5.71%), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (n = 2, 5.71%), limited cutaneous systemic sclerosis (n = 2, 5.71%), and diffuse cutaneous systemic sclerosis (n = 1, 2.86%), ankylosing spondylitis (n = 1, 2.86%), other spondyloarthritis (n = 1, 2.86%), undifferentiated connective tissue disease (UCTD) (n = 1, 2.86%). Comorbidities in patient with AIRDs are generally well-managed and their conditions are not worsening.

Disease-Modifying Antirheumatic Drugs (DMARDs) are a specific type of immunosuppressant that aims to modify the disease process, while all DMARDs are immunosuppressants, not all immunosuppressants are DMARDs and that are classified as either conventional synthetic DMARDs (csDMARDs) or biological DMARDs. A total of 32 (91.4%) patients were using immunosuppressive drugs (87.5% ongoing treatment with csDMARDs and 12.5% ongoing treatment with other immunosuppressive drugs that are mycophenolate mofetil (MMF) and azathioprine (median dose of MMF 2,500 (2000, 3000) mg/day and median dose of azathioprine 75 (50, 100) mg/day) and none of the patients were receiving biological DMARDs including biosimilar). Seventeen (48.6%) patients were receiving ongoing treatment with prednisone, classify prednisolone dosage is low dose (less than 7.5 mg per day) is 16 patients, moderate dose (between 7.5 mg and 40 mg per day) is 1 patient and no patient use high dose of prednisolone (more than 40 mg per day), median dose of prednisolone was 5.00 (2.50, 5.00) mg/day. Disease activity at baseline was considered low disease activity (Table 1).

Table 1 Demographic and clinical characteristics of patients with AIRDs

Characteristic	Patients with AIRDs (N = 35)	Control group (N = 70)
Sex, N (%)		
Male	5 (14.29)	10 (14.29)
Female	30 (85.71)	60 (85.71)
Age (years), median (IQRs)	61 (59, 67)	61.50 (56, 66)
Disease duration (years), median (IQRs) (At the time of 1st vaccination)	3 (1, 7)	
Autoimmune disease, N (%)		
Rheumatoid arthritis	17 (48.57)	
Sjögren's syndrome	5 (14.29)	
SLE	3 (8.57)	
Psoriatic arthritis	2 (5.71)	-
ANCA-associated vasculitis	2 (5.71)	
Limited cutaneous systemic sclerosis	2 (5.71)	
Diffuse cutaneous systemic sclerosis	1 (2.86)	
UCTD	1 (2.86)	
Ankylosing spondylitis	1 (2.86)	
Other spondyloarthritis	1 (2.86)	
Comorbidities, N (%)		
Diabetes mellitus	3 (8.57)	

Characteristic	Patients with AIRDs (N = 35)	Control group (N = 70)
CKD	3 (8.57)	
Cardiovascular disease	3 (8.57)	-
Solid cancer	2 (5.71)	
Cirrhosis	1 (2.86)	
Hematologic malignancy	1 (2.86)	
Immunosuppressants, N (%)		
Conventional synthetic DMARDs	28 (87.50)	
csDMARD monotherapy	17 (53.12)	
csDMARD combination therapy	11 (34.38)	-
Immunosuppressive drugs	4 (12.50)	
Azathioprine	2 (6.25)	
Mycophenolate mofetil	2 (6.25)	
Prednisolone-equivalent glucocorticoids, N (%)		
<7.5 mg/day	16 (94.12)	
7.5 mg - 40 mg/day	1 (5.88)	
Prednisolone (dose), median (IQRs)		
Prednisolone (mg/day)	5.00 (2.50, 5.00)	-
Disease activity at baseline, N (%)		
Remission	8 (22.86)	
Minimal or low disease activity	17 (48.57)	-
Moderate disease activity	8 (22.86)	
Severe or high disease activity	2 (5.71)	
Disease activity at baseline, median (IQRs)		
PGA	3 (0, 8)	-
PhGA	3 (0, 8)	

CKD, chronic kidney disease; csDMARD, conventional synthetic Disease-Modifying Antirheumatic Drugs included: methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine; Immunosuppressive drugs included: azathioprine and mycophenolate mofetil

ChAdOx1 vaccine shows immunogenicity in patients with AIRDs

The results of SARS-CoV-2 IgG antibody detection in study subjects with or without AIRDs are shown in Tables 2 and in Figure 1. The GMC of SARS-CoV-2 IgG antibodies at 1 month after the second vaccination was not significantly different (P = 0.484) than that in the healthy control group with a mean anti-SARS-CoV-2 IgG of 814.08 BAU/mL (95% CI = 668.45-991.44). Patients with AIRDs exhibited lower levels of anti-SARS-CoV-2 IgG (mean 647.05 BAU/mL; 95% CI = 341.91-1224.50) (Table 2 and Figure 1), but the GMC of SARS-CoV-2 IgG antibodies at 3 months after the first vaccination of ChAdOx1 vaccine was significantly (P = 0.002) lower in

patients with AIRDs (21.82 BAU/mL, 95% CI = 11.46-41.54) than that in the healthy control group (Table 2 and Figure 1).

Two patients with AIRDs had no detectable anti-SARS-CoV-2 IgG at 3 months after the first vaccination and 1 patient with AIRDs at 1 month after the second dose of ChAdOx1 vaccine. This patient was a 75-year-old female with diagnosed ANCA-associated vasculitis who was receiving treatment with mycophenolate mofetil 3 g/day, and prednisolone 5 mg/day.

Table 2 Geometric mean ratio of anti-SARS-CoV-2 spike protein RBD antibodies

Group	N (%)	Geometric mean concentration (95% CI), (BAU/mL)	Geometric mean ratio (95% CI)	*P* value
At 1 month after the second dose of ChAdOx1 vaccine				
Patients with AIRDs	35 (33.33)	647.05 (341.91–1224.50)	0.79 (0.41–1.52)	
Control group	70 (66.67)	814.08 (668.45–991.44)	Ref.	0.484
At 3 months after the first dose of ChAdOx1 vaccine				
Patients with AIRDs	33 (37.93)	21.82 (11.46–41.54)	0.33 (0.17-0.65)	
Control group	54 (62.07)	66.01 (50.53–86.22)	Ref.	0.002

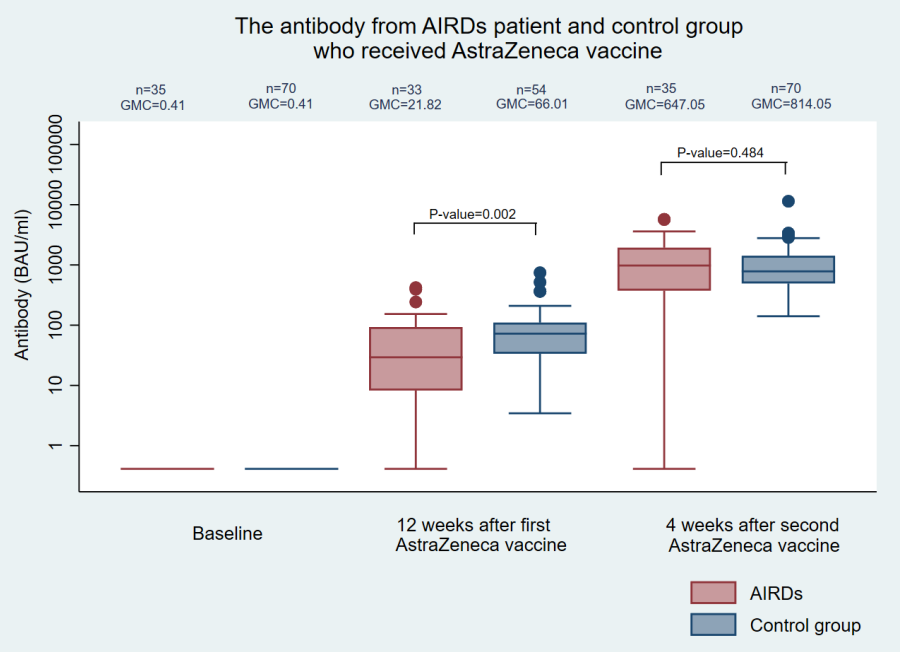

Figure 1 Anti-SARS-CoV-2 spike protein RBD antibodies after a single dose and two dose of the ChAdOx1 vaccine in patients with AIRDs and healthy controls.

Seroconversion of antibodies after the second vaccine dose

Before vaccination, all patients were confirmed to be seronegative for anti-SARS-CoV-2 spike protein IgG antibodies (<0.8 BAU/mL). Positive antibody response developed in 94.3% of all participants approximately 1 month after the second dose of ChAdOx1 vaccine. The seroconversion rate was higher in the control group than that in the patients with AIRDs group (Table 3).

Table 3 Seroconversion rate; before (Day 0) and after the second dose (1 month after the second vaccination) of ChAdOx1 vaccine in patients with AIRDs and control group

Antibody level at 1 month after the 2nd vaccination / Group	Antibody (BAU/mL)		Antibody (BAU/mL)	
	<0.8	≥0.8	<133	≥133
Patients with AIRDs	1 (2.90)	33 (97.10)	4 (11.76)	30 (88.24)
Control group	0 (0.00)	70 (100.00)	0 (0.00)	70 (100.00)

There was no significant difference in GMC of SARS-CoV-2 IgG antibodies between therapeutic groups (immunosuppressive drug vs no immunosuppressive drug use) that none of the patients were receiving biological DMARDs. In subgroup analysis, comparing between patients with prednisolone (N=17) and patients without prednisolone (N=18), there was a significant difference between the steroid treatment group and the no-steroid treatment group (313.77 BAU/mL [95% CI = 98.72-997.28] vs. 1334 BAU/mL [95% CI = 862.12-2065.1], $P = 0.018$) (Supplemental Table 1).

Reactogenicity

Adverse events recorded at 7 days after ChAdOx1 vaccination are presented in Table 4. Overall, mild adverse reactions, such as injection site reaction, fatigue, and myalgia, were found in patients with AIRDs. Mild to moderate fever was more common in healthy controls than in patients with AIRDs at 7 days after the first dose of ChAdOx1 vaccination ($P = 0.022$). Headache was more common in patients with AIRDs than in healthy controls at 7 days after the second dose of ChAdOx1 vaccination ($P = 0.011$) but was of mild severity.

Table 4 Reactogenicity after the first and second vaccination in patients with AIRDs and healthy controls a documented 7 days after the ChAdOx1 vaccination

Symptoms	1st Vaccination		P-value	2nd Vaccination		P-value
	Control group	Patients with AIRDs		Control group	Patients with AIRDs	
Injection Site Reaction			0.182[1]			0.055[1]
No	61 (87.14)	26 (74.29)		68 (97.14)	30 (85.71)	
Mild	6 (8.57)	4 (11.43)		1 (1.43)	4 (11.43)	
Moderate	3 (4.29)	4 (11.43)		1 (1.43)	1 (2.86)	
Severe	0 (0.00)	1 (2.86)		0 (0.00)	0 (0.00)	

Symptoms	1st Vaccination		P-value	2nd Vaccination		P-value
	Control group	Patients with AIRDs		Control group	Patients with AIRDs	
Fever			0.022[1]			0.116[1]
No	48 (68.57)	29 (82.86)		68 (97.14)	31 (88.57)	
Mild	10 (14.29)	0 (0.00)		1 (1.43)	3 (8.57)	
Moderate	7 (10.00)	1 (2.86)		1 (1.43)	1 (2.86)	
Severe	5 (7.14)	5 (14.29)		0 (0.00)	0 (0.00)	
Headache			0.560[1]			0.011[1]
No	55 (78.57)	27 (77.14)		68 (97.14)	31 (88.57)	
Mild	8 (11.43)	3 (8.57)		0 (0.00)	4 (11.43)	
Moderate	4 (5.71)	1 (2.86)		2 (0.00)	0 (0.00)	
Severe	3 (4.29)	4 (11.43)		0 (0.00)	0 (0.00)	
Fatigue			0.636[1]			0.107[1]
No	56(80.00)	27 (77.14)		68 (97.14)	32 (91.43)	
Mild	5 (7.14)	5 (14.29)		1 (1.43)	3 (8.57)	
Moderate	7 (10.00)	2 (5.71)		1 (1.43)	0 (0.00)	
Severe	2 (2.86)	1 (2.86)		0 (0.00)	0 (0.00)	
Myalgia			0.288[1]			1.000[1]
No	52 (74.29)	27 (77.14)		67 (95.71)	33 (94.29)	
Mild	4 (5.71)	5 (14.29)		1 (1.43)	1 (2.86)	
Moderate	7 (10.00)	1 (2.86)		1 (1.43)	1 (2.86)	
Severe	7 (10.00)	2 (5.71)		1 (1.43)	0 (0.00)	
Nausea or Vomiting			0.139[1]			0.551[1]
No	62 (88.57)	35 (100.00)		68 (97.14)	35 (100.00)	
Mild	5 (7.14)	0 (0.00)		2 (2.86)	0 (0.00)	
Moderate	3 (4.29)	0 (0.00)		0 (0.00)	0 (0.00)	
Severe	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
Diarrhea			1.000[1]			1.000[1]
No	66 (94.29)	33 (94.29)		69(98.57)	34 (97.14)	
Mild	4 (5.71)	2 (5.71)		1 (1.43)	1 (2.86)	
Moderate	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
Severe	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	

[1] Fisher's exact test

Disease activity

Most patients have minimal or low disease activity at baseline (Table 1). The change of PGA and PhGA scores between pre- and postvaccination at 7 days after the first dose of ChAdOx1 vaccination was significantly lower in patients with AIRDs after vaccination (median PGA of 3.00 (2.00, 5.00) vs 2.00 (0.00, 5.00) [$P = 0.003$] and median PhGA of 3.00 (2.00, 5.00) vs 2.00 (0.00, 3.00) [$P = 0.002$]). However, there was no difference in the change of CDAI in the context of pre- and postvaccination (7 days after ChAdOx1 vaccination) (Supplemental table 2). The glucocorticoid or immunosuppressive therapies were not modified before or after vaccination.

Discussion

This study showed that patients with AIRDs had a lower humoral immune response to ChAdOx1 vaccine and tended to have lower levels of anti-SARS-CoV-2 spike RBD antibodies and lower seroconversion rates as compared with those in healthy controls, although this was not significant at 1 month after the second vaccination, probably because of the smaller number of AIRDs patients. Our findings were consistent with other studies with ChAdOx1 vaccine and other COVID-19 vaccines[11,14,15].

Our study demonstrated that the GMC of SARS-CoV-2 IgG antibodies at 3 months after the first dose of ChAdOx1 vaccine was significantly lower in patients with AIRDs than that in the healthy control group. This may be because the immunogenicity of patients with AIRDs is transient and lacks sustained antibody responses, and their antibody levels may diminish more rapidly than in healthy controls. This indicates a potential risk in delaying the second dose or having longer intervals between additional doses of ChAdOx1 vaccine in these patients. The antibody level postvaccination may be decreased in patients with AIRDs depending on the vaccine and immunosuppressive therapy[16,17].

Adenovirus vectors encoding the spike protein enter dendritic cells (DCs) at the injection site or within lymph nodes. RNA sensors, such as Toll-like receptor 9 (TLR9), are triggered by the adenovirus vector vaccine. The resultant activated DCs present antigen and co-stimulatory molecules to spike protein-specific naive T cells, which become activated and differentiated into effector cells to form cytotoxic T lymphocytes or helper T cells. T follicular helper cells help spike protein-specific B cells to differentiate into antibody-secreting plasma cells and promote the production of high affinity anti-spike protein antibodies. Following vaccination, spike protein-specific memory T cells and B cells develop and circulate along with high affinity SARS-CoV-2 antibodies, which together help prevent subsequent infection with SARS-CoV-2[18].

Several traditional DMARDs, biologic agents, and corticosteroids interfere with the immune response to vaccines in many mechanisms, including the inhibition of B cells, nucleotide synthesis in T cells, cytokines, and intracellular signaling pathways[19]. Baseline data showed low disease activity, and all patients were receiving only conventional DMARD therapy. No patient was receiving B cell-depleting therapy, which is known to decrease vaccination response. Therefore, generalizing from these data may be inappropriate.

Antibody responses between those patients with AIRDs on immunosuppressive drugs did not significantly differ from those patients not taking immunosuppressive drugs. Immunosuppressive drug use only included conventional synthetic DMARD therapy, without biological drugs. Because 50% of all patients were not receiving steroids, the size of these cohorts may be why there was no significant difference between the groups. However, a previous study showed that the immune response to the polysaccharide pneumococcal vaccine may be reduced among patients receiving ≥20 mg of prednisolone per day for ≥2 weeks as there was a significant difference in immune response between the steroid treatment group receiving a median glucocorticoid dose of 5 mg/day and the no-steroid treatment group[20].

Overall, mild adverse reactions were found in the patients with AIRDs cohort. Our findings were consistent with other studies[11,13,21]. The reduction in systemic side effects, such as fever, in these patients compared with those in the healthy control group may indicate stronger immune reactions in healthy individuals and that the medication taken by patients with AIRDs may affect the incidence of adverse reactions. However, even patients with AIRDs displayed more severe headache after the first vaccination than that in the healthy controls.

There was no significant evidence of disease flares after each vaccination that was consistent with other studies [13,21], and this trended to a lower score at 7 days after each ChAdOx1 vaccination compared with that prevaccination may be low disease activity at baseline, although PGA and PhGA scores did significantly decrease postvaccination. No patient with AIRDs needed to adjust DMARD or glucocorticoid therapy.

The limitations of our study include its small sample size and limited immunosuppressive

regimens that may not apply to patients who receive biologic therapy. Therefore, generalizing from these data might be inappropriate. Other limitations in this study included a lack of cellular immunity testing and of neutralizing antibody testing, which are thought to represent the best correlate of protection following vaccination. However, antibodies against the spike protein RBD have been revealed to confer neutralizing activity against SARS-CoV-2 with an optimized cutoff.

In conclusion, patients with AIRDs tended to have lower antibody responses than healthy individuals but this was not significant at 1 month after the second vaccination in our study. Validation of this study using a larger sample size and a broader spectrum of disease activity is required. Almost all the patients with AIRDs safely tolerated vaccinations without significant side effects or flares.

Supplemental Materials:

Supplement Table 1 (Table S1): Anti-SARS-CoV-2 Spike RBD antibodies against SARS-CoV-2 at 1 month after second vaccination of ChAdOx1 vaccine comparing the largest therapeutic groups.

	N (%)	Geometric mean concentration (95% CI), (BAU/mL)	Anti-SARS-CoV-2 Spike RBD antibodies	P value
Treatment				
On immunosuppressive drug	32 (91.43)	651.16 (322.75, 1313.76)	1.07 (0.46, 2.50)	0.864
No immunosuppressive drug	3 (8.57)	606.02 (191.99,1912.89)	Ref.	
Steroid				
On steroid treatment	17 (48.67)	313.77 (98.72, 997.28)	0.24 (0.07, 0.77)	0.018
No steroid treatment	18 (51.43)	1334 (862.12, 2065.15)	Ref.	

Supplement table 2 (Table S2): Inflammatory disease activity in patients with AIRDs at the time point of vaccination, and 7 days after ChAdOx1 vaccination.

Disease activity	1st vaccination		P value	2nd vaccination		P value
	D0	D7 after vaccination		D0	D7 after vaccination	
DAS 28 ESR	2.86 (1.81, 4.22)			3.19 (2.60, 4.00)		
CDAI	7.50 (1.00, 14.00)	6.00 (0.00, 13.00)	0.123[2]	6.50 (0.50, 16.50)	6.50 (0.00, 16.50)	0.922[2]
PGA	3.00 (2.00, 5.00)	2.00 (0.00, 5.00)	0.003[2]	3.00 (1.00, 5.00)	2.00 (0.00, 4.00)	0.056[2]
PhGA	3.00 (2.00, 5.00)	2.00 (0.00, 3.00)	0.002[2]	3.00 (0.00, 5.00)	2.00 (0.00, 4.00)	0.187[2]

[2] Wilcoxon signed rank test

DAS28, disease activity score 28; CDAI, Clinical Disease Activity Index; PGA, Patients Global Assessment; PhGA, Physician Global Assessment

Supplement table 3 (Table S3): AIRD patients with immunosuppressive therapy

Patient	Sex	Age	Diagnosis	DMARDs/ Immunosuppressants
1	Female	61	Rheumatoid arthritis	Methotrexate, Hydroxychloroquine
2	Female	73	SLE	-
3	Female	65	Sjögren's syndrome	Azathioprine, Hydroxychloroquine
4	Female	72	Psoriatic arthritis	Methotrexate
5	Female	54	UCTD	Hydroxychloroquine
6	Female	61	Sjögren's syndrome	Hydroxychloroquine
7	Female	61	Rheumatoid arthritis	Methotrexate, Sulfasalazine, Leflunomide, Hydroxychloroquine
8	Female	61	Psoriatic arthritis	Methotrexate
9	Female	62	Rheumatoid arthritis	Methotrexate, Sulfasalazine
10	Female	61	Spondyloarthritis	Methotrexate
11	Female	67	Rheumatoid arthritis	Methotrexate
12	Female	58	Sjögren's syndrome	Hydroxychloroquine
13	Female	60	Rheumatoid arthritis	Hydroxychloroquine
14	Female	49	Rheumatoid arthritis	Methotrexate, Sulfasalazine, Hydroxychloroquine
15	Female	75	AAV	Mycophenolate mofetil
16	Female	64	Rheumatoid arthritis	Methotrexate
17	Female	70	Rheumatoid arthritis	Methotrexate, Sulfasalazine
18	Female	62	Sjögren's syndrome	Hydroxychloroquine
19	Female	57	SLE	Azathioprine, Hydroxychloroquine
20	Female	69	LcSSc	Methotrexate
21	Male	70	Rheumatoid arthritis	Methotrexate, Sulfasalazine
22	Female	64	Rheumatoid arthritis	Methotrexate, Hydroxychloroquine
23	Female	67	Rheumatoid arthritis	Leflunomide
24	Female	67	AAV	Mycophenolate mofetil
25	male	70	Rheumatoid arthritis	Methotrexate, Sulfasalazine, Hydroxychloroquine
26	Male	55	Ankylosing spondylitis	Leflunomide, Sulfasalazine
27	Male	40	Rheumatoid arthritis	Methotrexate
28	Female	60	Rheumatoid arthritis	Methotrexate, Sulfasalazine
29	Female	59	Rheumatoid arthritis	-
30	Female	51	Rheumatoid arthritis	Methotrexate, Leflunomide, Hydroxychloroquine

Patient	Sex	Age	Diagnosis	DMARDs/ Immunosuppressants
31	Female	65	DcSSc	Hydroxychloroquine
32	Female	61	Rheumatoid arthritis	Methotrexate
33	Female	61	LcSSc	Hydroxychloroquine
34	Female	59	SLE	Hydroxychloroquine
35	Male	60	Sjögren's syndrome	-

SLE, systemic lupus erythematosus; UCTD, undifferentiated connective tissue disease; AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; LcSSc, limited cutaneous systemic sclerosis; DcSSc, diffuse cutaneous systemic sclerosis

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee for Human Research of Chulabhorn Research Institute (reference number: 056/2564). In addition, this study was registered at thaiclinicaltrials.org (TCTR20211228003) and was conducted in compliance with the International Conference for Harmonization Good Clinical Practice Guideline.

Informed Consent statement: Informed consent was obtained from all subjects involved in the study.

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Author's contributors

Chartisathian W and Tawinprai K: Conceptualization and study design. Chartisathian W analyzed and interpreted the data. Chartisathian W drafted the first version of the manuscript. This paper was revised and edited by Chartisathian W and Tawinprai K. All authors have read and agreed to the published version of the manuscript.

Data sharing

The datasets analysed during the current study are available from the corresponding author on reasonable request.

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