



Research Article

# Safety of SARS-CoV-2 Vaccines in Patients with Autoimmune Diseases

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## Abstract

**Background:** several vaccines have been developed against SARS-CoV-2 showing good safety profile. However, patients with autoimmune diseases or other conditions undergoing immunosuppressive treatments have been excluded from the clinical trials resulting in the approval of vaccines. Therefore, the safety profile of SARS-CoV-2 vaccines in this group of patients is unknown. The main was to analyze the short-term safety of vaccines against SARS-CoV-2 in a cohort of patients with autoimmune diseases.

**Materials and Methods:** We carried out a cross-sectional study consisting of telephone interviews of patients with autoimmune diseases who received any vaccine for SARS-CoV-2. Contact was made after a minimum of 15 days following the application of the first or second vaccine dose. A standard questionnaire was applied.

**Results:** 150 patients, 74.6% women with a mean age of 60 years, were included. Main diseases of the interviewed patients were systemic lupus erythematosus (27.3%), vasculitis (18.7%), systemic sclerosis (16%), and antiphospholipid syndrome (8.7%). 40% patients received Pfizer/BioNTech (BNT162b2) vaccine, 38.7% Moderna (mRNA-1273), and 20.7% Oxford-AstraZeneca (ChAdOx1). Overall, 73.3% presented any adverse event associated with vaccination. The most common side effect was local pain (70%), followed by musculoskeletal symptoms and fatigue (54.5%), fever (34.5%), and headache (19%). In 78.2% of patients, symptoms resolved within 48 hours.

**Conclusions:** SARS-CoV-2 vaccines are safe in patients with systemic autoimmune diseases. Although vaccine-related adverse effects are common, they tend to be mild and rapidly vanish. The vaccines have a high safety profile, and the benefit clearly outweighs the risks.

**Keywords:** Autoimmune diseases; COVID-19; Safety; SARS-CoV2; Vaccine

## Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 130 million cases of the COVID-19 (coronavirus disease 2019) and nearly 3 million deaths worldwide [1]. After the first cases of SARS-CoV-2 were reported in Wuhan (China), the disease spread worldwide and was declared a pandemic (WHO, 11 March 2020) [2,3].

Although there was no specific treatment for COVID-19 between March and June 2021, technological improvements have allowed the rapid development of vaccines that have shown high efficacy in preventing the risk of developing overt or severe forms of the disease. At the time of this study, three types of vaccines were available in Spain: Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), and Oxford-AstraZeneca (ChAdOx1). All three showed high efficacy in preventing SARS-CoV-2 infection (95% for Pfizer, 94% for Moderna, and >70% for AstraZeneca) [4-6]. Adverse reactions to the vaccines were observed in up to 90% of patients, but these were mild (low-grade fever, malaise, local pain and erythema, myalgia, and arthralgia) and usually resolved within 24-48 hours. Serious effects have been observed in only 0.1% of cases [4-6]. Notably, patients with autoimmune diseases and those receiving immunosuppressive treatment were excluded from vaccine trials. Similarly, recent reports of thrombotic events in vaccinated patients, presumably due to an autoimmune mechanism, have raised concerns among the autoimmune community and physicians [7,8]. The present study aimed to evaluate the short-term safety of SARS-CoV-2 vaccines in patients with systemic autoimmune disease.

## Materials and Methods

A descriptive and cross-sectional study was conducted on patients with autoimmune diseases followed up at the Department of Autoimmune Diseases, Hospital Clínic of Barcelona, between 1 March and 31 May 2021. Patients who had received at least one dose of any of the SARS-CoV-2 vaccines licensed in Spain were interviewed by telephone using a 32-questions questionnaire

administered between 15 and 90 days after vaccination. The questionnaire was administered by the same author (JMGC) and included the following variables: sex, age, type of autoimmune disease, immunosuppressive treatment, use of glucocorticoids and oral anticoagulants, previous SARS-CoV-2 infection, type of vaccine, vaccine-related adverse events, occurrence of disease exacerbation, and SARS-CoV-2 infection after vaccination. Consensus was reached with other study authors (OA and GE) in case of doubts about adverse effects or flares. Patients were re-contacted six months after vaccination to identify those who developed SARS-CoV-2 infection during this period. Informed consent was obtained from all individuals before enrolment, and the project was approved by the Research Ethics Committee of the Hospital Clínic of Barcelona (HCB/2021/0432). Patient information was de-identified prior to the analysis, and all procedures were performed in accordance with the ethical principles of the 2013 Declaration of Helsinki.

## Statistical Analysis

Absolute and relative frequencies, expressed as numbers and percentages, were used to characterise the samples according to the categorical variables. Quantitative variables with a parametric distribution are expressed as mean and Standard Deviation (SD), and those with a non-parametric distribution are expressed as median and Interquartile Range (IQR). Frequency analysis (independent samples) was used to compare adverse effects of immunosuppressive glucocorticoid treatment. The statistical program JAMOVI 1.6.23.0 was used for data analysis and processing. A confidence level of 95% was used.

## Results

### General characteristics

One hundred and fifty patients were included; 112 (74.6%) were female, and the mean age was 60 years (17.3). Thirty-five (23.3%) patients received one dose and 115 patients (76.6%) received two doses. The most common autoimmune disease in the surveyed cohort was systemic lupus erythematosus (SLE) (41 patients; 27.3%), followed by vasculitis (28 patients; 18.7%) and systemic sclerosis (25 patients, 16.6%). Table 1 summarises the general characteristics of the included patients.

Characteristics	N = 150
Age (years) - mean ± SD	60 ± 17.3
Gender (female) - n (%)	112 (74.6)
Type of vaccine - n (%)	
Pfizer-BioNTech	60 (40)
Moderna	58 (38.7)
Oxford/AstraZeneca	31 (20.7)
Autoimmune diseases - n (%)	
Systemic lupus erythematosus	41 (27.3)
Vasculitis	28 (18.7)
Systemic sclerosis	25 (16.6)
Antiphospholipid syndrome	13 (8.7)
Autoimmune hepatitis	13 (8.7)
Behçet's disease	8 (5.3)
Non-infectious uveitis	7 (4.7)
Inflammatory myopathy	5 (3.3)
Sarcoidosis	3 (2)
Rheumatoid arthritis	2 (1.3)
Sjögren's syndrome	2 (1.3)
Inflammatory bowel disease	1 (0.7)
Common variable immunodeficiency	1 (0.7)
Autoinflammatory disease	1 (0.7)
Treatments - n (%)	
Corticosteroids	72 (48)
<5mg/d	57 (38)
5-10mg/d	10 (6.7)
>10mg/d	5 (3.3)
Hydroxychloroquine	31 (20.7)
Immunosuppressive therapy	89 (59.3)
Azathioprine	21 (14)
Methotrexate	19 (12.7)
Mycophenolate	11 (7.3)
Rituximab	7 (4.7)
Adalimumab	5 (3.3)
Tacrolimus	3 (2)

Data for categorical variables are expressed as n (%), and those for continuous variables are expressed as mean ± SD.

**Table 1:** General characteristics of the vaccinated patients.

### Adverse effects associated with SARS-CoV2 vaccines

Overall, 110 (73.3%) patients presented with vaccine-related adverse effect (Table 2). The most common symptom was local pain, present in 77 (70%) patients, followed by general symptoms and fatigue in 60 (54.5%), fever in 38 (34.5%), headache in 21 (19%), chills in 19 (17.2%), myalgia in 19 (17.2%), and arthralgia in 8 (7.2%). Adverse effects resolved within 48 h in most patients (78.2%), between 3 and 5 days in 19.2%, and persisted between 6 and 15 days in only 3 (2.7%) patients. Table 3 summarises the most common vaccine-related adverse effects according to patients' diseases. Local pain was the main symptom observed in patients with vasculitis, antiphospholipid syndrome, and Behçet's disease, whereas general symptoms and fatigue were the main symptoms observed in patients with SLE and systemic sclerosis. Diarrhoea occurred in only two (1.3%) patients, all with Behçet's disease.

Adverse effects - n° (%)	N = 110
Local pain	77 (70)
General symptoms and fatigue	60 (54.5)
Fever	38 (34.5)
Headache	21 (19)
Chills	19 (17.2)
Myalgia	19 (17.2)
Arthralgia	8 (7.2)
Lymphadenopathy	4 (3.6)
Local itchy and rash	3 (2.7)
Diarrhoea	2 (1.8)
Dizziness	2 (1.8)
Local swelling	1 (0.9)
Insomnia	1 (0.9)
Dysgeusia	1 (0.9)
Dysphagia	1 (0.9)

**Table 2:** Adverse effects associated with SARS-CoV2 vaccines.

Adverse effects - n (%)	SLE N=33	Vasculitis N=17	APS N=9	SSc N=16	BD N=7
Local pain	18 (54.5)	14 (82.3)	7 (77.7)	8 (50)	6 (85.7)
General symptoms and fatigue	24 (72.7)	6 (35.2)	4 (44.4)	9 (56.2)	4 (57.1)
Fever	12 (36.3)	4 (23.5)	6 (66.6)	5 (31.2)	1 (14.2)
Chills	6 (18.1)	3 (17.6)	1 (11.1)	1 (6.2)	3 (42.8)
Arthralgia	7 (21.2)	1 (5.8)	1 (11.1)	0	3 (42.8)
Myalgia	4 (12.1)	1 (5.8)	1 (11.1)	2 (12.5)	0
Headache	10 (30.3)	2 (11.7)	1 (11.1)	3 (18.7)	2 (28.5)
Diarrhea	0	0	0	0	2 (28.5)

**Abbreviations:** APS: antiphospholipid syndrome; BD: Behçet’s disease; SLE: systemic lupus erythematosus; SSc: systemic sclerosis.

**Table 3:** Main adverse effects associated with SARS-CoV2 vaccines according to autoimmune disease.

Adverse effects were more frequent in patients vaccinated with Moderna (91.4%), followed by AstraZeneca (64.5%), and Pfizer-BioNTech (61.7%) ( $p < 0.001$ ) (Table 4). According to patient age, adverse effects were more frequently observed in patients younger than 60 years than in those older than 60 years (84.4% vs. 65.1%,  $p = 0.008$ ). Neither the use of glucocorticoids (70.8% vs. 75.6%,  $p = 0.5$ ) nor additional immunosuppressive agents (65% vs. 78.9%,  $p = 0.06$ ) showed any effect on the development of adverse effects.

Adverse effects - n (%)	Moderna N=58	Pfizer-BioNTech N=60	Oxford/Astrazeneca N=31
Local pain	37 (63.7)	25 (41.6)	15 (48.3)
General symptoms and fatigue	30 (51.7)	22 (36.6)	12 (38.7)
Fever	26 (44.8)	7 (11.6)	5 (16.1)
Chills	15 (25.8)	3 (5)	0
Arthralgia	9 (15.5)	3 (5)	0
Myalgia	6 (10.3)	5 (8.3)	1 (3.2)
Headache	16 (27.5)	3 (5)	4 (12.9)
Diarrhoea	1 (1.7)	1 (1.6)	0
Lymphadenopathy	1 (1.7)	3 (5)	0

**Table 4:** Main adverse effects associated with SARS-CoV2 vaccines according to vaccine type.

### Disease activity after SARS-CoV-2 vaccination

One patient (0.6 %) experienced a flare-up of autoimmune disease after vaccination. The patient had Behçet’s disease and developed oral ulcers after being vaccinated with Pfizer-BioNTech. These lesions resolved without any changes in treatment.

### SARS-CoV-2 infection after vaccination

Only four patients (3%) had COVID-19 infection after vaccination (Supplementary Table 1). No death occurred during the follow-up period.

Case	Age (years)	Sex	Autoimmune Disease	ISS therapy	Corticosteroid dosing	Vaccination date	Infection date	COVID19 severity*
1	81	F	ANCA-vasculitis	Reslizumab	5mg/d	Pfizer March-2021	July 2021	Mild
2	35	F	Behçet's disease	Azathioprine	<5mg/d	Pfizer April-2021	July 2021	Mild
3	82	F	Systemic sclerosis	None	No	Pfizer April-2021	June 2021	Mild
4	85	M	Systemic sclerosis	None	No	Moderna April-2021	July 2021	Mild

\*According to World Health Organization (2021). COVID-19 clinical management: living guidance, 25 January 2021. <https://apps.who.int/iris/handle/10665/338882>

**Abbreviations:** ISS: immunosuppressive

**Supplementary Table 1:** SARS-CoV-2 infection after vaccination in patients with autoimmune disease.

## Discussion

In our study, SARS-CoV2 vaccines were effective and safe for patients with autoimmune diseases. The adverse event profile was similar to that described in the general population, and in most patients, adverse events were mild and resolved within 48 h. However, the proportion of relapses after vaccination was low. In the absence of an effective treatment against SARS-CoV-2, face masks, social distancing, and the massive application of vaccines have shown efficacy. Vaccines were 85% effective in preventing SARS-CoV-2 infection, 97% effective in preventing symptomatic COVID-19, 93% in preventing hospitalisation, 96% in preventing intensive care unit admission, and 95% effective in preventing COVID-19-related death [9]. Serious adverse events from vaccine use are less than 1%; therefore, the benefits of using vaccines clearly outweigh the risks of not using them [10,11]. Our results are consistent with the published information. In our study, the adverse effects were similar but less frequent than those described in clinical trials involving the general population [12]. In clinical trials of Moderna and Pfizer-BioNTech vaccines, local pain, fatigue, headache, and myalgia were the most common adverse events (92% vs. 84.1%, 70% vs. 62.9%, 64.7% vs. 55.1%, and 61.5% vs. 38.3%, respectively) [4-5,13]. In our study, the most common adverse events were local pain (70%), general symptoms and fatigue (54.5%), fever (34.5%), and headaches (19%).

In a recent German study, the adverse effects of these vaccines were very similar in patients with chronic inflammatory diseases compared with a healthy population control group. The most common symptoms were fatigue, myalgia, and headache (53.8%, 42.3%, and 38.5% respectively) [14]. Another study involving 325 patients with autoimmune diseases evaluated the safety of the first dose of mRNA vaccine in patients with autoimmune diseases. Of these, 51% received Pfizer vaccines, and 49% received Moderna vaccines. The most common adverse reaction was local pain

(89%), followed by general symptoms (such as asthenia and fatigue) in 69% of the cases [15]. The EULAR COVAX Registry is a European paediatric and adult registry that reports the outcomes of COVID-19 patients with rheumatic/autoimmune diseases [16]. At the update of 5 October 2021 of the 6589 patients included, 69% had received Pfizer-BioNTech, 18% Oxford/AstraZeneca, and 9% Moderna, and 25% of patients had received only one dose. The predominant autoimmune diseases analysed were rheumatoid arthritis (33%), spondyloarthritis (14%), psoriatic arthritis (10%), and SLE (7%). Following vaccination, 38% of the patients experienced an adverse event, 4% experienced a disease flare, and 1% developed COVID-19. The most common adverse event was local pain at the injection site (18%), followed by fatigue (12%), fever (9%), generalised myalgia (7%), and headache (6%) [17].

SLE was the most common autoimmune disease observed in our study. In this sense, the results of VACOLUP (an international registry to evaluate the adverse effects of SARS-CoV-2 vaccines in patients with SLE) have been published. Overall, vaccine-related adverse events were reported in 53% of patients, with no sex or age differences. Only 3% of patients develop a SLE flare after vaccination, leading to a change in treatment in 71% of patients [18]. Regarding the age of the patients in our study, those younger than 60 years presented a higher frequency of vaccine-related adverse events, which is similar to the secondary effects described in the general population (without autoimmune diseases). Similar to the healthy population, adverse reactions in the majority of our cases (78.2%) usually resolve within 48 h, and only a small percentage of patients may present with symptoms up to 2 weeks after vaccination. Furthermore, the adverse events observed in our autoimmune patients did not lead to changes in treatment, and no cases of short-term mortality were identified. Moreover, adverse events were not associated with the use of glucocorticoids or additional immunosuppressive agents (conventional or biological). Therefore, from a safety point of view, it does not seem justified

to discontinue basic treatment before or during the COVID-19 vaccination. If changes in treatment are required, they must be individualised [19,20]. Our study has several important advantages over similar studies. The survey was conducted by the same author, reducing the risk of interpretation bias. In doubt, a consensus was reached by other authors. In addition, the study was a telephone survey and not a registry where patients submit data (such as the VACOLUP registry), which can lead to problems in interpreting adverse effects or disease flares. However, our study has several limitations, such as the small number of patients analysed, the fact that some patients only received a single dose of the vaccine, and the lack of long-term follow-up.

## Conclusions

The results of our study confirm that vaccination against SARS-CoV-2 can be recommended for the population with autoimmune diseases (with or without immunosuppressive treatment) owing to its very good safety profile. These results suggest that the benefits of COVID-19 vaccination in patients with autoimmune diseases outweigh the risks of non-vaccination.

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