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COVID-19 Vaccines in a Cohort of Egyptian Patients with Auto-Immune Rheumatic Diseases

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Abstract

Background: The COVID-19 pandemic is considered a global health problem with paramount importance. However, limited data are available regarding safety and efficacy of COVID-19 vaccines on patients with autoimmune rheumatic diseases (AIRDs).

Aim of Study: To study the efficacy and safety of COVID-19 vaccinations among a cohort of Egyptian patients with auto-immune rheumatic diseases (AIRDs).

Patients and Methods: 43 patients with different AIRDs, and 43 age-and sex-matched controls were enrolled in the study. All participants have been vaccinated using the two-dose regime of COVID-19 vaccines. Post-vaccination disease activity and measurement of serum IgG antibodies against SARS-CoV-2 trimeric spike proteins S1/S2 in patients with AIRDs compared to healthy controls were done two to six weeks after the second dose of the vaccine. All participants completed a survey to assess the safety and adverse effects of the vaccines.

Results: The mean serum IgG antibody levels in patients with AIRDs was 6753.6±9117.8 BAU/ml compared to 10538.1±13333.9 BAU/ml in the control group with no significant difference. As regard adverse events, arthralgia after the first dose and local pain after the second dose were statistically higheramong the patients' group. Patients who received Pfizer's vaccine developed higher levels of serum IgG antibodies compared to those who received Sinopharm and Sinovac vaccine (p=0.004 and 0.016 respectively). A statistically lower level of serum IgG antibody was found in patients with AIRDs who received glucocorticoid dose more than 10mg/day compared to who received glucocorticoid dose equal or less than 10mg/daily (p=0.039).

Conclusions: The results of the study confirm the efficacy, safety and tolerability of SARS-CoV-2 vaccines, thus they should be strongly recommended in patients with AIRDs.

Key Words: *COVID-19 – Vaccines – Auto-immune – Rheumatic diseases.*

Introduction

THE COVID-19 pandemic is considered a global health problem with paramount importance. Covid-19 patients develop many rheumatic-like manifestations that are difficult to differentiate from that of auto-immune rheumatic diseases (AIRDs), it is not yet clear if these manifestations are virus-induced or a flare of the autoimmune disease. Moreover, the underlying pathogenesis in both conditions is a combination of hyperinflammatory response and dysregulation of the immune system **[1]**.

However, limited data are available regarding many aspects related to vaccination in patients with AIRDs. First, the efficacy and immunogenicity of the different COVID-19 vaccines in patients with AIRDs. Second, what is the best vaccine for those patients. Third, the impact of the immunosuppressive drugs used in management of AIRDs on the antibody level production in these patients. Due to its role in immunomodulation, patients who receive immunosuppressive treatment were excluded from phase III trials of the vaccines, in adherence to the recommendations of the Food and Drug Administration (FDA) and European Medicines Agency (EMA) **[2]**. The American College of rheumatology guidelines considered patients with AIRDs as a high-risk group and prioritized for vaccinations against SARS-CoV-2 during the pandemic **[3]**.

The paucity of data regarding COVID-19 vaccination and AIRDs in general, and the usage of different vaccines in different countries had prompted the present study on the efficacy and safety of COVID-19 vaccinations among a cohort of Egyptian patients with AIRDs.

Patients and Methods

This is an observational, analytic, case-control study conducted on 86 participants, of whom 43 were patients with different AIRDs, and 43 age-and sex-matched controls. All patients were recruit-

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ed from the outpatient clinic and inpatient unit of the Rheumatology Department, Cairo University Hospitals between September 2021 and March 2022. Healthy controls were medical staff, workers, and medical students. All participants have been vaccinated using the two-dose regime of Pfizer, Astra Zeneca, Sinopharm or Sinovac vaccines and measurement of serum IgG antibody was done two to six weeks after the second dose.

Those with Previous COVID-19 infection, who received only one dose of vaccine, and those with more than six weeks elapsed after the second dose of vaccination were excluded from the study. Pregnant women andpatients with chronic diseases such as diabetes, heart disease, end-stage renal disease (ESRD) were also excluded.

AIRDs included patients with rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), Behcet's disease (BD), ankylosing spondylitis (AS), Sjogren's syndrome (SS), juvenile idiopathic arthritis (JIA), undifferentiated arthritis (UA), psoriatic arthritis (PsA), familial Mediterranean fever (FMF), idiopathic inflammatory myositis (IIM) and primary antiphospholipid syndrome (APS). Patients wereclassified according to the classification criteria of the different international societies **[4-14]**.

All patients were subjected to a review of their personal data, medical history, medical records, clinical presentation, and drug history. An in-person clinical examination to assess the post-vaccination disease activity within 2-6 weeks after the second vaccine dose was performed. Pre-vaccination disease activity was retrieved from the patients' medical records. Disease activity was assessed using an appropriate index such as Disease Activity Score 28 (DAS28-ESR/CRP) for RA patients **[15]** and, Systemic lupus Disease Activity Index (SLEDAI) for SLE patients **[16]**. Moreover, a questionnaire was given to all patients to evaluate any change or worsening of disease symptoms after vaccination compared to the pre-vaccination status.

Evaluating efficacy of the COVID-19 vaccines:

Levels of serum IgG antibodies against SARS-CoV-2 trimeric spike proteins S1/S2 in patients with AIRDs compared to healthy controls were measured two to six weeks after the second dose of the vaccine. Participants with a serum level of more than 18 BAU/ml (binding antibody unit/ml) were considered to have a positive response.

Evaluating the safety of the COVID-19 vaccines:

All participants were required to complete a survey to assess the safety and adverse effects of the vaccines. Patients and healthy controls completed a questionnaire about the most common adverse events of COVID-19 vaccines. Adverse effects were classified into four groups **[3]**: local reactions, systemic reactions, rheumatic symptoms, and others. All participants were asked explicitly about the following symptoms after each dose of vaccination:

- Local reactions: Local pain and swelling, local redness, and local numbness.
- Systemic reactions: Fever, anorexia, nausea and vomiting, fatigue, headache, runny nose, sore throat, diarrhea, hypersensitivity, high blood pressure, and lymphadenopathy.
- Rheumatic symptoms: Such as myalgia, arthralgia, joint swelling, skin rash, uveitis, hair loss, oral ulcers, chest pain, back pain, acrocyanosis, and thromboembolic events.
- Others: Including any symptoms not mentioned above that might be linked to COVID-19 vaccines such assystemic and local thrombosis, oral herpes, and herpes zoster infection.

Reports of adverse events following the vaccination were recorded.

Ethics:

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and in accordance with the 1964 Helsinki declaration and its later amendments.

Statistical analysis:

All data were analyzed and entered using Statistical Program for Social Science (SPSS) version 28 (IBM Corp, Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency and relative frequency (percentage) for categorical data. Comparisons between quantitative were made using the non-parametric Karuskal-Wallis and Man-Whitney tests. The non-parametric Wilcoxon signed-rank test was used to compare serial measurements within each patient **[17]** for comparing categorial data, Chi-square test was performed. The exact test was used instead when the expected frequency was less than 5 **[18]**. *p*-values less than 0.05 were considered statistically significant.

Results

Demographics and clinical characteristics:

Forty-three patients with different AIRDs (36 females and 7 males) with a mean age 43.1±11.8

years and 43 healthy controls (35 females and 8 males) with a mean age 41.5±11.2 years were enrolled in the study. Among the group of AIRDs, 21 patients (48.8%) had rheumatoid arthritis, 9 patients (20.9%) had systemic lupus erythematosus, 3 patients (7%) with Behcet's disease, 3 patients (7%) with ankylosing spondylitis, 2 patients (4.7%) had psoriatic arthritis and 1 patient (2.3%) with each of the following diseases: Sjogren's syndrome, primary antiphospholipid syndrome, juvenile idiopathic arthritis, undifferentiated arthritis, and inflammatory muscle disease.Sixteen patients (37.2%) were on glucocorticoids, 19 patients (44.2%) on methotrexate, 11 patients (25.6%) on hydroxychloroquine, 6 patients (14%) on leflunomide, 5 patients (11.6%) on TNF inhibitors, 2 patients (4.7%) on azathioprine, 1 patient (2.3%) on cyclosporine. Four patients (9.3%) were not receiving any immunosuppressive therapy and another 4 patients (9.3%) were receiving combinations of glucocorticoids and/or hydroxychloroquine with the other DMARDs. Eighteen patients (41.9%) received Astra Zeneca vaccine, 11 patients (25.6%) received Pfizer's vaccine, 11 patients (25.6%) received Sinopharm and 3 (7%) received Sinovac vaccine compared to 22 (51.2%), 13 (30.2%), 7 (16.3%) and 1 (2.3%) of the control group respectively.

Efficacy of the COVID-19 vaccines in patients with AIRDs:

All patients tested positive for serum IgG antibodies against SARS-CoV-2 spike proteins within 2-6 weeks of the second dose. No non-responders were found in both groups. The mean serum IgG antibody levels in patients with AIRDs was 6753.6 ±9117.8 BAU/ml compared to 10538.1±13333.9 BAU/ml in the control group. Although the mean level was higher in the control group compared to AIRDs patients, the difference was not statistically significant (p=0.349) Fig. (1).

There was no statistically significant difference as regard the serum IgG level among patients with rheumatoid arthritis compared to the level among patients with systemic lupus erythematosus (p=0.263) Fig. (2).

Moreover, the study results showed variation in serum IgG antibodies against SARS-CoV-2 spike protein levels in patients with AIRDs according to the type of the vaccine (p-value <0.001), as shown in Table (1). In addition, tracing variation in serum IgG antibody levels by vaccine type demonstrated no statistically significant difference in patients with AIRDs compared to control group (p=0.338).

Evaluating the safety of the COVID-19 vaccines:

Although there were more common adverse events in the patients' group such as fever and fatigue, the differences were not statistically significant except for arthralgia after the first dose (p<0.008) and local pain after the second dose (p=0.008).

In addition, Table (2) shows the absence of any significant change in disease activity after vaccination in patients with rheumatoid arthritis and patients with systemic lupus erythematosus compared to the pre-vaccination disease activity. The number of patients with other AIRDs was too small to allow any statistical analysis.

Effect of different immunosuppressive drugs on vaccine immunogenicity:

There was no statistically significant difference in serum IgG antibody levels against SARS-CoV-2 spike proteins in patients receiving conventional and biological drugs (p=0.413). On the other hand, a statistically lower level of serum IgG antibody was found in patients with AIRDs who received glucocorticoid dose more than 10mg/day compared-to who received glucocorticoid dose equal or less than 10mg/daily (p=0.039). Fig. (3).

Table (1): Relation between vaccine type and IgG level in patients with AIRDs.

	Serum IgG antibodies against SARS-CoV-2 spikes protein level after the second dose					p-value
	Mean BAU/mL	Standard Deviation	Median	Minimum	Maximum	
Vaccine type:						
Pfizer	14663.33	15296.87	9058.80	580.30	40000.00	<0.001
AstraZeneca	5852.48	1984.46	5730.05	2909.40	12245.80	
Sinopharm	1902.11	1456.76	1455.80	812.50	5757.20	
Sinovac	947.63	604.67	801.10	429.70	1612.10	

Table (2-A): Disease activity in patients with RA (A) and SLE (B) pre-and post-vaccination.

	RA					*p*-value
	Mean	SD	Median	Minimum	Maximum	
Disease activity before the vaccine	4.43	3.61	3.70	2.70	20.00	0.095
Disease activity after vaccine	4.11	0.57	3.90	3.20	5.10	

Table (2-B): Disease activity in patients with RA (A) and SLE (B) pre-and post-vaccination.

	SLE					*p*-value
	Mean	SD	Median	Minimum	Maximum	
Disease activity before the vaccine	2.44	0.88	2.00	2.00	4.00	0.157
Disease activity after vaccine	2.89	1.45	2.00	2.00	6.00	

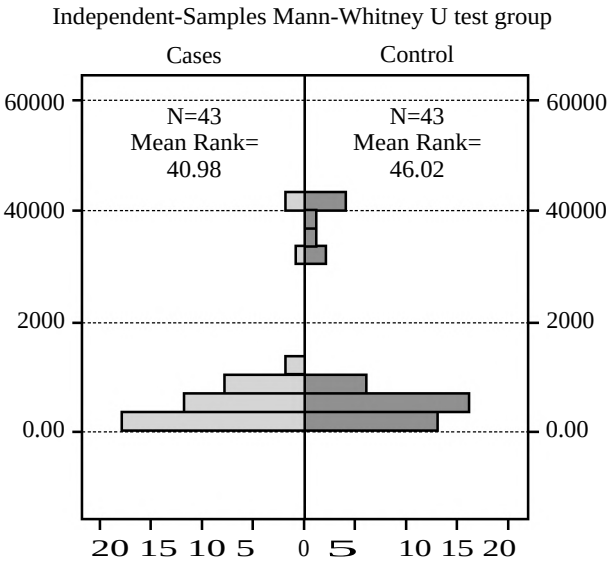

Fig. (1): Serum IgG antibody levels in patients with AIRDs compared to control.

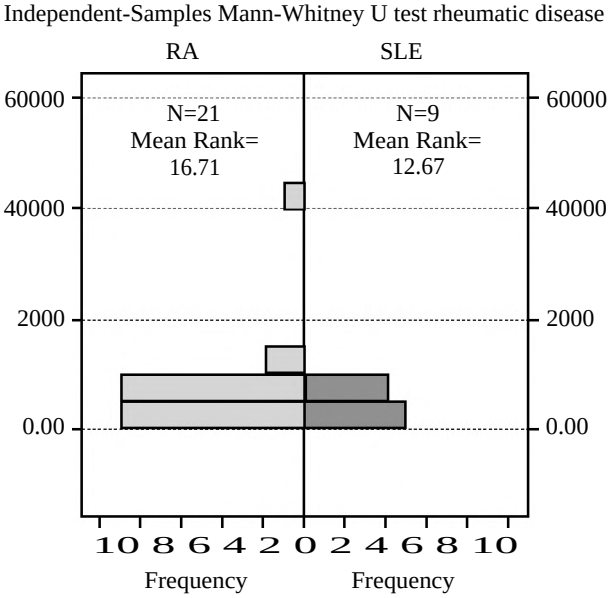

Fig. (2): Serum IgG antibody levels in patients with rheumatoid arthritis compared to patients with systemic lupus erythematosus.

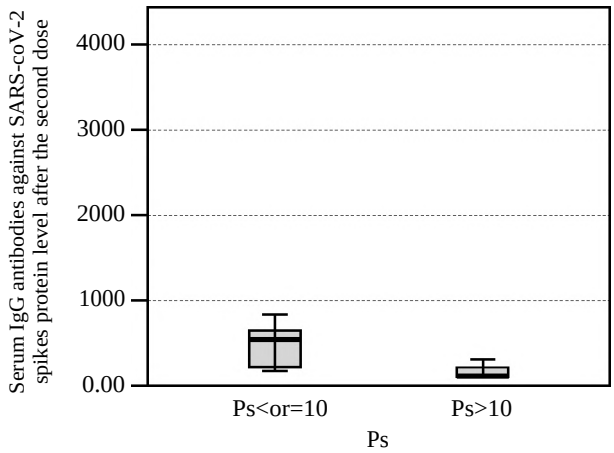

Fig. (3): Serum IgG levels in patients taking glucocorticoids.

Discussion

COVID-19 pandemic remains a global threat to humanity. To end the pandemic, vaccination has been shown to be an effective measure. The available vaccines differ from one country to another. The main four COVID-19 vaccines widely used in Egypt include the mRNA vaccines (BNT162b2 -Pfizer-BioNTech), viral-vector vaccines (ChAdOx1-AstraZeneca), Ad26.COV2.S (Johnson & Johnson) and killed-virus vaccines (Sinopharm). The mRNA-1273 (Moderna), Gam-COVID-Vac (also known as Sputnik V), killed-virus vaccines (CoronaVac-Sinovac) are used on a limited scale. Unfortunately, individuals with autoimmune inflammatory rheumatic diseases (AIRDs) who are immunocompromised by their disease and therapy were excluded from participation in the large vaccine registration trial. The efficacy and safety of the different types of vaccines in these vulnerable individuals was therefore not well known. However, prioritization of vaccination of patients with AIRDs to receive SARS-CoV-2 vaccination with any of

the vaccines approved in their country was endorsed recently by EULAR [19].

This study examined the efficacy and safety of COVID-19 vaccination among a cohort of Egyptian patients with AIRDs. All participants in both groups tested positive for the serum IgG antibodies against SARS-CoV-2 spike proteins within 2-6 weeks of the second dose. Although the mean serum IgG antibody levels was higher in the control group compared to the mean level of the AIRDs group, the difference was not statistically significant (p<0.349). Initial observations published in 2021 showed that COVID-19 vaccines are safe and effective in patients with AIRDs and other immune-mediated inflammatory diseases [2,20,21]. In a recent study published in 2022, the concentration of antiSARS-Cov-2 serum antibodies were moderately lower in patients with AIRDs than in those without, but there was no difference in seroconversion, in addition, the neutralizing capacity against the virus and the ability to generate rapid and satisfactory response on re-exposure to antigen did not differ between individuals with or without AIRDs [21]. The number of patients with various AIRDs in this study allows only comparison between the mean serum antibody level in patients with rheumatoid arthritis (n=21) and systemic lupus erythematosus (n=9). There was no significant difference between the mean serum IgG antibody levels in both diseases. In the same context, the humoral immune responses inpatients with various AIRDs, such as RA, SpA, soft connective tissue diseases, and vasculitides, who were treated with immunomodulatory or immunosuppressive drugs or combination did not vary in the different AIRDs [22]. Moreover, it seems from our results that patients who received Pfizer-BioNTech (BNT162b2) vaccine developed higher levels of serum IgG antibodies against SARS-CoV-2 compared to those who received Sinopharm and Sinovac vaccine (p 0.004 and 0.016, respectively), while there was no statistically significant difference between serum IgG antibody levels in patients who received Pfizer vaccine compared to those who received AstraZenica vaccine. However, patients with AIRDs should be strongly advised to receive a SARS-CoV-2 vaccination with any of the available vaccines approved in their country.

The adverse events of the vaccines were evaluated by asking all participants to complete a detailed questionnaire about the most common adverse events of COVID-19 vaccines after each dose of the vaccine. There were more common adverse events in the patients with AIRDs compared to individuals without AIRDs. However, significant difference was found only as regard arthralgia following the first dose (p<0.008) and local injection site pain after the second dose (p<0.008). Patient-reported adverse events following SARS-CoV-2 vaccination were comparable to those reported in the general population, with rheumatic disease flares requiring medication changes occurring in less than 5% [20], and a third SARS-CoV-2 vaccination was not associated with increased risk of adverse events compared to the second vaccination [23].

Pre-vaccination disease activity score (DAS28-ESR/CRP) for RA patients and systemic lupus disease activity index (SLEDAI) for SLE patients was retrieved from the patients' medical records and compared to disease activity after the two doses of vaccination. Moreover, the questionnaire given to all patients included questions regarding any change or worsening of disease symptoms after vaccination compared to the pre-vaccination status. There was no significant change in disease activity after vaccination in patients with RA or patients with SLE compared to the pre-vaccination disease activity. In general, current evidence doesn't support the increased risk of disease flare after COVID-19 vaccination. However, the disease flare of rheumatic diseases (RDs) may be triggered by COVID-19 vaccinations, especially for patients with high disease activity [24]. Most of these flares after vaccination are mild and need no treatment escalation. Considering the benefits and risks, RD patients are recommended to receive the COVID-19 vaccination but should be vaccinated when the RDs are in stable states [24].

As the type of vaccine used in different studies varied, a question of arises whether the type of vaccine matter in inducing diseases flares. Direct comparisons between several different mRNA and adenovirus-based vaccines, found no difference in terms of flare-up development (p=0.43) [25]. Another study conducted on 2132 RD's patients who received mRNA vaccinationand 695 RD's patients who received adenovirus-based vaccination. Flare rates was similar in both groups [26]. On the other hand, adenovirus-based vaccine was associated with higher flare riskrelative to mRNA vaccine in another study (OR1.44, 95% Cl 1.08-2.48) [27]. Most studies were done on mRNA, and data on AIRDs after killed and adenovirus- based vaccine are scanty,on comparing mRNA vaccines with killed vaccine, similar rates of disease flares was found [28,29].

Regarding the effect of immunomodulatory immunosuppressive drugs on the immune response

in the studied cases, the study revealed no statistically significant difference on the levels of serum IgG against SARS-CoV-2 in patients receiving biologics compared to patients receiving conventional DMARDs (p=0.413). Previous data on the effect of immunosuppressive treatment on vaccination reported limited but acceptable immune response to the vaccines. Even in the absence of antibodies, cellular immune response against SARS-CoV-2 spike proteins may exist **[30]**. Likewise, to our study, regarding the immune response in patients taking TNF-inhibitors and conventional synthetic DMARDs, there were no significant difference between IgG levels in patients receiving different therapies **[2]**. Methotrexate had no impact on the immune response to COVID-19 vaccines in patients with AIRDs **[31]**. Other studies showed improved vaccines' immunogenicity with a two-week pause of methotrexate **[32,33]**. On the other hand, Furer and his colleagues reported that treatment with glucocorticoids, mycophenolate mofetil, and abatacept was significantly associated with a lack of humoral response **[21]**. Our study also showed significant difference in patients with AIRDs who received glucocorticoid dose more than 10mg/day compared to those on glucocorticoid dose equal or less than 10mg/day (p<0.039). Apart from the risk connected to GCs use, the COVID-19 Global Rheumatology Alliance physician registry foundthat patients with RA treated with rituximab and JAK inhibitors are associated with a higher burden of COVID-19 severity and mortality [34]. On the other hand, TNF inhibitors carry a lower risk of adverse outcomes of COVID-19,particularly when administered as monotherapy [35].None of our patients were on rituximab. The B-cell depleting agentsrepresent a particular challenge for vaccination in patients with AIRDs **[36-40]**. Although, switching to another DMARD with different mode of action may be feasible in some situations to allow successful immunization, this approach may be difficult in some diseases such as in remission induction and maintenance of ANCA-associated vasculitis (AAV). Although the humoral responseto the vaccine is impaired in patients receiving rituximab, data suggests that the cellular response is not **[39]**. Lower dosages and vaccination delay since last rituximab infusion should be encouraged (when clinically feasible) **[40]**.

There are some limitations of this study; the first is related to the relatively small number of patients in the group AIRDs, in view of the fact that this number does not represent a single disease entity but various types rheumatic diseases. Secondly, the inclusion of the various AIRDs with different immunologic pathogenesis in one group, may have an impact on the immunogenicity of different vaccines. Thirdly, four patients were receiving a combination of glucocorticoids and/or hydroxychloroquine together with their disease-modifying antirheumatic drugs which complicate the relative impact of each drug on vaccine immunogenicity. However, the current study had several strengths: It represents a step forward towards unveiling the efficacy and safety of SARS-CoV-2 vaccines in patients with AIRDs. In addition this study may add some knowledge related to efficacy and safety of the inactivated or killed vaccines which are not available in many countries. Overall, the results of the study reconfirm that SARS-CoV-2 vaccines should be strongly recommended in patients with AIRDs, since safety and tolerability of these vaccines have been confirmed in many studies.

Conflict of interest:

The authors declare that they have no conflict of interest.

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لقاحات كوفيد-١٩ لمجموعة من المرضى المصريين المصابين بأمراض المناعة الذاتية الروماتيزمية

يتشارك كوفيد–١٩ وأمراض المناعة الذاتية الروماتيزمية فى العديد من المظاهر السريرية والمناعية، ويتميز كلاهما بالاستجابة المناعية الالتهابية المفرطة وعدم التنظيم المناعى. قد تتأثر الإستجابة المناعية عند مرضى المناعة الذاتية الروماتيزمية بعدة عوامل بما فى ذلك نوع مرض الروماتيزم المناعى الذاتى، وجود أمراض مصاحبة، ونوع العلاج المثبط للمناعة، ونوع اللقاح. لهذا السبب، كانت سلامة وفعالية لقاحات كوفيد–١٩ فى المرضى الذين يعانون من أمراض المناعة الذاتية الروماتيزمية تحظى بأبحاث مكثفة.

لذلك، كان الهدف من الدراسة الحالية هو تقييم مناعية وسلامة لقاحات كوفيد–١٩ فى المرضى الذين يعانون من أمراض المناعة الذاتية الرو ماتزمية.

هذه دراسة تحليلية أجريت على مجموعة ٨٦ من مشاركاً منهم ٤٣ مريضاً يعانون من أمراض المناعة الذاتية الروماتيزمية على العلاج المثبط للمناعة. أجريت الدراسة فى العيادات الخارجية وأجنحة القصر العينى، قسم الروماتيزم والتأهيل.

أظهرت الدراسة أن لقاحات كوفيد–١٩ كانت آمنة وفعالة فى المرضى الذين يعانون من أمراض المناعة الذاتية الروماتيزمية. كانت سلامة وفعالية اللقاح لديهم مشابهة لتلك التى عند الاشخاص الاصحاء. لا يوجد فرق فى الاستجابة المناعية للقاحات فى المرضى الذين يتلقون متشابهات بيولوجية مقارنة بالمرضى الذين يتناولون مضادات الرو ماتيزم التقليدية. أضافة إلى ذلك، كان نشاط المرض ثابتاً بعد التطعيم فى معظم الحالات.