Humoral Response of Different Types of SARS-CoV-2 Vaccines in Patients with Autoimmune Rheumatic Diseases: Experiences from a Serbian Cohort

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ABSTRACT **Background:** Data are scarce on the immunogenicity of coronavirus disease 2019 vaccines in patients with autoimmune rheumatic diseases (ARD).

Objectives: To measure the immunoglobulin G (IgG) response after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunization and to evaluate clinical characteristics associated with seropositivity.

Methods: Samples were collected after the second and third doses of the three different types of vaccines in ARD patients. Seroconversion rates and IgG antibody S1/S2 titers were measured.

Results: The type of ARD diagnosis and previous treatment had no significant impact on the serum IgG antibody levels measured after the second (P = 0.489 and P = 0.330, respectively) and boost dose (P = 0.441 and P = 0.446, respectively). What made a significant difference regarding serum IgG antibody levels after the second dose was the type of SARS-CoV-2 vaccine. The difference was highly statistically significant for all vaccine types (P = 0.001 with the highest odds ratio for the mRNA vaccine). After the boost with the mRNA vaccine, all patients achieved a high level of serum IgG antibody levels (t = 10.31, P = 0.001). No ARD patients experienced serious post-vaccinal reactions. Eight patients developed COVID-19 before the boost dose.

Conclusions: In ARDs patients, the highest level of serum IgG antibody against S1/S2 proteins was achieved with the mRNA vaccine, irrespective of the therapy applied or the type of the disease. We recommend a booster dose with mRNA vaccine in all ARDs for the highest SARS-CoV-2 protection without serious post-vaccinal reactions observed.

IMAJ 2023; 25: 590–594

KEY WORDS: antiphospholipid syndrome, autoimmune disease, coronavirus disease 2019 (COVID-19) vaccine, rheumatic disease, seroconversion

Rheumatic diseases (RD) comprise plenty of chronic inflammatory conditions of the connective tissue disease and musculoskeletal system including autoimmune rheumatic diseases (ARDs) and inflammatory diseases. These conditions differ regarding clinical presentation, disease severity, co-morbidities, treatment, and organ involvement. The patients are more susceptible to coronavirus disease 2019 (COVID-19) infection due to the immunomodulatory treatment of the primary disease and increased vulnerability due to the presence of the disease itself. A higher risk of COVID-19 infection carries more infected patients and, therefore if there are more infected patients, there would be a more with severe clinical presentation The severity of the disease might be weakened by the widespread application of safe and effective vaccination. Patients diagnosed with ARD, malignancy, and human immunodeficiency virus (HIV) are generally excluded from vaccine safety and efficacy studies. There are clear and uniform worldwide recommendations that strongly support vaccination in ARD patients to reduce the rate of the disease in this population [1-4]. Smaller differences refer to the recommendations on adjusting or delaying the drugs used in the treatment of these patients. Despite the fear of infection or developing severe clinical effects, only 54.2% of ARD patients were willing to get vaccinated against COVID-19 [5]. They were undecided about vaccination due to the lack of background information regarding vaccines and a possible flare of their disease, side effects, and local reactions.

An updated systematic review and meta-analysis of 47 studies demonstrated that COVID-19 vaccination was effective in protecting rheumatic patients from severe illness caused by the virus and involved a low incidence of disease flares after vaccination [6]. Data on SARS-CoV-2 vaccine efficacy after the second dose revealed the potential need for a booster vaccine.

In this study, we measured the immunoglobulin G (IgG) re-

sponse of the various SARS-CoV-2 vaccines after the second dose and the booster dose administered to patients with ARD and evaluated clinical characteristics and treatments associated with seropositivity.

PATIENTS AND METHODS

This prospective observational cohort study was conducted between 1 March 2021 and 31 March 2022 among outpatient ARD patients during regular appointments with a rheumatologist at Special Hospital "Dr Zutic", Belgrade, Serbia.

The ARD patients with pre-vaccination negative COVID-19 serology were voluntarily vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with two regular doses one month apart and a booster dose after 6 months via the Serbian national vaccine program. The patients were offered one of the following vaccines available in the Serbian healthcare system: mRNA vaccine, Pfizer BioNTech; non-replicating viral vector vaccines, Oxford-AstraZeneca and Sputnik V; or inactivated whole virus, Sinopharm Beijing Institute of Biological Products. The patients were vaccinated irrespective of the ARD treatment, but rather with the patient's preference of the chosen vaccine. Exclusion criteria were history of allergic reaction to vaccine components, heart failure (NYHA III-IV), history of vaccination in the previous 6 weeks, or other known chronic viral illness (e.g., hepatitis B, hepatitis C, HIV). Patients who underwent organ transplant were also excluded. The study was conducted under the Declaration of Helsinki rules and was approved by the Ethics Committee of Special Hospital "Dr Zutic". All patients signed informed consent without any participant compensation.

The following data were collected: type and date of four different SARS-CoV-2 vaccinations, demographics, type of ARD, concurrent treatment, co-morbidities, COVID-19 outbreak among vaccinated patients, and outcomes. Vaccination efficacy, safety, and disease activity were assessed within 6 weeks after the booster dose.

Overall, 40 ARD patients were included: 37 female (92.7%) and 3 male (7.3%), with an average age of 49.5 ± 15.1 years. Among all ARD patients, there were 7 patients diagnosed with primary antiphospholipid syndrome (PAPS) (17.5%), 16 with systemic lupus erythematosus (SLE) (40%) (7 with the associated antiphospholipid syndrome), 6 with rheumatoid arthritis (RA) (15.0%), 4 with Sjögren's syndrome, 2 with Morbus Still (5.0%), 2 with Polymyalgia rheumatic (5.0%), 2 with reactive arthritis (morbus Reiter) (5.0%), and 1 with granulomatosis Wegener (2.5%).

To assess humoral immunogenicity, blood sampling was obtained from all participants 4 weeks after the second dose (before booster dose) and 4 weeks after booster dose. Sera were stored at -70°C. A chemiluminescent immunoassay was applied to measure IgG antibodies against S1 and S2 proteins in the receptor binding site domain (RBD). Serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins were analyzed by ELISA method 2 weeks after the second and booster doses of different SARS-CoV-2 vaccines. Results were defined as negative if titer levels were below 50 AU/ml, low if 50–100 AU/ml, and medium if 100–1000 AU/ml. Levels above 1000 AU/ml were considered high. Post-vaccine reactions were analyzed and compared with ongoing therapy.

STATISTICAL ANALYSIS

For normally distributed continuous data, mean and standard deviation were applied, for non-normal distribution median and interquartile range, and for categorical variable percentage and proportion. The categorical variable was analyzed using the Chi-square test and Mann-Whitney for the non-parametric continuous variables. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Statistical significance was defined as $P < 0.05$.

RESULTS

VACCINATION IN ALL PATIENTS

The patient characteristics are presented in Table 1. The distribution of patients receiving different types of SARS-CoV-2 vaccines was similar without a statistically significant difference: 15 (37.5%) received the mRNA vaccine, 13 (32.5%) the viral vector, and 12 (30.0%) the vaccine with the inactivated whole virus. The booster dose was of the same type as the previous two. Seroconversion after the second dose was achieved in 29 patients (72.5%) ($P = 0.007$) and after the booster dose in 39 (97.5%) ($P < 0.001$) [Figure 1]. There was a statistically significant difference in seroconversion comparing the type of the vaccine. Almost all patients achieved seroconversion after the second dose of the mRNA vaccine, but only two were vaccinated using the whole virus vaccine ($P < 0.001$).

There was no serum IgG antibody against SARS-CoV-2 spike S1/S2 proteins in 11 patients (27.5%) after the second dose, and high levels were measured in 13 (32.5%) ($P = 0.007$). Almost all patients had high levels of IgG antibody against SARS-CoV-2 spike S1/S2 proteins (37/92.5%) after the booster dose.

What made a significant difference regarding serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins after the second dose was the type of SARS-CoV-2 vaccine. The difference was highly statistically significant for all types ($P = 0.001$) with highest odds ratio for mRNA vaccine. After the boost with the mRNA vaccine, all patients achieved a high level of serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins [Figure 2].

Post-vaccine reactions were seen in 29 patients (72.5%). None of the ARD patients experienced serious post-vaccinal reactions. However, the majority of the reactions were mild. The most common events were pain at the injection site, fatigue, and headache.

Eight patients developed COVID-19 before the booster dose, 75% had been previously vaccinated with the whole virus vaccine, all of them with mild form without long-COVID conditions observed.

VACCINATION AND DIAGNOSIS

There was no statistically significant difference considering the patient diagnosis and chosen type of vaccine ($P = 0.661$) and the seroconversion at both points of time [Table 2]. The patient diagnosis had no significant impact on the level of serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins measured after the second ($P = 0.489$) and the booster dose ($P = 0.441$) in our study group. There were no cases of hospitalization due to COVID-19 or worsening of the underlying disease. No serious post-vaccinal reactions were observed after any type of vaccines.

VACCINATION AND TREATMENT

All patients were in a stable form of the disease. Most of them were treated with combined therapy of which 48.7% had low doses of prednisolone (5–20 mg), 74.4% hydroxychloroquine (200 mg), and 17.9% low dose of methotrexate (7.5–10 mg). Only 3 (7.5%) were without immunosuppressive treatment.

Table 1: Clinical and demographic characteristics, and the vaccination pattern of the cohort

Type of ARD	Number	Age in years	Co-morbidity	Vaccine type		
				mRNA	Vector	Whole
PAPS	7 (17.5%)	43.4 ± 12.7	3 (42.8%)	3 (42.9%)	3 (42.9%)	1 (14.2%)
SLE	9 (22.5%)	49.3 ± 9.9	2 (22.2%)	4 (44.4%)	3 (33.3%)	2 (22.3%)
SLE with APS	7 (17.5%)	47.9 ± 11.8	1 (14.3%)	2 (28.6%)	2 (28.6%)	3 (42.8%)
RA	6 (15%)	67.3 ± 4.5	4 (66.7%)	2 (33.3%)	3 (50%)	1 (16.7%)
Morbus Sjögren's syndrome	4 (10%)	49.2 ± 18.1	0/0	2 (50%)	0/0	2 (50%)
Polymyalgia rheumatica	2 (5%)	64.5 ± 4.9	1 (50%)	1 (50%)	0/0	1 (50%)
Morbus Reiter	2 (5%)	19.0 ± 2.3	0/0	1 (50%)	0/0	1 (50
Morbus Still	2 (5%)	34.5 ± 3.5	0/0	0/0	2 (100%)	0/0
Wegener	1 (2.5%)	61	0/0	0/0	0/0	1 (100%)

APS = antiphospholipid syndrome, ARD = autoimmune rheumatic diseases, PAPS = primary antiphospholipid syndrome, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus

Table 2: Seroconversion related to diagnosis

Type of ARD	Seroconversion after the second dose	Seroconversion after the booster
PAPS	6 (85.7%)	6 (85.7%)
SLE	7 (77.8%)	9 (100%)
SLE + APS	3 (42.9%)	7 (100.0%)
RA	6 (100.0%)	6 (100.0%)
Morbus Sjögren's syndrome	2 (50.0%)	4 (100.0%)
Polymyalgia rheumatica	1 (50.0%)	2 (100.0%)
Morbus Reiter	1 (50.0%)	2 (100.0%)
Morbus Still	2 (100.0%)	2 (100.0%)
Wegener	1 (100.0%)	1 (100.0%)
Total	29 (72.5%)	39 (97.5%)
P-value	**0.320**	**0.775**

APS = antiphospholipid syndrome, ARD = autoimmune rheumatic diseases, PAPS = primary antiphospholipid syndrome, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus

Figure 1. Seroconversion after the second dose of different types of SARS-CoV-2 vaccines in ARDs patients

ARD = autoimmune rheumatic diseases, IgG = immunoglobulin G, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

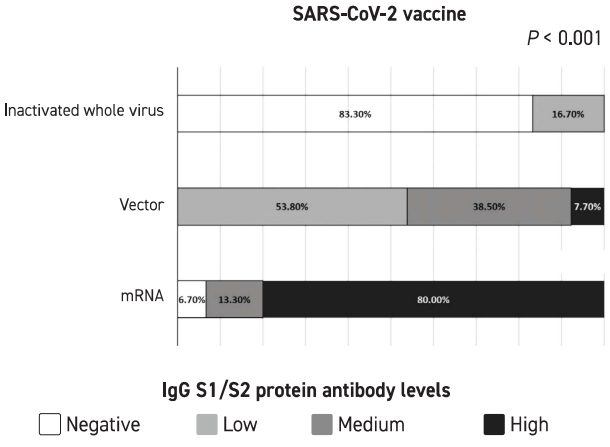
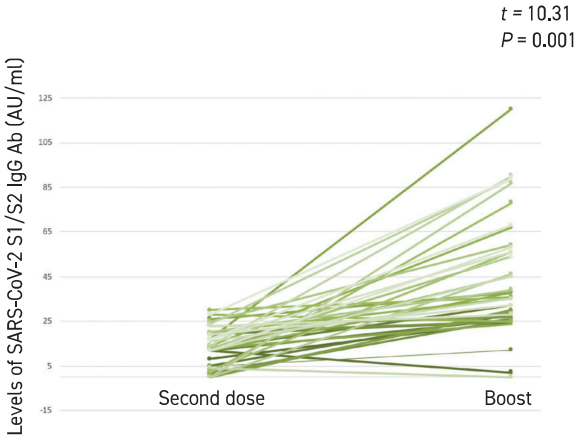


Figure 2. Seroconversion after the boost dose with mRNA SARS Co-V2 vaccine in ARDs patients

ARD = autoimmune rheumatic diseases, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2



There was no statistically significant difference considering treatment and chosen vaccine ($P = 0.908$), seroconversion after the second dose ($P = 0.381$), seroconversion after the booster dose ($P = 0.740$), level of antibodies after the second dose ($P = 0.330$), level of antibodies after the booster dose ($P = 0.446$).

DISCUSSION

In this rather small group of ARD patients, we demonstrated that vaccination is highly safe and effective against COVID-19 infection. There were no cases of hospitalization due to COVID-19 or worsening of the underlying disease. Post-vaccinal reactions were seen in 72.5% of patients but they were in the category of mild (pain at the injection site, fatigue, and headache). Eight patients developed COVID-19 before the booster dose, 75% were previously vaccinated with the whole virus vaccine, all of them with mild form without long-COVID conditions observed. Seroconversion after the second dose was achieved in 72.5% of patients and after the booster dose in 97.5% of patients. There was a statistically significant difference in seroconversion among the type of the vaccine. Almost all patients achieved seroconversion after the second dose of the mRNA vaccine, but only two had been vaccinated using the whole virus vaccine. After the boost with the mRNA vaccine, all patients achieved a high level of serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins.

The SARS-CoV-2 virus became a reality 3 years ago and has not yet passed. At the peak of the pandemic, the number of estimated cases exceeded 2 million per day. Considering that at least 1% of the population has an autoimmune rheumatic disease and an autoinflammatory disease could indicate the magnitude of the problem ahead [7]. It was shown that the burden of the disease could be abbreviated by the global program of effective and safe vaccination [8]. The VAXICOV study demonstrated that despite the reported median score of 8 (scale of 0–10) for being afraid to get infected by SARS-CoV-2 or to develop a severe clinical presentation with a median score of 9 (0–10), only 54.2% of ARD patients were willing to get vaccinated against COVID-19 [9]. The willingness increased to 62.8% when vaccination was recommended by the physician (rheumatologist or internist). The main reasons for not vaccinating are the lack of information about vaccines, fear of the vaccination, undecided, fear of a flare, side effects, and local reactions [10].

There are existing guidelines about vaccination for rheumatic patients [11]. A systematic review and meta-analysis of 47 studies demonstrated that COVID-19 vaccination was effective in protecting ARD patients from severe illness caused by the virus despite the impaired humoral and cellular immunogenicity of vaccines [6]. The data have not suggested ARDs as an independent risk factor for severe COVID-19 [12,13]. The susceptibility of ARD patients to COVID-19 infection is influenced by host factors: age, co-morbidities, and certain medications used in treatment. The vaccination against COVID-19 is strongly recommended for patients with rheumatic diseases [1-4]. There are slight differences in recommendations for delaying or stopping regular treatment. The consensus agreement is that there is no need to adjust or delay most of the medications used in the treatment of ARD patients (except for anti-CD 20 antibodies and mycophenolate mofetil close to planned COVID-19 immunization).

The coronavirus enters the human cells through binding of its S protein to the angiotensin-converting 2 receptor, which is located mainly on the surface of the alveolar type II cells and epithelial cells of the oral cavity. The host's immune response begins to generate nearly simultaneously IgM and IgG antibodies to the S1 and S2 domains of the S protein with a median time of 2 weeks. The amount and chronological appearance of antibodies are very individual and host dependent.

The patients were offered with one of the following vaccines available in the Serbian healthcare system: mRNA vaccine, Pfizer BioNTech; non-replicating viral vector vaccines, Oxford-AstraZeneca and Sputnik V; or inactivated whole virus, Sinopharm Beijing Institute of Biological Products. The mechanism of activity of each of these vaccines is different, and some are completely new, like mRNA vaccines. The patients were encouraged to get vaccinated; however, initially there were no additional recommendations on the type of vaccine to choose, which was one of the reasons for delaying vaccination.

Data about seroconversion in rheumatic patients have been summarized. The relative risks between rheumatic patients and healthy control in terms of seroconversion after the first and second dose are 0.42 (95% confidence interval 0.34–0.52) and 0.86 (95% confidence interval 0.84–0.87), respectively [6]. Humoral response after the first dose of mRNA-based vaccines is achieved at 53%, and the proportion increased after the second dose to 79%. Only a few

studies have demonstrated the effectiveness of other vaccines. Seroconversion after vector vaccine is achieved in 49% after the first dose, and those after the first and second dose of whole vaccines are 19% and 70%, respectively [14,15]. The data about seroconversion after the booster dose are scarce. We found just one study that demonstrated that the third dose of the mRNA vaccine led to a seroconversion of 88% (15/17) in rheumatic arthritis patients who had an absent or low response to the first and second doses [16].

Despite coincidental reports of different COVID-19 post-vaccine side effects onset of autoimmune diseases such as ocular myasthenia gravis [17], inflammatory myopathy [18], inflammatory arthritis [19], and immune thrombocytopenia [20], none were noticed in this group of patients during follow-up.

Our results agree with previous results regarding the response to the third dose in ARD patients. The limitations of our study are a small group of patients and lack of the control group of healthy individuals, but the advantage is a single center experience since all patients were strictly followed and blood samples were conducted as planned. Based on our data, the highest level of serum IgG antibody against SARS-CoV-2 spike S1/S2 proteins was achieved with the mRNA vaccine, irrespective of the therapy applied and the type of the disease.

CONCLUSIONS

The best results of seroconversion were seen after the third booster dose of the mRNA vaccine. Therefore, we strongly recommend a booster dose with available mRNA vaccine in all ARDs patients for the highest protection against SARS-CoV-2 with no serious post-vaccinal reactions observed.

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A few cobras in your home will soon clear it of rats and mice. Of course, you will still have the cobras.
William Jacob Cuppy (1884–1949), humorist and literary critic known for his satirical books about nature and historical figures