

COVID-19 vaccination in patients with rheumatic diseases leads to a high seroconversion rate and reduced self-imposed isolation and shielding behaviour

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ABSTRACT

Objectives: We investigated the effect of a two-dose messenger ribonucleic acid (mRNA) vaccine on antibody levels against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and patient behaviour and shielding concerning fear of coronavirus disease 2019 (COVID-19) in patients with systemic lupus erythematosus or rheumatoid arthritis.

Methods: Three hundred and three patients and 44 blood donors were included. All patients received two doses of an mRNA vaccine and had total antibodies against SARS-CoV-2 measured before vaccination and 2 and 9 weeks after the second vaccination. Further, patients answered an electronic questionnaire before and after vaccination concerning behaviour, anxiety, and symptoms of depression (Patient Health Questionnaire-9).

Results: Significantly fewer patients (90%) had measurable antibodies against SARS-CoV-2 compared to blood donors (100%) after the second vaccination ($P < .001$). Treatment with rituximab was the strongest predictor of an unfavourable vaccine response, as only 27% had measurable antibodies. Nearly all patients (97%) not treated with rituximab experienced seroconversion. Prednisone and methotrexate had a negative effect on seroconversion, but no effect of age or comorbidity was observed. Patients experienced significant improvement after vaccination in 10 out of 12 questions regarding behaviour and fear of COVID-19, while no change in Patient Health Questionnaire-9 or anxiety was observed.

Conclusion: We find a very high seroconversion rate among rheumatic patients and reduced self-imposed isolation and shielding after COVID-19 vaccination.

KEYWORDS: COVID-19; Rheumatoid arthritis; systemic lupus erythematosus; patient-reported outcome measures; SARS-CoV-2 antibodies

Introduction

The promise of a vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December of 2020 brought hope to the world. The phase 3 vaccine trials of the SARS-CoV-2 mRNA vaccines were encouraging but excluded most patients with rheumatic diseases (RDs) and patients treated with immunosuppressive therapy [1, 2]. However, the fear of severe coronavirus disease 2019 (COVID-19) in RD patients soon out-weighted the concern of not knowing the vaccine effect or reactivity in these patients.

Reports of a more severe COVID-19 course in patients with RDs prompted strategies for expediting vaccination of RD patients in most countries [3–6]. We now know that

severe COVID-19 in patients with RDs is related to specific treatments and the general risk factors like age, obesity, hypertension, and diabetes [7]. Recent data suggest that vaccinated patients with RDs who experience breakthrough COVID-19 perform better compared with unvaccinated RD patients with similar characteristics of disease and treatment [8].

A widely accessible way of assessing vaccine response is by measuring antibodies against the vaccine [9]. In mRNA vaccines, the humoral response correlated well with the cellular response [10]. And in healthcare workers, 98% developed a significant antibody response against SARS-CoV-2 spike protein after two doses of the BNT162b2 mRNA

vaccination [11]. Thus far, studies show that particularly B-cell depletin therapy is associated with impaired vaccine responses [12–14]. Time since the last rituximab treatment seems imperative for a humoral response, and B-cell reconstitution is a promising predictor of response [14, 15].

In addition to the impact experienced by most people of the pandemic, patients with RDs were adversely impacted by the potential risk of severe COVID-19 due to their disease and immunosuppressive treatment. In Denmark, no special precautions were recommended for patients with RDs, as was the case in, e.g. UK. Here, patients identified as being ‘clinically extremely vulnerable’ were advised to shield [16]. With or without governmental recommendations, fear of COVID-19 led to disproportionate anxiety, self-isolation, and shielding behaviour for many RD patients at the beginning of the pandemic [17, 18]. There is still no evidence of whether vaccination has lifted patients’ fear or changed their behaviour.

We investigated antibody levels in serum against SARS-CoV-2 after a two-dose vaccination with an mRNA vaccine in 303 patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) from the COPANARD (Corona PANdemic Autoimmune Rheumatic Disease) cohort [18]. Further, we examined how vaccination influenced patient behaviour with regard to fear of COVID-19 and shielding.

Patients and methods

Patients

Patients were recruited from the COPANARD cohort [13, 18–20]. Outpatients with SLE or RA were identified through hospital records at the Department of Rheumatology, Aarhus University Hospital (AUH), Denmark. SLE patients fulfilled the 1997 updated American College of Rheumatology (ACR) criteria for SLE. RA patients fulfilled either the 1987 ACR or 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) Classification Criteria and received treatment with either a biologic or small molecule disease-modifying anti-rheumatic drug.

Disease characteristics, treatment, and Charlson Comorbidity Index were obtained from the electronic health record.

All patients from the COPANARD cohort ($n = 405$) who wanted to receive a two-dose mRNA vaccine offered by the Danish Health Authorities were asked to participate in the study.

Patients were included between weeks 4 and 6 of 2021 and received their vaccination between February and August 2021. All included patients followed the national vaccination schedule managed by the Danish National Health Authorities. Patients received two doses of an mRNA vaccine, either BNT162b2 (Pfizer/BionTec) or mRNA-1273 (Moderna), by intramuscular injection in the deltoid muscle 3 weeks apart.

Blood donors

Forty-four randomly selected blood donors, but matched on sex, from the Danish Blood Donor Study, all vaccinated with an mRNA vaccine, had antibodies measured post-vaccination. These measurements were included to have an indication of a normal antibody response in immunocompetent persons after vaccination using the assay described here.

Patient involvement

Two patient research partners and two advisers from The Danish Rheumatism Association collaborated in study planning to ensure the patient perspective. Results will be communicated through the member network sources.

Questionnaires

After informed consent, patients completed an electronic questionnaire concerning their mental and physical health, exercise, and behaviour (the questionnaire was answered between weeks 4 and 6 of 2021). Symptoms of depression were assessed using the Patient Health Questionnaire-9 (PHQ-9) [21], and signs of anxiety were evaluated using a national anxiety symptom questionnaire. The same questionnaire was sent to patients 8 weeks after their last vaccination.

Two patient research partners and two patient advisers from The Danish Rheumatism Association participated in creating the questions. All questions were answered on a visual analogue scale from 0 to 10.

SARS-CoV-2 total antibody assay

Patients had antibodies against SARS-CoV-2 measured before vaccination at inclusion and 2 and 9 weeks after the second vaccination using the routine assay for total antibodies at AUH. We have previously reported week 2 antibody levels for 134 patients from the COPANARD cohort [13]. Serum total antibodies against recombinant SARS-CoV-2 spike S1 protein were measured in a commercial assay (VITROS Immunodiagnostic Products, Rochester, NY, USA). According to the manufacturer’s instructions, all analyses were performed by experienced staff at the Department of Clinical Microbiology, AUH.

Assay performance characteristics were determined in a Danish validation study [22] and had a sensitivity of 95.3% and a specificity of 100%. No cross-reactivity was observed.

The patients were not informed about the results of the anti-SARS-CoV-2 antibody titers.

Local and systemic reactogenicity

Seven days after the second vaccination, the patients reported local and systemic reactogenicity through an electronic questionnaire. Reactogenicity data regarding the current cohort have previously been published [20].

Statistics

All values reported are medians with interquartile range unless otherwise stated. The statistical significance of differences was assessed using the Mann–Whitney nonparametric test for continuous variables and Pearson’s chi-square test for categorical variables. Wilcoxon signed-rank test was used to test differences in patient behaviour before and after vaccination.

Regression analyses were performed to investigate which factors impacted the presence of SARS-CoV-2 antibodies 9 weeks after vaccination. Analysis was divided into two groups: the first with ‘classic covariates’ of vaccine response (age, sex, diagnosis, comorbidity, and treatment) and the second with local and systemic ‘reactogenicity covariates’. Last observation carried forward was used; e.g. if antibody measurement 9 weeks after vaccination was missing, the antibody measurement 1 week after vaccination was used.

A similar analysis strategy was used for both the classic and reactivity covariates. Univariate logistic regression analyses were performed with SARS-CoV-2 antibodies as the dependent variable after vaccination. Afterward, multiple logistic regression analyses for both the classic and reactivity covariates were performed with backward selection, using the criterion of $P \geq .05$ for removal from the model. The multiple logistic regression models included all significant ($P < .05$) variables in the univariate analysis.

Ethics

This project was approved by The Danish Data Protection Agency (1-16-02-19-21). The Central Denmark Region Committee on Health Research Ethics was consulted concerning the present study (Ref. nr. 1-10-72-1-21).

The Danish Blood Donor Study was approved by The Danish Research Ethics Committees (1-10-72-95-13, SJ-740) and the Danish Data Protection Agency (P-2019-99).

Table 1. Demographics, disease characteristics, and treatment details for the 303 patients included in the study.

	SLE		RA	
Patients included, <i>n</i>	142		161	
Female sex, <i>n</i> (%)	127	89%	113	70%
Age, years (IQR)	54	41–62	64	56–71
BMI, kg/m ² (IQR)	24.7	21.6–28.5	26.3	23.0–29.4
Disease duration, years (IQR)	13	7–26	14	8–22
Charlson score (IQR)	2	1–3	3	2–4
Active/previous/never smoker (%)	9/37/54		12/54/34	
SARS-CoV-2 antibody positive pre-vaccination, <i>n</i> (%)	4/131	3.1	1/154	0.7
Caucasian, <i>n</i> (%)	138	97.2	158	98.1
RA				
Anti-CCP positivity, <i>n</i> (%)			122/158	77.2
IgM-RF positivity, <i>n</i> (%)			112	69.6
Erosive disease on X-ray, <i>n</i> (%)			129	80.1
DMARD				
Methotrexate po/sc, <i>n</i> (%)			84	52.2
Salazopurine, <i>n</i> (%)			8	5.0
Hydroxychloroquine, <i>n</i> (%)			2	1.2
Prednisone, <i>n</i> (%)			11	6.8
Prednisone dose mg, median (IQR)			5	3.75–6.25
Leflunomide, <i>n</i> (%)			14	8.7
Azathioprine, <i>n</i> (%)			3	1.9
Biologics and small molecules				
Number of biologics tried, <i>n</i> (IQR)			2	1–3
TNF inhibitors, <i>n</i> (%)			83	51.6
Rituximab, <i>n</i> (%)			23	14.3
JAK inhibitor, <i>n</i> (%)			19	11.8
Anti-IL-6, <i>n</i> (%)			22	13.7
Abatacept, <i>n</i>			10	6.2
SLE				
ACR classification criteria				
Malar rash, <i>n</i> (%)	89	62.7		
Discoid rash, <i>n</i> (%)	10	7.0		
Photosensitivity, <i>n</i> (%)	71	50.0		
Oral ulcers, <i>n</i> (%)	39	27.5		
Nonerosive arthritis, <i>n</i> (%)	120	84.5		
Pleuritis or pericarditis, <i>n</i> (%)	41	28.9		
Renal disorder, <i>n</i> (%)	39	27.5		
Neurologic disorder, <i>n</i> (%)	11	7.8		
Haematologic disorder, <i>n</i> (%)	109	76.8		
Immunologic disorder, <i>n</i> (%)	133	93.7		
Positive antinuclear antibody, <i>n</i> (%)	140	98.6		
SLICC score, median (IQR)	1	0–2		
Treatment				
Hydroxychloroquin, <i>n</i> (%)	99	69.7		
Prednisone, <i>n</i> (%)	54	38.0		
Prednisone dose in milligrams, median (IQR)	5	3.75–5		
Azathioprin, <i>n</i> (%)	28	19.7		
Mycophenolatemofetil, <i>n</i> (%)	24	16.9		
Methotrexat, <i>n</i> (%)	12	8.5		
Rituximab, <i>n</i> (%)	6	4.2		
Belimumab, <i>n</i> (%)	5	3.5		
Other (privigen, tacrolimus, and taltz), <i>n</i> (%)	6	4.2		
No treatment, <i>n</i> (%)	18	12.7		

Abbreviations: anti-CCP, anti-citrullinated protein antibody; anti-IL-6, interleukin 6 inhibitor; BMI, body mass index; DMARD, disease-modifying anti-rheumatic drug; IgM-RF, Immunoglobulin M rheumatoid factor; IQR, interquartile range; JAK, Janus kinase; SLICC/ACR, Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

Results

Patients

Out of the 405 patients originally included in the COPANARD cohort [18], 65 were not included. The reasons for non-inclusion were as follows: (1) did not want to receive the vaccine ($n = 3$), (2) had received other types of vaccines than mRNA ($n = 18$), and (3) had already been vaccinated or did not wish to participate at the time of inclusion ($n = 44$). Three hundred and forty eligible patients gave their written informed consent to inclusion. Thirty-seven, however, did not have their blood samples drawn as planned and had to be excluded. Finally, 303 patients (75% of the COPANARD cohort) were included for data analysis.

Patients were predominantly female (F/M = 240/63) with a mean age of 57 years (SD = 13.8). One hundred and sixty-one patients with RA (53%) and 142 with SLE (47%) were included. Five patients tested positive for SARS-CoV-2 prior to vaccination. Ninety-eight percent of included patients were Caucasian. Patients with RA were anti-CCP positive (77%), and the majority (52%) received methotrexate combination therapy most often with a tumour necrosis factor (TNF) inhibitor. SLE patients were antinuclear antibody (ANA) positive (99%) and treated with hydroxychloroquine (70%) either in monotherapy or with other immunosuppressants. RA patients had a significantly higher Charlson Comorbidity Index of 3 compared to 2 for the SLE patients ($P > .001$). Patient characteristics are found in Table 1.

Blood donors, included as a reference, were predominantly female (F/M = 36/8) with a mean age of 42 (SD = 12.6). Data on these blood donors have previously been published (REF).

Vaccination effect on patient behaviour

Concerns of falling sick with COVID-19 decreased significantly for RD patients post-vaccination ($P < .001$) (Table 2). Fear of leaving home, self-perceived need to isolate, and worry about socializing dropped dramatically after vaccination (P values all $< .001$). Media information about COVID-19 did not have the same negative effect post-vaccination as pre-vaccination ($P < .001$), and patients' thoughts were less dominated by the pandemic post-vaccination ($P > .001$).

The vaccination changed both patient experience of pain and limitation in physical activity (P values $< .001$ and $.02$, respectively), whereas patient perception of disease activity was not influenced ($P = .73$).

Vaccination effect on symptoms of depression and anxiety

There was no difference in RD patients with symptoms of moderate depression evaluated by a PHQ-9 score ≥ 10 before (21.8%) and after (23.6%) vaccination ($P = .62$). Similarly, we observed no difference in anxiety symptoms that affected the daily function of RD patients before (7.7%) and after (6.1%) vaccination ($P = .46$).

Serological response to mRNA vaccine

In patients, antibodies against SARS-CoV-2 were detectable in 84% of patients 2 weeks after the second vaccine and in 90% 9 weeks after the second vaccine [Figure 1(a)]. All included blood donors showed seroconversion 5 weeks after the second mRNA vaccine. Patients generally showed lower serum levels of SARS-CoV-2 antibodies compared to blood donors (Figure 1(b)). Nine weeks after the last vaccination, the median concentration in patients was 211 AU/ml compared to 935 AU/ml in blood donors ($P < .0001$).

Serological response and treatment

In the initial univariate regression analysis examining factors with potential impact on the presence of SARS-CoV-2 antibodies 9 weeks after vaccination, we found seven significant covariates (diagnosis, rituximab, TNF inhibitor, prednisone, methotrexate, leflunomide, and hydroxychloroquine) (Table 3). All were included in the initial multiple regression model with stepwise backward selection. The factors significantly impacting seroconversion in the final model were rituximab ($P < .001$), prednisone in a dose-dependent manner ($P < .001$), and methotrexate ($P = .01$) (Table 3). In the univariate analysis, neither age, comorbidity, nor pausing medication influenced the ability to seroconvert after vaccination (P values = $.37$, $.09$, and $.74$, respectively).

Table 2. Changes in behaviour, shielding, and fear of COVID-19 on a numerical rating scale.

	Before vaccination, $n = 298$		After vaccination, $n = 246$		P value
How worried are you getting sick with Corona?	6.5	(3–8)	3	(1–6)	$< .001$
How scared are you to leave your home because of Corona?	3	(0–5)	1	(0–3)	$< .001$
How important do you think it is at the moment to stay isolated?	7	(4–8)	1	(0–3)	$< .001$
How worried are you about hanging out with people outside your 'social bubble'/closest circle of friends?	7	(5–9)	2	(1–4)	$< .001$
How much does the Corona pandemic limit your physical activity?	5	(2–7)	1.5	(0–4)	$< .001$
How much pain do you experience daily?	4	(2–6)	3	(1–5)	$.02$
How active is your disease at the moment?	3	(1–5)	2	(1–5)	$.73$
How much does the media's corona information negatively affect you?	5	(2–7)	2	(0–4)	$< .001$
How worried are you about being infected by your close relatives (children/spouse/cohabitant)?	3	(1–6)	1	(0–2)	$< .001$
To what extent do your worries cause restrictions for your close relatives?	3	(1–6)	0	(0–3)	$< .001$
As a person living with a chronic illness, to what extent do you perceive yourself as part of the community of society?	7	(5–9)	4	(2–7)	$.06$
How much are your daily thoughts filled with the Corona pandemic?	4	(2–7)	2	(1–3)	$< .001$

Patients were asked the questions twice, before vaccination and 8 weeks after vaccination. Questions were answered on an 11-point numeric rating scale, from 0 to 10. Values are median with IQR in parentheses. Wilcoxon signed-rank test was used to calculate the difference.

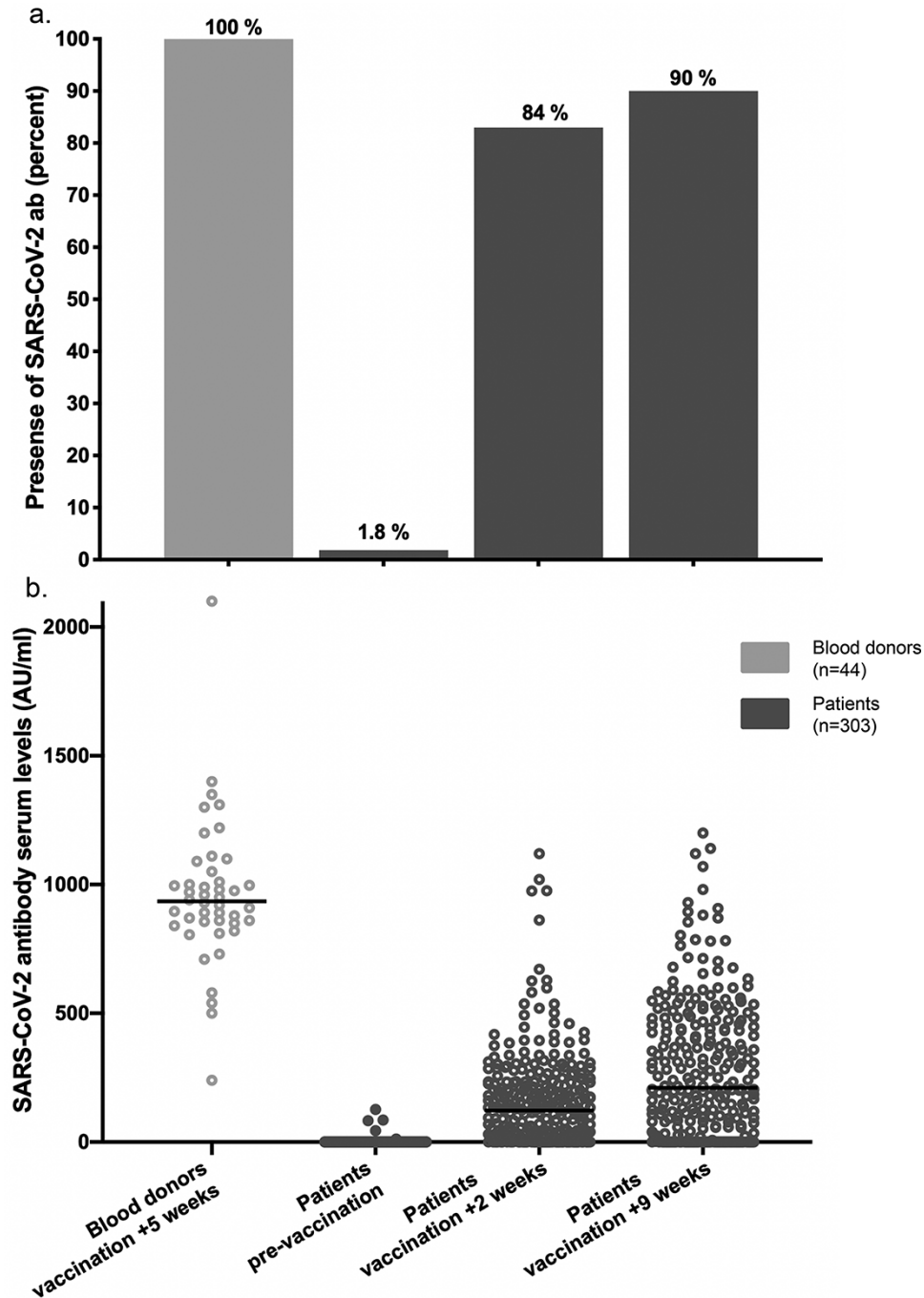


Figure 1. Total antibody response against SARS-CoV-2 before and after two mRNA vaccines. Antibody response against mRNA COVID-19 vaccine pre-vaccination, 2 and 9 weeks after in patients with rheumatic diseases, and 5–6 weeks after vaccination in blood donors. (a) Percentage of patients with positive SARS-CoV-2 antibody results after vaccination. (b) Levels of SARS-CoV-2 antibodies in serum.

We stratified RD patients into participants receiving or not receiving rituximab. In the subgroup of patients not receiving rituximab, 97% of patients were seropositive 9 weeks after the second vaccination, whereas the same was true for only 27% of patients treated with rituximab [Figure 2(a)] ($P < .001$). SARS-CoV-2 antibody levels were universally lower in rituximab-treated patients than non-rituximab-treated patients (Figure 2(b)). There was a significant difference when comparing serum levels 9 weeks after the last vaccination between the two groups ($P < .001$).

Prednisone was examined in the same manner as rituximab. In the subgroup of patients not receiving prednisone, 92% of patients were seropositive 9 weeks after the second vaccination, whereas the same was true for 80% of patients treated with prednisone (Figure 2(c)) ($P = .01$). There was no statistically significant difference in SARS-CoV-2 antibody levels 9 weeks after the second vaccination in patients receiving and not receiving prednisone ($P = .18$) (Figure 2(d)).

Combination therapy with methotrexate predominantly seems to influence seroconversion and serum SARS-CoV-2

Table 3. Univariate logistic regression and multivariate logistic regression analysis with stepwise backward selection.

	OR	95% CI	P value
Univariate logistic regression analysis			
Sex, female = ref.	0.61	0.26–1.39	.24
Age, years	0.99	0.96–1.02	.37
Diagnosis, SLE = ref.	0.36	0.15–0.83	.02
Charlson Comorbidity Index score	0.81	0.64–1.03	.09
Pause with medicine before vaccination	0.84	0.30–2.38	.74
Biologic treatment			
Rituximab	0.01	0.005–0.04	<.001
TNF inhibitor	6.15	1.42–26.38	.02
JAK inhibitor	0.97	0.21–4.40	.97
Abatacept	1.03	0.13–8.38	.98
DMARD treatment			
Prednisone, dose in milligrams	0.88	0.78–0.99	.03
Methotrexate	0.45	0.21–0.96	.04
Leflunomide	0.26	0.08–0.88	.03
Hydroxychloroquine	2.84	1.06–7.62	.04
Mycophenolate	1.28	0.29–5.71	.75
Azathiorine	0.74	0.24–2.29	.61
Initial model—multiple logistic regression analysis—stepwise backward			
Diagnosis, SLE = ref.	0.23	0.03–1.73	.16
Rituximab	0.01	0.003–0.05	<.001
TNF inhibitor	3.73	0.62–22.57	.15
Prednisone, dose in milligrams	0.69	0.57–0.85	<.001
Methotrexate	0.22	0.06–0.85	.03
Leflunomide	1.27	0.16–9.88	.82
Hydroxychloroquine	0.82	0.12–5.50	.84
Final model—multiple logistic regression analysis—stepwise backward			
Rituximab	0.007	0.002–0.03	<.001
Prednisone, dose in milligrams	0.73	0.61–0.87	<.001
Methotrexate	0.20	0.06–0.68	.01

Treatment with IL-6 inhibitor ($n = 22$) and belimumab ($n = 6$) was omitted from analysis as all patients treated had an antibody response. All significant variables from the univariate analysis were included in the multiple logistic regression model, which was performed with stepwise backward selection. The first and final models of the multiple regression analyses are presented. Abbreviations: JAK, Janus kinase; DMARD, disease-modifying anti-rheumatic drug; OR, odds ratio.

antibody levels in RD patients treated with either rituximab or abatacept (Supplementary Figure S1).

Discussion

In a Danish cohort of 303 patients with RD recruited from the University Hospital of Aarhus, we found that 90% of patients had detectable antibodies against SARS-CoV-2 after two doses of an mRNA vaccine. Patients not treated with Rituximab (RTX) had a 97% seroconversion rate compared to 27% in RTX-treated patients, with a negative impact of prednisone and methotrexate treatment. Positive changes in patient behaviour with regard to reduced isolation, fear of COVID-19, pain, and increased physical ability after vaccination were significant in 10 out of 12 questions. In contrast, we found no change in the number of patients with symptoms of moderate depression or anxiety symptoms.

Vaccination has changed patient behaviour. From our results, it is clear that receiving the vaccine has led to less isolation, fear, and shielding behaviour for patients with RD. The consequences of isolation and shielding faced by many RD patients at the beginning of the pandemic were for the majority of patients disproportionate [17, 18, 23]. Nevertheless, there is a persistent concern of the vaccine providing a false sense of protection for the minority of patients who are unable to generate a humoral response to vaccination, particularly patients treated with rituximab [12, 14]. The communication of this somewhat ambiguous information to

our patients represents a challenge going forward in the pandemic.

We found no change in the number of patients with symptoms of depression (21.8–23.6%) and anxiety (7.7–6.1%) after vaccination despite reduced isolation, fear of COVID-19, pain, and increased physical ability. Previously published data from this cohort collected at the start of the pandemic in May 2020 reported similar values for depression (19.0%) and anxiety (5.2%), while blood donors scored significantly lower for depression (6.8%, $P < .001$) but not anxiety (4.9%, $P = .83$) [18]. It is well established that patients with RDs have an increased prevalence of depression (15–38%) and anxiety (14–62%) depending on the method of case definition [24–27]. There are several plausible explanations for the observed lack of change regarding depression and anxiety. Particularly depression rates are high in SLE and RA, and smaller changes would likely not be reflected in the questionnaires, as the PHQ-9 questionnaire is effective at detecting a moderate-to-large change in symptoms [28]. Further, 8 weeks post-vaccination observation period could be a too short time period to detect relevant changes. In contrast, symptoms of depression and anxiety captured by validated questionnaires may tap into more chronic and general mood states, which could be less affected by pandemic-related changes in isolation, fear, and shielding behaviour, at least on the group level [29].

Our findings confirm that the majority of patients with RD mount a humoral response after vaccination with an

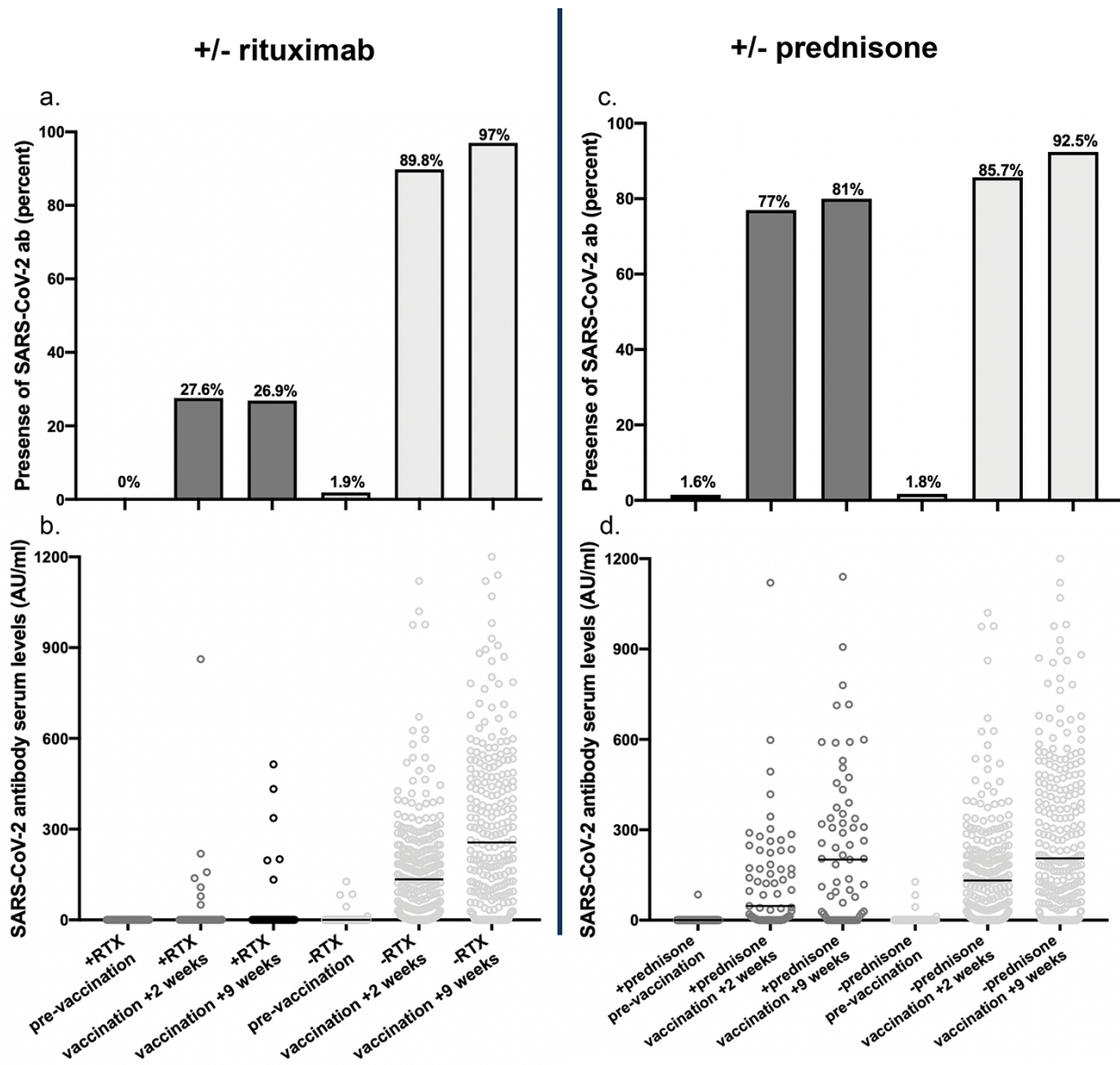


Figure 2. Vaccine response in patients divided by rituximab and prednisone treatment. Antibody response against mRNA COVID-19 vaccine pre-vaccination and 2 and 9 weeks after in patients with rheumatic diseases divided by treatment with rituximab (a) + (b) and prednisone (c) + (d). Percentage of patients with positive SARS-CoV-2 antibody results after vaccination (a) + (c). Levels of SARS-CoV-2 antibodies in serum (b) + (d).

SARS-CoV-2 mRNA vaccine [12, 13, 30, 31]. The leading cause of a lower or missing serological response to the vaccine is immunosuppressive treatments like rituximab, methotrexate, and glucocorticoids. It is reassuring that 97% of patients with RD not treated with rituximab had measurable antibodies.

Several studies have confirmed an adverse effect of rituximab and glucocorticoids on the serological response after SARS-CoV-2 vaccination [12, 13, 31–33], whereas the effect of methotrexate has been more ambiguous [12, 34]. Rituximab was the treatment associated with the lowest response to the vaccine in the present study, with only 27% having detectable antibodies 9 weeks after the second vaccine. This phenomenon is known from studies on both influenza and pneumococcal vaccines [35]. Although it is a recommendation by EULAR that vaccines in patients receiving rituximab be

administered 1 month before or 6 months after treatment [36], this has not been possible for all RD patients during the pandemic. In the current study, RD patients on combination therapy with rituximab and methotrexate seemed to have the lowest serological response after vaccination. This raises the idea that combination therapy impedes vaccine response more than monotherapy, at least for some treatments.

A previous study demonstrated that pausing methotrexate 2 weeks prior to influenza vaccination resulted in higher antibody levels in RD patients [37]. EULAR recommendations have been to continue methotrexate while getting vaccinated with the COVID vaccine [36], as the risk of disease flare is higher than a potential lower vaccine response in a few individuals. From our data, we could not see an effect on seroconversion when comparing patients who did and did not pause their medication. However, pausing was

not done systematically. It was done at the patient's discretion. Thus, we cannot make specific conclusions based on the data.

We found a significantly reduced serological response after SARS-CoV-2 vaccination in RD patients compared with immunocompetent blood donors, also reported by others [12, 13, 31, 34]. The titer of SARS-CoV-2 antibodies that convey protection against infection has still not been defined, and the consequences of the lower antibody level in RD patients, therefore, remain unclear. It has, however, become evident that patients lacking a serological response can still have T-cell-mediated protection [32, 38]. In healthy individuals, a robust SARS-CoV-2 T-cell response was associated with lower COVID-19 severity [39], and in animal models, SARS-CoV-2-specific T-cell response conveyed protection when serological responses were inadequate [40].

Thus, although patients with RDs have lower SARS-CoV-2 antibodies, we cannot per se conclude that they lack protection against severe COVID-19 entirely. However, undetectable antibodies after vaccination pose a concern since antibodies are essential in the early phases of SARS-CoV-2 infection [40].

Antibody presence increased in RD patients from weeks 1 to 9 after the second vaccination, demonstrating that RD patients need more time to seroconvert than in a recent study of healthy controls, where all seroconverted within 14 days of the first mRNA vaccination [41]. We need kinetic studies of antibody presence and levels in RD patients to avoid bias when comparing different studies of humoral responses to COVID-19, as the optimal timepoint for antibody measurement after vaccination in RD patients has not been established [33]. These data would further guide the decision of the number and timing of booster vaccinations.

The current study is a large study in a well-defined cohort of patients with RDs on the impact of vaccination on serological response and behaviour. The study has limitations. The study did not include data about disease activity at the time of vaccination, which could have potentially influenced our results. Patients in this cohort were predominantly Caucasian, and thus, extrapolations of the results to other ethnic groups are questionable. Data concerning the incidence of COVID-19 post-vaccination were unfortunately not available. We measured antibodies against SARS-CoV-2 in this study, but we lack knowledge on the minimal protective antibody level against SARS-CoV-2. Further, neither data on B-cell repopulation at the time of vaccination nor characterization of memory B- and T-cells was available in this cohort. Finally, immunosuppressed patients might create lower affinity or less effective antibodies, which could have been demonstrated by measuring neutralizing antibodies compared with healthy controls.

Conclusions

Most patients with RA or SLE develop a serological response against SARS-CoV-2 after two doses of mRNA vaccines. Vaccination impacted the behaviour and fear of COVID-19 by reducing self-imposed isolation, shielding, and increasing physical activity but not the symptoms of depression and anxiety. Our findings warrant encouragement of vaccination against COVID-19 for patients with RD, as patients benefit from both a serological immune response and reduced self-imposed isolation and shielding.

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Supplementary data

Supplementary data are available at *Modern Rheumatology* online.

Conflict of interest

None declared.

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