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Research Letter

Impaired Humoral Immunogenicity of SARS-CoV-2 Vaccination in Patients With Rheumatoid Arthritis

To the Editor:

Humoral immunogenicity of SARS-CoV-2 vaccination in rheumatoid arthritis (RA) seems impaired depending on the underlying immunosuppressive agents, especially with rituximab (RTX), glucocorticoids, and abatacept (ABA), but data are still scarce.[1–9] Identifying an impairment could lead to treatment adaptation or a vaccine booster dose to improve vaccine response.

We studied SARS-CoV-2 humoral immunogenicity after 2 doses of mRNA or ChAdOx1 nCoV-19 vaccine in patients with RA receiving different immunosuppressive regimens by monitoring the anti–SARS-CoV-2 spike-specific antibody titers post vaccination.

This prospective monocentric study was conducted between April and August 2021 at the Rheumatology Department of Hôpital Erasme, Brussels, Belgium. Inclusion criteria were as follows: age ≥ 18 years; RA diagnosis according to the American College of Rheumatology/European Alliance of Associations for Rheumatology 2010 criteria; vaccination with 2 doses of SARS-CoV-2 mRNA (BNT162b2 or mRNA-1273) or ChAdOx1 nCoV-19 vaccine according to the Belgian vaccination campaign; and current medication of glucocorticoids, conventional synthetic (cs-) disease-modifying antirheumatic drugs (DMARDs), biologic (b-) DMARDs, and/or targeted synthetic (ts-) DMARDs. Exclusion criteria included history or clinical suspicion of SARS-CoV-2 infection prior to vaccination, pregnancy, and breastfeeding. One month after the second vaccine dose, anti–SARS-CoV-2 spike IgG antibodies were quantified by the LIAISON SARS-CoV-2 TrimericS IgG (DiaSorin) assay with titers ≥ 33.8 binding antibody units (BAU)/mL indicating the presence of antibodies. Descriptive statistics, Fisher, Mann-Whitney, and Kruskal-Wallis nonparametric tests were performed, with $P < 0.05$ considered statistically significant.

This study complies with the Declaration of Helsinki and was approved by the local ethics committee (Ethics Committee of Hôpital Erasme, P2021-238/SRB2021099). Written informed consent was obtained from all study participants prior to study initiation.

We enrolled 104 patients with RA (median age 61 yrs, 79.8% female, median disease duration 8.5 yrs, 60.6% with seropositive RA, and 55.8% with erosive disease). Among them, 79.8% received mRNA vaccines and 20.2% ChAdOx1 nCoV-19 vaccines (Table 1). At first vaccination dose, 78.8% were on csDMARDs, mainly methotrexate (MTX); and 72.1% were on b/tsDMARDs, mainly anti–tumor necrosis factor (TNF) and ABA. Ten patients received RTX within 12 months before vaccination. More than 50% were on csDMARD and b/tsDMARD combination therapy and > 25% were on prednisone (PDN).

Anti–SARS-CoV-2 IgG was detected in 84.6% of patients. ChAdOx1 nCoV-19 vaccine was associated with a lower anti–SARS-CoV-2 IgG seropositivity rate ($P < 0.01$; Table 1) and lower titers ($P < 0.01$; Figure 1A). All patients on monotherapy or combination of csDMARDs without PDN presented detectable anti–SARS-CoV-2 IgG with significantly higher titers compared to patients on csDMARDs associated with b/tsDMARDs with or without PDN ($P < 0.05$; Figure 1B). Seropositivity rates were 88.2% with b/tsDMARDs monotherapy, 86.1% with b/tsDMARDs combined with csDMARDs without PDN and 55.6% with b/tsDMARDs combined with csDMARDs and PDN. Adding PDN to csDMARD and b/tsDMARD combination therapy revealed a lower seropositivity rate ($P < 0.05$). Nearly all nonresponders were on b/tsDMARDs, mostly ABA and RTX. Global seropositivity rate of patients on ABA was 66.7%. This rate was 57.9% in case of ABA combined with MTX and 37.5% when adding PDN. Of the patients treated with RTX within 12 months before vaccination, immunogenicity was 60.0%. Among them, 6 received their last RTX dose within 6 months before vaccination with only 33.3% serological responders. Seropositivity rates with anti-TNF, anti-interleukin (IL)-6, and Janus kinase inhibitors (JAKi) were 100%, 85.7% and 88.9%, respectively. The only nonresponder on JAKi was taking MTX and PDN.

Patients vaccinated with ChAdOx1 nCoV-19 were older compared to those vaccinated with mRNA vaccine (median age 65 and 60 yrs, respectively; $P < 0.01$). Regarding all vaccines, a weak negative correlation between anti–SARS-CoV-2 IgG titers and age was observed ($r = -0.28$, $P < 0.01$). During this short-term study, no patient reported coronavirus disease 2019 (COVID-19) post vaccination.

Impaired humoral immunogenicity in RA was observed after 2-dose regimen SARS-CoV-2 vaccination, and was more pronounced with ChAdOx1 nCoV-19 vaccine; these results are consistent with the previous trials.[1,4–7] The lower anti–SARS-CoV-2 seropositivity rate and IgG titers with ChAdOx1 nCoV-19 vaccination could be explained in part by the patient's older age in this population. In our cohort, immunogenicity was 100% in patients on monotherapy or csDMARD combination therapy. However, the combination of csDMARDs with b/tsDMARDs was associated with a weaker immunogenicity and lower anti–SARS-CoV-2 IgG titers. Adding PDN induces a more pronounced impairment, and has been reported previously.[1,9] Patients on ABA and RTX had the lowest seropositivity rates, consistent with previous trials.[1,2,3,8,9,10] Seropositivity rates of patients on anti-TNF, anti–IL-6, or JAKi monotherapy were 100%. As shown in previous studies, SARS-CoV-2 vaccine response with those biologics seems satisfactory.[1,9]

A strength of our study is the inclusion of a homogenous RA cohort taking several immunosuppressants. Different SARS-CoV-2 vaccines were administered with diverse time

Table 1. Demographic, clinical, and treatment characteristics of study participants, with seropositivity rates and IgG anti–SARS-CoV-2 titers after 2-dose regimen SARS-CoV-2 vaccination.

	Entire Cohort	Seropositivity for Anti–SARS-CoV-2 IgG	Anti–SARS-CoV-2 IgG Titers, BAU/mL, Median (IQR)
Patients, n (%)	104 (100)	88 (84.6)	699.5 (283.4–1363.8)
Female sex, n (%)	83 (79.8)	70 (84.3)	
Age, yrs, median (IQR)	61 (52–68)	61 (51–67)	
BMI, kg/m^2, median (IQR)	27.3 (23.6–31.9)	27.3 (23.4–32.0)	
Ethnicity			
White, n (%)	75 (72.1)	61 (81.3)	
Arab, n (%)	22 (21.2)	20 (90.9)	
Other[a], n (%)	7 (6.7)	7 (100)	
RA			
Disease duration, yrs, median (IQR)	8.5 (5–18)	9 (5–18)	
RA seronegativity, n (%)	35 (33.7)	29 (82.9)	
RF seropositivity, n (%)	63 (60.6)	54 (85.7)	
ACPA seropositivity, n (%)	58 (55.8)	49 (84.5)	
Erosive disease on radiograph, n (%)	58 (55.8)	48 (82.8)	
SARS-CoV-2 vaccine, n (%)			
mRNA	83 (79.8)	74 (89.2)[b]	839.0 (376.8–1482.5)[c]
BNT162b2 mRNA	74 (71.2)	65 (87.8)	800.0 (370.0–1440.0)
2-dose interval, days, median (IQR)	32 (27–35)	33 (28–35)	
mRNA-1273	9 (8.7)	9 (100)	1435.2 (841.0–2060.0)
2-dose interval, days, median (IQR)	28 (28–31)	28 (28–31)	
ChAdOx1 nCoV-19	21 (20.2)	14 (66.7)[b]	404.0 (159.8–681.8)[c]
2-dose interval, days, median (IQR)	81 (79–84)	81 (79–84)	
Immunosuppressive therapy, n (%)			
csDMARDs	82 (78.8)	68 (82.9)	638.3 (234.5–1310.0)
Monotherapy or combination csDMARDs	23 (26.1)	23 (100)	1170.0 (665.3–1984.5)[d]
MTX	76 (73.1)	63 (82.9)	624.0 (228.0–1320.0)
MTX monotherapy	15 (17.0)	15 (100)	1170.0 (613.5–1984.5)
MTX weekly dose, mg, median (IQR)	15 (10–15)	15 (10–15)	
csDMARDs + PDN	5 (4.8)	4 (80.0)	1680.0 (1026.3–5470.0)
b/tsDMARDs	75 (72.1)	60 (80.0)	549.5 (212.0–1062.5)
Anti-TNF	18 (17.3)	18 (100)	764.0 (383.0–1105.0)
Anti–IL-6	14 (13.5)	12 (85.7)	1085.0 (675.0–1560.0)
Abatacept	24 (23.1)	16 (66.7)	476.0 (144.4–788.0)
RTX < 12 months before vaccine	10 (9.6)	6 (60.0)	231.9 (77.8–394.8)
RTX < 6 months before vaccine	6 (5.7)	2 (33.3)	221.3 (146.9–295.6)
JAKi	9 (8.7)	8 (88.9)	237.5 (148.8–366)
b/tsDMARDs monotherapy	17 (16.3)	15 (88.2)	1030.0 (623.5–1437.6)
b/tsDMARDs + PDN	4 (3.8)	4 (100)	575.5 (324.0–1213.3)
csDMARDs + b/tsDMARDs	54 (51.9)	41 (75.9)	403.0 (150.0–828.0)
csDMARDs + b/tsDMARDs without PDN	36 (34.6)	31 (86.1)[e]	525.0 (157.0–845.0)[d]
csDMARDs + b/tsDMARDs + PDN	18 (17.3)	10 (55.6)[e]	332.6 (125.7–434.8)[d]
PDN	28 (26.9)	19 (67.9)	410.0 (225.5–1265.0)
PDN daily dose, mg, median (IQR)	5 (5.0–5.0)	5 (2.5–5.0)	

[a] Black, Asian, or Hispanic. [b] SARS-CoV-2 seropositivity rate of vaccination with 2-dose regimen mRNA vaccine was significantly higher compared to that with 2-dose regimen ChAdOx1 nCoV-19 vaccine. ($P < 0.01$). [c] Anti–SARS-CoV-2 IgG titers were significantly higher in patients vaccinated with 2-dose regimen mRNA vaccine compared to patients with 2-dose regimen ChAdOx1 nCoV-19 vaccine ($P < 0.01$). [d] Anti–SARS-CoV-2 IgG titers were significantly higher in patients treated with csDMARDs monotherapy or with a combination of csDMARDs compared to patients treated with csDMARDs associated with b/tsDMARDs with or without PDN ($P < 0.05$). [e] SARS-CoV-2 seropositivity rate of combination therapy of b/tsDMARDs and csDMARDs without PDN was significantly higher compared to that of b/tsDMARDs and csDMARDs with PDN ($P < 0.05$). ACPA: anticitrullinated protein antibody; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; IL: interleukin; JAKi: Janus kinase inhibitor; MTX: methotrexate; PDN: prednisone; RA: rheumatoid arthritis; RF: rheumatoid factor; RTX: rituximab; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TNF: tumor necrosis factor; tsDMARD: targeted synthetic DMARD.

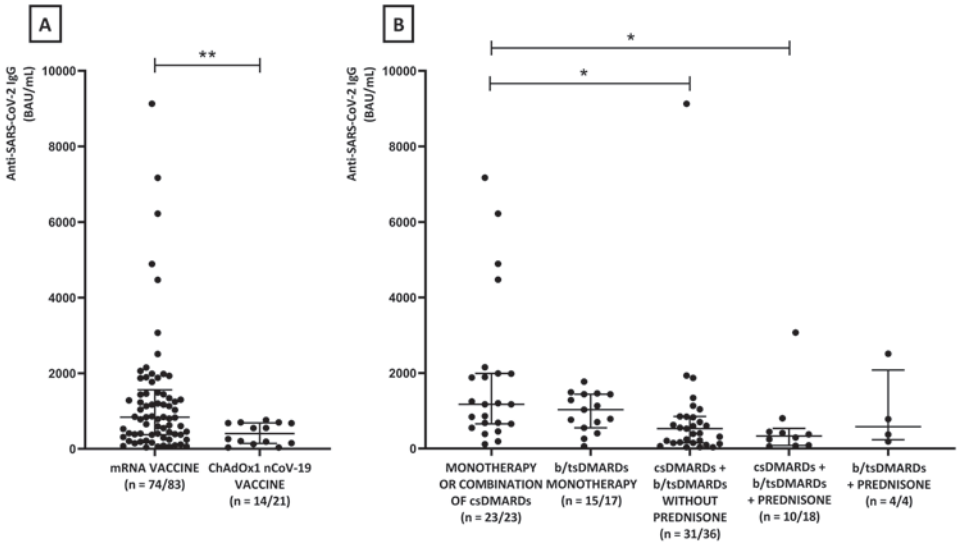

Figure 1. (A) Titers of anti–SARS-CoV-2 IgG antibodies after 2-dose regimen SARS-CoV-2 vaccination in patients with RA depending on the type of vaccine. Results are represented as dot plots with median and IQR for each treatment group. ** $P < 0.01$. (B) Titers of anti–SARS-CoV-2 IgG antibodies after 2-dose regimen SARS-CoV-2 vaccination in patients with RA depending on the type of immunosuppressive treatments in monotherapy and combination therapy. Results are represented as dot plots with median and IQR for each treatment group. * $P < 0.05$. bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; tsDMARD: targeted synthetic DMARD.

intervals between the vaccine doses; these are representative of our daily medical practice and improve the generalizability of our results.

Study limitations include the absence of a control group and the lack of neutralizing antibody testing. Another limitation is the absence of anti–SARS-CoV-2 spike protein antibody testing before vaccination and anti–SARS-CoV-2 nucleocapsid antibody testing during the trial, both of which possibly led to the inclusion of participants with asymptomatic COVID-19 infection.

Further studies are required to explore the long-term humoral immunogenicity impairment of SARS-CoV-2 vaccination in RA. Moreover, the effects of withholding antirheumatic treatment and administering an additional vaccine dose, currently recommended in Belgium, should be investigated to optimize vaccine response.

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The authors declare no conflicts of interest relevant to this article.

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DATA AVAILABILITY

Data are available upon request from the corresponding author.

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