Immunogenicity of COVID-19 vaccination in patients with ankylosing spondylitis: a monocentric prospective belgian cohort study

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Dear Editor,

Vaccination is cardinal in restraining the pandemic of COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The increased risk of severe COVID-19 infection in patients with inflammatory rheumatic diseases (IRD) makes vaccination particularly relevant in this population (1). There is scarce data regarding immunogenicity of SARS-CoV-2 vaccines in axial spondyloarthritis (AxSpA). Most of the studies, focused on cohorts of mixed IRD patients and on mRNA vaccines with short-term follow-ups, showing an impaired immunogenicity in these patients relative to healthy controls with lower anti-SARS-Cov-2 spike-specific IgG antibodies (anti-S Ab) levels (2-6). We aimed to prospectively evaluate the vaccine responsiveness in a homogeneous monocentric Belgian cohort of patients with AxSpA. This study, conducted between June and October 2021, complied with the Declaration of Helsinki and was approved by the local ethics committee. Informed written consent was obtained from all patients.

Patients (aged ≥ 18 years) with AxSpA according to the ASAS classification criteria followed in our department without any history of COVID-19 disease (nor PCR or antibodies positivity nor high clinical suspicion history) and fully vaccinated against SARS-CoV-2 (2 doses of mRNA vaccines or ChAdOx1 nCoV-19 or one dose of Ad26.COV2.S) were invited to participate. Vaccination was not part of the study. Demographic and clinical characteristics as well as AxSpA specific data were collected from medical records. The humoral immune response of vaccination was evaluated by measuring the anti-S Ab levels at one (36.8 days ± 8.8 SD) and three (96.1 days ± 9.8 SD) months respectively after complete vaccination using the LIAISON® SARS-CoV-2 TrimericS IgG (DiaSorin, Stillwater, USA) assay. Data were presented as percentage for qualitative variables and as median with minimal and maximal values for non-normally distributed data. We used Wilcoxon-Mann-Whitney's test (paired samples), Mann-Whitney non-parametric test (continuous variables) and Spearman's correlation test as appropriate. P-values below 0.05 were considered statistically significant. A total of 36 patients were included (median age 47 years, 47.2% females, median AxSpA disease duration 11 years, 91.7 % fulfilling the NY criteria), of whom 27 patients were on immunosuppressive therapy (25 patients under anti-TNF and 2 patients under anti-IL 17 biotherapy, all in monotherapy) (**Table 1**). No patient was taking corticosteroids. Twenty-six patients (72.2%) were vaccinated with mRNA vaccine (22 (61.1%) with BNT162b2 and 4 (11.1%) with mRNA-1273). Ten patients

(27.8%) were vaccinated with viral vectored vaccine (9 (25%) with ChAdOx1 nCoV-19 and one (2.8%) with Ad26.COV2.S vaccine). No underlying treatment was modified during the peri-vaccination period.

The patients were stratified into two groups according to their treatment: 9 patients (25%) without immunosuppression versus 27 patients (75%) with immunosuppression. Both groups were similar except for an over-representation of females in the group without immunosuppression (77.8% versus 37%). Anti-S Ab were detected in 35/36 (97.2%) patients at one month and 33/36 (91.7%) patients at three months. One patient, a man aged 67 years with skin psoriasis and ≥ 2 comorbidities, treated with infliximab was a non-responder. Two patients (56 and 67 years old, both under anti-TNF biotherapy) dropped their antibody levels below the positivity threshold at 3 months. Antibody levels decreased significantly between one and three months ($p < 0.0001$) without any significant statistical difference between the two groups. At one month, anti-S Ab levels in the sub-group vaccinated with mRNA vaccine was significantly higher in patients without immunosuppression compared to the group on immunosuppression (2940 BAU/ml versus 1410 BAU/ml, $p = 0.0362$). Patients vaccinated with mRNA vaccine had significantly higher median anti-S Ab titres either at one and three months post-vaccination compared to patients vaccinated with viral vectored vaccine (median, 1635 BAU/ml versus 208 BAU/ml at one month; $p < 0.0001$ and 560 BAU/ml versus 121.8 BAU/ml at three months; $p = 0.0069$)(**figure 1**). The drop of antibody levels between one and three months was also significantly greater with mRNA vaccination compared to viral vectored vaccine administration (median of difference 996.5 BAU/ml for mRNA vaccine versus 112.2 BAU/ml for non-mRNA vaccine, $p < 0.0001$). There was no difference in humoral response between the two mRNA vaccines. During this short-term study follow-up after SARS-CoV-2 vaccination, no patient reported a COVID-19 symptomatic disease. This study is limited by the absence of a control group, the small size of the cohort and the low median age of the participants.

We conclude that the main factor influencing anti-SARS-CoV-2 spike-specific IgG antibody levels in AxSpA patients is the type of vaccine rather than the patient's level of immunosuppression, although the maintenance of the biotherapy during the perivaccination period could be a potential confounder. While antibody levels persisted 3 months after complete vaccination in the majority of patients, the rapid decrease in these levels is an argument for an

additional dose of vaccine in the upcoming months in this population. The effect of this additional vaccine dose has to be investigated.

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Table 1 Demographic and clinical characteristics

	All patients	Not on immunosuppression	On immunosuppression
Patients included, n	36	9	27
Females, n (%)	17 (47.2)	7 (77.8)	10 (37)
Age, median (min,max), years	47 (22-67)	54 (45-67)	45 (22-67)
BMI, median (min,max), kg/m²	24.2 (15.82-34.41)	23.03 (15.82-33.25)	24.25 (17.87-34.41)
Ethnicity			
Caucasian, n (%)	30 (83.3)	7 (77.8)	23 (85.2)
Comorbidities			
No comorbidity	17 (47.2)	4 (44.4)	13 (48.1)
1 comorbidity	13 (36.1)	3 (33.3)	10 (37)
≥2 comorbidities	6 (16.7)	2 (22.2)	4 (14.8)
AxSpA			
Disease duration, median (min, max), years	11 (0.5-33)	8 (3-19)	14 (0.5-33)
HLAB27 positivity, n (%)*	21/30 (70)*	2/7 (28.6)*	19/23 (82.6)*
Fulfilling NY criteria, n (%)	33 (91.7)	9 (100)	24 (88.9)
Non radiographic AxSpA (NMR positive)	3 (8.3)	0 (0)	3 (11.1)
Spondylarthropathy extra-articular manifestations			
Uveitis, n (%)	7 (19.4)	2 (22.2)	5 (28.5)
IBD, n (%)	9 (25)	2 (22.2)	7 (25.9)
Crohn disease, n (%)	5 (13.9)	1 (11.1)	4 (14.8)
UC disease, n (%)	1 (2.8)	1 (11.1)	0 (0)
Skin psoriasis, n (%)	10 (27.8)	4 (44.4)	6 (22.2)
Hidrosadenitis, n (%)	2 (5.6)	1 (11.1)	1 (3.7)
Treatment			
No treatment, n (%)	2 (5.6)	2 (22.2)	NA
NSAID, n (%)	6 (16.7)	6 (66.7)	NA
csDMARDs, n (%)	1 (2.8)	1 (11.1)	NA
sulfasalazine			
bDMARDs, n (%)	27 (75)	NA	27 (100)
Anti-TNF, n (%)	25 (69.4)	NA	25 (92.6)
Anti-IL-17, n (%)	2 (5.6)	NA	2 (7.4)
SARS-CoV-2 vaccine			
mRNA, n (%)	26 (72.2)	7 (77.8)	19 (70.4)
BNT162b2 mRNA, n (%)	22 (61.1)	6 (66.7)	16 (59.3)
Interval between 2 doses, median (min, max), d	30.5 (21-40)	32.5 (29-35)	29 (21-40)
mRNA-1273, n (%)	4 (11.1)	1 (11.1)	3 (11.1)
Interval between 2 doses, median (min, max), d	28.5 (27-30)	30 (NA)	28 (27-29)
Viral vectored, n (%)	10 (27.8)	2 (22.2)	8 (29.6)
ChAdOx1 nCoV-19, n (%)	9(25)	2 (22.2)	7 (25.9)
Interval between 2 doses, median (min, max), d	78 (56-114)	71.5 (65-78)	80 (56-114)
Ad26.COV2.S, n (%)	1 (2.8)	0 (0)	1 (3.7)
Seropositivity at one month, n (%)	35 (97.2)	9 (100)	26 (96.3)
IgG anti-SARS-CoV2, median (min, max), BAU/ml	1255 (11.20-22900)	1960 (52.60-14000)	1120 (11.20-22900)
Seropositivity at three months, n (%)	33 (91.7)	9 (100)	24 (88.9)
IgG anti-SARS-CoV2, median (min,max), BAU/m	434 (5.08-12600)	1020 (35.80-1410)	284 (5.08-12600)

*HLAB27 status was available only for 30 patients

Abbreviation: d, days; min, minimum; max, maximum; BMI, body mass index; AxSpA, axial spondyloarthritis ; NMR, nuclear magnetic resonance; IBD, inflammatory bowel disease; UC, ulcerative colitis ;; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2;NSAID, Non-steroidal anti-inflammatory drugs;csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs, biological DMARDs; TNF, tumor necrosis factor; IL-17, interleukin 17.

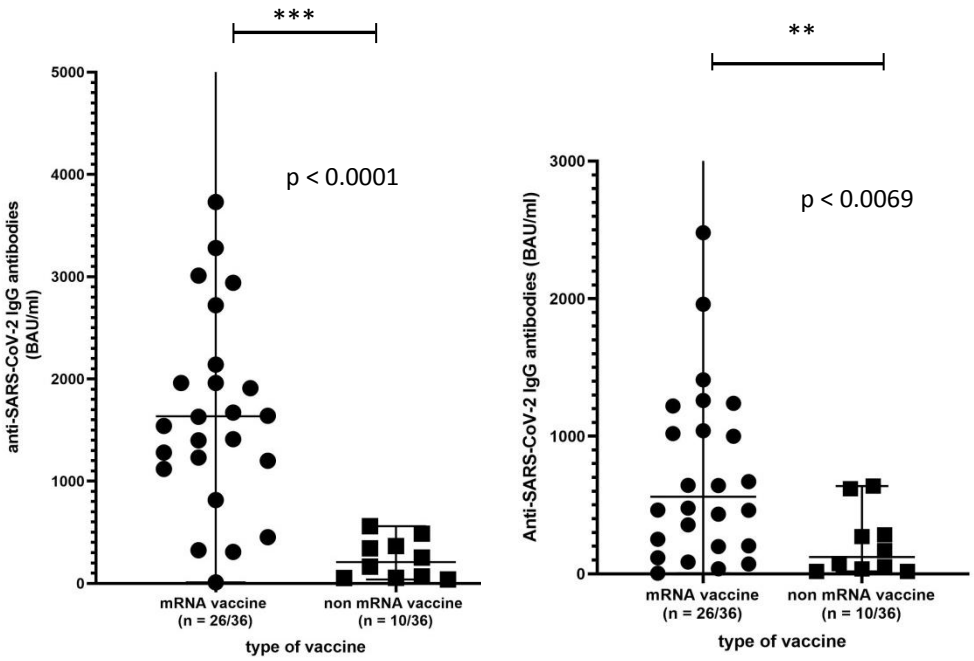

Figure 1. *Antibodies levels depending of the type of vaccine.*
Anti-SARS-CoV-2 antibodies levels in binding antibody units (BAU)/mL after complete vaccination in patients with AS at one and three months depending of the type of vaccine received.