Waning humoral immunity of SARS-CoV-2 vaccination in a rheumatoid arthritis cohort and the benefits of a vaccine booster dose

C. Le Moine[1], M.S. Soyfoo[1], L. Mekkaoui[2], H. Dahma[2], L. Tant[1]

[1]Department of Rheumatology, Hôpital Erasme, Université Libre de Bruxelles, Brussels; [2]Microbiology Department, Laboratoire Hospitalier Universitaire de Bruxelles, Universitair Laboratorium Brussel (LHUB-ULB), Université Libre de Bruxelles, Brussels, Belgium.

Abstract

Objective

We aimed to assess SARS-CoV-2 spike-specific antibody kinetics postvaccination and the benefit of a mRNA vaccine booster dose in rheumatoid arthritis (RA) patients treated with immunosuppressive drugs.

Methods

Consecutive RA patients on immunosuppressive therapies, with no known history of SARS-CoV-2 infection or high-risk contact, vaccinated with 2 doses SARS-CoV-2 mRNA, BNT162b2 or mRNA-1273, or viral vectored ChAdOx1 nCoV-19 vaccine were recruited during their routine rheumatology consultation. Anti-SARS-CoV-2 IgG spike-specific antibodies were quantified at 1, 3 and 6 months respectively following the second vaccine dose. The incidence of SARS-CoV-2 infection postvaccination during this 6-month longitudinal study was also assessed.

Results

Of the 104 RA patients included, 79 patients completed the 6-month trial follow-up. A significant decrease in anti-SARS-CoV-2 spike-specific IgG titres was observed between 1-month and 3-month postvaccination ($p<0.01$). Among the 46 patients (46/79) receiving a booster dose, all developed detectable anti-SARS-CoV-2 spike-specific IgG antibodies at the 6-month follow-up with significantly higher titres compared to 1-month ($p<0.001$) and 3-month ($p<0.0001$) post-vaccination. Conversely, the antibody titres among the 33 patients (33/79) not receiving a booster dose decreased significantly at the 6-month follow-up compared to 1-month ($p<0.0001$) and 3-month ($p<0.01$) post-vaccination. The incidence of COVID-19 disease postvaccination was 8.9% without severe forms.

Conclusion

To our knowledge, this is the first study to report on anti-SARS-CoV-2 spike-specific antibody kinetics postvaccination and the effect of a booster dose in a cohort of RA patients. The latter is essential given the waning humoral immunity observed in vaccinated RA patients and the increased incidence of COVID-19 diseases postvaccination in this 6-month longitudinal study.

Key words

rheumatoid arthritis, humoral immune response, coronavirus, vaccination, booster immunisation

Camille Le Moine, MD
Muhammad S. Soyfoo, MD, PhD
Leila Mekkaoui, MD
Hafid Dahma
Laure Tant, MD

Please address correspondence to:
Camille Le Moine,
Department of Rheumatology,
Hôpital Erasme,
Université Libre de Bruxelles,
808 Route de Lennik,
1070 Brussels, Belgium.
E-mail: camille.le.moine@erasme.ulb.ac.be

ORCID iD: 0000-0002-8199-6772

Received on February 22, 2022; accepted in revised form on March 25, 2022.

Funding: this work was supported by the Rheumatology Department of Hôpital Erasme (Brussels, Belgium).

Competing interests: none declared.

Introduction

An impaired immunogenicity of SARS-CoV-2 vaccination is observed in patients with rheumatoid arthritis (RA) treated with immunomodulating agents, especially B-cell depleting agents (1-4). Besides, there is a progressive decrease in vaccine's efficacy characterised by a continuous decline in anti-SARS-CoV-2 spike-specific and neutralising antibodies, more pronounced among immunosuppressed patients (5). This waning immunity of SARS-CoV-2 vaccination has led to a resurgence of the COVID-19 pandemic, supporting the administration of a third SARS-CoV-2 vaccine booster dose to improve vaccine's effectiveness (6). Currently, the approval of this booster dose is widely spreading and there is no shadow of doubt of its benefit in immunocompromised patients. Data regarding the antibody kinetics postvaccination are still scarce, especially the effect of this additional booster dose in RA. Most available studies focus on mixed cohorts of inflammatory rheumatic diseases.

Here, we investigate the SARS-CoV-2 spike-specific antibody kinetics up to 6 months after two-dose regimen SARS-CoV-2 vaccination in a cohort of RA patients on different immunosuppressive therapies of conventional synthetic (cs-), biological (b-) and/or targeted synthetic (ts-) disease-modifying anti-rheumatic drugs (DMARDs). A proportion of this cohort received a third SARS-CoV-2 mRNA vaccine booster dose in this time frame according to the national vaccination campaign. To our knowledge, this is the first prospective study to report on anti-SARS-CoV-2 spike-specific antibody kinetics postvaccination and the effect of a booster dose in RA. The incidence of SARS-CoV-2 infection during this 6-month postvaccination follow-up was also investigated.

Methods

Participants

This 6-month longitudinal prospective monocentric study was conducted between April 2021 and February 2022 at the Rheumatology Department of Hôpital Erasme (Brussels, Belgium). Patients were eligible to participate if they were at least 18 years old, diagnosed with RA according to the ACR/EULAR criteria 2010, treated with the following immunosuppressive drugs in monotherapy or combination therapy: glucocorticoids, csDMARDs (methotrexate, hydroxychloroquine, leflunomide and sulfasalazine), bDMARDs (anti-TNF, anti-IL6, abatacept and rituximab) and/or tsDMARDs (JAK inhibitors), and vaccinated according to the Belgian national vaccination campaign with 2 doses of SARS-CoV-2 mRNA vaccine, BNT162b2 or mRNA-1273, or viral vectored ChAdOx1 nCoV-19 vaccine from March to August 2021. Any history of documented SARS-CoV-2 infection, defined as a positive SARS-CoV-2 RT-PCR test or a known positivity for anti-SARS-CoV-2 antibodies, or any high clinical suspicion of SARS-CoV-2 infection prior to vaccination were exclusion criteria for trial participation. Pregnant and breastfeeding women were excluded.

Consecutive patients were recruited during their routine rheumatology consultation. Demographic and clinical characteristics, RA-specific clinical and therapeutic data and vaccination data were collected from their medical records.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethical committee (the Ethics Committee of Hôpital Erasme) (P2021-238/SRB2021099). Informed consent was obtained from all study participants prior to the initiation of the study.

Anti-SARS-CoV-2 IgG assays

Humoral immunogenicity was investigated with the LIAISON® SARS-CoV-2 TrimericS IgG (DiaSorin, Stillwater, USA), a chemiluminescence immunoassay measuring IgG antibodies against the SARS-CoV-2 trimeric spike-specific protein of the SARS-CoV-2 performed 1 month, 3 months and 6 months after the administration of the second vaccine dose. This serology assay was performed according to the manufacturer's protocol at the University-Hospital Laboratory Brussels (LHUB-ULB). The measuring ranges were between 4.81 and 2080 binding antibody units (BAU)/mL. Seropositivity was defined as IgG titres ≥33.8 BAU/mL. Blood samples

Table I. Demographic, clinical, treatment and SARS-CoV-2 vaccination characteristics of study participants.

	Patients completing 1-month follow-up (n=104)	Patients completing 3-month follow-up (n=92)	Patients completing 6-month follow-up (n=79)
Female sex, n (%)	83 (79.8)	75 (81.5)	63 (79.7)
Age, median (IQR), years	61.0 (52.0-68.0)	61.0 (51.8-68.0)	61.0 (52.5-68.0)
BMI, median (IQR), kg/m²	27.3 (23.6-31.9)	27.3 (23.6-31.9)	26.8 (23.4-31.6)
Ethnicity			
Caucasian, n (%)	75 (72.1)	67 (72.8)	59 (74.7)
Arab, n (%)	22 (21.2)	19 (20.7)	16 (20.3)
Other, n (%)*	7 (6.7)	6 (6.5)	4 (5.1)
RA			
Disease duration, median (IQR), years	8.5 (5.0-18.0)	8.0 (6.0-18.0)	8.0 (5.0-18.0)
RA seronegative, n (%)	35 (33.7)	31 (33.7)	27 (34.2)
RF seropositivity, n (%)	63 (60.6)	56 (60.9)	47 (59.5)
ACPA seropositivity, n (%)	58 (55.8)	52 (56.5)	43 (54.4)
Initial SARS-CoV-2 vaccination (2 doses)			
mRNA, n (%)	83 (79.8)	75 (81.5)	63 (79.7)
BNT162b2, n (%)	74 (71.2)	66 (71.7)	54 (68.4)
Interval between 2 doses, median (IQR), days	32.0 (27.0-35.0)	31.5 (25.0-35.0)	33.0 (28.0-35.0)
mRNA-1273, n (%)	9 (8.7)	9 (9.8)	9 (11.4)
Interval between 2 doses, median (IQR), days	28.0 (28.0-31.0)	28.0 (28.0-31.0)	28.0 (28.0-31.0)
ChAdOx1 nCoV-19, n (%)	21 (20.2)	17 (18.5)	16 (20.3)
Interval between 2 doses, median (IQR), days	81.0 (79.0-84.0)	80.0 (79.0-83.0)	80.0 (78.8-83.3)
Third SARS-CoV-2 mRNA vaccine booster dose, n (%)			46 (58.2)
Interval between 2nd dose and booster dose, median (IQR), days			133.0 (111.5-140.8)
Immunosuppressive therapy			
csDMARDs, n (%)	82 (78.8)	73 (79.3)	64 (81.0)
Methotrexate, n (%)	76 (73.1)	68 (73.9)	60 (75.9)
b/tsDMARDs, n (%)	75 (72.1)	65 (70.7)	55 (69.6)
Anti-TNF, n (%)	18 (17.3)	16 (17.4)	14 (17.7)
Anti-IL-6, n (%)	14 (13.5)	10 (10.9)	10 (12.7)
Abatacept, n (%)	24 (23.1)	21 (22.8)	16 (20.3)
Rituximab <12 months before vaccine, n (%)	10 (9.6)	9 (9.8)	7 (8.9)
Rituximab <6 months before vaccine, n (%)	6 (5.7)	6 (6.5)	4 (5.1)
JAKi, n (%)	9 (8.7)	9 (9.8)	8 (10.1)
csDMARDs + b/tsDMARDs, n (%)	54 (51.9)	47 (51.1)	41 (51.9)
csDMARDs + b/tsDMARDs + prednisone, n (%)	18 (17.3)	15 (16.3)	13 (16.5)
Prednisone, n (%)	28 (26.9)	24 (26.1)	21 (26.6)
≤5 mg, n (%)	24 (23.1)	20 (21.7)	17 (21.5)
>5 and <10 mg, n (%)	2 (1.9)	2 (2.2)	2 (2.5)
≥10 mg, n (%)	2 (1.9)	2 (2.2)	2 (2.5)
Daily dose, median (IQR), mg	5.0 (5.0-5.0)	5.0 (2.5-5.0)	5.0 (2.5-5.0)

*African, Asian or Hispanic
IQR: interquartile ranges; BMI: body mass index; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs: biological DMARDs; tsDMARDs: targeted synthetic DMARDs; TNF: tumour necrosis factor; IL-6: interleukin 6; JAKi: Janus kinase inhibitors.

with IgG titers ≥2080 BAU/mL were diluted using the LIAISON® TrimericS IgG Diluent Accessory with a dilution factor of 1:20.

The incidence of COVID-19 disease postvaccination during the 6-month study follow-up was also assessed, as well as the related hospitalisations.

Statistical analysis

Patient's characteristics and immunogenicity were summarised using descriptive statistics reported as median and interquartile range (IQR) for continuous variables and as frequency and percentage for categorial variables. Assessing statistical differences was done using Mann-Whitney non-parametric test for continuous variables and Friedman non-parametric test for repeated measures with Dunn's *pot-hoc* multiple comparison test to compare individual groups. *p*-values less than 0.05 were considered statistically significant. All analyses were performed using GraphPad Prism 8.

Results

Of the 104 patients included, 104 patients performed the 1-month anti-SARS-CoV-2 spike-specific IgG assay postvaccination, 92 patients performed the 1- and 3-month anti-SARS-CoV-2 spike-specific IgG assays postvaccination and 79 patients performed the 1-, 3- and 6-month anti-SARS-CoV-2 spike-specific IgG assays postvaccination. Baseline characteristics are summarised in Table I. At 1-month follow-up, anti-SARS-CoV-2 spike-specific

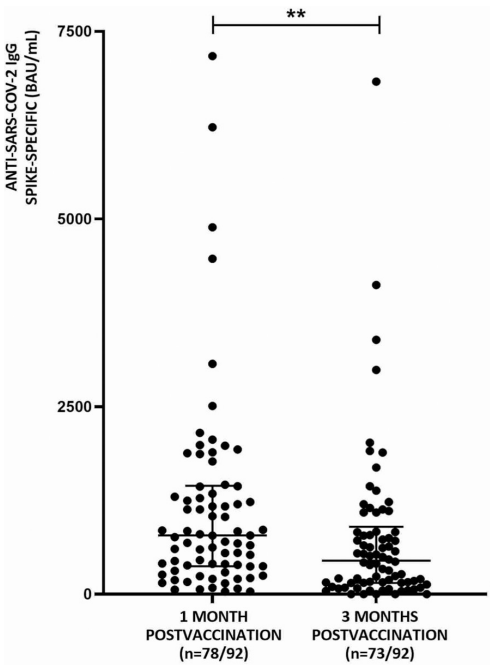

Fig. 1. Titres of anti-SARS-CoV-2 spike-specific IgG antibodies 1 month and 3 months after two-dose regimen SARS-CoV-2 vaccination in 92 patients with RA; 78 patients were seropositive at 1-month post-vaccination and 73 patients remain seropositive at 3 months post-vaccination. Results are represented as median and IQR for each treatment group.
**$p<0.01$.

IgG antibodies were detected in 84.6% of the patients (88/104). All of the non-responders except for 1, were on b/tsDMARDs, mostly abatacept and rituximab. These preliminary results have already been published elsewhere (8).

Among the 92 patients performing the 1-month and 3-month anti-SARS-CoV-2 spike-specific IgG assays, 78 patients (84.8%; 78/92) were seropositive at 1-month postvaccination with 73 patients (79.3%; 73/92) remaining seropositive at 3-month postvaccination. All patients who became seronegative at 3-month follow-up were treated with csDMARDs in combination with either abatacept (3/5) or rituximab (2/5). Between 1-month and 3-month postvaccination, a significant decrease in anti-SARS-CoV-2 spike-specific IgG titres was observed with median titres of 782.5 BAU/mL and 447.5 BAU/mL, respectively ($p<0.01$) (Fig. 1).

Of the 79 patients who completed the 6-month follow-up, 46 patients (58.2%; 46/79) received a mRNA vaccine booster dose within this time frame. These 46 patients were all seropositive for anti-SARS-CoV-2 spike-specific IgG antibodies at 6-month follow-up with significantly increased IgG titres compared to 1-month and 3-month postvaccination ($p<0.001$ and $p<0.0001$, respectively) (Fig. 2A). Conversely, the anti-SARS-CoV-2 spike-specific IgG antibody titres among the 33 other patients (41.8%; 33/79) who did not receive a booster dose during the trial follow-up decreased significantly at 6-month follow-up compared to 1-month and 3-month postvaccination ($p<0.0001$ and $p<0.01$, respectively) (Fig. 2B).

In this cohort, 6 patients (7.6%; 6/79) were seronegative for anti-SARS-CoV-2 spike-specific IgG antibodies at 6-month follow-up. None of them received a booster dose. They were all treated with a combination therapy of methotrexate and a bDMARD: abatacept (3/6), rituximab (2/6) and anti-IL6 (1/6).

In terms of infection, 7 of the 79 patients (8.9%; 7/79) who completed the 6-month follow-up developed a non-severe COVID-19 disease, confirmed by a positive SARS-CoV-2 RT-PCR test. None required hospitalisation. All COVID-19 diseases occurred between 3-month and 6-month postvaccination, although 4 of these 7 patients had already received the booster dose. Among the 7 COVID-19 cases, only 3 patients, who had been vaccinated with the viral vectored ChAdOx1 nCoV-19 vaccine, were seronegative for anti-SARS-CoV-2 spike-specific IgG antibodies at 1-month and 3-month follow-up. Concerning these 3 patients, 2 patients treated with methotrexate and abatacept in combination therapy, had received a booster dose before contracting COVID-19 disease and 1 patient treated with methotrexate and prednisone, had not received a booster dose before being infected with SARS-CoV-2.

Discussion

Given the increased risk of infections and the impaired humoral immunogenicity of SARS-CoV-2 vaccination in RA patients on immunosuppressive therapies (1-4), improving vaccine effectiveness in this immunocompromised population is essential. In this prospective study conducted in a real-life RA cohort, we observed a progressive decline in anti-SARS-CoV-2 IgG antibody titres after the administration of 2 doses of SARS-CoV-2 mRNA vaccine, BNT162b2 or mRNA-1273, or viral vectored ChAdOx1 nCoV-19 vaccine, consistent with previous studies (5, 9, 10). Some patients became even seronegative for anti-SARS-CoV-2 IgG antibodies just 3 months after vaccination, all treated with a combination therapy of csDMARDs and bDMARDs. The administration of a third SARS-CoV-2 mRNA vaccine booster dose induced a significant increase in anti-SARS-CoV-2 spike-specific IgG antibodies, regardless of the underlying immunosuppressive treatments. Although neutralising assays correlate with protective immunity in SARS-CoV-2 infection (11, 12), they are nonetheless complex, time-consuming and expensive, and were not performed in this trial. However, the positive correlation observed between anti-SARS-CoV-2 spike-specific IgG antibodies and neutralising antibody titres (5) suggests a protective character of these anti-SARS-CoV-2 spike-specific IgG antibodies.

The incidence of COVID-19 disease postvaccination during this 6-month trial follow-up was 8.9%, which is slightly higher compared to vaccinated healthy subjects (13). Reassuringly, all had a mild form, even those who were serological non-responders.

The strength of our study is the prospective design of a real-life RA cohort facing the COVID-19 pandemic with a vaccination campaign evolving over time. Our observations are there-

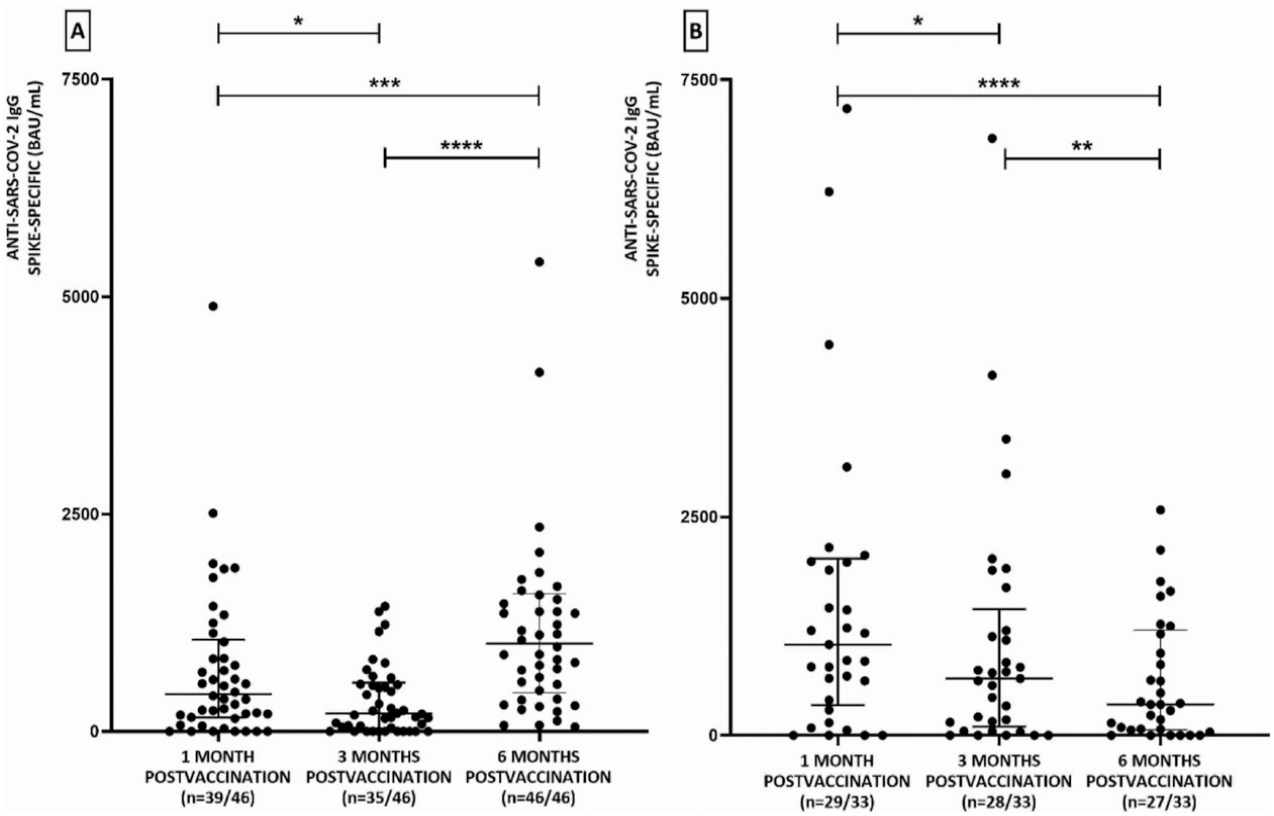

Fig. 2. A: Titres of anti-SARS-CoV-2 spike-specific IgG antibodies 1 month, 3 months and 6 months after two-dose regimen SARS-CoV-2 vaccination in 46 patients with RA receiving a mRNA vaccine booster dose before between 3-month and 6-month follow-up. Results are represented as median and IQR for each treatment group. *p<0.05; ***p<0.001; ****p<0.0001.
B: Titres of anti-SARS-CoV-2 spike-specific IgG antibodies 1 month, 3 months and 6 months after two-dose regimen SARS-CoV-2 vaccination in 33 patients with RA who did not receive a mRNA vaccine booster dose. Results are represented as median and IQR for each treatment group.
*p<0.05; ****p<0.0001; **p<0.01.

fore representative of the daily medical practice. The main limitations are the heterogeneity of the therapeutic regimens and the number of patients lost to follow-up. Indeed, 25 patients did not complete the 6-month study follow-up. The latter is mainly explained by the health measures and restrictions imposed by the still active COVID-19 pandemic limiting the healthcare contacts at the hospital, challenging our medical practice (14).

To our knowledge, this is the first study to report on the anti-SARS-CoV-2 spike-specific antibody kinetics post-vaccination in a cohort of patients with RA treated with different immunosuppressive regimens. Moreover, the effect of an additional vaccine booster dose in RA has not been reported previously.

In conclusion, we observe a waning humoral immunity over time in RA patients vaccinated with SARS-CoV-2 mRNA vaccine, BNT162b2 or mRNA-1273, or viral vectored ChAdOx1 nCoV-19 vaccine. The administration of a mRNA vaccine booster dose improves the vaccine humoral responsiveness in RA. This latter is essential given the lower vaccine effectiveness in immunocompromised patients and the increased incidence of COVID-19 disease postvaccination, even if no severe forms were observed in this 6-month longitudinal study.

Key messages

- SARS-CoV-2 vaccine humoral responsiveness in RA patients on immunomodulating agents is impaired with a waning immunity over time.
- The administration of an additional vaccine booster dose in RA improves vaccine humoral effectiveness.
- SARS-CoV-2 vaccination should be encouraged especially given the increased incidence of COVID-19 disease postvaccination in our cohort, even if no severe forms were observed.

Acknowledgements

We thank Dr Céline La and Mrs Sandra Kleimberg of the Rheumatology Department of Hôpital Erasme (Brussels, Belgium) for their participation in the recruitment of trial participants and all the patients who participated to the study. We also thank the staff of the University-Hospital Laboratory Brussels (LHUB-ULB) for their laboratory work.

References

1. FURER V, EVIATAR T, ZISMAN D *et al*.: Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis* 2021; 80(10): 1330-8. https://doi.org/10.1136/annrheumdis-2021-220647
2. SIEIRO SANTOS C, CALLEJA ANTOLIN S, MORIANO MORALES C *et al*.: Immune responses to mRNA vaccines against SARS-CoV-2 in patients with immune-mediated inflammatory rheumatic diseases. *RMD Open* 2022; 8(1): e001898. https://doi.org/10.1136/rmdopen-2021-001898
3. DEEPAK P, KIM W, PALEY MA *et al*.: Effect of

Immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2: a prospective cohort study. *Ann Intern Med* 2021; 174(11): 1572-85. https://doi.org/10.7326/m21-1757

4. PRENDECKI M, CLARKE C, EDWARDS H *et al*.: Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. *Ann Rheum Dis* 2021; 80(10): 1322-9. https://doi.org/10.1136/annrheumdis-2021-220626
5. LEVIN EG, LUSTIG Y, COHEN C *et al*.: Waning immune humoral response to BNT162 b2 Covid-19 vaccine over 6 months. *N Engl J Med* 2021; 385(24): e84. https://doi.org/10.1056/nejmoa2114583
6. BARDA N, DAGAN N, COHEN C *et al*.: Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 2021; 398(10316): 2093-100. https://doi.org/10.1016/s0140-6736(21)02249-2
7. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62(9): 2569-81. https://doi.org/10.1002/art.27584
8. LE MOINE C, SOYFOO MS, MEKKAOUI L, DAHMA H, TANT L: Impaired humoral immunogenicity of SARS-CoV-2 vaccination in rheumatoid arthritis patients. *J Rheumatol* 2022; 49(7): 855-58. https://doi.org/10.3899/jrheum.211270
9. ABU-RADDAD LJ, CHEMAITELLY H, BERTOLLINI R: Waning mRNA-1273 vaccine effectiveness against SARS-CoV-2 infection in Qatar. *N Engl J Med* 2022; 386(11): 1091-3. https://doi.org/10.1056/nejmc2119432
10. KATIKIREDDI SV, CERQUEIRA-SILVA T, VASILEIOU E *et al*.: Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: a retrospective, population-based cohort study in Scotland and Brazil. *Lancet* 2022; 399(10319): 25-35. https://doi.org/10.1016/s0140-6736(21)02754-9
11. KHOURY DS, CROMER D, REYNALDI A *et al*.: Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; 27(7): 1205-11. https://doi.org/10.1038/s41591-021-01377-8
12. EARLE KA, AMBROSINO DM, FIORE-GARTLAND A *et al*.: Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* 2021; 39(32): 4423-8. https://doi.org/10.1016/j.vaccine.2021.05.063
13. BERGWERK M, GONEN T, LUSTIG Y *et al*.: Covid-19 breakthrough infections in vaccinated health care workers. *N Engl J Med* 2021; 385(16): 1474-84. https://doi.org/10.1056/nejmoa2109072
14. PUXEDDU I, FERRO F, BARTOLONI E *et al*.: COVID-19: the new challenge for rheumatologists. One year later. *Clin Exp Rheumatol* 2021; 39(1): 203-13. https://doi.org/10.55563/clinexprheumatol/si106e