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Concise report

Strong response after fourth dose of mRNA COVID-19 vaccine in autoimmune rheumatic diseases patients with poor response to inactivated vaccine

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Abstract

Objectives. To assess immunogenicity of a heterologous fourth dose of an mRNA (BNT162b2) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine in autoimmune rheumatic diseases (ARD) patients with poor/non-response to inactivated vaccine (Sinovac-CoronaVac).

Methods. A total of 164 ARD patients who were coronavirus disease 2019 (COVID-19) poor/non-responders (negative anti-SARS-CoV-2 S1/S2 IgG and/or neutralizing antibodies—NAb) to the third dose of Sinovac-CoronaVac received an additional heterologous dose of mRNA (BNT162b2) 3 months after last dose. IgG and NAb were evaluated before and after the fourth dose.

Results. Significant increases were observed after the fourth dose in IgG (66.4 *vs* 95.1%, $P < 0.001$), NAb positivity (5.5 *vs* 83.5%, $P < 0.001$) and geometric mean titre (29.5 *vs* 215.8 AU/ml, $P < 0.001$), and 28 (17.1%) remained poor/non-responders. Patients with negative IgG after a fourth dose were more frequently under rituximab ($P = 0.001$). Negative NAb was associated with older age ($P = 0.015$), RA ($P = 0.002$), SSc ($P = 0.026$), LEF ($P = 0.016$) and rituximab use ($P = 0.007$). In multiple logistic regression analysis, prednisone dose $\geq$7.5 mg/day (OR = 0.34; $P = 0.047$), LEF (OR = 0.32, $P = 0.036$) and rituximab use (OR = 0.19, $P = 0.022$) were independently associated with negative NAb after the fourth vaccine dose.

Conclusions. This is the largest study to provide evidence of a remarkable humoral response after the fourth dose of heterologous mRNA SARS-CoV-2 vaccination in ARD patients with poor/non-response to the third dose of an inactivated vaccine. We further identified that treatment, particularly rituximab and prednisone, impaired antibody response to this additional dose.

Trial registration. ClinicalTrials.gov, https://clinicaltrials.gov, CoronavRheum #NCT04754698.

Key words: autoimmune diseases, COVID-19, vaccination, therapy

BASIC SCIENCE

Rheumatology key messages

- There were no large studies of immunogenicity of fourth SARS-CoV-2 vaccine dose in autoimmune rheumatic disease (ARD) patients.
- The fourth heterologous vaccination dose provided a robust immunogenicity response in ARD patients with poor/non-response to the third dose.
- Rituximab and prednisone use were associated with reduced antibody response to the additional dose.

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Introduction

Severe breakthrough coronavirus disease 2019 (COVID-19) infections are still a matter of concern during the ongoing pandemic, especially in autoimmune rheumatic disease (ARD) patients [1]. Brazilian health authorities recently approved the fourth severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine dose to immunocompromised patients in view of the recent new peak of SARS-CoV-2 infections by the Omicron variant.

Few reports in transplant recipients have indicated that a fourth dose of COVID-19 vaccine produced an overall increase in antibody responses, but only half of them reached the cut-off level [2, 3]. A recent case series including 18 ARD patients described good antibody responses to two additional SARS-CoV-2 vaccine doses [4]. In addition, the booster vaccination against 2009 H1N1 influenza virus in ARD patients under rituximab treatment improved antiviral T cell response in patients with low B cells [5]. Similarly, for hepatitis B virus vaccine, booster doses were required for achievement of adequate responses in ARD patients on biological therapy, particularly rituximab [6]. With regard to anti-SARS-CoV-2 vaccination, prime immunization may be especially impaired by age $\geq$60 years, prednisone, and some specific immunosuppressive and biological drugs [1, 7, 8], reinforcing the need for additional doses. Both homologous and heterologous third dose of anti-SARS-CoV-2 vaccination have been associated with robust humoral response in this population [9, 10]. Furthermore, a recent small sized study of a fourth anti-SARS-CoV-2 dose demonstrated enhanced immunogenicity in ARD patients, although still impaired by MMF [4].

We recently reported a substantial increase in antibody response after a third dose of Sinovac-CoronaVac in a large cohort of ARD patients. However, almost 20% of patients were still negative for anti-SARS-CoV-2 IgG or neutralizing antibodies (NAb) after three-dose homologous vaccination [10], and possibly remained at high risk for severe COVID-19 [11]. The analysis of factors associated with a reduced third dose response in our cohort of 875 patients revealed that older age, prednisone $\geq$5 mg/day, MMF and biologic drugs, particularly abatacept, belimumab and rituximab, were the main factor impairing vaccine-induced antibody response [10].

Therefore, the aim of this study was to assess whether an additional, fourth dose of an mRNA (BNT162b2) heterologous SARS-CoV-2 vaccine would improve immunogenicity in poor/non-responders ARD patients previously vaccinated with the third dose of a SARS-CoV-2 inactivated vaccine.

Methods

Study design and population

Patients $\geq$18 years old diagnosed according to the international disease classification criteria were included [1]. All patients had previously received a two-dose scheme of the inactivated Sinovac-CoronaVac vaccine (Sinovac Life Sciences, Beijing, China, batch #20200412) with 28 days interval in February–March 2021 and a third (booster dose) 6 months later (September 2021). We defined poor response as absence of anti-SARS-CoV-2 S1/S2 IgG or NAb, and no-response as absence of both tests 30 days after the third dose. Heterologous vaccination with mRNA (BNT162b2) vaccine was performed in a single dose 90 days after the third inactivated vaccine dose (December 2021). As part of standard of care, based on ACR Guidelines for COVID-19 vaccination [12] patients with low disease activity/inactive disease at last visit (up to 2 months) were instructed to withhold MTX and/or MMF after their fourth vaccine dose (two weekly doses for MTX and one week for MMF).

Exclusion criteria for vaccination and immunogenicity were described previously [1, 10]. The study was performed in accordance with the principles of the declaration of Helsinki and approved by the National (Comissão Nacional de Ética em Pesquisa—CONEP) and Institutional Ethical Committee (Comissão de Ética para Análise de Projetos de Pesquisa—CAPPesq) of Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil (ID CAAE: 42566621.0.0000.0068). Written informed consent was obtained from all participants. A rigorous follow-up of COVID-19 incident cases and vaccine-related adverse events was performed at final visit, as previously reported [1].

Primary and secondary outcomes

Primary outcome was defined as humoral immunogenicity assessed by the presence of IgG and NAb 30 days after the fourth dose. Secondary outcomes were geometric mean titre (GMT) of IgG and median of NAb activity after the fourth dose. The influence of demographic data, ARD diagnosis and current therapy on immune response was also evaluated.

Serologic assays

Blood samples were collected 30 days after the third dose and 30 days after the fourth dose. Serologic assays included total IgG against the SARS-CoV-2 S1 and S2 proteins (chemiluminescent immunoassay on the ETI-MAX-3000, LIAISON® SARS-CoV-2 S1/S2 IgG kit, DiaSorin, Saluggia, VC, Italy), and measurement of circulating NAb using the SARS-CoV-2 sVNT Kit (GenScript, Piscataway, NJ, USA) [13]. Patients with $\geq$15.0 AU/ml for total IgG and with $\geq$30% inhibition in neutralizing assay were considered seropositive according to the manufacturer's guide. The value of 1.9 AU/ml was attributed to undetectable levels of IgG.

Data and statistical analysis

Data were presented as number (%) for categorical variables, and as mean (S.D.) or medians (interquartile ranges) for continuous variables, whereas IgG titres were expressed as geometric means with 95% CI. Comparisons were performed by the χ^2 or Fisher's exact

tests for categorical variables, and by Student's *t*-test or Mann–Whitney test for continuous variables. Seropositivity rates were compared before and after the fourth dose using McNemar's test and mean of the Napierian logarithm (ln)-transformed IgG titres and NAb activity using paired *t*-test. Multivariate logistic regression analyses were performed using seropositivity after the fourth dose as a dependent variable, and, as independent variables, those with $P < 0.2$ in each univariate analysis. Statistical significance was set as $P < 0.05$. Most statistical analyses were performed using Statistical Package for the Social Sciences, version 20.0 (IBM-SPSS for Windows, 20.0, Chicago, IL, USA).

Results

A total of 210 poor/non-responder ARD patients 30 days after the third Sinovac-CoronaVac vaccine dose were invited for a fourth dose of heterologous vaccine. From these, 182 (87%) patients attended the fourth dose vaccination. Ten patients were excluded due to real-time reverse transcriptase (RT)-PCR-confirmed COVID-19 during the study, one patient for taking a vaccine platform other than BNT162b2 (Pfizer) and seven patients who missed the final visit. Therefore, the final study sample consisted of 164 poor/non-responder ARD patients who received the fourth dose of heterologous COVID-19 vaccine (BNT162b2) and returned after 30 days for blood collection. Demographic data and current treatment of ARD patients are described in supplementary Table S1, available at *Rheumatology* online. Patients' mean current age was 55.6 (12) years, with 137 (83.5%) of females, and mostly represented by RA (46.3%) {median age 63.3 [interquartile range (IQR) 56.2–70.7]}, SLE (23.2%) [median age 43.1 (IQR 36.8–50.0)] and SpA (10.4%) [median age 55.3 (IQR 47.3–61.8)]. Regarding current treatment, 93 (56.7%) of patients were under prednisone, 53 (32.3%) MTX, 24 (14.6%) LEF, 22 (13.4%) AZA, 21 (12.8%) MMF and 81 (49.4%) biologic drug [29 (17.7%) anti-TNF, 19 (11.6%) abatacept, 11 (6.7%) tocilizumab, 11 (6.7%) rituximab, 10 (6.1%) belimumab and 1 (0.6%) ustekinumab]. Most of the RA (71.8%) and SLE (86.8%) patients were under immunosuppressive drugs, while biologic therapy was used by 70.5% of RA and 26.3%, respectively. According to ACR guidelines [12], 27 patients on low disease activity/inactive disease withheld MTX for 2 weeks and 22 patients withdrew MMF for 1 week after vaccination.

Analysis of immune response to the fourth vaccine dose in poor/non-responder ARD patients are presented in Table 1. Robust increases were observed in anti-S1/S2 IgG and NAb positivity rates after fourth dose vaccination compared with the levels before vaccination ($P < 0.001$). Also, a relevant increase of GMT [29.5 (23.3–37.4) *vs* 215.8 (180.5–257.9) AU/ml, $P < 0.001$] was observed after vaccination, whereas for NAb activity the higher levels did not reach statistical significance (49.2 *vs* 90.6%, $P = 0.101$). Twenty-eight (17.1%) patients remained poor/non-responsive after the fourth dose. The subgroup of 46 non-responder ARD patients after the third dose demonstrated a significant increase in IgG positivity to 84.8% ($P < 0.001$), with GMT of 106 AU/ml (95% CI 68.2, 167), and NAb positivity of 82.6% ($P < 0.001$) with median NAb activity of 78.7% (IQR 53.5–95.2).

Among ARD patients on MTX treatment, the apparent higher rates in patients who withdrew the drug for 2 weeks ($n = 27$) after a fourth vaccine dose for positive anti-SARS-CoV-2 S1/S2 IgG [26 (96.3%) *vs* 22 (84.6%), $P = 0.192$], GMT [273.3 (95% CI 185.6, 402.2) *vs* 137.8 (95% CI 71.5, 265.5), $P = 0.143$], NAb positivity [22 (81.5%) *vs* 18 (69.2%), $P = 0.300$] and NAb activity [85.5% (68.9–95.8) *vs* 79.9% (56.5–93.8), $P = 0.463$] did not reach statistical significance. With regard to MMF, patients who withheld MMF ($n = 22$) and those who maintained the drug ($n = 6$) after the fourth dose had comparable frequencies of IgG [20 (90.9%) *vs* 6 (100%), $P = 1.0$] and NAb positivity [20 (90.9%) *vs* 4 (66.7%), $P = 0.192$].

Table 1 Humoral immunogenicity before and after fourth dose of COVID-19 heterologous vaccination in poor/non-responders ARD patients

Groups	After third dose	After fourth dose	*P*-value
Anti-S1/S2 IgG positivity, *n* (%)	109 (66.4)	156 (95.1)	**<0.001**
Anti-S1/S2 IgG GMT (95% CI), AU/mL	29.5 (23.3, 37.4)	215.8 (180.5, 257.9)	**<0.001**
NAb positivity, *n* (%)	9 (5.5)	137 (83.5)	**<0.001**
Neutralizing activity, median (IQR), %	49.2 (38.1–83.3)	90.6 (66.2–96.2)	**0.101**

Frequencies of subjects with positive anti-SARS-CoV-2 S1/S2 IgG and NAb are expressed as number (%). Positivity for anti-SARS-CoV-2 S1/S2 IgG was defined as post-vaccination titre ≥15 AU/mL by Indirect ELISA (LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Positivity for NAb was defined as a neutralizing activity ≥30% (cPass sVNT Kit, GenScript, Piscataway, NJ, USA). Anti-S1/S2 IgG antibody titres are expressed as GMT with 95% CI and percentage of neutralizing activity of NAb are expressed as medians [interquartile range (IQR)]. Frequencies of antibodies positivity 30 days after third dose and 30 days after fourth dose were compared using McNemar's test. The mean of the neperian logarithm-transformed IgG titres and NAb activity were compared between timepoints (30 days after third dose and 30 days after fourth dose) using paired *t*-test. $P < 0.05$ are highlighted in bold. ARD: autoimmune rheumatic diseases; GMT: geometric mean titres (AU/mL).

Analysis of factors associated with absence of IgG or NAb after the fourth vaccine dose is presented in Table 2. Patients with negative IgG were more frequently under rituximab ($P = 0.001$). Negative NAb was associated with older age ($P = 0.015$), RA ($P = 0.002$), SSc ($P = 0.026$), LEF ($P = 0.016$) and rituximab use ($P = 0.007$). Multiple logistic regression analysis revealed that prednisone dose $\geq$7.5 mg/day (OR = 0.34, $P = 0.047$), LEF (OR = 0.32, $P = 0.036$) and rituximab use (OR = 0.19, $P = 0.022$) were independently associated with lower NAb positivity after the fourth vaccine dose.

No serious adverse event was reported. Patients presented mostly local reactions including pain (43.3%), swelling (13.4%), induration (10.4%), erythema (6.1%) and pruritus (6.1%). The most frequent systemic reactions were headache (13.4%), myalgia (11.6%), fatigue (10.4%), arthralgia (9.8%), malaise (9.8%), back pain (9.1%), muscle weakness (7.9%) and somnolence (8.5%).

Table 2 Baseline characteristics of ARD patients seropositive and seronegative for IgG/NAb after fourth COVID-19 heterologous vaccination

	Anti-S1/S2 IgG			NAb		
	Seronegative ($n = 8$)	Seropositive ($n = 156$)	*P*-value	Seronegative ($n = 27$)	Seropositive ($n = 137$)	*P*-value
Demographic data						
Current age, years	55.8 (10.7)	55.6 (12.9)	0.970	61.1 (12.3)	54.5 (12.6)	**0.015**
Current age $\geq$60 years	3 (37.5)	68 (43.6)	>0.99	17 (63.0)	54 (39.4)	**0.024**
Female sex	6 (75.0)	131 (84.0)	0.504	25 (92.6)	112 (81.8)	0.165
White race	5 (62.5)	82 (52.6)	0.724	14 (51.9)	73 (53.3)	0.892
ARD						
RA	5 (62.5)	71 (45.5)	0.473	20 (74.1)	58 (40.9)	**0.002**
Axial SpA	0	8 (5.1)	>0.99	0	8 (5.8)	0.355
PsA	0	9 (5.8)	>0.99	0	9 (6.6)	0.358
SLE	1 (12.5)	37 (23.7)	0.683	1 (3.7)	37 (27.0)	**0.006**
Systemic vasculitis	1 (12.5)	7 (4.5)	0.336	2 (7.4)	6 (4.4)	0.619
Idiopathic inflammatory myopathies	0	8 (5.1)	>0.99	0	8 (5.8)	0.355
SSc	1 (12.5)	1 (0.6)	0.095	2 (7.4)	0	**0.026**
Primary SS	0	6 (3.8)	>0.99	2 (7.4)	4 (2.9)	0.257
Primary APS	0	6 (3.8)	>0.99	0	6 (4.4)	0.591
Current therapies						
HCQ	3 (37.5)	40 (25.6)	0.433	4 (14.8)	39 (28.5)	0.159
SSZ	0	10 (6.4)	>0.99	1 (3.7)	9 (6.6)	>0.99
Prednisone	5 (62.5)	88 (57.9)	>0.99	15 (55.6)	78 (58.6)	0.767
Prednisone dose	7.5 (4.4–12.5)	5 (5-10)	0.574	7.5 (5–10)	5 (5-0)	0.157
Prednisone $\geq$7.5 mg/day	3 (37.5)	31 (19.9)	0.364	9 (33.3)	25 (18.2)	0.077
Number of DMARDs	2 (2–2)	1 (1–2)	**0.018**	2 (1–2)	1 (1–2)	0.094
Immunosuppressive	8 (100)	108 (69.2)	0.106	22 (81.5)	94 (68.6)	0.179
MTX	5 (62.5)	48 (30.8)	0.113	13 (48.1)	40 (29.2)	0.054
LEF	0 0	24 (15.4)	0.605	8 (29.6)	18 (11.7)	**0.016**
AZA	1 (12.5)	21 (13.5)	>0.99	2 (7.4)	20 (14.6)	0.536
MMF	2 (25.0)	19 (12.2)	0.272	3 (11.1)	18 (13.1)	>0.99
Tofacitinib	0	5 (3.2)	>0.99	1 (3.7)	4 (2.9)	>0.99
Tacrolimus	1 (12.5)	3 (1.9)	0.183	0	4 (2.9)	>0.99
CYC	0	2 (1.3)	>0.99	0	2 (1.5)	>0.99
Ciclosporin	0	2 (1.3)	>0.99	0	2 (1.5)	>0.99
Biologic drug	6 (75.0)	75 (48.1)	0.165	14 (51.9)	67 (48.9)	0.780
Anti-TNF	0	29 (18.6)	0.353	2 (7.4)	27 (19.7)	0.170
Abatacept	2 (25.0)	17 (10.9)	0.233	6 (22.2)	13 (9.5)	0.059
Tocilizumab	0	11 (7.1)	>0.99	1 (3.7)	10 (7.3)	0.694
Belimumab	0	10 (6.4)	>0.99	0	10 (7.3)	0.371
Rituximab	4 (50.0)	7 (4.5)	**0.001**	5 (18.5)	6 (4.4)	**0.007**
Ustekinumab	0	1 (0.6)	>0.99	0	1 (0.7)	>0.99

Results are expressed in mean (S.D.), median (interquartile range) and *n* (%). Seropositivity for anti-SARS-CoV-2 S1/S2 IgG was defined as post-vaccination titre $\geq$15 AU/mL by Indirect ELISA (LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Positivity for NAb was defined as a neutralizing activity $\geq$30% (cPass sVNT Kit, GenScript, Piscataway, NJ, USA). $P < 0.05$ are highlighted in bold. ARD: autoimmune rheumatic diseases; NAb: neutralizing antibodies.

Discussion

This is the largest study to provide evidence of a remarkable humoral response to the fourth dose of heterologous mRNA SARS-CoV-2 vaccination in poor/non-responder ARD patients after the third dose of an inactivated vaccine.

The restricted inclusion of patients who were poor/non-responders to third dose of homologous inactivated COVID-19 vaccine and that subsequently received the BNT162b2 mRNA heterologous vaccine scheme allowed a more accurate evaluation of vaccine-induced immune response. In addition, the rigorous control of timeframe for vaccination and blood collection provided a homogeneous evaluation of immunogenicity, contrasting with the variable intervals described in previous case reports [2–4]. A limitation was the lack of data on cellular immune response, but neutralizing antibodies were reported to be highly predictive of immune protection [14].

Most ARD patients included in this study were negative for NAb. Of note, the fourth heterologous SARS-CoV-2 vaccination resulted in a significant increase in overall antibody response. Given that NAb is the most widely accepted marker of disease protection [14], it is encouraging that >80% of poor/non-responsive patients either seroconverted or increased IgG titres and NAb positivity after the fourth dose. The apparent increase in neutralizing activity from 49.2% to 90.6% after the fourth dose was not statistically significant and this is likely a power issue. Regardless of this aspect, previous evidence indicates neutralization titre as an important predictor of clinical protection from SARS-CoV-2 infection and suggests that neutralization levels for protection from severe infection are significantly lower than the 20% level required for protection [14] against general SARS-CoV-2 infection.

This finding reinforces that ARD patients with poor/no-response to the Sinovac-CoronaVac vaccine may benefit from a fourth additional heterologous dose to achieve their full potential of immunogenicity, contrasting with prior studies in solid organ transplant recipient non-responders [3, 15]. The higher immunosuppression state in transplant recipients with concomitant use of immunosuppressive drugs in most of them may explain this divergent result. Also, the homologous vaccination scheme with m-RNA vaccine in the study by Kamar *et al.* [15] may have limited vaccine response, in contrast to the heterologous strategy used in the present report. In fact, heterologous boosting seems to induce greater antibody increase than homologous boosting, with similar reactogenicity profile [16]. Importantly, the fourth vaccine dose was safe in ARD patients evaluated herein.

The detrimental effect of immunosuppressive therapy on antibody production has been previously demonstrated in ARD patients [1, 7, 8, 17]. We identified that prednisone in doses ≥7.5 mg/day and rituximab have a negative impact on immune response after the fourth dose in poor/non-responder patients, as also reported by our group after prime vaccination [7, 10, 17]. With regard to LEF, its negative effect on immunogenicity observed in the present study is probably related to the fact that all patients used this drug in association with other DMARDs, as observed in an RA population immunized with Sinovac-CoronaVac vaccine [7]. In contrast to SSc and RA, SLE patients tended to have higher rates of positive antibody responses. The younger age and lower frequency of biologic therapy in the latter group may explain these findings.

The ACR recommendation to withhold MTX and MMF [12] did not result in a significant difference among studied groups. The small sample size precluded a definitive conclusion about the apparent immunogenicity increase, particularly for the MTX withheld group.

In conclusion, this study demonstrated that a heterologous fourth dose of an mRNA SARS-CoV-2 vaccination was safe and provided a remarkable antibody response in ARD patients with poor/no-response to third dose. We further identified that some specific immunosuppressive drugs (rituximab and glucocorticoid) reduced antibody response to this additional dose.

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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