



Role of booster with BNT162b2 mRNA in SARS-CoV-2 vaccination in patients with rheumatoid arthritis

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Abstract

Only case reports and small clinical series report the effects of booster vaccination with BNT162b2 in patients with rheumatoid arthritis (RA). We studied 200 patients with RA in clinical remission evaluated with the DAS28. All patients were vaccinated for SARS CoV-2 with the BNT162b2 mRNA vaccine. The value of anti-SARS-CoV 2 Spike RBD IgG antibodies was determined at T1 (3 weeks after first vaccination) and T2 (3 weeks after booster). In addition, patients underwent assessment of lymphocyte subpopulations by flow cytometry analysis before starting the vaccination cycle (T0). Furthermore, the serum antibody levels of 96 health care workers (HCWs) were analyzed for comparison. DAS28 values at T0, T1, and T2 indicated remission or low disease activity in all patients. Levels of anti-SARS CoV-2 IgG at T1 were higher in HCWs than in patients' groups: 1562.00 BAU WHO/mL [975.00–1632.00] vs 416.00 BAU WHO/mL [110.00, 1581.00], $p < 0.001$. Anti-SARS COV2 IgG levels at T1 and at T2 were slightly lower in patients taking b/tsDMARDs than in patients under csDMARDs. Regression analysis evidenced age, treatment with abatacept (ABA), JAK inhibitors, and rituximab (RTX) as negative predictors of higher anti-SARS CoV-2 IgG levels at T1. Moreover, treatment with anti-IL6, anti-JAK, and anti-tumor necrosis factor (TNF) emerged as positive predictors of higher levels of anti-SARS CoV-2 IgG at T2. Our data show that despite the booster vaccine with BNT162b2, seroconversion in patients with rheumatoid arthritis is influenced by the background therapy, particularly for patients being treated with ABA and RTX.

Keywords Vaccination SARS-CoV-2 · Rheumatoid arthritis · mRNA BNT162b2

Introduction

SARS-CoV-2 infection is responsible for the coronavirus disease-2019 (COVID-19) pandemic with a severe acute respiratory syndrome and a severe impact on global health and difficult clinical management [1–3]. Mass vaccination is the most effective measure for controlling the COVID-19 pandemic and globally an effort to develop and distribute

an effective vaccine has produced important infection containment results. Several data are currently available on the efficacy of mRNA platform vaccines, namely BNT162b2 and mRNA-1273, in inducing strong antibody-mediated and cellular immune responses in naïve healthy subjects [4–6]. The ability to elicit a coordinated induction of the immune response is critical for an effective fight against SARS CoV-2 infection [7, 8]. Currently available data suggest that patients with autoimmune inflammatory rheumatic diseases have a slightly higher prevalence of SARS CoV-2 infections, and risk of hospitalization and death from COVID-19 compared to the general population, and were considered a priority target for the administration of the vaccine [9, 10]. Recently, some encouraging data on mRNA vaccination in rheumatoid arthritis (RA) patients have emerged from small studies and a large observational prospective multi-center study has evaluated the immunogenicity and safety of BNT162b2 compared to control subjects without rheumatic diseases [11–13]. Overall, these studies demonstrated that

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BNT162b2 vaccine is immunogenic in most RA patients (86–100%), but it elicits delayed and reduced response compared to controls. Also, the results on the impact of immunosuppressive therapy on the vaccine's immunogenicity is not homogeneous, with most studies showing that RTX followed by ABA, mycophenolate mofetil, corticosteroids (CCS), and methotrexate (MTX) can induce a significant reduction in seropositivity and antibody levels [14]. The aim of our study was to evaluate the induction of a specific immune response after SARS-CoV-2 booster vaccination in terms of anti-SARS CoV-2 anti-region binding domain (RBD) antibody response against spike and vaccination safety in terms of clinical impact on disease activity. A cohort of Health Care Workers (HCWs) were used as a control group.

Methods

We studied 200 RA patients defined according to the ACR/EULAR 2020 criteria [15] in clinical remission according to DAS28 score and enrolled at the Rheumatology Unit of the San Giovanni di Dio Hospital (Florence). All patients were vaccinated for SARS-CoV-2 with the BNT162b2 mRNA vaccine. For patients treated with methotrexate, leflunomide, abatacept, rituximab, treatment was discontinued following the ACR 2021 guidelines [16]. The study cohort underwent assessment of lymphocyte subpopulations (CD3 +, CD3 + / CD4 +, CD3 + / CD8 +, CD4 + / CD8 +, CD3– / CD19 +, CD3– / CD56 + CD16 +) by flow cytometry analysis (FACS CANTO II, BD Biosciences) before starting the vaccination cycle (T0). The value of anti-SARS CoV-2 Spike RBD IgG (FEIA ThermoFisher, Uppsala, Sweden) was assessed 3 weeks after the second vaccine dose (T1) and then 3 weeks after the booster (T2). In addition, the serum antibody levels of 96 HCWs were assessed after the second vaccine dose (T1). All patients expressed their written informed consent based on the prospective nature of the study according to the Declaration of Helsinki and Italian legislation (Privacy Guarantor No. 9, 12 December 2013).

Statistical Analysis

Statistical analysis was performed using software R 3.5.2 GUI 1.70 El Capitan build (7612). For the descriptive statistics, continuous variables were tested for normality (Kolmogorov-Smirnov) and represented by indicating the average and standard deviation if normally distributed. Non-normal variables were represented as median (inter-quartile range); categorical variables were described by frequency distribution. Demographic characteristics (age and sex) were compared between patients and controls by *T* test and chi-squared test as appropriate. DAS 28 values at T0, T1,

and T2 were compared between patients taking different b/tsDMARDs using one-way ANOVA, corrected with Welch test. DAS28 values differences between T0, T1, T2 were assessed by Wilcoxon test. Values of lymphocyte subpopulations (CD3 +, CD3 + / CD4 +, CD3 + / CD8 +, CD4 + / CD8 +, CD3– / CD19 +, CD3– / CD56 + CD16 +) were compared using *T* test between patients taking b/tsDMARDs (biological DMARDs, targets synthetic DMARD) vs patients taking only csDMARDs (conventional synthetic DMARDs); patients taking vs not taking methotrexate; patients taking vs not taking steroids; patients not taking antiTNF bDMARDs vs other bDMARDs. Serum levels of lymphocyte subpopulations were also compared using one-way ANOVA, between patients taking different DMARDs (overall and separately in patients taking and not taking b/tsDMARDs). Levels of anti-SARS CoV-2 IgG at T1 were compared through Kruskal-Wallis test between patients vs HCWs' control group; patients taking b/tsDMARDs vs patients taking only csDMARDs; patients taking vs not taking methotrexate; patients taking vs not taking steroids. Levels of anti-SARS CoV-2 IgG at T1 were then compared using Kruskal-Wallis test, between patients taking different DMARDs (overall and separately in patients taking and not taking b/tsDMARDs). Levels of anti-SARS CoV-2 IgG at T2 were compared through Kruskal-Wallis test between patients taking b/tsDMARDs vs patients taking only csDMARDs; patients taking vs not taking methotrexate; patients taking vs not taking steroids; patients taking different DMARDs; patients taking antiTNF bDMARDs vs other bDMARDs. Difference in levels of anti-SARS CoV-2 IgG at T1 vs T2 was assessed by Wilcoxon test. Linear regression analysis was performed to assess any predictive variables associated to higher levels of anti-SARS CoV-2 IgG at T1; higher levels of anti-SARS CoV-2 IgG at T2; higher difference between anti-SARS CoV-2 IgG levels at T1 vs at T2.

Results

Two hundred patients affected by RA were included in this study; mean age was 67.82 (SD 13.29) vs 50.54 years, SD 11.66, $p < 0.001$ in HCW. Of them, 156 (78%) were females and 44 (22%) were males. Patients who under treatment with b or ts DMARDs were 184 (92%): 64 (32%) were taking an IL-6 inhibitor, 43 (21.5%) anti-TNF inhibitors, 35 (17.5%) ABA, 24 (12%) JAK inhibitors, 18(9%) RTX. In this group of patients, 78 (42.4%) were also taking MTX.

Further details on employed drugs are shown in Table 1.

Furthermore, 16 patients (8%) were taking csDMARDs; 10 MTX alone (62.5%) and 6 in combination with LFN (37.5%).

DAS28 values at T0, T1, and T2 did not differ between patients undergoing different treatments and indicated

Table 1 Distribution of b/tsDMARDs in patients' group

b/tsDMARD	n (%)
Abatacept	35 (19.0)
Adalimumab	12 (6.5)
Baricitinib	15 (8.2)
Certolizumab	6 (3.3)
Etanercept	23 (12.5)
Golimumab	1 (0.5)
Infliximab	2 (1.1)
Rituximab	18 (9.8)
Sarilumab	9 (4.9)
Tocilizumab	52 (28.3)
Tofacitinib	4 (2.2)
Upadacitinib	7 (3.8)

Table 2 Comparison of antibodies' levels at T1 between health care workers and patients

Anti-SARS-COV-2 antibodies. BAU WHO/mL (median [IQR])		
HCW T1	Patients T1	P value
1562.00 [975.00, 1632.00]	416.00 [110.00, 1581.00]	<0.001

remission status. There were no significant changes in DAS 28 values from T0 to T1 (p 0.759), nor from T1 to T2 (p 0.847).

Serum levels of lymphocyte subpopulations (CD3 +, CD3+ / CD4 +, CD3 + / CD8 +, CD4 + / CD8 +, CD3– / CD19 +, CD3– / CD56 + CD16 +) did not significantly differ between patients taking b/tsDMARDs vs patients taking only csDMARDs, neither between patients taking vs not taking methotrexate. Patients taking steroids (5 mg/day of prednisone) showed lower levels of CD 19+ (139.91 ± 108.5 vs 198.71 ± 120.30 , p 0.013).

When compared across patients taking different b/tsDMARDs, serum levels of lymphocytes CD3+, CD3+/CD4+; CD19+ significantly varied (p 0.010, p <0.001, p 0.01 respectively, Table S1) with the higher values associated with patients taking anti-TNF bDMARDs. A comparison was then made between patients taking antiTNF and patients taking other b/tsDMARDs than anti-TNF: CD

3+, CD3+CD4+, and CD 19+ had higher values in the first group (p 0.01, p <0.01, and p 0.03 respectively).

Levels of anti-SARS CoV-2 IgG at T1 were higher in HCWs than in patients' groups (Table 2).

Anti-SARS CoV-2 IgG levels at T1 were slightly lower in patients taking b/tsDMARDs than in patients under csDMARDs (380.00 [0.70, 1632.00] vs 1480.00 [40.00, 1632.00], p 0.045).

Antibody production was lower in patients taking both b/tsDMARDs and MTX than in patients treated with b/tsDMARDs alone (208.00 [0.70, 1632.00] vs 488.00 [0.70, 1632.00], p 0.004).

No difference was found depending on the use of prednisone.

Kruskal-Wallis test comparing Anti-SARS CoV-2 IgG levels at T1 between different b/tsDMARDs was significant (p 0.011) as shown in Table 3 and Figure 1 with lower antibodies' level in patients taking ABA and RTX. Anyway, after the post hoc Steel test, only the difference between patients treated with ABA vs patients treated with anti-IL-6 maintained significance (p 0.28).

No difference in antibody levels was found between patients taking anti-TNF and patients taking other b/tsDMARDs than anti-TNF.

Regression analysis in the overall group of patients evidenced age, treatment with ABA, with JAK inhibitors, and RTX as negative predictors of higher anti-SARS CoV-2 IgG levels.

When restricted to patients taking b/tsDMARDs, regression analysis showed age as a negative predictor of higher anti-SARS CoV-2 IgG levels, while, between different b/tsDMARDs, none maintained significance in predicting antibody levels at T1.

Serum levels of lymphocyte subpopulations CD3+, CD3+CD4+, CD3+CD8+, CD19+, CD3–CD16*CD56+ did not correlate with antibody levels at T1 nor at T2.

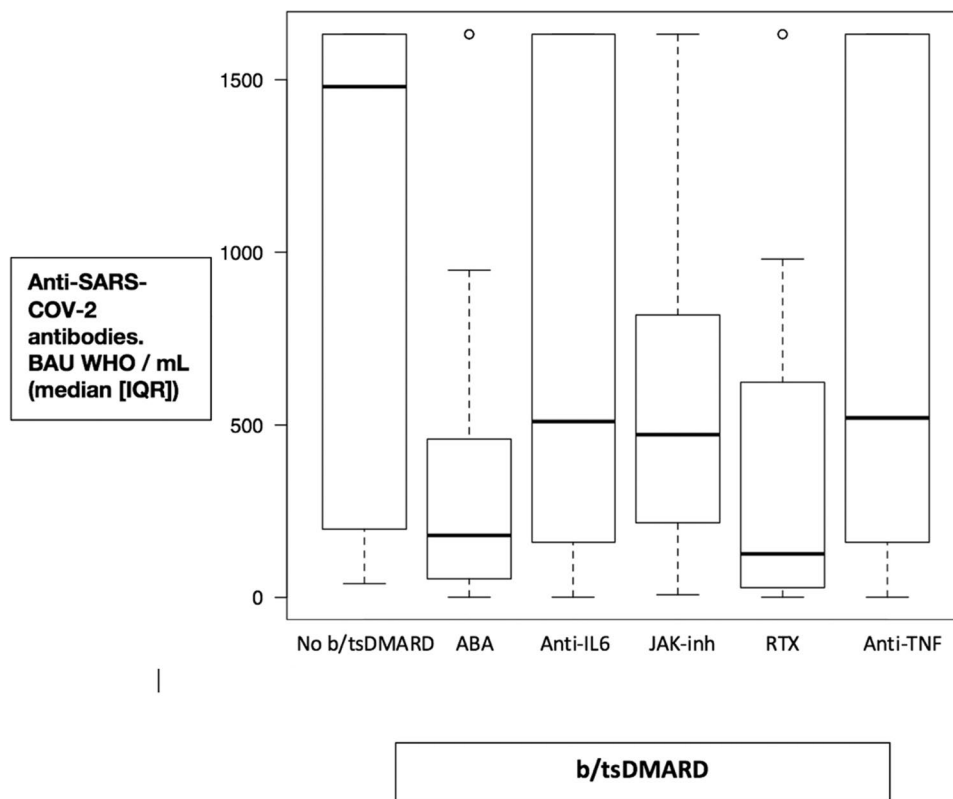
Anti-SARS CoV-2 IgG levels at T2 were lower in patients taking b/tsDMARDs than in patients under csDMARDs (445.50 [9.00, 1632.00] vs 1450.00 [56.00, 1632.00], p 0.032).

As for antibody levels at T1, IgG values at T2 were lower in patients taking in combination b/tsDMARD and MTX

Table 3 Median level of anti-SARS CoV-2 IgG at T1 in patients taking different b/tsDMARDs

b/tsDMARDs						p value
	Abatacept	Anti-IL6	Anti-JAK	Rituximab	Anti-TNF	
N°	35	64	24	18	43	
Anti-SARS-COV-2 antibodies	180.00 [0.70, 1632.00]	510.00 [0.70, 1632.00]	472.00 [218.25, 789.00]	126.50 [29.55, 568.25]	520.00 [0.70, 1632.00]	0.011
BAU WHO/mL (median [IQR])						

Fig. 1 Median level of anti-SARS CoV-2 IgG at T1 in patients taking different b/tsDMARDs



than in patients treated with b/tsDMARDs alone (562.00 [12.00, 1632.00] vs 231.50 [9.00, 1632.00], $p < 0.001$).

The intake of prednisone did not make any difference in antibody production for patients under both b/tsDMARDs and csDMARDs.

Kruskal-Wallis test comparing anti-SARS CoV-2 IgG values at T2 between patients taking different b/tsDMARDs was significant ($p < 0.001$), with lower values expressed by patients taking RTX and ABA (see Table 4). When post hoc Steel test was performed, significance was maintained by ABA vs anti-IL6 ($p < 0.001$), ABA vs Anti-Jak ($p 0.005$), ABA vs anti-TNF ($p 0.003$), RTX vs anti-IL6 ($p 0.04$).

Regression analysis in the overall group of patients showed level of antibodies at T1 to be a positive predictor of higher levels of antibodies at T2, while treatment with ABA was a negative predictor.

When restricted to patients taking b/tsDMARDs, regression analysis showed treatment with anti-IL6, anti-JAK, and anti-Tnf as positive predictors of higher levels of anti-SARS CoV-2 IgG at T2.

Serum levels of lymphocyte subpopulations CD3+, CD3+CD4+, CD3+ CD8+, CD19+, CD3–CD16+CD56+ did not correlate with antibody levels at T1 nor at T2.

Median levels of anti-SARS CoV-2 IgG significantly increased between T1 and T2 (p value < 0.0001) in overall group of patients and separately in patients taking b/tsDMARDs but not in patients taking only csDMARDs.

Linear regression analysis evidenced treatment with ABA as a negative predictor of higher differences between anti-SARS CoV-2 IgG levels at T1 and T2 in the overall group of patients (t value -2.03 , $p 0.043$) while treatment with anti-IL6 and anti-TNF were predictive of increased antibodies

Table 4 Median level of anti-SARS CoV-2 IgG at T2 in patients taking different b/tsDMARDs

	b/tsDMARDs					<i>p</i> value
	Abatacept	Anti-IL6	Anti-JAK	Rituximab	Anti-TNF	
<i>N</i> °	35	64	24	18	43	
Anti-SARS-CoV-2 antibodies	156.00	565.00	543.00	112.00 [9.00, 1632.00]	632.00 [12.00, 1632.00]	< 0.001
BAU WHO / mL (median [IQR])	[11.00, 1632.00]	[12.00, 1632.00]	[67.00, 1632.00]			

levels from T1 to T2 (t value 2.25, p 0.026, and t value 2.56, p 0.011, respectively).

Discussion

In light of the current evidence, our research is specific on full booster vaccination for SARS CoV-2 in patients with rheumatoid arthritis. Patients in clinical remission at baseline showed no increase in DAS28 values after vaccination with two doses of BNT162b2 mRNA nor after the booster. The studies evaluating the immunogenicity of SARS CoV-2 vaccines in RMD patients also briefly described the reactivation rate (ranging from 0 to 5%), and one multicentric study reported few cases of flare-up or new onset of immune-mediated diseases identified from the post-vaccination surveillance [11, 12, 17]; indeed, Watad et al. described 17 flares (and 10 new onset) of immune-mediated diseases identified among the adverse event report forms from multiple academic centers located in 3 countries [18]. More recently, the Global Rheumatology Alliance (GRA) carried out a survey to investigate RMD patients' perceptions and outcomes related to COVID-19 vaccines showing a 13.4% rate of flare after the vaccination in patients with different RMDs, with only about one-third (4.6% of the whole cohort) requiring medication changes [19]. The trials evaluating the immunogenicity and safety of the mRNA vaccine for SARS CoV-2, enrolling overall 1000 patients with different chronic inflammatory diseases, showed a low rate of disease reactivation during the observational time ranging from 2 to 8 weeks of follow-up [11, 12]. While Geisen et al. and Braun-Moscovici et al. reported no flare at all, Furer et al. reported a worsening of the symptoms of underlying RMD in 2.53% of patients after the first dose and 1.79% after the second one [17]. Data from telephone interviews on adverse vaccination events of 126 patients with RMD revealed 5 suspected cases. RMDs were subsequently confirmed in 3 of them, 2 women with psoriatic arthropathy and 1 with rheumatoid arthritis. The incidence rate of RMD reactivation was of 0.007 person/month [20]. It has recently been shown in mouse models that BNT162b2 induces immunization of natural killer cells and CD8 + T cells in draining lymph nodes which are the main producers of circulating IFN- γ . Vaccine-induced CD8 + T cell response is dependent on type I interferon-dependent MDA5 signal [21]. The short-term persistence of humoral immunity, together with the reduced neutralizing capacity compared to the currently prevalent SARS-CoV-2 variants, may explain reinfections. Long-lived memory B lymphocytes and CD4 + T lymphocytes can protect against the development of serious disease. A booster dose restores optimal anti-spike immunity in naïve individuals, while the need for vaccinated individuals cured of COVID-19 has yet to be defined [22]. It is not currently known the impact of

drug therapies in memory B cell and CD4 + T cell of RA subjects. In our study, serum levels of CD3 +, CD3+CD4 +, CD3+ CD8 +, CD19 +, CD3-CD16+CD56 + lymphocytes did not differ significantly between patients taking b/tsDMARD compared to patients taking csDMARD alone, nor between patients taking and not taking methotrexate. Patients taking steroids (prednisone 5 mg/day) showed lower levels of CD 19+. This may explain the role that chronic prednisone intake played in reducing antibody production [23, 24]. When comparing patients taking different b/tsDMARDs, the serum levels of CD3 +, CD4 + lymphocytes, and CD19 + varied significantly with the higher values represented by patients taking anti-TNF bDMARD. Literature data show that TNF antibodies do not have an impact on antibody production after vaccination [11–13, 17, 25, 26]. And, in fact, the comparison between different b/tsDMARDs showed higher antibody levels in patients taking anti-TNF and anti-IL-6, even if there was no difference between patients taking anti-TNF with a group including patients taking other b/tsDMARDs than anti-TNF. Antibody production was lower in patients taking b/tsDMARD and MTX together than in patients taking b/tsDMARD alone. Other literature data have demonstrated the role of MTX in reducing antibody production after SARS-CoV-2 vaccination [14–27]. The median anti-SARS CoV-2 Spike RBD IgG antibody levels in the rheumatoid arthritis patient cohort at T1 was 416.00 [110.00, 1581.00], while the median serum level of the HCW group was 1562.00 BAU WHO/mL [IQR 975.00, 1632.00], significantly higher than the patients' group ($p < 0.001$). It is to note that patients were medially older than controls (mean age was 67.82, SD 13.29, vs 50.54 years, SD 11.66, $p < 0.001$) and this could be a limitation of the study as in similar studies as well [26]. Anyway, linear regression analysis revealed age as a negative predictor of concentration levels in patients' cohorts while no association emerged between age and IgG levels in HCW. Therefore, age-related immune-senescence associated with immunomodulatory treatments may also contribute to lower IgG levels in patients' but not in controls' group. A limitation of our study could be the absence of data on HCW antibodies levels after their booster (T2) that could have allowed further comparison. Moreover, we did not use the virus neutralization assay since it was not available.

Nevertheless, the data on the booster highlighted interesting aspects of the research. T1 antibody values after vaccination affects T2 values after the booster. Our study highlights that patients undergoing the booster while in treatment with anti-TNF, anti-JAK, and anti-IL-6 showed a significant increase in antibody production after the booster, while patients treated with ABA and RTX did not show an increase in antibody production after the booster. A deficit in humoral and cellular T response mediates by IL-2 and IFN γ in RA patients receiving ABA after SARS CoV-2 vaccination

has been demonstrated [28]. Moreover, no improvement was found in patients on ABA with the booster despite the 3-week suspension. Based on these results and considering that ABA blocks the activation of T lymphocytes by binding with high affinity CD80+ / CD86+ molecules thus interfering with the co-stimulation signals delivered through the antigen submitted [29, 30], it may be reasonable to extend the suspension to more than one month. This approach can improve the induction of a specific immune response especially at the level of T lymphocytes. For RTX, it has been seen that reduced or absent antibodies production depends on time between the last infusion and the vaccination, with an average 9 months [31] needed to elicit a molecular response, while an IGRA cellular T response was also observed in patients without circulating antibodies [32, 33]. A strength of our study is the numerosity of sample size. In fact, in literature, data on the booster comes from extremely small cohorts in comparison with our case series. A case report shows the presence of antibodies after a booster with BNT162b2 in a patient with rheumatoid arthritis treated with upadacitinib and initial negative antibodies response [34]. A second case of a patient receiving etanercept 50 mg/week, leflunomide 20 mg/day had no antibody response after vaccination with mRNA-1273 vaccine (Moderna) and had antibody but not cellular response after a booster with one dose of the Ad26. COV2.S viral vector SARS-CoV-2 vaccine (Johnson & Johnson) [35]. An antibody production after booster was demonstrated in 12 of 17 patients with rheumatoid arthritis treated with b-DMARD and b/tsDMARDs [36], while in a study of 18 patients with autoimmune diseases without significant immune response after the initial vaccination, the absence of antibody production persisted in two RA patients taking mycophenolate or RTX [37]. A recent study involved 90 patients treated with RTX of which 49 patients were given a third dose of the vaccine. Nineteen (21.8%) of 87 patients produced antibodies since the last rituximab infusion (median 267 days [IQR 222–324]). After two vaccine doses, 10 (53%) of 19 patients had CD3+ CD4 + lymphocyte response and 14 (74%) had CD8 + lymphocyte response. A third dose of vaccine induced serological responses in eight (16.3%) of 49 patients, but induced a CD3+CD4 + and CD3+CD8 + response in all patients evaluated ($n = 12$) [38]. Recent CoronaVac data on 597 patients with autoimmune rheumatic disease (ARD) showed that the third dose increases the anti-S1/S2 IgG seropositivity rate from day 210 (60%) to day 240 (93%) ($p < 0.0001$) in patients with ARD. Neutralizing antibody positivity also increased: 38% (day 210) vs 81.4% (day 240) ($p < 0.0001$). Negatively correlated factors with antibody production were doses of prednisone > 5mg, abatacept, mycophenolate, rituximab, and MTX despite 2-week discontinuation. Interestingly in this study, the number of infections after the booster was small [39]. We observed 4 cases of moderate infection

in our cohort, in the post-vaccination time, higher than the rate reported by the EULAR-COVID-19 and COVAX registries which suggest that the breakthrough rate is low (1%) in fully vaccinated individuals with inflammatory RMD [40]. Actually, further studies are needed to clarify the impact of these variants on vaccines' efficacy, both in healthy subjects and in patients with RMDs.

Conclusion

Our study shows that despite the booster vaccine with BNT162b2, seroconversion in patients with rheumatoid arthritis is conditioned by the background therapy in particular for those patients being treated with ABA and RTX. Considering that guidelines are available on suspension time of the two bDMARDs before and after every vaccine dose, these results could contribute to their modification in order to optimize serological response. Moreover, antibody production showed to be lower in patients taking b/tsDMARD and MTX in combination, so that these patients may deserve special attention in vaccination schedule, maybe with adjunctive boosters. Finally, based on literature data, also the evaluation of T cell response provides further information on drugs effect in immunological reaction to vaccination. So it may be included within the routine tests to be performed in patients affected by RA as well as by other inflammatory diseases, treated with immunosuppressive drugs.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12026-022-09283-y>.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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