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Basic science

Rituximab, but not other biologics, impairs humoral immunity in patients with rheumatoid arthritis—a study using CoVariant protein arrays

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Abstract

Objectives: RA is an autoimmune disease characterized by chronic inflammation and joint destruction. Biologics are crucial to achieving treat-to-target goals in patients with RA. The global spread and continuous variation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) necessitate the monitoring of variant-specific humoral responses post-vaccination. The aim of this study was to investigate how different biologic treatments for vaccinated RA patients might affect their neutralizing antibodies against multiple SARS-CoV-2 variants.

Methods: We recruited RA patients who had received three doses of conventional SARS-CoV-2 vaccines and were treated with various biologics, e.g. TNF inhibitor (etanercept), IL-6 inhibitor (tocilizumab), CTLA4-Ig (abatacept) or anti-CD20 (rituximab). Serum samples were used to profile the binding and neutralizing antibodies using our own SARS-CoV-2 variant (CoVariant) protein array, developed previously.

Results: Compared with healthy controls, only RA therapy with rituximab showed a reduction in neutralizing antibodies capable of targeting spike proteins in SARS-CoV-2 wild-type and most variants. This reduction was not observed in binding antibodies against SARS-CoV-2 wild-type or its variants.

Conclusion: After receiving three doses of SARS-CoV-2 vaccination, RA patients who underwent rituximab treatment generated sufficient antibodies but exhibited lower neutralizing activities against wild-type and multiple variants, including current Omicron. Other biological DMARDs, e.g. TNF inhibitor, IL-6 inhibitor and CTLA4-Ig, did not show obvious inhibition.

Lay Summary

What does this mean for patients?
This research examined the impact of various biologic treatments (a type of drug) on the immune response of rheumatoid arthritis (RA) patients to coronavirus disease 2019 (COVID-19) vaccination. The study revealed that RA patients treated with rituximab had significantly lower levels of neutralizing antibodies against various severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, including Omicron, even after receiving three vaccine doses. Neutralizing antibodies defend the body from organisms that cause disease, such as viruses, by preventing them from entering cells. In contrast, RA patients receiving other biologic therapies, including TNF inhibitors, IL-6 inhibitors or CTLA4-Ig, did not experience the same reduction in neutralizing antibodies. No significant difference was found in serum antibodies, regardless of the specific biologic therapy (TNF inhibitors, IL-6 inhibitors, CTLA4-Ig or anti-CD20). This study highlights the different immune responses to COVID-19 vaccination in patients with RA treated with various biologics. Therefore, individuals with RA who are considering or are currently undergoing biologic treatment should engage in thorough discussions with their health-care providers regarding vaccination strategies. In summary, this study underscores the necessity for personalized vaccination strategies for RA patients based on their specific treatment regimens to ensure robust protection against evolving COVID-19 variants.

Keywords: rheumatoid arthritis, SARS-CoV-2 variants, protein microarray, DMARDs, rituximab, neutralizing antibody.

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Key messages

- This study reveals the impact of biologics on humoral responses against multiple SARS-CoV-2 variants in vaccinated RA patients.
- For patients with a three-dose history of the SARS-CoV-2 vaccine, rituximab, but not other biologics, inhibited neutralizing antibodies against multiple SARS-CoV-2 variants, including Omicron.

Introduction

RA is a systemic autoimmune disease that can result in joint destruction and disability. Although the pathogenesis of RA is incompletely understood, advances in understanding have fostered the development of new medications, including biologics. Early diagnosis and treatment with DMARDs, including biologic DMARDs (bDMARDs), are crucial in controlling disease and preventing joint destruction. Although bDMARDs are important in RA treatment, they could increase the risk of infection [1].

The RNA nature of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has produced multiple variants and a broad global spread. Vaccination is the most efficient strategy for preventing severe coronavirus disease 2019 (COVID-19) in healthy individuals. In patients with RA, vaccination is generally safe and efficacious. However, the immune responses after SARS-CoV-2 vaccination can be blunted in RA patients treated with bDMARDs, especially those treated with B-cell-depleting therapy [2, 3]. During the SARS-CoV-2 pandemic, patients with autoimmune diseases, particularly those treated with rituximab, exhibited a higher mortality rate than the general population [4]. Previous studies have also shown that rituximab and other immunosuppressants can affect the efficacy of SARS-CoV-2 vaccines in patients with autoimmune diseases [5]. The variant-specific immune responses in RA patients treated with different biologics are not fully understood.

A functional protein microarray is a high-throughput tool that captures native proteins on the surface for profiling humoral immunities [6]. To quantify the humoral responses against multiple SARS-CoV-2 variants simultaneously, our team recently developed a high-throughput tool named SARS-CoV-2 variant (CoVariant) protein microarray [7]. With this tool, we aimed to analyse the impact of bDMARDs on the humoral responses against multiple SARS-CoV-2 variants after vaccinations.

Methods

Participants and blood sampling

Consecutive patients with RA who were ≥20 years old and receiving treatment with biologic DMARDs, including rituximab (anti-CD20), etanercept (TNF inhibitor), tocilizumab (IL-6 inhibitor) or abatacept (CTLA4-Ig), were included from 1 March 2022 to 30 September 2022 in the rheumatology outpatient department of National Cheng Kung University Medical Center. All subjects without SARS-CoV-2 infection were vaccinated three times with mRNA vaccine (BioNTech and Moderna) or protein vaccine (Novavax). All participants gave written informed consent according to the approval of the ethics committee at National Cheng Kung University Hospital Taiwan (approval number: A-ER-110–263). In addition to six healthy controls, the RA patients included in this study were eight treated with etanercept, six with tocilizumab, six with abatacept and eight with rituximab. Blood samples were collected in 8.5 ml SST-II tubes (BD, catalog no. 367953) and kept for 15 min at room temperature before centrifugation at 2000 xg for 10 min to separate the sera. Sera were divided into several aliquots and stored immediately in a −80°C refrigerator until detection.

CoVariant protein microarray

The design of the CoVariant protein microarray was based on previous publication with some modifications [7]. Briefly, a collection of spike receptor-binding domains (RBDs) or extracellular domains (ECDs) from SARS-CoV-2 wild-type and nine variants (B.1.1.7/Alpha, B.1.351/Beta, P.1/Gamma, B.1.617.2/Delta, B.1.617.3/Delta+, B.1.1.529/Omicron, BA.2.12.1/Omicron, BA.4/Omicron and BA.5/Omicron) were included. Protein samples were prepared in 30% glycerol and printed in triplicates onto aldehyde-coated slides using a contact printer (CapitalBio, #SmartArrayer 136). Each focused CoVariant protein microarray consisted of 14 identical blocks for independent assays. The protein arrays were immobilized overnight, then stored at −80°C. Quality control of CoVariant protein arrays was achieved using anti-6xHis tag and angiotensin-converting enzyme 2 (ACE2) staining.

Serum profiling using CoVariant protein arrays

The pre-made CoVariant protein arrays were removed from the −80°C refrigerator and defrosted at room temperature. The detailed assay procedures were described previously [8]. Briefly, arrays were blocked, incubated with 50 µl of 50× diluted serum samples in tris-buffered saline with 0.1% tween 20 (TBST) with 0.1% BSA for 1 h, washed three times, incubated with Cy3-labelled anti-human IgG/IgA/IgM and Cy5-labelled ACE2 cocktails for 1 h, washed three times, and dried. The fluorescence images were acquired by a laser scanner (Caduceus Biotechnology, #SpinScan) with 25% 532 nm laser power and 30% 633 nm laser power. The raw signal intensity of each spot was extracted by GenePix Pro software and analysed and exported as the foreground minus background. The surrogate neutralizing activities were measured using the Cy5 fluorescence: 1 − (ACE2 signals with serum/ACE2 signals without serum) × 100% [7, 8]. For binding antibodies, the signals of the Cy3-labelled anti-human were adjusted according to anti-His signals to normalize the amount of protein and presented as the relative fluorescence intensity (RFI).

Statistical analysis

To compare different groups, a one-way ANOVA followed by Tukey's *post hoc* test was performed. Statistical significance was defined as a *P*-value of <0.05. Data were calculated with GraphPad Prism software ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ and $^{****}P < 0.0001$). Data are presented as the mean ± SD, where *n* represented the number of subjects.

Results

Cohorts and participant characteristics

A total of six healthy control patients (33.34% females, mean age 44 ± 15 years), and 28 RA patients treated with bDMARDs, including TNF inhibitor (etanercept, $n = 8$), IL-6 inhibitor (tocilizumab, $n = 6$), CTLA4-Ig (abatacept, $n = 6$) and anti-CD20 (rituximab, $n = 8$), were recruited. Baseline characteristics of patients in our study are summarized in Supplementary Table S1, available at *Rheumatology Advances in Practice* online. Most of the patients on bDMARDs were concomitant with at least one conventional synthetic DMARD. None was treated with AZA, MMF or CYC. All study participants were vaccinated three times (fully vaccinated) with either mRNA or protein vaccines. Blood was samples ≥30 days after their third vaccine (Supplementary Table S1, available at *Rheumatology Advances in Practice* online).

Neutralizing antibody against multiple SARS-CoV-2 variants in fully vaccinated RA patients

To understand the neutralizing effects in RA patients treated with different bDMARDs after three doses of vaccine, we separated RA patients treated with different bDMARDs and added healthy controls for the comparisons. By using CoVariant protein microarrays, we were able to detect simultaneously serum antibodies and surrogate neutralizing antibodies against multiple variants (Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online). The extracellular domain of spike protein interacted with ACE2, whereas the RBD was the key part to dock with ACE2. The surrogate neutralizing antibodies could be calculated based on the interaction between RBD and ACE2 (Fig. 1; Supplementary Fig. S2, available at *Rheumatology Advances in Practice* online) or between ECD and ACE2 (Supplementary Figs S3 and S4, available at *Rheumatology Advances in Practice* online).

The surrogate neutralizing activity assays for viral RBD and viral ECD showed slightly different results. Compared with healthy vaccinated subjects, RA patients treated with anti-CD20 (rituximab) showed significantly lower neutralizing antibodies against multiple variants, including RBDs from wild-type, Alpha, Beta, Gamma, Delta, Delta+ and Omicrons (Fig. 1). Similar observations were made for neutralizing antibodies against ECDs (Supplementary Fig. S3, available at *Rheumatology Advances in Practice* online). Comparing different bDMARD-treated RA patients, the TNF inhibitor (etanercept) showed better neutralizing activity than anti-CD20 against RBDs from wild-type, Gamma, Delta and Omicron/B.1.1.529 (Fig. 1). TNF inhibitor also showed better neutralizing activities than anti-CD20 against ECDs from wild-type, Alpha, Beta, Gamma, Delta and Delta+ (Supplementary Fig. S3, available at *Rheumatology Advances in Practice* online).

Given that disease duration is important for antibody production, we investigated the correlation between neutralizing antibodies against variants and periods of bDMARDs exposure (Supplementary Fig. S5, available at *Rheumatology Advances in Practice* online) and found that the TNF inhibitor showed a negative correlation with most variants except Beta, Gamma and Delta ECD (Supplementary Fig. S5A, available at *Rheumatology Advances in Practice* online). IL-6 inhibitor showed a positive correlation with Gamma, Omicron/

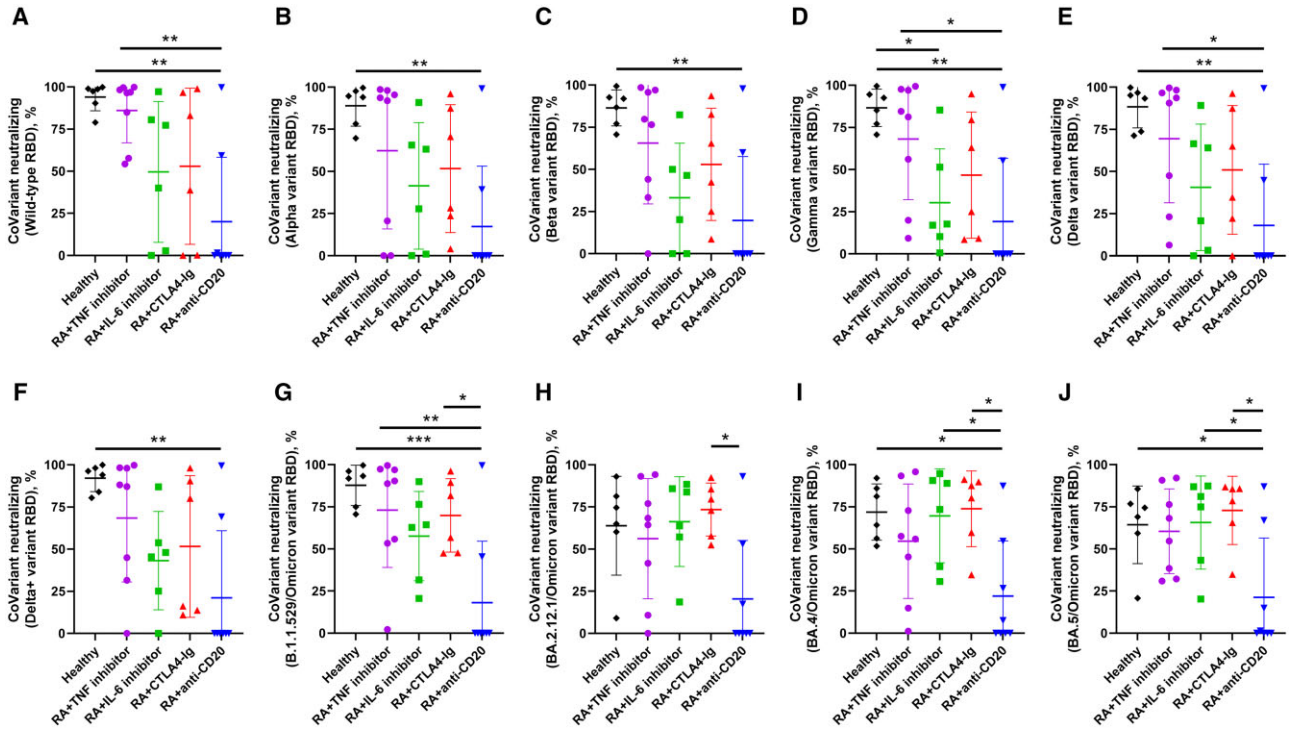

Figure 1. Surrogate neutralizing antibody against severe acute respiratory syndrome coronavirus 2 receptor-binding domains in vaccinated healthy and vaccinated RA patients. Spike receptor-binding domains from wild-type (**A**), Alpha variant (**B**), Beta variant (**C**), Gamma variant (**D**), Delta variant (**E**), Delta+ variant (**F**), B.1.1.529/Omicron (**G**), BA.2.12.1/Omicron (**H**), BA.4/Omicron (**I**) and BA.5/Omicron (**J**) were used to determine the neutralizing antibodies in vaccinated healthy or vaccinated RA patients undergoing therapy with biologic DMARDs. Data were analysed by one-way ANOVA followed by Tukey's *post hoc* test. The threshold of significance was $P < 0.05$. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, as indicated on the plots

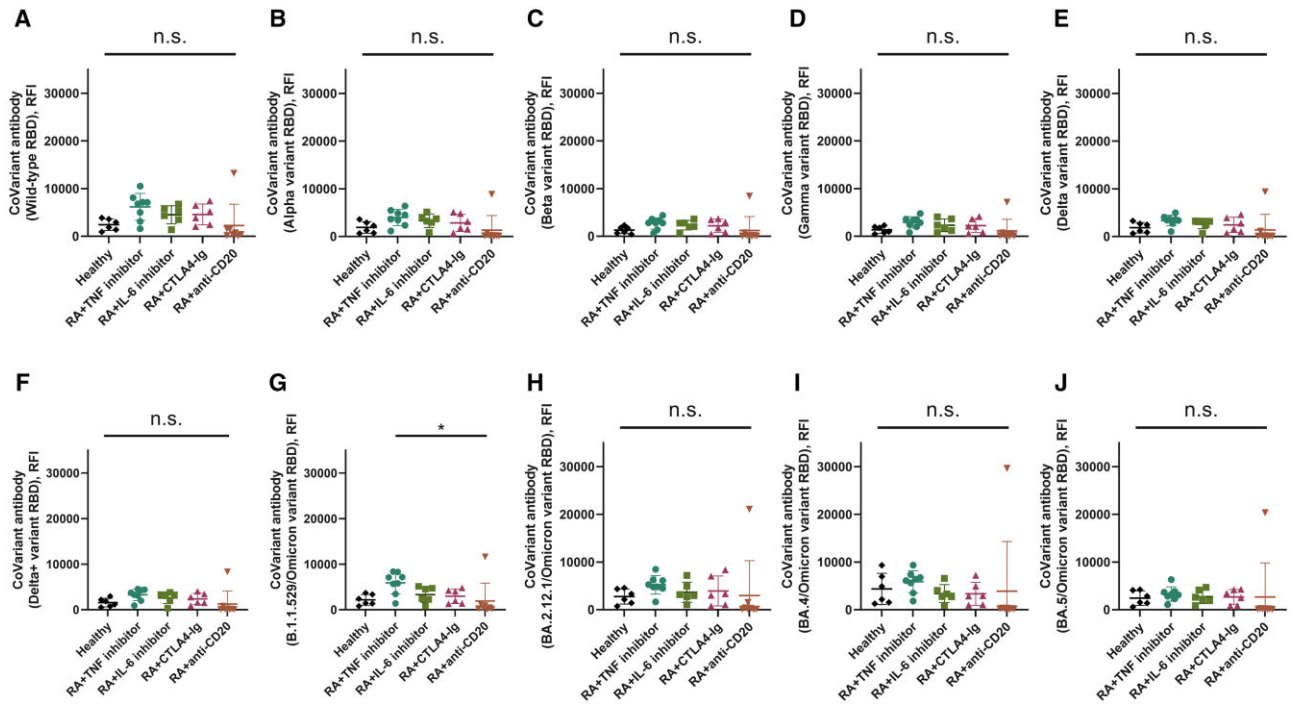

Figure 2. Serum antibody against severe acute respiratory syndrome coronavirus 2 receptor-binding domains in vaccinated healthy and vaccinated RA patients. Spike receptor-binding domains from wild-type (**A**), Alpha variant (**B**), Beta variant (**C**), Gamma variant (**D**), Delta variant (**E**), Delta+ variant (**F**), B.1.1.529/Omicron (**G**), BA.2.12.1/Omicron (**H**), BA.4/Omicron (**I**) and BA.5/Omicron (**J**) were used to quantify the binding antibodies in vaccinated healthy or vaccinated RA patients undergoing therapy with biologic DMARDs. Data were analysed by one-way ANOVA followed by Tukey's *post hoc* test. The threshold of significance was $P < 0.05$, and n.s. indicates no significant differences

BA.2.12.1, Omicron/BA.4, Omicron/BA.5 ECD and Gamma RBD (Supplementary Fig. S5C, available at *Rheumatology Advances in Practice* online). CTLA4-Ig showed a positive correlation only with Omicron/B.1.1.529 ECD (Supplementary Fig. S5E, available at *Rheumatology Advances in Practice* online). Anti-CD20 was positively correlated with most variants except wild-type, Alpha, Beta, Gamma, Delta, Delta+ and Omicron/BA.4 ECD (Supplementary Fig. S5G, available at *Rheumatology Advances in Practice* online).

Serum antibody against multiple SARS-CoV-2 variants in fully vaccinated RA patients

To understand the number of antibodies against SARS-CoV-2 in the RA patients treated with different bDMARDs, we quantified the serum antibodies against RBDs (Fig. 2; Supplementary S6, available at *Rheumatology Advances in Practice* online) and ECDs (Supplementary Figs S7 and S8, available at *Rheumatology Advances in Practice* online) from multiple SARS-CoV-2 variants. Although there were differences in levels of neutralizing activity between groups for RBDs or ECDs regarding surrogate neutralizing antibodies (Fig. 1; Supplementary Fig. S3, available at *Rheumatology Advances in Practice* online), there were almost no differences between groups in serum antibodies against spike RBDs or ECDs (Fig. 2; Supplementary Fig. S7, available at *Rheumatology Advances in Practice* online). The impact of bDMARDs on fully vaccinated RA patients was more significant for neutralizing antibodies than binding antibodies.

We also examined the relationship between serum antibodies against different variants and the duration of treatment with various bDMARDs (Supplementary Fig. S5, available at *Rheumatology Advances in Practice* online). TNF inhibitors and CTLA4-Ig showed no significant correlation (Supplementary Fig. S5B and F, available at *Rheumatology Advances in Practice* online). However, IL-6 inhibitors were positively correlated with Alpha ECD, Omicron/BA.2.12.1 and Omicron/BA.4 RBD variants (Supplementary Fig. S5D, available at *Rheumatology Advances in Practice* online). Anti-CD20 treatment was positively correlated with most variants, except Beta, Gamma and Delta+ ECD (Supplementary Fig. S5H, available at *Rheumatology Advances in Practice* online).

Discrimination between bDMARD-treated RA patients and healthy controls after vaccination

Given that the impact of neutralizing antibodies was more significant than that of binding antibodies, neutralizing antibodies were selected to discriminate RA patients on bDMARDs from healthy controls. The performance of each neutralizing marker could be quantified using receiver operating characteristic curves. RA patients treated with TNF inhibitor were the least discernible from healthy controls in data for multiple neutralizing RBDs and ECDs [area under the curve (AUC) $<$ 0.8; Supplementary Figs S9 and S10, available at *Rheumatology Advances in Practice* online]. RA patients treated with IL-6 inhibitor, CTLA4-Ig and anti-CD20 were easily discernible from healthy controls in most neutralizing RBDs and ECDs, except for a few RBDs in Omicron (AUC $>$ 0.8; Supplementary Figs S9 and S10, available at *Rheumatology Advances in Practice* online). In the neutralizing RBDs, RA patients treated with anti-CD20 displayed the best discriminatory power *vs* healthy controls from wild-type to Omicron (AUC $>$0.8; Supplementary Fig. S9, available at

Rheumatology Advances in Practice online). These aligned with the better neutralizing activity of RA patients treated with TNF inhibitor than with anti-CD20 (Fig. 1; Supplementary Fig. S3, available at *Rheumatology Advances in Practice* online).

Discussion

The results of our study showed lowered neutralizing antibodies against SARS-CoV-2 variants in RA patients treated with rituximab (anti-CD20), but not etanercept (TNF inhibitor), tocilizumab (IL-6 inhibitor) or abatacept (CTLA4-Ig). Previous studies have shown an increased risk of poor outcomes related to SARS-CoV-2 infection, including deaths, in RA patients [9] and in those treated with MTX, JAK inhibitors [10], and in particular, among those treated with anti-CD20 [11] with or without conventional synthetic DMARDs, when compared with the general population.

B Cells play a critical role in the development of humoral immune responses. In a recent French cohort study of 63 patients treated with rituximab, 13 (21%) died of COVID-19 compared with 76 (7%) of 1027 patients without rituximab [11]. Anti-CD20 (rituximab) therapy depletes B cells with decreased humoral immune response to recall antigens. Our data are in line with others showing that rituximab affects neutralizing antibodies to COVID-19 vaccination [12–14]. We proved that in RA patients undergoing treatment with rituximab, even in patients receiving three doses of SARS-CoV-2 vaccinations, the neutralizing antibodies are still significantly lower than in healthy controls. In our study, even after a third dose, the number of binding antibodies appeared normal in RA patients treated with rituximab, but neutralizing activities against multiple variants were still inhibited. mAb treatment needs to be considered in RA patients treated with rituximab in the event of SARS-CoV-2 exposure [15].

Other bDMARD treatments in RA patients, such as TNF inhibitor, IL-6 inhibitor or CTLA4-Ig, did not exhibit obvious inhibition in neutralizing activities against multiple variants. Our findings were aligned with others showing no adverse outcomes for RA patients treated with TNF inhibitor, IL-6 inhibitor or CTLA4-Ig [10].

The significant strength of our study is the CoVariant array, allowing for high-throughput screening of serum antibodies and neutralizing antibodies against multiple SARS-CoV-2 variants and providing a valuable tool for monitoring the humoral responses and vaccine efficacy. As the global pandemic continues, such platforms could play a crucial role in understanding the immune responses to ongoing mutations, helping to guide clinical decision-making.

Our study has some limitations. First, only 34 individuals were included. Despite such limits of size, our study results still identified the significant differences of immune response in different subjects. Second, as SARS-CoV-2 variants constantly change, the development of new CoVariant arrays might be necessary in the future. Third, because various bDMARDs have different routes and durations of administration, a risk of selection bias exists. For instance, patients on rituximab were older and more likely to be exposed to CSs. Dosing periods and the cumulative dose might also affect the immune response of the patient following SARS-CoV-2 vaccinations.

Conclusion

Despite receiving three doses of SARS-CoV-2 vaccination, RA patients who underwent rituximab treatment generated sufficient antibodies but exhibited lower neutralizing activities against wild-type and multiple variants, including current Omicrons. Other biological DMARDs, e.g. TNF inhibitor, IL-6 inhibitor and CTLA4-Ig, did not show obvious inhibition.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The datasets generated in this study are available from the corresponding author upon reasonable request.

Author contributions

W.-H.L., P.-X.D., P.-S.T., B.B.K., W.-Y.S., N.-Y.L., W.-C.K., P.-C.L., H.-C.S., M.-Y.W. and G.-D.S. performed the experimental work. W.-H.L., M.-Y.W. and G.-D.S. contributed to the manuscript preparation. M.-Y.W. and G.-D.S. contributed their expertise and supervision to the entire project.

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