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Antibody response to SARS-CoV-2 mRNA vaccines in patients with rheumatic diseases in Japan: Interim analysis of a multicenter cohort study

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Abstract

Background: To evaluate the impact of medication on antibody response to SARS-CoV-2 mRNA vaccines in Japanese patients with rheumatic diseases.

Methods: This prospective multicenter cohort study evaluated the humoral response in 12 different medication groups. Antibody levels before the first vaccination and 3-6 weeks after the second vaccination were measured using the Elecsys Anti-SARS-CoV-2 S assay. Statistical analysis included comparing antibody titers among the different medication groups using the Kruskal–Wallis test followed by the Bonferroni–Dunn test for multiple comparisons and multiple linear regression analysis.

Results: Three hundred and seventy-two patients receiving treatment for rheumatic diseases were enrolled, and 295 patients were analyzed. The seroconversion rate was 92.2% and the median antibody titer was 255 U/ml (interquartile range; IQR, 34.1-685) after the second mRNA vaccination. Antibody levels were significantly lower in the groups treated with TNF inhibitor (TNFi) with methotrexate (MTX) (median, 104 U/ml; IQR, 33.2-260), abatacept (median, 48.2 U/ml; IQR, 17.9-182), mycophenolate mofetil (MMF) (median, 3.24 U/ml; IQR, 0-34), MMF or mizoribine (MMF/MZR) combined with calcineurin inhibitor (CNI) (median, 5.5 U/ml; IQR, 0-21), and rituximab or cyclophosphamide (RTX/CPA) (median, 19.5 U/ml; IQR, 0-142) compared with those treated with sulfasalazine and/or bucillamine (median, 831 U/ml; IQR, 451-1451.5) or CNI (median, 833 U/ml; IQR, 164-1882) ($p<0.01$).

Conclusions: Additional early vaccination is required in patients treated with TNFi and MTX, ABT, MMF, MMF or MZR combined with CNI and CPA/RTX. However, patients treated with CNI and sulfasalazine and/or bucillamine may be safer among patients with rheumatic diseases.

Background

Vaccination is one of the most important preventive strategies against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In December 2021, the vaccination rate was more than 60% in many countries [1], and many patients with rheumatic disease treated with immunosuppressive or antirheumatic agents had already received vaccination. Most of these are mRNA vaccines and are created using relatively new technology. They have proven efficacy in healthy individuals. However, little information is available about the immunogenicity of mRNA vaccines in patients with rheumatic disease, especially in Asians [2].

The novelty of mRNA vaccines provide a unique opportunity to observe the immune responses of many patients to novel antigens in a real clinical setting. Many types of immunosuppressive agents and anti-rheumatic drugs are used to treat rheumatic diseases. The mechanisms of action are different, and their effects on adaptive immunity are also different in theory. However, it was difficult to interpret the actual effects of drugs on patients` adaptive immunity because large numbers of patients were not simultaneously exposed to new antigens. Although influenza and pneumococcal vaccines are administered to patients with rheumatic diseases, they should have been exposed to these antigens

throughout their lives. SARS-CoV-2 is a novel human infection, and its protein has never elicited an immune response in unaffected individuals. By monitoring the immune response before and after the SARS-CoV-2 vaccination, we observed the actual effect of the drugs on adaptive immunity.

Most previous reports have insufficiently interpreted the effects of drugs because the participants were registered regardless of medication intake and the number of patients receiving specific medications was small [3]. Furer et al. reported the seroconversion rate in 686 patients with rheumatic disease in Israel, but their report included only a small number of cases treated with interleukin-6 inhibitor (IL6i) monotherapy and abatacept (ABT) monotherapy [4]. Moreover, it did not contain a number of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as bucillamin (BUC), iguratimod (IGUR), mizoribine (MZR), and calcineurin inhibitors (CNIs), which are commonly used for rheumatic diseases in Japan and the Asia-Pacific region [4, 5]. In order to resolve these problems, we defined 12 different medication groups in Japanese patients with rheumatic diseases and planned to measure antibody levels before vaccination and 3-6 weeks and six months after the second SARS-CoV-2 mRNA vaccination to study its humoral immunogenicity. Here, we report the results of the interim analysis up to 3-6 weeks after the second vaccination.

Methods

Patients

All patients were Japanese outpatients from Kyushu University Beppu Hospital, Kyushu University Hospital, Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, and Osaka Minami Medical Center. We defined 12 medication groups according to the inclusion criteria as follows: 1. Sulfasalazine (SSZ) and/or BUC (SSZ/BUC); 2. Methotrexate (MTX); 3. IGUR; 4. tumor necrosis factor inhibitors (TNFi) with MTX; 5. TNFi without MTX; 6. IL6i without MTX; 7. ABT without MTX; 8. Janus kinase inhibitors (JAKis) without MTX; 9. CNI; 10. Mycophenolate mofetil (MMF); 11. MMF or MZR (MMF/MZR) combined with CNI; and 12. Rituximab (RTX) or cyclophosphamide (CPA) was administered within the previous year (RTX/CPA). Patients taking glucocorticoids > 10 mg/day (prednisone equivalent) or belimumab were excluded. Concomitant use of hydroxychloroquine, SSZ, BUC, and glucocorticoids with a prednisone-equivalent dose of 10 mg/day or less was allowed in all groups. Concomitant use of immunosuppressive agents other than MTX was allowed in groups including biologic therapy, JAKis, MMF/MZR combined with CNI, or RTX/CPA. The exclusion criteria were severe anemia, history of COVID-19, age < 20 years, and an absence of paired serum. Up to 50 patients receiving each treatment and mRNA vaccination were eligible from four institutions.

Immunogenicity of the mRNA vaccine

Serum samples were collected before vaccination and at 3-6 weeks after the second vaccination. This was an interim study up to 3-6 weeks after the second vaccination; a planned third sample at six months post-vaccination will be reported in a future study. Serum samples were stored at -80 °C, and antibody titers were measured using Elecsys Anti-SARS-CoV-2 S assays (Roche Diagnostics, Basel, Switzerland) at

Kyushu University Hospital. Elecsys anti-SARS-CoV-2 S assays are chemiluminescent immunoassays measuring antibodies against a recombinant protein comprising the receptor-binding domain (RBD) of the S antigen. The quantitative results are interpreted as follows: <0.8 U/mL: negative or ≥0.8 U/mL: positive. The major outcomes of this study were seroconversion rate and antibody titers after the second mRNA vaccination in all patients. This was an exploratory analysis of 12 groups.

This multicenter prospective cohort study was approved by the ethics committee of Kyushu University [#2021-128] and written informed consent was obtained from all patients before inclusion.

Statistical analysis

The results were analyzed using Stata Statistical Software Release 14 (StataCorp, College Station, TX, USA). Continuous variables are reported as median (interquartile range [IQR]). Categorical and continuous variables were compared using Fisher's exact test and the Mann-Whitney U test. Antibody titers among the medication groups were compared using the Kruskal–Wallis test followed by the Bonferroni–Dunn test for multiple comparisons. Multiple linear regression analysis was performed to evaluate the effects of treatment on antibody titers after adjustment for sex, age, and glucocorticoid dose, following log (x + 1) data transformation of antibody titers. A quantile-quantile (QQ) plot was used to check the normality of the residuals. Statistical significance was set at $P < 0.05$.

Results

Between May and November 2021, 372 patients were enrolled and 300 paired titers of antibodies were measured before vaccination and 3-6 weeks after the second mRNA vaccination (273 patients were vaccinated with BNT162-2b (Pfizer/Biontech) twice, 6 with mRNA-1273 (Moderna) twice, and 21 with either of the two mRNA vaccines, twice). Patients seropositive before vaccination (n =1), receiving other immunosuppressive therapy of specified treatment (n =3), and affected by COVID-19 (n =1) were excluded. Therefore, 295 patients were included in the analysis.

Patients and major outcomes

Patient characteristics are shown in Table 1. All patients were Japanese, and the median age was 57 (IQR, 48-67). The seroconversion rate of anti-SARS-CoV-2 RBD antibody 3-6 weeks after the second mRNA vaccination was 92.2% (272/295), and the median antibody titer was 255 (IQR, 34.1-685) U/ml in total patients. Medication group, immunologic diagnosis, and glucocorticoid dose were statistically associated with the seroconversion rate ($p<0.01$; Fisher's exact test). The seroconversion rates were lower in the MMF, MMF/MZR combined with CNI, and RTX/CPA groups (64.3%, 57.9%, and 66.7%, respectively) than in the SASP/BUC group (100%). However, the seroconversion rates were > 90% in the other groups.

Table 1: Displayed at the end of the file.

Medication group and antibody titers

Details of drugs and demographic characteristics among the medication groups are shown in Supplementary Table 1 and Supplementary Table 2. TNFi with MTX, ABT without MTX, MMF, MMF/MZR combined with CNI, and RTX/CPA group patients showed significantly lower antibody titers than those in the SSZ/BUC group and the CNI group ($p<0.01$) (Figure 1, Supplementary Table 3). Multiple linear regression analysis included the medication groups with significantly higher or lower antibody titer in Bonferroni-Dunn test as variables. Consequently, SSZ/BUC and CNI were correlated with high anti-SARS-CoV-2 RBD antibody, and TNFi with MTX, ABT without MTX, MMF, MMF/MZR combined with CNI, and RTX/CPA were correlated with low anti-SARS-CoV-2 RBD antibody titers after adjusting for age, sex, and glucocorticoid dose ($p<0.01$) (Table 2). Immunologic diagnoses were excluded from the analysis because they were correlated with the medication groups (Supplementary Table 2). The QQ plot of the residuals was almost linear (Supplementary Figure 1).

Figure 1 an Table 2: Displayed at the end of the file.

Discussion

This is the first large-scale demonstration of mRNA vaccine responsiveness in Asian patients with rheumatic diseases. For an accurate evaluation of the effect of treatments on antibody titer, the background of each group was made as uniform as possible. The absence of a history of COVID-19 was assessed not only by patient interviews but also by measuring antibody titers before vaccination. Patients treated with high-dose glucocorticoids and belimumab were excluded. Low racial diversity is suitable for assessing purely drug-induced effects. Our study findings demonstrate that drugs elicit different adaptive immune responses in patients with rheumatic diseases, with some keeping the antibody response while others markedly diminishing it.

CNI is one of the most used drugs for rheumatoid arthritis and other rheumatic diseases in the Asia-Pacific region. [4-6] To the best of our knowledge, this is the first report to examine the effect of CNI on humoral response to the mRNA vaccine in patients with rheumatic diseases. Rozen-Zvi et al. reported lower CNI blood level (less than $\leq$7 ng/ml) was associated with antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients. [7] In our report, the CNI group showed good humoral response; the median dose of tacrolimus was 3 mg/day (IQR, 2-3), and that of cyclosporine was 150 mg/day (IQR, 150-200). These results suggest that low doses of CNI used for rheumatic diseases do not reduce humoral response.

In most studies on seroconversion rates of mRNA vaccination in patients with rheumatic disease, MMF and RTX have been reported to reduce seroconversion rates after the second vaccination [3, 8, 9], which is consistent with the results of our study. ABT has also been reported to reduce the seroconversion rate in two large-scale studies [3, 8], whereas the seroconversion rate remained at 90.5% in our patients. Furer et al. reported a seroconversion rate of 40% (2/5) for ABT with MTX and 71% (5/7) for ABT monotherapy [3]. Inconsistencies in our findings from those in previous reports may be largely owing to the exclusion of patients with concomitant MTX use in our study.

Whether MTX reduces the seroconversion rate remains controversial. Although Haberman et al. reported a decrease in adequate vaccine response to MTX, the adequate response in the study was assessed by the presence of antibody production above a certain level, not by true non-response [10]. Bugatti et al. also reported that MTX was associated with a lower seroconversion rate after the first mRNA vaccination, but this was not evaluated after the second vaccination [11]. On the other hand, in large-scale studies referring to seroconversion rate after the second mRNA vaccination, univariate analysis of seroconversion rates showed significant differences, and these differences disappeared in multivariate analysis [3, 8]. In our study, we also observed a high seroconversion rate in MTX monotherapy after the second vaccination. In the present study, MTX alone failed to reduce the seroconversion rate because of a lower dose of MTX used in Japan than that in other countries. For example, the median MTX dose was 10 mg/week (IQR, 8-12). We also revealed that the antibody titer significantly decreased in patients treated with TNFi in combination with MTX, which was not observed with TNFi alone. MTX in combination with other drugs may further reduce the antibody titer and seroconversion rate after the second mRNA vaccination.

Anti-SARS-CoV-2 RBD antibody titer measured by the Elecsys assay correlates with the effectiveness in preventing viral infections in ex vivo experiments [12], although it remains unclear what level of anti-SARS-CoV-2 RBD antibody titer would be effective in preventing severe disease or disease onset in the general population and in immunosuppressed patients. In a large observational study that included patients receiving immunosuppressive treatment, a third vaccination administered five months after the second vaccination was also reported to reduce the risk of severe illness and death [13]. Even in post-renal transplant patients without antibody response to the second mRNA vaccination, seroconversion was observed in 27-38% after a third mRNA vaccination was received one month after the second vaccination [14, 15]. Our results indicate that an early third vaccination is desirable in patients under treatment that significantly reduce antibody titers.

There are limitations to this study. Foremost, this is an observational study. There may be bias relating to the type of mRNA vaccine used, as more than 90% of vaccinations in this study used BNT162b2, healthy controls were not included, and confounding factors other than sex, age, and glucocorticoid dose have not been considered. Additionally, although the Bonferroni-Dunn test is a robust method of analysis, it is difficult to achieve statistical significance. No significant differences were observed in treatments other than those in the five groups outlined previously; however, other study designs may have observed differences in other treatments, especially MTX.

Conclusions

Patients with rheumatic disease treated with TNFi and MTX, ABT, MMF, MMF or MZR combined with CNI, and RTX or CPA had significantly lower anti-SARS CoV-2 RBD antibody levels after the second mRNA vaccination. Strict precautions should be taken to prevent infection, even after vaccination, and an early third vaccination is recommended for patients receiving these treatments. Meanwhile, patients treated with CNI or SASP and/or BUC alone may be safer among patients with rheumatic diseases.

Abbreviations

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; IL6i, interleukin-6 inhibitor; ABT, abatacept; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; BUC, bucillamin; IGUR, iguratimod; MZR, mizoribine; CNI, calcineurin inhibitor; SSZ, sulfasalazine; MTX, methotrexate; TNFi, tumor necrosis factor inhibitor; JAKi, Janus kinase inhibitor; MMF, mycophenolate mofetil; RTX, rituximab; CPA, cyclophosphamide; RBD, receptor-binding domain; IQR, interquartile range; QQ, quantile-quantile

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committee of Kyushu University [#2021-128]. The patients signed an informed consent form for recruitment in the study. Patients were not directly involved in the experimental design or in performing the study.

Consent for publication

All patients provided written informed consent for the publication of information resulting from the trial without any personally identifying information.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

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Authors' contributions:

YuK, YaK, SO, TT, and TakH designed the study and interpreted the data. YuK and MA contributed to the data analysis. TaeH and DK contributed to the antibody measurement. TS, KI, SN, JH, QW, SK, MA, HM, NO, YA, HN, KA, and SO contributed to data collection and interpretation. All authors contributed intellectual content during the drafting and revision of the manuscript and approved the final version for publication.

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References

1. Our world in data Coronavirus (COVID-19) vaccinations. 2021. Global Change Data Lab. Available from: https://ourworldindata.org/covid-vaccinations (Accessed 31 Dec 2021).
2. Jena A, Mishra S, Deepak P, Kumar-M Praveen, Sharma A, Patel Y, et al. Response to SARS-CoV-2 vaccination in immune mediated inflammatory diseases: systematic review and meta-analysis. Autoimmun Rev 2022;21:102927. Doi: 10.1016/j.autrev.2021.102927.
3. Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky 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;80:1330–8.
4. Lau CS, Chia F, Dans L, Harrison A, Hsieh TY, Jain R, et al. 2018 update of the APLAR recommendations for treatment of rheumatoid arthritis. Int J Rheum Dis 2019;22:357–75.
5. Kameda H, Fujii T, Nakajima A, Koike R, Sagawa A, Kanbe K, et al. Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis. Mod Rheumatol 2019;29:31–40.
6. Rafael-Vidal C, Altabás I, Pérez N, Rodríguez CM, Pego-Reigosa JM, Garcia S. Calcineurin and systemic lupus erythematosus: The rationale for using calcineurin inhibitors in the treatment of lupus nephritis. Int J Mol Sci 2021;22:1263.
7. Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. Clin Microbiol Infect 2021;27:1173.e1-1173.e4.
8. Braun-Moscovici Y, Kaplan M, Braun M, Markovits D, Giryes S, Toledano K, et al. Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2. Ann Rheum Dis 2021;80:1317–21.
9. Ruddy JA, Connolly CM, Boyarsky BJ, Werbel WA, Christopher-Stine L, Garonzik-Wang J, et al. High antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis 2021;80:1351–2.
10. Haberman RH, Herati R, Simon D, Samanovic M, Blank RB, Tuen M. et al. Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease. Ann Rheum Dis 2021 ;80 :1339–44.
11. Bugatti S, De Stefano L, Balduzzi S, Greco MI, Luvaro T, Cassaniti I, et al. Methotrexate and glucocorticoids, but not anticytokine therapy, impair the immunogenicity of a single dose of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic inflammatory arthritis. Ann Rheum Dis 2021;80:1635–8.
12. Rus KR, Korva M, Knap N, Županc TA, Poljak M. Performance of the rapid high-throughput automated electrochemiluminescence immunoassay targeting total antibodies to the SARS-CoV-2 spike protein receptor binding domain in comparison to the neutralization assay. J Clin Virol 2021;139.104820.

13. Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, 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;398:2093–100.
14. Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, Fafi-Kremer S, et al. Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. JAMA 2021;326:1063–5.
15. Bertrand D, Hamzaoui M, Lemée V, Lamulle J, Laurent C, Etienne I, et al. Antibody and T-cell response to a third dose of SARS-CoV-2 mRNA BNT162b2 vaccine in kidney transplant recipients. Kidney Int 2021;100:1337–40.

Tables

Table 1. Demographic characteristics of patients and anti-SAR-CoV2 RBD antibody after the second mRNA vaccination

Characteristics	Total number of patients	Seroconversion		p value	Anti-SARS-CoV2 RBD antibody titer
		Number	Rate (%)		
Gender					
Male	78	74	94.9	0.46	250.5 (64.5-641)
Female	217	198	91.2		255 (24.9-718)
Age					
20-39	36	34	94.4	0.95	572 (67.3-1657)
40-64	169	155	91.7		317 (51.5-800)
≥ 65	90	83	92.2		134.5 (23.8-325)
Race					
Asian	295	-	-		-
Immunologic diagnosis					
Rheumatoid arthritis	176	172	97.7	<0.01	250.5 (51.7-641.5)
Systemic lupus erythematosus	43	33	76.7		122 (2.09-674)
Spondyloarthritis	15	15	100		536 (246-763)
Polymyositis/Dermatomyositis	14	12	85.7		80.7 (13-1954)
Scleroderma	7	6	85.7		31.9 (2.7-481)
Vasculitis	7	4	57.1		19.5 (0-194)
Behçet's disease	7	7	100		288 (111-475)
Mixed connective tissue disease	6	5	83.3		206 (49.8-2159)
Castleman disease	5	4	80		126 (78.2-1124)
Other	15	14	93.3		824 (338-1683)
Medication group					
SSZ and/or BUC	20	20	100	<0.01	831.5 (451-1451.5)
MTX	40	40	100		228.5 (59.5-742.5)
IGUR	11	11	100		457 (245-1170)
TNFi with MTX	42	41	97.6		104 (33.2-260)*

TNFi without MTX	24	24	100		317.5 (169.5-594.5)
IL6i without MTX	43	41	95.4		348 (131-857)
ABT without MTX	21	19	90.5		48.2 (17.9-182)*
JAKi without MTX	14	13	92.9		310.5 (71.2-626)
CNI	38	37	97.4		833 (164-1882)
MMF	14	9	64.3		3.24 (0-34)*
MMF or MZR combined with a CNI	19	11	57.9		5.5 (0-21)*
RTX or CPA in the past year	9	6	66.7		19.5 (0-142)*
Glucocorticoid dose (prednisone equivalent)					
0 mg/day	147	146	99.3	<0.01	317 (104-820)
>0 ≤ 5 mg/day	111	98	88.3		193 (22.4-674)
>5 ≤ 10 mg/day	37	28	75.7		15.5 (2.1-338)

P-values were calculated using Fisher's exact test. The asterisked treatment groups had significantly lower antibody titers than the SSZ/BUC and CNI groups ($p<0.01$, Kruskal–Wallis test followed by Bonferroni-Dunn test). RBD, receptor-binding domain; SSZ, sulfasalazine; BUC, bucillamin; IGUR, iguratimod; MTX, methotrexate; TNFi, tumor necrosis factor inhibitor; IL6i, interleukin-6 inhibitor; ABT, abatacept; JAKi, Janus kinase inhibitor; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MZR, mizoribine; RTX, rituximab; CPA, cyclophosphamide

Table 2. Multiple linear regression analysis for log transformed SARS-CoV2 RBD antibody titers

Variable	Beta coefficient (95% CI)	p value
Gender: female	-0.04 (-0.24 to 0.16)	0.71
Age: per 1 year increase	-0.01 (-0.02 to -0.01)	<0.01
Glucocorticoid dose: per 1 mg/body increase (prednisone equivalent)	-0.08 (-0.12 to -0.04)	<0.01
Medication group		
Other than below	0 (Ref.)	-
SSZ or BUC	0.54 (0.18-0.90)	<0.01
CNI	0.43 (0.14-0.73)	<0.01
TNFi with MTX	-0.50 (-0.77 to -0.23)	<0.01
ABT without MTX	-0.65 (-1.00 to -0.29)	<0.01
RTX or CPA	-0.80 (-1.35 to -0.25)	<0.01
MMF or MZR combined with a CNI	-1.21 (-1.61 to -0.80)	<0.01
MMF	-1.26 (-1.70 to -0.82)	<0.01

Adjusted R2 = 0.34. All variables are adjusted by each other. RBD, receptor-binding domain; SSZ, sulfasalazine; BUC, bucillamin; CNI, calcineurin inhibitor; TNFi, tumor necrosis factor inhibitor; MTX, methotrexate; ABT, abatacept; RTX, rituximab; CPA, cyclophosphamide; MMF, mycophenolate mofetil; MZR, mizoribine

Figures

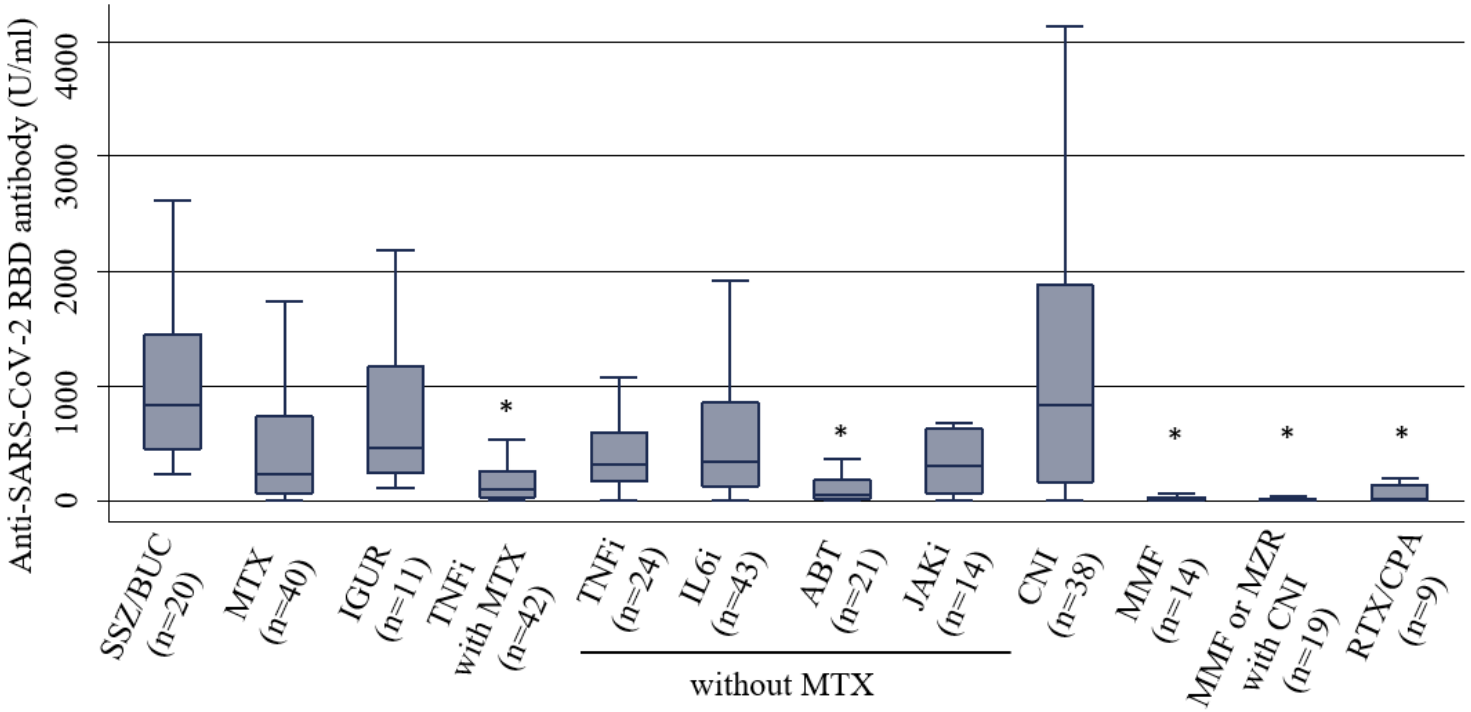

Figure 1

Box plot distribution of anti-SARS-CoV2 RBD antibody titers among medication groups.

The asterisked treatment groups had significantly lower antibody titers than the SSZ/BUC and CNI groups ($p<0.01$, Kruskal-Wallis test followed by Bonferroni-Dunn test). Data are represented as median and interquartile range. RBD, receptor-binding domain; SSZ, sulfasalazine; BUC, bucillamin; IGUR, iguratimod; MTX, methotrexate; TNFi, tumor necrosis factor inhibitor; IL6i, interleukin-6 inhibitor; ABT, abatacept; JAKi, Janus kinase inhibitor; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MZR, mizoribine; RTX, rituximab; CPA, cyclophosphamide

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