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Medium-term impact of the SARS-CoV-2 mRNA vaccine against disease activity in patients with systemic lupus erythematosus

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ABSTRACT

Objectives Numerous case reports have referred to new onset or flare of SLE after SARS-CoV-2 messenger RNA (mRNA) vaccines. Several observational studies showed that the short-term flare rate of SLE after SARS-CoV-2 vaccination is low. However, well-controlled clinical surveys are unavailable and the medium-term impact of the SARS-CoV-2 mRNA vaccines against the flare of SLE is uncertain. Therefore, we aimed to analyse the association between vaccination and medium-term subjective and objective disease activities of SLE and flares using matched pair methods.

Methods Altogether, 150 patients with SLE from the Kyoto Lupus Cohort were included. Patients who received two doses of the SARS-CoV-2 mRNA vaccines were 1:1 matched with unvaccinated patients based on the first vaccination date. The outcome measures were the SLE Disease Activity Index-2000 (SLEDAI-2K), the Japanese version of the SLE Symptom Checklist Questionnaire (SSC-J) and the Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI flare index at 30, 60 and 90 days after vaccination.

Results SLEDAI-2K levels were not significantly different in vaccinated and unvaccinated patients with SLE at 30, 60 and 90 days after the second vaccination (adjusted estimate (95% CI): 30 days: −0.46 (−1.48 to 0.56), p=0.39; 60 days: 0.38 (−0.64 to 1.40), p=0.47; 90 days: 0.40 (−0.54 to 1.34), p=0.41). Similar results were observed in the SSC-J score (adjusted estimate (95% CI), 30 days: 0.05 (−1.46 to 1.56), p=0.95; 60 days: −0.63 (−2.08 to 0.82), p=0.40; 90 days: 0.27 (−1.04 to 1.58), p=0.69) and flare index (adjusted OR (95% CI), 30 days: 0.81 (0.36 to 1.85), p=0.62; 60 days: 1.13 (0.50 to 2.54), p=0.77; 90 days: 0.85 (0.32 to 2.26), p=0.74).

Conclusion SARS-CoV-2 vaccination did not significantly influence the medium-term subjective and objective disease activities or flares of SLE until 90 days after the second vaccination.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The flare rate of SLE after SARS-CoV-2 messenger RNA (mRNA) vaccination is reported to be approximately 10%, but the evaluation was mostly based on interviews or questionnaires.
⇒ The exact impact on flares is unknown because no studies have included matched SLE patients who were not vaccinated.
⇒ There have been reports related to the short-term relapse rate of the SARS-CoV-2 mRNA vaccine, but its medium-term to long-term impact is unknown.

WHAT THIS STUDY ADDS

⇒ Using matched pair methods, SARS-CoV-2 mRNA vaccination was found not to influence the medium-term subjective and objective disease activities or flares compared with those of the SARS-CoV-2 mRNA vaccinated and unvaccinated control groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The SARS-CoV-2 mRNA vaccine may be safe for patients with SLE with medium-term disease activity and flares.
⇒ The results of this study reassure patients with SLE who have not yet received the vaccine.

INTRODUCTION

Recently, the frequency of adverse reactions in autoimmune inflammatory rheumatic disease after vaccination has been similar to that in healthy subjects,[1–3] and the autoimmune inflammatory rheumatic disease relapse rate is low.[1 2 4] However, most of these studies focused on rheumatoid arthritis and did not examine flares in patients with SLE. Regarding the relationship between SLE and the SARS-CoV-2 vaccine, numerous case reports of new-onset or flare after vaccination suggest that vaccination might worsen SLE.[5–7] Type I interferonopathy, the primary pathogenesis of SLE, is also triggered by the SARS-CoV-2 vaccination, which causes the onset or flare of SLE.[8]

A few observational studies have reported that the relapse rate of SLE after vaccination

is low.[9–11] However, there are several problems, such as the inadequate evaluation of SLE disease activities based on non-validated questionnaires and patient self-reports; the difficulty in distinguishing between adverse reactions and SLE disease activities in a short period after vaccination and the inability to establish a strict control group. Hence, the influence of vaccination on disease activity in patients with SLE is not thoroughly understood.

In the present matched-pair study, we investigated the medium-term impact of vaccination on disease activity in patients with SLE using physicians' objective assessment of disease activity, laboratory tests and a validated questionnaire.

METHODS

Inclusion criteria

All patients with SLE who fulfilled the following inclusion criteria were included in the study:

1. Patients in the Kyoto Lupus Cohort,[12] who visited Kyoto University Hospital and who had a minimum of two visits between 1 January 2021 and 1 December 2021 (considering the vaccination situation in Japan).
2. Patients with the 1997 American College of Rheumatology[13] or the 2012 Systemic Lupus, as well as those who met the International Collaborating Clinics classification criteria.[14]
3. Patients whose disease activity was measured.

The sample size was not estimated.

Matching methods

The first vaccination date during two doses of vaccination was defined as the index date. The patients with SLE who had completed their second vaccination were grouped as vaccinated patients. Among patients with SLE, every vaccinated patient was matched to one unvaccinated patient whose disease activities were assessed on the same index date as that with replacement, which consists of selecting one match for each control and returning the matched controls to the pool of observations. Patients who did not match were excluded.

Disease activities

Disease activities were assessed before the first vaccination and after the second vaccination using the SLE Disease Activity Index-2000 (SLEDAI-2K) as an objective parameter[15]; the Japanese version of the SLE Symptom Checklist Questionnaire (SSC-J) as a subjective parameter and[12] physician-visual analogue scale (Ph-VAS), patient-VAS (Pt-VAS) and laboratory data. The flare of SLE was evaluated using the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI flare index.[16] Disease activities up to 3 months before the index date were defined as baseline.

Outcomes

Primary outcomes

The primary outcome was SLEDAI-2K scores at 30 days after the second vaccination.

Secondary outcomes

The secondary outcomes were as follows:

1. SLEDAI-2K scores at 60 and 90 days after the second vaccination.
2. SSC-J scores at 30, 60 and 90 days after the second vaccination.
3. SELENA-SLEDAI flare index at 30, 60 and 90 days after the second vaccination.
4. Ph-VAS and Pt-VAS scores at 30, 60 and 90 days after the second vaccination.
5. SLEDAI-2K arthritis categories and SSC-J arthralgia at 30 days after the second vaccination.
6. Serological activities at 30 days after the second vaccination, including white blood cell count ($\times 10^3/\mu L$), platelet count ($\times 10^3/\mu L$), C3 (mg/dL), C4 (mg/dL), CH50 (CH50/mL), anti-DNA antibody titre (IU/mL) and urine protein-to-creatinine (P/C) ratio (g/gCre).
7. SLEDAI-2K and SSC-J scores at 30, 60 and 90 days after the second vaccination in patients with high disease activity (SLEDAI-2K>10).

Missing value

The missing values were adjusted using the simple imputation method to assign the mean of the values preceding and following the missing value.

Statistical analysis

The χ^2 and Wilcoxon rank-sum tests were used for categorical and continuous variables, respectively. Linear and logistic mixed-effect models were used to calculate estimates, ORs and 95% CIs. JMP software V.14, R software V.3.4.1 and GraphPad Prism V.9.3.1 were used for analysis or drawing figures. The level of statistical significance was set at $p<0.05$.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Of the 150 patients who fulfilled the inclusion criteria, 74 vaccinated and 74 unvaccinated patients were selected based on the 1:1 match on the index date. The prefirst vaccination data of 32 patients in the vaccinated group were registered in the unvaccinated group (figure 1).

Table 1 shows the characteristics of the patients in the vaccinated and unvaccinated groups. There were no significant differences in patients' characteristics, including age, sex, disease duration and medications, between the two groups. The baseline serological disease activity and disease activity scores did not differ. In the vaccinated group, 16 out of 74 (21%) patients had high disease activity (SLEDAI-2K>10).

Primary outcome

The quantitative changes in SLEDAI-2K scores from the prefirst vaccination baseline to 30 days after the second

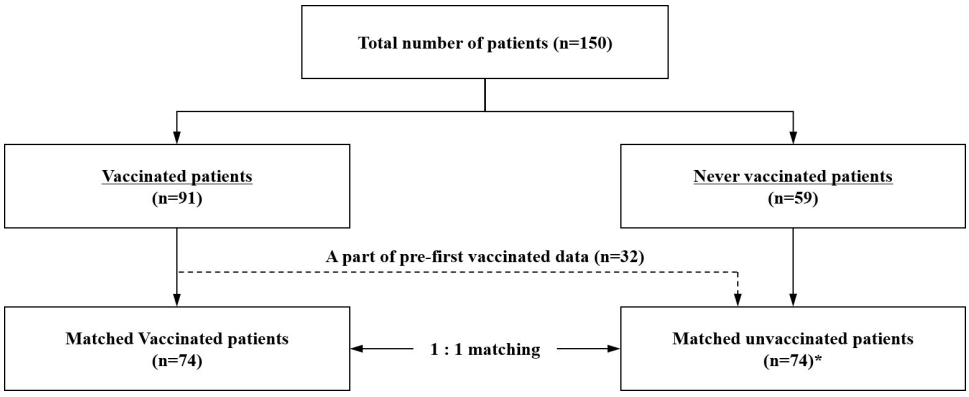

Figure 1 Flow chart of patients included in the present study. Altogether, 150 patients with SLE were included. The patients were divided into two groups: the vaccinated group (n=91) and the never-vaccinated group (n=59). The prefirst vaccination data of the 32 patients in the vaccinated group was registered in the unvaccinated group. Then, we selected 74 vaccinated and 74 unvaccinated patients by 1:1 matching with replacement. *'Matched unvaccinated patients' referred to 42 never-vaccinated patients and 32 patients in the vaccinated group before their first vaccination.

vaccination were not significantly different between the vaccinated and unvaccinated groups (ΔSLEDAI-2K (mean±SD): vaccinated vs unvaccinated group (−0.3±4.6) vs (0.2±5.5), p=0.93, respectively) (figure 2A). The slope graph of SLEDAI-2K scores between the two time points was similar (online supplemental figure 1A,B). The linear mixed-effects models showed no significant difference in SLEDAI-2K scores 30 days after the second vaccination between the groups (estimate (95% CI) −0.53 (−1.22 to 0.16), p=0.13) (table 2). A similar result was obtained after adjusting for age, sex, SLEDAI-2K at baseline, and immunosuppressive drug or biological agent use (adjusted estimate (95% CI) −0.46 (−1.48 to 0.56), p=0.39).

Secondary outcomes

The linear mixed-effects model showed no significant difference between the vaccinated and unvaccinated groups in the SLEDAI-2K scores at 60 and 90 days after the second vaccination (adjusted estimate (95% CI), 60 days: 0.38 (−0.64 to 1.40), p=0.47; 90 days: 0.40 (−0.54 to 1.34), p=0.41) (table 2).

The change in SSC-J scores from prefirst vaccination baseline to 30 days after the second vaccination was not significantly different between the two groups (ΔSSC-J (mean±SD): vaccinated vs unvaccinated group (0.04±8.85) vs (−0.49±5.06), p=0.61, respectively) (figure 2B). The slope graph of SSC-J scores between the two time points was similar (online supplemental figure 1C,D). The mixed-effects models, adjusted for age, sex, baseline SSC-J score and immunosuppressive drug or biological agent use, did not show significant variation in the SSC-J score after the vaccination (adjusted estimate (95% CI), 30 days: 0.05 (−1.46 to 1.56), p=0.95; 60 days: −0.63 (−2.08 to 0.82), p=0.40; 90 days: 0.27 (−1.04 to 1.58), p=0.69) (table 2).

The rate of SLE flares 30 days after the second vaccination was 20.3% (mild or moderate, 20.3% (n=15/74); severe, 0.0% (n=0/74)) and 23.3% (mild or moderate, 20.3% (n=15/74); severe, 4.1% (n=3/74)) in the vaccinated and unvaccinated groups, respectively. The flare rates at 60 and 90 days are similar in the two groups (online supplemental table 1). The linear mixed-effects model, adjusted for age, sex and immunosuppressive drug or biological agent use, showed no significant association between the vaccination and flares at 30, 60 and 90 days after the second vaccination (adjusted OR (95% CI), 30 days: 0.81 (0.36 to 1.85), p=0.62; 60 days: 1.13 (0.50 to 2.54), p=0.77; 90 days: 0.85 (0.32 to 2.26), p=0.74) (table 3).

The subanalyses showed that the categories of 'arthritis' in SLEDAI-2K and 'arthralgia', the subjective symptoms evaluated in SSC-J, were not associated with vaccination. The scores at 30 days after the second vaccination were (adjusted OR (95% CI) (arthritis (SLEDAI-2K)): 0.88 (0.20 to 3.85), p=0.87; (arthralgia (SSC-J)): 1.92 (0.70 to 5.29), p=0.20) (online supplemental table 3).

The Ph-VAS scale at 30, 60 and 90 days and Pt-VAS scale at 30 and 60 days were similar in both the groups; however, the Pt-VAS scale at 90 days was significantly lower in the vaccinated group (adjusted estimate (95% CI) −3.43 (−6.49 to −0.37) mm, p=0.03) (online supplemental table 4).

Serological disease activity indices showed no clinically significant differences at 30 days after vaccination; however, platelet count was lower by $1.6\times10^3/\mu L$ (95% CI −2.64 to −0.56), p=0.003) and C3 was higher by 1.1 mg/dL (95% CI −0.02 to 2.22, p=0.05) in the vaccinated group compared with that in the unvaccinated group. The other parameters were not significantly different between the two groups (online supplemental table 5).

The linear mixed-effects model adjusting for age, sex, SLEDAI-2K at baseline and immunosuppressive drug or biological agent use, showed no significant differences in SLEDAI-2K or SSC-J scores after the second vaccination between vaccinated and unvaccinated groups in patients with high disease activity (SLEDAI-2K: adjusted estimate (95% CI), 30 days: −0.95 (−3.13 to 1.23), p=0.40; 60 days: 0.50 (−2.32 to 3.32), p=0.73; 90 days: 1.22 (−1.31 to 3.75), p=0.35; SSC-J: adjusted estimate (95% CI), 30 days: 0.74

Table 1 Patient characteristics of the vaccinated and unvaccinated groups

	Vaccinated	Unvaccinated	P value
Number, *n*	74	74	–
Female, *n* (%)	71 (96)	73 (99)	0.62
Age, years, mean (SD)	50 (14)	44 (14)	0.11
Disease duration, years	19.5 (10.75, 27.5)	17 (8.75, 25.25)	0.45
Body mass index	20.8 (18.8, 22.5)	19.8 (19.4, 21.98)	0.65
Complications			
Lupus nephritis, *n* (%)	37 (50.0)	41 (55.4)	0.62
Antiphospholipid antibody syndrome, *n* (%)	7 (9.5)	3 (4.1)	0.33
Comorbidity			
Rheumatoid arthritis, *n* (%)	6 (8.1)	4 (5.4)	0.75
Sjögren's syndrome, *n* (%)	6 (8.1)	9 (12.2)	0.59
Mixed connective tissue disease, *n* (%)	3 (4.1)	2 (2.7)	1.00
Systemic sclerosis, *n* (%)	3 (4.1)	7 (9.5)	0.33
Treatment			
Glucocorticoid, *n* (%)	64 (89.9)	69 (93.2)	0.28
Prednisolone dose (mg)	5 (3, 8)	6 (4, 8)	0.19
Hydroxychloroquine, *n* (%)	27 (36.5)	28 (37.8)	1.00
Immunosuppressant or biologics, *n* (%)	52 (70.3)	54 (73.0)	0.86
Tacrolimus, *n* (%)	26 (35.1)	30 (40.5)	0.61
Azathioprine, *n* (%)	11 (14.9)	9 (12.2)	0.81
Mycophenolate mofetil, *n* (%)	10 (13.5)	15 (20.3)	0.38
Methotrexate, *n* (%)	6 (8.1)	7 (9.5)	1.00
Mizoribine, *n* (%)	6 (8.1)	7 (9.5)	1.00
Ciclosporin A, *n* (%)	4 (5.4)	4 (5.4)	1.00
Belimumab, *n* (%)	9 (12.2)	14 (18.9)	0.36
Serological disease activity			
Anti-DNA antibody (IU/mL)	5 (2.25, 14.5)	7 (4, 11)	0.56
C3 (mg/dL)	82.9 (71.8, 94.3)	88.9 (71.7, 102.5)	0.35
CH50 (CH50/mL)	41 (35, 46.3)	41 (36, 46.3)	0.46
Disease activity score			
SLEDAI-2K score	6 (2, 10)	6 (4, 12)	0.60
Disease activity			
None (SLEDAI-2K: 0), *n* (%)	14 (18.9)	6 (8.1)	0.09
Low (SLEDAI-2K: 1–5), *n* (%)	18 (24.3)	30 (40.5)	0.053
Moderate (SLEDAI-2K: 6–10), *n* (%)	26 (35.1)	19 (25.7)	0.28
High (SLEDAI-2K: 11–19), *n* (%)	13 (17.6)	14 (18.9)	1.00
Very high (SLEDAI-2K: <19), *n* (%)	3 (4.1)	5 (6.8)	0.72
SSC-J score	29 (11, 49)	35 (10, 53)	0.77
Physician VAS (mm)	17 (7.5, 33.25)	20 (9.75, 33)	0.67
Patient VAS (mm)	45.5 (22, 59)	54 (29, 67.5)	0.06
SARS-CoV-2 vaccination			
BNT162b2 (Pfizer/BioNTech), *n* (%)	65 (88)	–	–
mRNA-1273 (Moderna), *n* (%)	9 (12)	–	–
COVID-19 infection	0 (0.0)	0 (0.0)	–

All glucocorticoids were converted to equivalent prednisolone doses. The χ^2 and Wilcoxon rank-sum tests were used for categorical and continuous variables, respectively. Continuous variables are expressed as IQRs.
mRNA, messenger RNA; SLEDAI-2K, SLE Disease Activity Index-2000; SSC-J, Japanese version of the SLE Symptom Checklist Questionnaire; VAS, visual analogue scale.

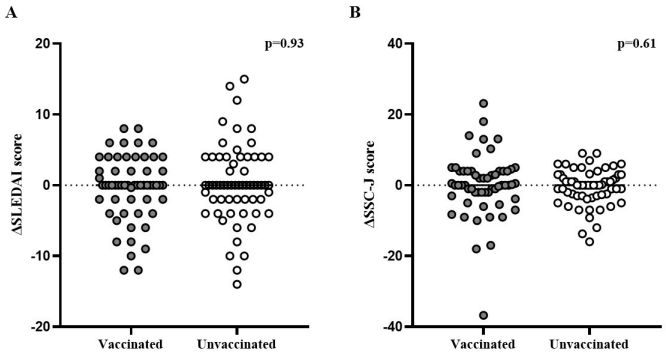

Figure 2 Quantitative change in the SLEDAI-2K and SSC-J scores in the vaccinated and unvaccinated groups at 30 days after the second vaccination. (A) ΔSLEDAI-2K, (B) ΔSSC-J. Analysed by using the Wilcoxon rank-sum test (ΔSLEDAI-2K (mean±SD): vaccinated group vs unvaccinated group, −0.3±4.6 vs 0.2±5.5 (p=0.93); ΔSSC-J (mean±SD): vaccinated group vs unvaccinated group, 0.04±8.85 vs −0.49±5.06 (p=0.61)). SLEDAI-2K, SLE Disease Activity Index-2000; SSC-J, Japanese version of the SLE Symptom Checklist Questionnaire. The value of statistical significance was set at p<0.05.

(−1.63 to 3.11), p=0.55; 60 days: −0.61 (−3.06 to 1.84), p=0.63; 90 days: −0.81 (−4.28 to 2.66), p=0.65).

DISCUSSION

Our study subjectively and objectively evaluated the medium-term influence of SARS-CoV-2 mRNA vaccination on SLE disease activities by comparing the vaccinated group with the unvaccinated group. There were no significant differences between the two groups in subjective or objective disease activities or flares until 90 days after the second vaccination. Previous reports have shown that musculoskeletal symptoms are the most common symptoms of short-term flare after vaccination.[10] In the present study, a subanalysis of musculoskeletal symptoms among SLEDAI-2K and SSC-J items, including arthritis and joint pain, showed no significant difference between the vaccinated and unvaccinated groups. In our study, 21% of patients in the vaccinated group had high disease activity before vaccination. However, there was no significant difference in disease activity at 30, 60 and 90 days after the second vaccination between vaccinated and unvaccinated patients. In general, disease activity in autoimmune inflammatory rheumatic diseases prior to vaccination should be controlled. The results of this study, in which prevaccination disease activity did not affect postvaccination disease activity, suggest that vaccination may be acceptable in urgent cases such as COVID-19, regardless of prevaccination disease activity. However, caution is needed for interpretation because the sample size was small.

Regarding the SARS-CoV-2 vaccine, data are adequate regarding its usefulness to policymakers, clinicians and patients in preventing infection, but not adequate regarding its side effects. Despite the benefits of the SARS-CoV-2 vaccinations, 28.2% of patients with SLE tend to hesitate in receiving them,[17] the primary reason being a flare of SLE due to vaccination (56%).[18] Our results will help alleviate patient concerns.

Previous studies showed 3%–10.6% short-term flare rates after vaccination within 7 days.[9–11] However, the assessments of disease activities were based on interviews or questionnaires, and the evaluation periods were short—not enough to distinguish SLE flares from reactions to vaccines. One study reported that the flare rate evaluated using SLEDAI was 11.4%.[19] However, the observation period was short (an average of 23.6 days) and did not establish appropriate controls. Our study has several strengths. First, we used the SLEDAI-2K as an objective measure and the SSC-J score as a validated subjective measure. Second, we compared vaccinated and

Table 2 Estimates in a linear mixed-effects model of vaccination effects for SLEDAI-2K and SSC-J score

	Unadjusted		Adjusted	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
30 days (15–61 days)				
SLEDAI-2K	−0.53 (−1.22 to 0.16)	0.13	−0.46 (−1.48 to 0.56)	0.39
SSC-J	0.21 (−0.32 to 0.74)	0.75	0.05 (−1.46 to 1.56)	0.95
60 days (28–120 days)				
SLEDAI-2K	0.29 (−0.51 to 1.09)	0.49	0.38 (−0.64 to 1.40)	0.47
SSC-J	−1.13 (−2.50 to 0.24)	0.07	−0.63 (−2.08 to 0.82)	0.40
90 days (56–189 days)				
SLEDAI-2K	0.48 (−0.44 to 1.40)	0.31	0.40 (−0.54 to 1.34)	0.41
SSC-J	0.09 (−1.20 to 1.38)	0.89	0.27 (−1.04 to 1.58)	0.69

Mixed-effects models were used to evaluate SLEDAI-2K and SSC-J scores between the groups at 30 days after the second vaccination. Adjustment variables: age, sex, SLEDAI-2K and SSC-J scores at baseline, and use of immunosuppressive drugs or biological agents. The missing values were adjusted using the simple imputation method to assign the mean of the values preceding and following the missing value ((SSC-J score at 30 days) n=2).
SLEDAI-2K, SLE Disease Activity Index-2000; SSC-J, Japanese version of the SLE Symptom Checklist Questionnaire.

Table 3 Estimated OR and 95% CI for the association between vaccination and flares at 30, 60 and 90 days after the second vaccination

	Unadjusted		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
30 days	0.85 (0.38 to 1.91)	0.70	0.81 (0.36 to 1.85)	0.62
60 days	1.10 (0.50 to 2.41)	0.81	1.13 (0.50 to 2.54)	0.77
90 days	0.76 (0.29 to 1.97)	0.57	0.85 (0.32 to 2.26)	0.74

Adjustment variables included age, sex and the use of immunosuppressive drugs or biological agents.

unvaccinated patients with SLE. Unlike the adverse reactions to vaccines, it is crucial to compare the two groups to assess the effect of vaccines on disease activity. Third, the vaccinated and unvaccinated patients were matched on the first vaccination date. Thus, more precise assessments of the changes in disease activity can be obtained. Finally, we evaluated disease activity in the present study for up to 3 months after the second vaccination.

Our study had several limitations. First, data were unavailable for all patients, as in previous studies. Second, the Kyoto Lupus Cohort contained many patients who had already received the vaccine. Therefore, we included prevaccination data of vaccinated patients in the unvaccinated group. Furthermore, the observation period was limited to 3 months. Since booster vaccination has already been started in Japan, further extended observation periods are challenging.

In this study, the prescription rate of hydroxychloroquine (HCQ) was 37 %, which is less frequent than that in the USA and Europe, and this might have influenced SLE disease activity. There are two reasons for the low prescription rate of HCQ in Japan. First, HCQ was approved by the Ministry of Health, Labour and Welfare in Japan only recently, in 2015. Second, HCQ exerts a higher risk of retinopathy, a side effect of HCQ, in Asians, including the Japanese.[20]

In conclusion, we observed that medium-term disease activities or flares of SLE did not worsen with the SARS-CoV-2 vaccination, which supports its use in patients with SLE. Further studies are needed to evaluate the long-term impact of vaccines over several years.

Contributors The study was designed, directed and coordinated by TY, the principal investigator. HT and AO are the co-investigators and in charge of the study conducted at all stages. All the coauthors recruited participants into the study and evaluated patients' prevaccination and postvaccination activity measures. TY, HT and AO wrote the article, which was critically reviewed by all coauthors. TY, HT, and AO are authors responsible for the overall content as the guarantor.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (R145). Written informed consent was obtained from all the patients.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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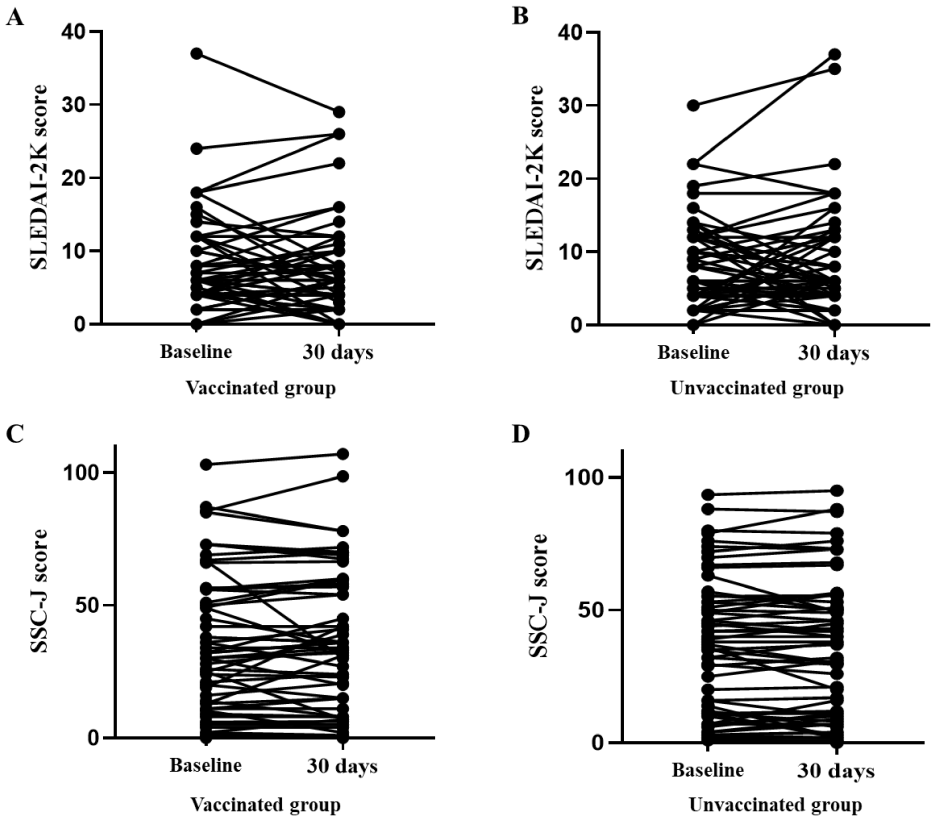
SUPPLEMENTAL FIGURE

Supplemental Figure 1: Slope graph of changes in SLEDAI-2K and SSC-J scores from baseline to 30 days after the second vaccination



[A-B] SLEDAI-2K score and [C-D] SSC-J score. Disease activities before the first vaccination were set as the baseline. SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; SSC-J, Japanese version of the Systemic Lupus Erythematosus Symptom Checklist Questionnaire

10 **SUPPLEMENTAL TABLES**

11 **Supplemental Table 1: Flare rates at 30, 60, and 90 days after the second vaccination**

12

	Vaccinated n = 74	Unvaccinated n = 74
30 days after the second vaccination		
Major flare, *n* (%)	0 (0.0)	3 (4.1)
Minor flare, *n* (%)	15 (20.3)	15 (20.3)
60 days after the second vaccination		
Major flare, *n* (%)	1 (1.4)	3 (4.1)
Minor flare, *n* (%)	18 (24.3)	14 (18.9)
90 days after the second vaccination		
Major flare, *n* (%)	1 (1.4)	2 (2.7)
Minor flare, *n* (%)	11 (14.9)	11 (14.9)

13

Supplemental Table 2: Estimates in a linear mixed-effects model of vaccination effects for SLEDAI-2K and SSC-J score in the high disease activity group (SLEDAI-2K>10)

	Unadjusted		Adjusted	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
30 days (15–61 days)				
SLEDAI-2K	-0.91 (-1.16–-0.66)	0.99	-0.95 (-3.13–1.23)	0.40
SSC-J	0.79 (-1.56–3.14)	0.66	0.74 (-1.63–3.11)	0.55
60 days (28–120 days)				
SLEDAI-2K	0.81 (-2.95–4.57)	0.68	0.50 (-2.32–3.32)	0.73
SSC-J	-1.42 (-4.07–1.23)	0.30	-0.61 (-3.06–1.84)	0.63
90 days (56–189 days)				
SLEDAI-2K	1.66 (1.09–2.23)	0.29	1.22 (-1.31–3.75)	0.35
SSC-J	-1.40 (-2.26–-0.54)	0.44	-0.81 (-4.28–2.66)	0.65

Mixed-effects models were used to evaluate SLEDAI-2K and SSC-J scores between the groups 30 days after the second vaccination. Adjustment variables: age, sex, SLEDAI-2K and SSC-J scores at baseline, and use of immunosuppressive drugs or biological agents.

CI, confidence interval; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; SSC-J, Japanese version of the Systemic Lupus Erythematosus Symptom Checklist Questionnaire.

The statistical significance level was set at $p<0.05$.

Supplemental Table 3: Estimated OR and 95% CI for the association between vaccination and arthritis or arthralgia 30 days after the second vaccination

	Unadjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Arthritis (SLEDAI-2K)	0.90 (0.26–3.09)	0.86	0.88 (0.20–3.85)	0.87
Arthralgia (SSC-J)	1.97 (0.74–5.29)	0.18	1.92 (0.70–5.29)	0.20

Mixed-effects logistic models were used to calculate the odds ratio and 95% CI in the present study. Adjustment variables included age, sex, arthritis or arthralgia rate at baseline, and use of immunosuppressive drugs or biological agents.

CI, confidence interval; OR, odds ratio; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000, SSC-J: Japanese version of the Systemic Lupus Erythematosus Symptom Checklist Questionnaire.

The statistical significance level was set at $p<0.05$.

Supplemental Table 4: Estimates in a linear mixed-effects model of vaccination effects on Ph-VAS and Pt-VAS

	Unadjusted		Adjusted	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
30 days (15–61 days)				
Ph-VAS	-0.27 (-2.60–2.06)	0.82	0.25 (-2.10–2.60)	0.84
Pt-VAS	1.35 (-1.77–4.47)	0.40	-0.98 (-4.00–2.04)	0.53
60 days (28–120 days)				
Ph-VAS	0.47 (-1.73–2.67)	0.68	-1.42 (-3.65–0.81)	0.54
Pt-VAS	-1.16 (-3.39–1.07)	0.31	0.88 (0.49–1.27)	1.00
90 days (56–189 days)				
Ph-VAS	0.34 (-2.33–3.01)	0.80	0.4 (-2.34–3.14)	0.78
Pt-VAS	-3.65 (-6.59–-0.71)	0.02	-3.43 (-6.49–-0.37)	0.03

Mixed-effects logistic models were used to calculate the estimate and 95% confidence interval. Adjusting factors included age, sex, Ph-VAS or Pt-VAS at baseline, and use of immunosuppressive drugs or biological agents. The missing values were adjusted using the simple imputation method to assign the mean of the values preceding and following the missing value ([Patient-VAS 0 days] n = 2; [Patient-VAS 30 days] n = 2).

CI, confidence interval; VAS, visual analog scale; Ph-VAS, Physician-VAS; Pt-VAS, Patient-VAS.

The statistical significance level was set at $p<0.05$.

52 **Supplemental Table 5: Estimates in a linear mixed-effects model of vaccination**

53 **effects for laboratory activity markers 30 days after the second vaccination**

54

	Unadjusted		Adjusted	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
WBC ($\times 10^3/\mu L$)	0.06 (-0.19–0.31)	0.66	0.03 (-0.36–0.42)	0.90
PLT ($\times 10^3/\mu L$)	-0.81 (-0.99–-0.63)	0.99	-1.60 (-2.64–-0.56)	0.003
CH50 (CH50/mL)	0.04 (-0.47–0.55)	0.87	-0.02 (-0.78–0.74)	0.96
C3 (mg/dL)	1.09 (0.17–2.01)	0.02	1.10 (-0.02–2.22)	0.05
C4 (mg/dL)	0.002 (-0.14–0.14)	0.97	0.01 (-0.42–0.44)	0.97
Anti-DNA antibody (IU/mL)	0.31 (-0.16–0.78)	0.21	0.33 (-0.16–0.82)	0.20
Protein/Creatinine ratio (g/gCr)	0.04 (0.001–0.08)	0.13	0.04 (0.001–0.08)	0.09

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56 Mixed-effect logistic models were used to calculate the estimate and 95% confidence

57 interval. Adjusting factors included age, sex, baseline values (including white blood cell

58 count, platelet count, CH50, C3, C4, anti-DNA antibody titer, and urine protein/creatinine

59 ratio), and use of immunosuppressive drugs or biological agents.

60 CI, confidence interval. WBC, white blood cells; PLT, platelet

61 The statistical significance level was set at $p<0.05$.

62

SUPPLEMENTAL FIGURE

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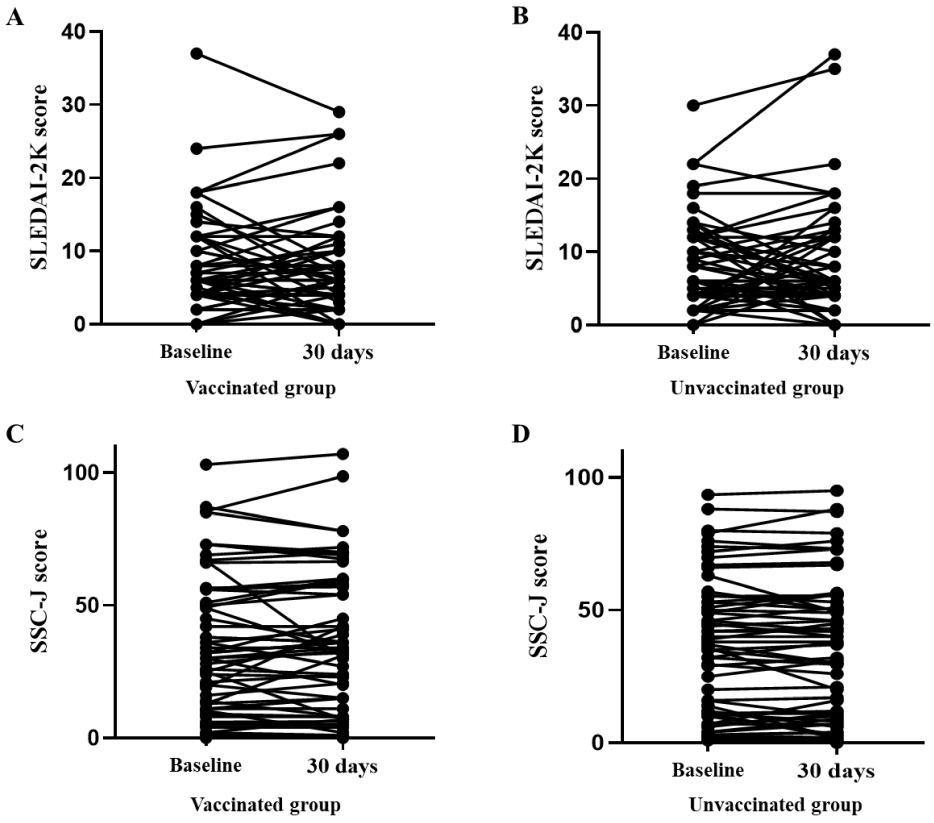

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