Attitudes towards and safety of the SARS-CoV-2 inactivated vaccines in 188 patients with systemic lupus erythematosus: a post-vaccination cross-sectional survey

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Abstract
Vaccination is key in mastering the COVID-19 pandemic. Data on attitudes towards and safety of the SARS-CoV-2 inactivated vaccines in patients with systemic lupus erythematosus (SLE) are limited. A post-vaccination cross-sectional survey was conducted to obtain data on attitudes towards and safety of the SARS-CoV-2 inactivated vaccines in SLE patients compared to healthy controls. A post-vaccination cross-sectional survey was conducted in 188 patients with SLE and in 190 healthy controls who had received at least one dose of SARS-CoV-2 inactivated vaccine to find out post-vaccination adverse event (AE) or SLE flares. A total of 188 patients with SLE and 190 healthy controls vaccinated with the two-dose regimen SARS-CoV-2 inactivated vaccine were enrolled in the study. The two groups were matched in age, sex, medical background, income, and education level. All the SLE patients were in disease remission or with low disease activity with a median age of 35 years, a sex constituent ratio of 87.4% female, and a median disease duration of 4 years. SLE patients had much more concerns about vaccination safety (44.7% vs. 15.8%, \( P < 0.001 \)), and were much less willing to get vaccinated (57.4% vs. 88.4%, \( P < 0.001 \)). SLE patients had more mild adverse events after the first vaccine dose (43.6% vs. 25.3%, \( P = 0.008 \)), and less mild adverse events after the second vaccine dose (19.8% vs. 34.9%, \( P = 0.024 \)), compared with healthy controls. The AEs were minor and there were no serious or major adverse events in both groups. In patients with SLE, the post-vaccination disease activity remained stable. One previously undiagnosed female progressed into symptomatic SLE after one week of vaccination. Although SLE patients had concerns about the safety of the SARS-CoV-2 vaccines, the inactivated vaccination was safe in patients with stable SLE.

Keywords Systemic lupus erythematosus · COVID-19 · SARS-CoV-2 · Vaccine · Adverse event

Abbreviations
SLE Systemic lupus erythematosus
AE Adverse event
GC Glucocorticoids
MMF Mycophenolate mofetil
CsA Cyclosporin A
LEF Leflunomide
AZA Azathioprine
MTX Methotrexate

Introduction
Vaccination is key in mastering the COVID-19 pandemic [1]. There are different types of vaccines including live attenuated, inactivated, protein-based, nucleic acid, and viral vector-based [2]. In China, inactivated vaccine is the first type of COVID-19 vaccine approved to be publicly used and there are over one billion doses of SARS-CoV-2 inactivated vaccines consumed so far. Patients with connective tissue diseases may be at higher risks for COVID-19 infection compared to the general population [3]. Although there are guidelines from different organizations on vaccination among patients with autoimmune diseases [3], data from the real world are limited. As the pandemic of COVID-19 goes on, we are facing massive consultation on vaccination from patients with SLE. Patients with SLE may change their attitude to COVID-19 vaccination if properly informed about risks and benefits by their trusted specialist [4]. Hence,
rheumatologists should inform their patients transparently considering their doubts and concerns during follow-up visits to influence the patient’s health-related choices. Then what concerns SLE patients have on vaccination? Is it safe for SLE patients to get vaccinated? This survey is trying to answer these questions.

Materials and methods

A post-vaccination cross-sectional survey was conducted in 188 patients with systemic lupus erythematosus (SLE) who had received at least one dose of SARS-CoV-2 inactivated vaccine to find out post-vaccination adverse event (AE) or disease flares of SLE. A similar survey was conducted in 190 healthy controls with no chronic diseases receiving the same vaccines.

Cases and controls

All patients and healthy controls are Chinese Han population from Hunan province. The cases were from Lupus Administration Group of the Second Xiangya Hospital, and they were diagnosed based on 1997 ACR classification criteria of SLE [5]. The healthy controls were recruited randomly through WeChat, and all the data were collected through participants’ online questionnaire (web questionnaire was attached in the supplement file 1). The median time between the first vaccine dose and survey response was 6 weeks, and the median time between the second vaccine dose and survey response was 4 weeks. To reduce the possible recalling bias, all the patients recalled AE within 3 months after the first dose.

Demographic characteristics, clinical data, and development of AEs (including disease flares) were collected. Vaccination safety was assessed within 6 weeks of the first and second vaccine dose. Disease activity was assessed at the vaccine administration date, and within 6 weeks after the first and/or second vaccination. The patients were not advised to reduce or stop the daily glucocorticoid dose to the vaccine administration. The disease activity was categorized as remission (SLEDAI ≤ 4), low disease activity (5 ≤ SLEDAI < 10), and moderate to high disease activity (SLEDAI ≥ 10) [6]. SLE flare was defined as one of the following: an increase in medication dosage or the introduction of new treatment in the presence of worsening of an already active system or in response to the activation of a new system; the use of the term flare in the physician’s notes; and new diagnosis of SLE.

This study followed ethical standards and the principles of Helsinki declarations. The ethics committee of the Second Xiangya Hospital approved this study with protocol number K011. All patients and healthy controls gave written informed consent about the nature and aim of the study, including consent to publish data.

Vaccination

All SLE patients and healthy controls were vaccinated with the two-dose regimen SARS-CoV-2 inactivated vaccine (Beijing Kexing Zhongwei Biotech Co., Ltd., 0.5 ml/person/time, interval between injections 14–28 days). In line with World Health Organization (WHO), AEs following immunization were classified as minor reactions (occurring within a short time of administration, complete resolution in a short period, can be local (pain, swelling, or redness at administration site) or systemic (fever, malaise, muscle pain, headache, or appetite loss)) and severe reactions (can be disabling and rarely life-threatening, including serious reactions such as death, inpatients hospitalization, persistent or significant disability, or life-threatening) [7].

Statistical analysis

The results were presented as median (range), and categorical variables were presented as absolute number and percentage for each category. The data normality was assessed using the Shapiro-Wilk’s test. We compared the clinical and laboratory data of study groups of patients using Student’s t test or Wilcoxon signed-rank test. Differences between categorical variables were tested for significance using the Chi-square test or Fisher’s exact test (as appropriate). Multiple logistic regression was applied in SLE patients and controls to determine the possible predictors of adverse events. The outcome variable was the participants with adverse events or not (1 or 0). The covariates were age, sex, medical background, income, and education level in healthy controls. In SLE patients, the covariates would also include the disease duration and glucocorticoid daily dose. Analyses were conducted using the IBM SPSS Statistics v23.0 (Armonk, NY, USA) and GraphPad Prism v8.0 (La Jolla, CA, USA). P values less than 0.05 were considered significant.

Results

Study population

A total of 188 patients with SLE and 190 healthy controls vaccinated with the two-dose regimen SARS-CoV-2 inactivated vaccine were enrolled in the study. There were no significant differences in age, sex, medical background, income, and education level between SLE group and the controls (Table 1). The median age of the patient group was 35
(18–69) years with a female (n = 166, 87.4%) majority and a median disease duration of 4 (0.5–21) years. All the SLE patients were in disease remission (94.7%, n = 178) or with low disease activity (5.3%, n = 10). A total of 100% (n = 188) of patients with SLE were treated with immunomodulatory medications (Table 2). Glucocorticoids (GC) were used in 93.6% (n = 176), and the median glucocorticoid daily dose was prednisone 10 mg. Hydroxychloroquine (HCQ) was used in 94.1% (n = 176). Immunosuppressive agents were used in 76.6% (n = 159), among which mycophenolate mofetil (MMF), cyclosporin A (CsA), leflunomide (LEF), azathioprine (AZA), and methotrexate (MTX) were commonly used. Biologics were used in combination with immunosuppressive agents in 3.2% (n = 6) (Table 2).

Attitudes towards the SARS-CoV-2 vaccines

There were no significant differences in knowledge about COVID-19, including the transmission ways and protection methods between SLE patients and controls. However, vaccine willingness was significantly different between the two groups: SLE patients had much more concerns about vaccination safety including AEs and SLE flares (44.7% vs. 15.8%), and were much less willing to get vaccinated compared with healthy controls (57.4% vs. 88.4%) (Table 3). Most SLE patients (83.0%, n = 156) consulted rheumatologists for advice before vaccination. SLE patients were more willing to get vaccinated if their doctor advised them to. Therefore, it is important for rheumatologists to understand the safety of the SARS-CoV-2 vaccination in SLE patients.

Safety of the SARS-CoV-2 inactivated vaccines

The prevalence of mild adverse events was significantly different in patients with SLE and controls. SLE patients had more mild adverse events after the first vaccine dose and less mild adverse events after the second vaccine dose (Fig. 1). However, the AEs were acceptable and there were no serious or major adverse events in both groups. In patients with SLE, the post-vaccination indices of disease activity remained stable (Table 4). There was a special SLE patient, who is a 46-year-old female and was once healthy, she was diagnosed with SLE after injection with two doses of SARS-CoV-2 inactivated vaccines. The patient might have an underlying immune system disorder (we could not confirm whether she had positive serum autoantibodies before vaccination), so the vaccine may be an induction factor. As indicated in the supplement Table 1, all of the P values of multiple regression analysis were more than 0.05. So, sex, age, medical background, income, education level, disease duration, and glucocorticoid daily dose were not the possible predictors of adverse events after the first vaccine dose.

Discussion

This is a large post-vaccination cross-sectional survey conducted to confirm safety of SARS-CoV-2 inactivated vaccines in patients with SLE compared with healthy controls. The special population with immune disorders and an administration of GC or immunosuppressive agents are used in 76.6% (n = 159), among which mycophenolate mofetil (MMF), cyclosporin A (CsA), leflunomide (LEF), azathioprine (AZA), and methotrexate (MTX) were commonly used. Biologics were used in combination with immunosuppressive agents in 3.2% (n = 6) (Table 2). Glucocorticoids (GC) were used in 93.6% (n = 176), and the median glucocorticoid daily dose was prednisone 10 mg. Hydroxychloroquine (HCQ) was used in 94.1% (n = 176). Immunosuppressive agents were used in 76.6% (n = 159), among which mycophenolate mofetil (MMF), cyclosporin A (CsA), leflunomide (LEF), azathioprine (AZA), and methotrexate (MTX) were commonly used. Biologics were used in combination with immunosuppressive agents in 3.2% (n = 6) (Table 2).
seriously considered for its safety and immunogenicity of COVID-19 vaccines. As was shown in our survey, SLE patients had much more concerns about safety of COVID-19 vaccination, the situation was similar in other autoimmune or inflammatory rheumatic diseases [8].

The vaccine was generally safe in terms of AEs both in patients with SLE and in controls. AEs after the first vaccine dose were similar to those after the second vaccine dose. AEs were generally minor reactions and acceptable, although the prevalence of mild AEs was significantly different between SLE group and control group. The top three common AEs were myalgia, fatigue, and pain/swelling/redness of injection sites. Assawasaksakul et al. also evaluated the safety of SARS-CoV-2 inactivated vaccine in lupus patients and revealed that none of the patients experienced an SLE flare, and the most common complaint was injection site pain followed by fatigue and fever [9]. AEs of SARS-CoV-2 inactivated vaccines are similar to those of other kinds of COVID-19 vaccines reported [10]. Other SARS-CoV-2 vaccines were reported to be safe in people with rheumatic and musculoskeletal diseases [11, 12].

Special attention should be paid to the previously non-SLE patient who developed symptomatic SLE after one week of vaccine injection. Both vaccine-induced humoral and cellular responses following vaccination are speculated as a possible mechanism of inducing SLE. Thus, people with underlying immune system disorder (with positive serum autoantibodies) but asymptomatic may progress into symptomatic autoimmune diseases after injection of vaccines. Other types of SARS-CoV-2 vaccines such as Pfizer/BioNTech (BNT162b2) [13], ChAdOx1 nCoV-19 vaccine (AZD1222) [14, 15] were reported to induce SLE. Not only SARS-CoV-2 vaccine, other vaccines, such as hepatitis B vaccine or meningococcal vaccine, were reported to induce or exacerbate SLE [16–18]. Vaccination-induced lupus may be one style of autoimmune/inflammatory syndrome induced by adjuvants [19]. This case highlights the importance of considering acute autoimmune reactions such as SLE and dermatomyositis in the differential diagnosis when assessing previously healthy patients presenting with systemic symptoms such as persistent fever, rash, fatigue, muscle pain, or

| Table 3 Attitudes towards the SARS-CoV-2 vaccines |
|-----------------------------------------------|
| Questions | Control (n = 190) | SLE (n = 188) | P values |
| Protection methods (agree with its efficacy) |
| Wash hands | 186 (97.9%) | 184 (97.9%) | 0.991 |
| Wear mask | 188 (98.9%) | 188 (100%) | 0.567 |
| Social distance | 174 (91.6%) | 178 (94.7%) | 0.399 |
| Disinfection | 170 (89.5%) | 162 (86.2%) | 0.487 |
| Ventilation | 172 (90.5%) | 176 (93.6%) | 0.432 |
| Spread methods (agree that it is one of the transmission way) |
| Respiratory | 190 (100%) | 188 (100%) | 0.994 |
| Contact | 142 (74.7%) | 146 (77.7%) | 0.637 |
| Aerosol | 98 (51.6%) | 94 (50.0%) | 0.828 |
| Gastrointestinal | 80 (42.1%) | 80 (42.6%) | 0.942 |
| Do you think vaccines would be effect to control the spreading of COVID-19? | 0.163 |
| Very effective | 106 (55.8%) | 76 (40.4%) |
| Effective | 68 (35.8%) | 102 (54.3%) |
| Unknown | 14 (7.4%) | 10 (5.3%) |
| No effect | 2 (1.1%) | 0 |
| Totally no effect | 0 | 0 |
| Do you prefer to get the vaccines? | < 0.001 |
| Yes | 168 (88.4%) | 108 (57.4%) |
| Unknown | 20 (10.5%) | 78 (41.5%) |
| No | 2 (1.1%) | 2 (1.1%) |
| Do you have any concerns about the vaccines? | < 0.001## |
| Safety (Side effects and disease flares) | 30 (15.8%) | 84 (44.7%) |
| Efficacy | 48 (25.3%) | 36 (19.1%) |
| None | 112 (58.9%) | 68 (36.2%) |

Significants were marked in bold

## Chi-square P value

Others were Fisher's exact P value
Fig. 1  Frequency of different adverse events in patients with SLE and healthy controls after the first A and second B dose of vaccine. SLE, systemic lupus erythematosus

Table 4  Adverse events of the SARS-CoV-2 inactivated vaccines in SLE and healthy controls

| Adverse events, n (%) | After the first vaccine dose | P values | After the second vaccine dose | P values |
|-----------------------|------------------------------|----------|------------------------------|----------|
|                       | Controls n = 190 | SLE n = 188 |                       | Controls n = 106 | SLE n = 116 |          |
| Pain/swelling/redness of injection site | 10 (5.3%) | 28 (14.9%) | 0.028 | 16 (15.1%) | 14 (12.1%) | 0.851 |
| Fever | 4 (2.1%) | 2 (1.1%) | 0.993 | 4 (3.8%) | 2 (1.7%) | 0.937 |
| Fatigue | 10 (5.3%) | 24 (12.8%) | 0.071 | 5 (4.7%) | 5 (4.3%) | 0.927 |
| Nausea/Vomiting | 2 (1.1%) | 4 (2.1%) | 0.993 | 0 | 0 | 0.949 |
| Myalgia | 18 (9.5%) | 16 (8.5%) | 0.817 | 10 (9.4%) | 0 | 0.035 |
| Arthralgia | 2 (1.1%) | 2 (1.1%) | 0.994 | 0 | 0 | 0.949 |
| Headache | 2 (1.1%) | 4 (2.1%) | 0.993 | 2 (1.8%) | 2 (1.7%) | 0.949 |
| Allergic reaction | 0 | 2 (1.1%) | 0.993 | 0 | 0 | 0.949 |
| Total minor reactions | 48 (25.3%) | 82 (43.6%) | 0.008 | 37 (34.9%) | 23 (19.8%) | 0.024 |
| Flare of lupus | – | 0 | 0.994 | – | 1(0.8%)* | 0.937 |
| Other symptoms | 0 | 0 | 0.994 | 1 (1.9%)* | 0 | 0.937 |

Significants were marked in bold

*A 46-year-old female was once healthy, and suffered from fever, fatigue and myalgia after the first vaccine dose. The adverse effects disappeared within one week. She suffered from persistent fever and arthralgia after the second vaccine dose and searched for medical help. The tests showed positive autoantibodies (Sm+, dsDNA+), proteinuria of 3 g per 24 h, and pleural effusion. She was diagnosed with SLE and was administered with mPSN 2 mg/kg/day, HCQ, and MMF, and she achieved complete remission after 3 months. We inferred that the patient had an underlying immune system disorder (with positive serum autoantibodies), and progressed into symptomatic SLE after injection of SARS-CoV-2 inactivated vaccine. The vaccine is considered to activate autoimmunity as an induction factor

*Cough

All P values were Chi-square P values
proteinuria (longer than one week) in the setting of recent COVID-19 vaccination. As an important dimension of safety, post-vaccination disease activity is highly concerned. In the survey, all patients of SLE are in remission or in low disease activity status, and no patient experienced disease relapse or deterioration after injection of the vaccines. Post-vaccination disease activity also remained stable in the majority of patients with rheumatic diseases after injection with other kinds of COVID-19 vaccines [20–22].

Immunogenicity of COVID-19 vaccines is also a widely concerned issue. Our survey provided limited information regarding the impact of glucocorticoids and various immunosuppressive treatments on vaccine-induced immunogenicity, since serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins were measured only in a small part of population surveyed. Previous studies showed immunogenicity was significantly impaired by glucocorticoids, immunosuppressive agents, and biologics [20, 23]. So, there was a recommended paradigm for vaccination of rheumatic disease patients with the SARS-CoV-2 vaccine aimed at achieving optimal vaccine benefit without interfering with disease activity status [24].

This study has several limitations. First, as a post-vaccination survey, there were recall bias. Second, there were limited data on SLE patients with active disease activity since all the SLE patients from our study were in disease remission or with low disease activity. Third, our study had limited data on immunogenicity of COVID-19 vaccines in SLE patients. Fourth, in the logistic regression, we did not include the smoking status [25] and some other confounders, which might be why we did not find the predictors of adverse events.

Conclusions

This post-vaccination cross-sectional survey showed SLE patients had more concerns about vaccination safety and were less willing to get vaccinated. AEs were acceptable and there were no serious or major adverse events in both SLE patients and healthy controls. In patients with SLE, the post-vaccination SLE disease activity remained stable. In total, SARS-CoV-2 inactivated vaccine was safe in stable patients with SLE.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10238-022-00832-1.

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Author contributions QT and JH were responsible for conceptualization, methodology, and resources. JK and JH carried out data curation. QT and FL wrote the original draft. FL and JH were involved in writing, reviewing, and editing. JH acquired the funding.

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Data Availability The detailed information on the data is available when be requested via email.

Declarations

Conflict of interest They all author declare that have no conflict of interest

Ethical approval Approval of this study was obtained from the ethics review board of the Hospital.

Informed consent Written informed consent has been obtained from the participants to publish this paper.

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