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Impact of Distinct Therapies on Antibody Response to SARS-CoV-2 Vaccine in Systemic Lupus Erythematosus

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Objective. To date, the only study that has assessed the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 mRNA) vaccine in systemic lupus erythematosus (SLE) observed a moderate response, but the sample size precluded an accurate analysis of the effect of individual drugs. Therefore, we evaluated the immunogenicity of an inactivated SARS-CoV-2 vaccine (Sinovac-CoronaVac) and the influence of different medications in SLE. Safety was also assessed.

Methods. We conducted a prospective controlled study of 232 SARS-CoV-2–naive SLE patients and 58 SARS-CoV-2–naive controls who were vaccinated with 2 doses of Sinovac-CoronaVac with a 28-day interval (day 0/day 28 [D0/D28]). Immunogenicity analysis at D0/D28 and D69 included anti-SARS-CoV-2 S1/S2 IgG seroconversion (SC) and neutralizing antibodies (NAb) positivity. The influence of individual drugs on immune response and safety was assessed.

Results. Patients and controls were well balanced for age ($P = 0.771$). At D69, SLE patients showed a moderate SC (70.2% versus 98.1%; $P < 0.001$) and moderate frequency of NAb positivity (61.5% versus 84.6%; $P = 0.002$), although both frequencies were lower than in controls. Factors associated with lower SC in univariate analysis at D69 were prednisone use (odds ratio [OR] 0.215 [95% confidence interval (95% CI) 0.108–0.427], $P < 0.001$) and mycophenolate mofetil (MMF) use (OR 0.201 [95% CI 0.107–0.378], $P < 0.001$), whereas hydroxychloroquine (HCQ) use led to a 2.5 increase in SC ($P = 0.011$). SLE patients who were receiving HCQ monotherapy had similar SC to controls at D69 (100% versus 98.1%; $P = 1.000$). In multivariate analysis, prednisone and MMF use were independently associated with lower SC ($P < 0.001$) and NAb positivity ($P < 0.001$). Safety analysis revealed no moderate/severe adverse events.

Conclusion. Sinovac-CoronaVac has a moderate immunogenicity in SARS-CoV-2–naive SLE patients with an excellent safety profile. We further demonstrate that HCQ may improve SC, whereas prednisone and MMF had a major deleterious effect in vaccine response, reinforcing the need to investigate the role of temporary MMF withdrawal or a vaccine-booster dose (ClinicalTrials.gov identifier: NCT04754698).

INTRODUCTION

The impact of COVID-19 in patients with autoimmune rheumatic diseases (ARDs) during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic remains a major concern, especially in systemic lupus erythematosus (SLE). Data are still controversial, with some studies showing that the number of organs involved, disease activity, and ARD itself are associated with COVID-19 poor outcome (1–3). In contrast, other studies have not confirmed this worse prognosis and have even suggested a lower risk of developing severe COVID-19 in these patients (4,5). A possible explanation for these discrepancies is

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SIGNIFICANCE & INNOVATIONS

- This large prospective control study focusing on SARS-CoV-2–naive systemic lupus erythematosus (SLE) patients' response to inactivated SARS-CoV-2 vaccine immunogenicity revealed a moderate antibody production, comparable to the immunogenicity reported for the mRNA/adenovirus vaccine, despite the high frequency of immunosuppression in this tertiary cohort.
- This is the first demonstration that mycophenolate mofetil and prednisone induce ~70–80% reduction in immunogenicity, reinforcing the need for novel strategies to improve vaccine-induced antibody production in this subgroup of SLE patients.
- Antimalarials seem to substantially increase the seroconversion, even in lupus patients with multiple drug therapy.

the overall ARD analysis, which may not be accurate in discriminating the effect of an individual ARD and its respective therapy in immune response (6). Reinforcing this finding, 1 study found twice the odds of hospitalization for COVID-19 in ARD patients using prednisone ≥10 mg/day, leading to higher admission rates in SLE patients (56%) (7), which was similar to the rate found in a larger sample SLE cohort (58%) (8).

In line with this hypothesis, we have previously demonstrated, in a large study of 1,668 patients with distinct ARD and their respective therapies, that these parameters differentially affected H1N1 vaccine response (9). Indeed, overall seroconversion (SC) rates for H1N1 vaccine were diminished in ARD patients (63.4%), including SLE, rheumatoid arthritis (RA), and psoriatic arthritis, whereas for systemic sclerosis, primary antiphospholipid syndrome, and primary Sjögren's syndrome, SC rates were comparable to the healthy control group (9). Regarding therapy, the analysis of 555 SLE patients who were undergoing different therapeutic regimens clearly identified that H1N1 vaccine response was reduced in those being treated with prednisone and immunosuppressive drugs, but the use of antimalarials seemed to improve vaccine immunogenicity (10).

There are, however, scarce studies that have evaluated SARS-CoV-2 vaccine response in SLE, mainly with mRNA vaccines, and most studies have included a small representation of this disease, precluding a subgroup analysis of the potential deleterious effect of therapy (11–15). A multicenter observational study of immune response and safety of the 2-dose regimen BNT162b2 mRNA vaccine, which included a large sample of 101 SLE patients, showed a seropositivity rate in this disease subgroup comparable to a nonbalanced, but age-adjusted control group (16). This study by Furer et al observed that, in the overall 686 patients with several ARDs, glucocorticoids, mycophenolate mofetil (MMF), rituximab, and abatacept were associated with reduced IgG response. No data are provided about the effect of the different drugs for each individual ARD. A recent study by Izmirly et al that focused exclusively on SLE patients evaluated immunogenicity after immunization with 3 different vaccines (2 mRNA and 1 adenovirus vaccines) compared to controls and reported a diminished vaccine response, but the sample size precluded a definitive conclusion regarding the influence of different therapies (17). Another study, by Simon et al, compared 64 SLE patients to 73 RA patients (without a healthy control group) and observed a global 77% response to the mRNA vaccine without a distinction between the 2 diseases. Rituximab was identified as the only drug associated with a pronounced reduction in immunogenicity (11).

The SARS-CoV-2 inactivated vaccine (Sinovac-CoronaVac) is accounted for in ~36% of all vaccinated subjects in Brazil. A recent cohort report from Chile that included 10.2 million people vaccinated with Sinovac-CoronaVac observed a significant impact in prevention of COVID-19–related hospitalization (87.5%), intensive care unit (ICU) admission (90.3%), and death (86.3%) (18). Recently, our group performed a phase 4 prospective controlled study with 910 SARS-CoV-2 seronegative ARD patients who received 2 doses of Sinovac-CoronaVac (19). A global moderate SC (70.4%) was observed in these patients (lower than in the control group [95.5%]), with a parallel decrease in symptomatic cases in the next 40 days after full vaccination. Prednisone, methotrexate, MMF, anti–tumor necrosis factor inhibitors, and abatacept were associated with the lower SC rates in the ARD patients overall. But the unbalanced distribution of disease and patient therapy does not allow for a precise identification of the effect of these factors in a specific disease subgroup (19). In addition, data on the possible influence of disease activity in vaccine-induced antibody response were not reported.

Therefore, the aim of the present study was to prospectively evaluate immunogenicity (anti-SARS-CoV-2 IgG and neutralizing antibodies [NAb]) to the Sinovac-CoronaVac vaccine in SARS-CoV-2 seronegative (naive) SLE patients compared to a control group and to determine the possible influence of different drugs in vaccine antibody production. Safety was also assessed.

PATIENTS AND METHODS

Study design. This prospective controlled trial is part of a larger phase IV study (CoronavRheum; ClinicalTrials.gov identifier: NCT04754698) that assessed immunogenicity and safety of the Sinovac-CoronaVac COVID-19 vaccine in a large sample of ARD patients (19), and it was conducted at a single tertiary center in Brazil. Data were collected and managed using REDCap electronic data capture tools hosted at our institution (20,21).

Participants. Consecutive SLE patients who fulfilled the Systemic Lupus International Collaborating Clinic (SLICC) classification criteria for SLE (22), were age ≥18 years and who were followed up at the outpatient SLE clinics (Hospital das Clinicas

HCFMUSP, Universidade de Sao Paulo) were invited to participate.

Subsequently, the maintenance/administrative hospital workers and their relatives were invited to comprise an age- (up to 5 years difference) and sex-balanced control group (1 control: 4 patients). None of the controls were previously immunized in the hospital's COVID-19 campaign. ARD diagnosis, use of immunosuppressors, or HIV infection were exclusion criteria for the control group, though other well-controlled diseases were allowed in the group. None of the patients included withdrew medications to increase vaccine immunogenicity.

The following exclusion criteria were applicable for all participants: acute febrile malady or symptoms suggestive of COVID-19 at baseline, previous anaphylactic response to vaccine components, demyelinating disease, severe heart failure (class III or IV), history of having received blood transfusion ≤6 months before study entry (to avoid false positive anti-SARS-CoV-2 antibodies), inactivated virus vaccine ≤14 days before, history of live virus vaccine ≤4 weeks before, not consenting to participate in the study, hospitalized patients, prior immunization with any SARS-CoV-2 vaccine, and pre-vaccination positive COVID-19 serology (anti-S1/S2 IgG) and/or NAb (for immunogenicity analysis). The protocol was approved by the National and Institutional Ethical Committee of Hospital das Clinicas HCFMUSP (n^{o} CAAE: 42566621.0.0000.0068). All participants agreed to a signed informed consent form before enrollment.

Vaccination protocol. The vaccination protocol for all participants included 2 doses of ready-to-use syringes loaded with the Sinovac-CoronaVac vaccine (Sinovac Life Sciences, batch #20200412), which consisted of 3 μg in 0.5 ml of β-propiolactone inactivated SARS-CoV-2 (resultant from the CN02 strain of SARS-CoV-2 grown in African green monkey kidney cells [Vero 25 cells]) with aluminum hydroxide as an adjuvant, applied in the deltoid muscle. The first vaccine dose was applied on February 9–10, 2021 (day 0 [D0]) and the second on March 9–10, 2021 (D28). After having the first vaccine dose, subjects with RT-PCR–confirmed COVID-19 were excluded from the immunogenicity analysis but remained in the safety evaluation.

Samples for immunogenicity evaluation. Blood samples (20 ml) were obtained from all participants at days D0 (baseline, before first vaccine injection), D28 (before second vaccine injection), and on D69 (April 19, 2021) (6 weeks after the last dose). Sera were stored in a –70°C freezer.

Anti-SARS-CoV-2 S1/S2 IgG antibodies. Analysis of anti-SARS-CoV-2 S1/S2 IgG antibodies was performed as described previously (17), including only SARS-CoV-2–naive participants. The SC rate was measured by positive serology (≥15.0 UA/ml) after vaccination. Geometric mean titers (GMTs) and 95% confidence intervals (95% CIs) of these antibodies were also determined at all time points, attributing the value of 1.9 UA/ml (half of the lower limit of quantification 3.8 UA/ml) to above lower levels (<3.8 UA/ml). The factor increase in GMTs is the ratio of the GMTs after immunization to the GMTs before immunization, which identified the increase in titers.

SARS-CoV-2 cPass virus-NAb. The evaluation of NAb were performed as described previously (19), including only in SARS-CoV-2–naive participants. The samples were cataloged as positive (inhibition ≥30%) or negative (inhibition <30%) according to the manufacturer's instructions (23). The frequency of seropositivity was recorded at all time points. Median values and interquartile ranges of the percentage of neutralizing activity were only measured for seropositive samples at all time points.

Vaccine adverse events (AEs) and incident cases of COVID-19. AEs were carefully followed throughout the study. In addition, an independent data safety monitoring board reviewed and evaluated the study protocol. Patients with SLE and controls were advised to report any side effects of the vaccine. On D0 (first dose) and on D28 (second dose), all participants received brochures to record local and systemic manifestations. AE severity was classified according to World Health Organization criteria (24).

In addition, to assess incident COVID-19 cases (exploratory outcome), all subjects were instructed to notify any symptom associated or not associated with COVID-19 (by telephone, smartphone instant messaging, or email). Suspected cases of COVID-19 were told to seek initial medical care in a local neighborhood and, if necessary, come to our institution for an in-person visit to collect SARS-CoV-2 RT-PCR in nasopharyngeal and oropharyngeal swabs using a laboratory-developed test (25). If tertiary care was required, participants were transferred to a referenced hospital. The standardized brochure of AE was rigorously revised with each participant on the day of the second dose (D28) and at the final visit (D69).

Disease assessment. The SLE Disease Activity Index 2000 (SLEDAI-2K) score (26) was retrospectively evaluated within 30 days before baseline (D0) and until 3 months after the second vaccine dose (D28), excluding those who developed COVID-19 during the study. Cumulative SLE manifestations were systematically evaluated, including cutaneous, articular, renal, hematologic, serositis, and neuropsychiatric manifestations, according to Systemic Lupus International Collaborating Clinics (SLICC) criteria (22). At entry, cumulative damage was also recorded and scored using the SLICC /American College of Rheumatology Damage Index (SDI) (27).

Statistical analysis. The sample size calculation was based on the previous 21% reduction of SC rate after primo immunization with the 2009 non-adjuvanted influenza A/H1N1

vaccine in a large cohort of SLE patients (10). Expecting SC rates of 59% in the SLE patient cohort and 80% in the control group, considering $\alpha = 5\%$ and power of 80%, with a 4:1 ratio in order to include more SLE patients, the minimum sample required would be 192 patients with SLE and 48 healthy age- and sex-balanced controls. Expecting a higher SC rate of 98% for this vaccine (28), such a sample size had a power of >99% to detect a 21% reduction in SC of patients with SLE. Due to the peak of the ongoing pandemic in Brazil during the immunization period, we invited more patients and controls, as we expected a high incidence of previously infected people and a high rate of COVID-19 during the study.

Categorical variables are shown as number (%) and compared using the chi-square or Fisher's exact tests, as appropriate. Only for patients with SLE, multivariate logistic regression analyses were performed using SC or presence of NAb at D69 (primary end points) as dependent variables and as independent variables those with $P < 0.2$ in each univariate analysis.

Continuous general data are shown as medians (interquartile ranges) and compared using the Mann-Whitney test for intergroup comparisons and Wilcoxon's signed rank test for before and after comparisons in the same group. Continuous data regarding anti-S1/S2 serology titers are shown as geometric mean (95% CI); their comparisons were performed using repeated measures analysis of variance, with 2 factors (2 groups [SLE and the control group] at 3 time points [D0, D28, and D69]) followed by Bonferroni's multiple comparisons in neperian logarithm (ln)-transformed data.

Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 20.0 (IBM SPSS for Windows, version 20.0).

Table 1. Baseline characteristics of SLE patients and controls*

	SLE patients (n = 232)	Controls (n = 58)	*P*
Demographic data			
Current age, median (IQR) years	40.5 (18–73)	41.5 (22–74)	0.771
Age at diagnosis, median (IQR) years	26 (7–62)	–	–
Disease duration, median (IQR) years	13 (1–54)	–	–
Female sex	208 (89.7)	52 (89.7)	>0.999
White race	97 (41.8)	31 (53.4)	0.110
Comorbidities	130 (56.0)	20 (34.5)	0.003
Pulmonary arterial hypertension	102 (44.0)	11 (19.0)	<0.001
Diabetes mellitus	10 (4.3)	4 (6.9)	0.490
Dyslipidemia	29 (12.5)	4 (6.9)	0.354
Obesity (BMI ≥30 kg/m^2)	70 (30.2)	19 (32.8)	0.703
Chronic cardiomyopathy	10 (4.3)	0	0.220
Chronic renal disease	4 (1.7)	0	0.587
Current smoking	13 (5.6)	6 (10.3)	0.192
Chronic obstructive pulmonary disease	0	0	>0.999
Asthma	5 (2.2)	1 (1.7)	>0.999
Interstitial lung disease	2 (0.9)	0	>0.999
Pulmonary hypertension	4 (1.7)	0	0.587
Hematologic disease	1 (0.4)	0	>0.999
Hepatic disease	2 (0.9)	0	>0.999
Current cancer	1 (0.4)	0	>0.999
Stroke	10 (4.3)	0	0.220
Current tuberculosis	0	0	–
HIV	0	0	–
Current therapies			
Hydroxychloroquine	187 (80.6)	–	–
Prednisone	126 (54.3)	–	–
Prednisone dose, median (IQR) mg/day	5 (0.5–60)	–	–
Prednisone ≥ 10 mg/day	48 (20.7)	–	–
Immunosuppressive drugs	173 (74.6)	–	–
Mycophenolate mofetil	73 (31.5)	–	–
Dose, median (IQR) mg/day	2 (0.5–3)	–	–
Azathioprine	62 (26.7)	–	–
Methotrexate	25 (10.8)	–	–
Calcineurin inhibitor	11 (4.7)	–	–
Cyclophosphamide	6 (2.6)	–	–
Leflunomide	3 (1.3)	–	–
Belimumab	32 (13.8)	–	–

* Values are the no. (%) except where indicated otherwise. BMI = body mass index; IQR = interquartile range; SLE = systemic lupus erythematosus.

Table 2. Seroconversion rates and anti-SARS-CoV-2 S1/S2 IgG titers before and after the first and the second dose of CoronaVac vaccination in SLE patients and controls*

	Before vaccine 1st dose	After vaccine 1st dose (D28)			After vaccine 2nd dose (D69)		
	GMTs	SC, no. (%)†	GMTs	FI-GMTs	SC, no. (%)	GMTs	FI-GMT
SLE patients (n = 215)	2.4 (2.2–2.6)	57 (26.5)	6.5 (5.5–7.7)	2.7 (2.3–3.2)	151 (70.2)	29.6 (24.8–35.4)	12.4 (10.3–14.8)
Controls (n = 53)	2.4 (2.1–2.8)	24 (45.2)	13.3 (9.3–19.0)	5.5 (4.1–7.3)	52 (98.1)	77.0 (64.5–91.8)	31.7 (26.1–38.7)
P (SLE patients versus controls)	>0.999	0.012‡	<0.001‡	<0.001‡	<0.001‡	<0.001‡	<0.001‡
P (time points for SLE patients and controls)§	<0.001‡		<0.001‡			<0.001‡	

* Values are the mean (95% confidence interval) except where indicated otherwise. Throughout the study period, the 2 groups had different dynamics of neperian logarithm (ln)–transformed geometric mean titers (GMTs; AU/ml) ($P < 0.001$ for interaction). FI-GMT = factor increase of GMTs; SLE = systemic lupus erythematosus.
† Seroconversion (SC) was defined as post-vaccination titer ≥15 AU/ml (indirect enzyme-linked immunosorbent assay [LIAISON], SARS-CoV-2 S1/S2 IgG [DiaSorin]).
‡ Statistically significant.
§ *P* time points included longitudinal comparisons of GMT for SLE patients and controls at day 28 (D28) and D69 versus baseline and at D69 versus D28.

RESULTS

Participants. A total of 262 consecutive SLE patients were invited to participate in the study, but 30 were excluded because of acute febrile illness at baseline (n = 5), history of demyelinating disease (n = 1), previous vaccination with any SARS-CoV-2 vaccine (n = 4), <2 weeks from another inactivated vaccine (n = 1), not wanting to participate in the study (n = 16), and hospitalizations (n = 3). Finally, 232 consecutive SLE patients and 58 age- and sex-matched controls were included and received 2 doses of the Sinovac-CoronaVac vaccine (Table 1).

Patients with SLE had a median disease duration of 13 years (IQR 1–54 years). The cumulative frequency of SLE manifestations included 80.2% cutaneous, 84.5% articular, 66.8% hematologic, 59.1% renal, 33.2% serositis, and 15.5% neuropsychiatric involvements. At baseline, 109 of 232 SLE patients (43.9%) had disease activity evaluation available within the last 1 month, with a median SLEDAI-2K score of 2 (range 0–19), and 20 of 109 SLE patients (18.3%) had scores ≥6. The median SDI score at baseline was 0 (range 0–6). Comorbidities were more often observed in patients with SLE ($P = 0.003$), mainly due to the high frequency of arterial hypertension (44% versus 19%; $P < 0.001$). A total of 187 SLE patients were taking hydroxychloroquine (HCQ) (80.6%), 54.3% were using prednisone with a median daily dose of 5 mg/day (IQR 0.5–60 mg/day), and 74.6% were taking immunosuppressive agents, with MMF being the most frequently used drug (31.5%), followed by azathioprine (26.7%) and methotrexate (10.8%). There was no patient receiving treatment with rituximab, and 32 (13.8%) were receiving belimumab (Table 1).

Immunogenicity assessment. For the immunogenicity outcome, we excluded 11 participants (9 SLE patients and 2 controls) with RT-PCR–confirmed COVID-19 after either the first or the second dose until D69, 2 participants (1 SLE patient and 1 control) for whom IgG serology was not collected at D69, and 5 participants (3 SLE patients and 2 controls) who were not tested for NAb at D69. Moreover, 7 SLE patients and 2 controls had pre-vaccination positive COVID-19 IgG serology and/or NAb positivity and were also excluded.

The immune response of the remaining 215 patients with SLE and 53 controls, who were all SARS-CoV-2–naive for anti-SARS-CoV-2 S1/S2 IgG antibodies and NAb, are shown in Tables 2 and 3. Analysis of SARS-CoV-2 S1/S2 IgG response revealed that 6 weeks after the second vaccine dose (D69), SC rates in SLE patients were moderate but lower than in controls (70.2% versus 98.1%; $P < 0.001$). GMTs (29.6 [24.8–35.4]

Table 3. Frequency of neutralizing antibodies and median percentage of neutralizing activity in positive cases, after the first and second dose of CoronaVac vaccination in SLE patients and controls*

	After vaccine 1st dose		After vaccine 2nd dose	
	Subjects with positive NAb	Neutralizing activity (%), median (IQR)	Subjects with positive NAb	Neutralizing activity (%), median (IQR)
SLE patients (n = 213)	58 (27.2)	52.1 (38.1–71.4)	131 (61.5)	56.2 (41.3–77.2)
Controls (n = 52)	19 (36.5)	43.7 (37.6–77.4)	44 (84.6)	65.9 (48.2–79.6)
P (SLE patients × controls)	0.232	0.786	0.002	0.132

* Values are the no. (%) except where indicated otherwise. Positivity for neutralizing antibodies (NAb) defined as a neutralizing activity ≥30% (cPass sVNT Kit [GenScript]). IQR = interquartile range; SLE = systemic lupus erythematosus.

versus 77.0 [64.5–91.8]; $P < 0.001$) were also significantly lower in patients with SLE compared to controls (Table 2).

After the first dose (D28), only one-fourth of SLE patients and 45.2% of controls developed anti-SARS-CoV-2 IgG antibodies, with lower titers in SLE patients compared to controls (6.5 versus 13.3; $P < 0.001$) (Table 2). Further analysis using Bonferroni's multiple comparison revealed that the mean behavior of the ln-transformed IgG titers was reduced on D28 compared to D69 in the SLE patient and control groups ($P < 0.001$). Mean IgG titers were similar at D0 in both groups ($P > 0.999$) and increased at each time point for SLE patients and controls ($P < 0.001$) (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24824/abstract).

Evaluation of the dynamics of NAb detection showed that, after the first dose (D28), a minority of participants had positive antibodies, and SLE patients had similar frequencies (27.2% versus 36.5%; $P = 0.232$) and similar median (IQR) activity (52.1% [38.1–71.4%] versus 43.7% [37.6–77.4%]; $P = 0.786$]) compared with controls (Table 3). At D69, neutralizing activity (56.2% versus 65.9%; $P = 0.132$) was similar between groups, and a moderate but lower NAb positivity was observed in SLE patients compared to controls (61.5% versus 84.6%; $P = 0.002$).

Factors associated with reduced immunogenicity among SLE patients. SLE patients who were receiving HCQ monotherapy showed similar SC rates compared to controls at D28 (46.0% versus 45.2%; $P = 0.942$) and D69 (100% versus 98.1%; $P = 1.000$). Table 4 shows the odds ratio (OR) for SC according to demographic data, SLEDAI-2K score, and current treatment. HCQ use had an OR of 2.476 (95% CI 1.228–4.993; $P = 0.011$) in favor of SC (Table 4). Of note, the association of HCQ to the immunosuppressive drugs + glucocorticoid combination provided an OR of 2.1 (95% CI 0.911–5.107; $P = 0.081$) of SC, comparing with SLE patients with the same drug combination but without HCQ association. Conversely, the use of immunosuppressive drugs had an OR of 0.03 (95% CI 0.004–0.224; $P < 0.001$) for SC, with use of MMF and prednisone decreasing the SC rate in ~80% of SLE patients (OR 0.201 [95% CI 0.107–0.378], $P < 0.001$ and OR 0.215 [95% CI 0.108–0.427], $P < 0.001$, respectively). Additionally, the median baseline SLEDAI-2K score of >4 was not statistically associated with lower SC ($P = 0.400$). Multivariate logistic regression analysis was performed using SC at D69 as the dependent variable and as independent variables those with $P < 0.2$ in the univariate analysis. Current age (OR 0.95 [95% CI 0.92–0.98], $P = 0.004$), prednisone use (OR 0.195 [95% CI 0.09–0.42], $P < 0.001$), and MMF use (OR 0.15 [95% CI 0.07–0.32], $P < 0.001$) were independently associated with the absence of SC in SLE patients.

Further analysis of factors associated with negative NAb in SLE after full vaccination (D69) showed that prednisone (OR 0.301 [95% CI 0.165–0.546], $P < 0.001$) and immunosuppressants use (OR 0.252 [95% CI 0.115–0.552], $P < 0.001$), particularly MMF (OR 0.361 [95% CI 0.199–0.656], $P < 0.001$), resulted in 70% lower chance of NAb positivity. Multivariate analysis

Table 4. Odds ratio for seroconversion according to current treatment in SLE patients*

	Anti-SARS-CoV-2 S1/S2 IgG SC			Neutralizing antibodies		
	OR	95% CI	*P*	OR	95% CI	*P*
Demographic data						
Current age >60 years	0.455	0.158–1.315	0.146	0.934	0.320–2.730	0.901
Female sex	1.036	0.405–2.654	0.941	1.870	0.784–4.462	0.158
White race	1.117	0.615–2.030	0.717	1.131	0.644–1.986	0.669
SLEDAI-2K score >4, (n = 80)†	0.656	0.246–1.751	0.400	0.863	0.337–2.210	0.759
Current therapies						
Hydroxychloroquine	2.476	1.228–4.993	0.011‡	1.690	0.850–3.359	0.135
Prednisone	0.215	0.108–0.427	<0.001‡	0.301	0.165–0.546	<0.001‡
Prednisone ≥10mg/day	0.458	0.233–0.900	0.024‡	0.685	0.354–1.326	0.262
Immunosuppressive drugs	0.030	0.004–0.224	<0.001‡	0.252	0.115–0.552	<0.001‡
Mycophenolate mofetil	0.201	0.107–0.378	<0.001‡	0.361	0.199–0.656	<0.001‡
Azathioprine	1.156	0.592–2.256	0.671	1.355	0.717–2.561	0.350
Methotrexate	0.830	0.336–2.049	0.686	0.711	0.302–1.672	0.435
Calcineurin inhibitor	0.729	0.206–2.583	0.489	1.101	0.312–3.884	0.881
Cyclophosphamide	2.158	0.247–18.845	0.695	1.260	0.226–7.038	0.792
Leflunomide	0.207	0.018–2.321	0.201	0.086	0.004–1.694	0.107
Belimumab	0.498	0.226–1.098	0.084	0.494	0.227–1.075	0.075

* Positivity for neutralizing antibodies defined as a neutralizing activity ≥30% (cPass sVNT Kit [GenScript]). Seroconversion (SC) defined as a positive serology (IgG titer ≥15 AU/ml) for anti-SARS-CoV-2 S1/S2 IgG antibodies after vaccination (indirect enzyme-linked immunosorbent assay [LIAISON], SARS-CoV-2 S1/S2 IgG [DiaSorin]). 95% CI = 95% confidence interval; OR = odds ratio; SLE = systemic lupus erythematosus.
† SLE Disease Activity Index 2000 (SLEDAI-2K) score in the last 30 days.
‡ Statistically significant.

Table 5. Adverse events after CoronaVac vaccination in SLE patients and controls*

	After vaccine 1st dose			After vaccine 2nd dose		
	SLE (n = 223)	Controls (n = 56)	*P*	SLE (n = 223)	Controls (n = 56)	*P*
No symptoms	91 (40.8)	31 (55.4)	0.050	118 (52.9)	28 (50.0)	0.696
Local reactions (at the injection site)	71 (31.8)	12 (21.4)	0.128	62 (27.8)	18 (32.1)	0.521
Pain	60 (26.9)	10 (17.9)	0.163	50 (22.4)	16 (28.6)	0.333
Erythema	8 (3.6)	1 (1.8)	0.692	11 (4.9)	2 (3.6)	1.000
Swelling	18 (8.1)	3 (5.4)	0.776	20 (9.0)	7 (12.5)	0.424
Bruise	10 (4.5)	2 (3.6)	1.000	11 (4.9)	2 (3.6)	1.000
Pruritus	9 (4.0)	0	0.212	7 (3.1)	6 (10.7)	0.016†
Induration	24 (10.8)	0	0.006†	16 (7.2)	6 (10.7)	0.380
Systemic reactions	109 (48.9)	23 (41.1)	0.295	82 (36.8)	24 (42.9)	0.402
Fever	5 (2.2)	2 (3.6)	0.631	10 (4.5)	3 (5.4)	0.729
Malaise	21 (9.4)	4 (7.1)	0.795	21 (9.4)	7 (12.5)	0.492
Somnolence	36 (16.1)	5 (8.9)	0.173	31 (13.9)	5 (8.9)	0.321
Lack of appetite	10 (4.5)	0	0.220	11 (4.9)	1 (1.8)	0.470
Nausea	14 (6.3)	2 (3.6)	0.747	21 (9.4)	6 (10.7)	0.769
Vomiting	0	1 (1.8)	0.201	5 (2.2)	0	0.587
Diarrhea	16 (7.2)	6 (10.7)	0.380	18 (8.1)	4 (7.1)	1.000
Abdominal pain	11 (4.9)	4 (7.1)	0.511	11 (4.9)	4 (7.1)	0.511
Vertigo	19 (8.5)	3 (5.4)	0.584	10 (4.5)	3 (5.4)	0.729
Tremor	8 (3.6)	1 (1.8)	0.692	5 (2.2)	2 (3.6)	0.631
Headache	59 (26.5)	10 (17.9)	0.182	37 (16.6)	15 (26.8)	0.080
Fatigue	29 (13.0)	4 (7.1)	0.353	30 (13.5)	9 (16.1)	0.667
Sweating	13 (5.8)	1 (1.8)	0.315	17 (7.6)	2 (3.6)	0.382
Myalgia	23 (10.3)	3 (5.4)	0.314	14 (6.3)	8 (14.3)	0.047†
Muscle weakness	14 (6.3)	2 (3.6)	0.747	17 (7.6)	5 (8.9)	0.746
Arthralgia	34 (15.2)	2 (3.6)	0.024†	22 (9.9)	6 (10.7)	0.850
Back pain	18 (8.1)	2 (3.6)	0.384	16 (7.2)	8 (14.3)	0.090
Cough	17 (7.6)	2 (3.6)	0.382	15 (6.7)	5 (8.9)	0.568
Sneezing	24 (10.8)	3 (5.4)	0.313	20 (9.0)	9 (16.1)	0.119
Coryza	25 (11.2)	7 (12.5)	0.787	17 (7.6)	9 (16.1)	0.052
Stuffy nose	16 (7.2)	3 (5.4)	0.774	21 (9.4)	7 (12.5)	0.492
Sore throat	24 (10.8)	4 (7.1)	0.619	17 (7.6)	5 (8.9)	0.746
Shortness of breath	7 (3.1)	1 (1.8)	1.000	5 (2.2)	2 (3.6)	0.631
Conjunctivitis	3 (1.3)	0	1.000	4 (1.8)	1 (1.8)	1.000
Pruritus	5 (2.2)	0	0.587	7 (3.1)	2 (3.6)	1.000
Skin rash	1 (0.4)	0	1.000	5 (2.2)	1 (1.8)	1.000

* Values are the number (%) except where indicated otherwise. SLE = systemic lupus erythematosus.
† Statistically significant.

confirmed prednisone use (OR 0.38 [95% CI 0.20–0.73], $P = 0.004$) and MMF use (OR 0.37 [95% CI 0.20–0.70], $P = 0.002$) as independent variables associated with the absence of NAb in SLE patients.

Vaccine safety and disease safety. Sinovac-CoronaVac vaccine safety analysis is shown in Table 5. No moderate or severe AEs were observed. Patients with SLE more often had arthralgia after the first dose (14.7% versus 3.4%; $P = 0.024$) but less myalgia after the second dose (6.5% versus 15.5%; $P = 0.025$). Only 4.7% of the SLE patients reported disease exacerbation after full immunization. There was no worsening of SLEDAI-2K score up to 3 months after full vaccination in 118 SLE patients (2.0 versus 2.0; $P = 0.07$).

COVID-19 incident cases. The evaluation period for incident cases was 80 days since D0. A total of 11 symptomatic cases of COVID-19 confirmed by RT-PCR were identified among SLE patients (n = 9) and controls (n = 2), and all of them occurred before 2 weeks of the complete vaccination. Only 1 SLE patient required hospitalization but did not require mechanical ventilation or ICU admission and no patient died.

DISCUSSION

This the first study to specifically analyze the impact of each drug in the SARS-CoV-2 vaccine immunogenicity of SLE patients. We demonstrated a moderate vaccine-induced antibody response to inactivated SARS-CoV-2 immunogen in this disease with an optimal safety profile. We further observed that glucocorticoid and MMF use negatively influences SARS-CoV-2 vaccine humoral response, whereas HCQ seems to increase SC conversion rates.

One of the strengths of the present study was to include a large number of SLE patients from a tertiary hospital who were seronegative for SARS-CoV-2 antibodies (serology and NAb), which allowed for a more precise definition of vaccine-induced immunogenicity. In fact, the majority of ARD patients were able to develop SARS-CoV-2 antibodies after COVID-19 natural infection, despite the use of immunosuppressive agents (29,30), and prevaccination seropositivity was reported to enhance vaccine-induced antibody production (31–34). The tertiary setting was important, in order to provide a substantial sample of patients receiving treatment with drugs that were reported to possibly affect vaccine response in autoimmune diseases overall (16,19). The balanced age and sex distribution was also an important issue to be considered, since both factors are known to impact vaccine response (11,35,36). In addition, blood collection for immunogenicity was obtained at the same time point for all participants, providing a comparable period for vaccine-induced antibody production herein, since the time elapsed from vaccination-influenced SC rates (11). The absence of this parameter in previous reports precludes a definitive conclusion about their findings (12,15). Another important advantage was that immunogenicity was assessed herein by both anti-SARS-CoV-2 S1/S2 IgG and by NAb, in contrast to most recent published studies which were limited to anti-S1/S2 IgG data (13,15,16). Recent reports have suggested that NAb are more directly associated with COVID-19 protection (37,38).

Our study identified that SLE patients had a moderate antibody-mediated response 6 weeks after the second dose (D69) of Sinovac-CoronaVac vaccination, although there was a lower response rate observed in our control group. Our findings are in line with previous reports with small samples of SLE patients after vaccination with mRNA vaccines (11,13,14,16) and a large study focusing exclusively on SLE (17). The comparable SC rates observed herein with the inactivated vaccine is encouraging, since our patients were highly immunosuppressed (75%) and nearly half of those reported by Izmirly et al were taking only HCQ or no drugs (17). On the other hand, the lower SC and NAb response after the first vaccine dose (D28) in our study highlights the importance of the Sinovac-CoronaVac second dose in these immunocompromised individuals. Regarding NAb, the frequency and activity detected herein were also moderate and comparable to the study by Izmirly et al of 90 lupus patients (17).

The present study specifically identified a deleterious effect of immunosuppressants and glucocorticoids in SARS-CoV-2 vaccine immunogenicity in SLE patients. Of note, MMF was the only immunosuppressant associated with a 70–80% reduction of vaccine response, while azathioprine and methotrexate did not affect the vaccine response measured by immunogenicity. The lower SC and NAb positivity observed in our SLE patients receiving belimumab therapy is probably explained by the concomitant use of other immunosuppressants, mainly MMF. Accordingly, the response after influenza vaccination revealed a significantly reduced SC in SLE patients treated with prednisone ≥20 mg, and further SC reduction was noted when associated with immunosuppressants such as MMF (10).

The SC rates of SLE patients taking HCQ more than doubled at D69 compared to those who were not taking this drug. It is possible that HCQ has a beneficial effect of restoring immunogenicity, as previously described for H1N1 vaccination in SLE patients (10). Reinforcing this finding, our study identified a tendency of higher SC in SLE patients under the combination of immunosuppressants and prednisone with HCQ versus those who were not taking HCQ ($P = 0.077$); this finding has also been reported for H1N1 vaccine (10). SLE patients receiving HCQ monotherapy also showed high and comparable SC rates compared to the control group at D69; however, this possible beneficial effect was not confirmed by multivariate analysis, which is likely related to the underrepresentation of the HCQ-monotherapy subgroup.

Importantly, our analysis identified that almost one-fourth of SARS-CoV-2–naive SLE patients did not develop SC, possibly remaining susceptible to SARS-CoV-2 infection. The immunogenicity responses obtained herein with an inactivated vaccine were similar to the results of mRNA or adenovirus vaccines recently reported in SLE patients (17). These data are reassuring, since the population studied herein is from a tertiary center, with 74.6% of patients taking immunosuppressants, whereas in this previous study 48% of the patients were receiving HCQ monotherapy or were not taking any medication (17).

Limitations of the present study were the lack of an SLE subgroup without therapy, which would help to distinguish the role of antimalarials and disease itself on the immune response of vaccination and the retrospective analysis of SLEDAI-2K to assess activity. The short-term observation period of vaccine immunogenicity also precludes any conclusion about persistence of antibodies in this population. In addition, we have not evaluated cellular immunogenicity, but the interferon gamma production was reported to have a parallel decrease with SC in SLE patients (17). Another limitation of the present study, as well as in other previous reports (11–19), is the unknown cutoff level of IgG antibodies for SARS-CoV-2 protection.

Inactivated vaccines are considered safe and suitable for patients with compromised immune systems, such as SLE patients (39). Accordingly, severe AEs were also not observed in other studies with mRNA vaccines (11,13,14,16,17). Reinforcing this finding, lupus disease remained stable during the 3 months post-vaccination. Also, the distinct dynamics of mild AE were shown with higher frequency in SLE patients after the first dose and in controls after the second dose.

In conclusion, we have demonstrated that SARS-CoV-2–naive lupus patients require 2 doses of inactivated Sinovac-CoronaVac SARS-CoV-2 vaccine to achieve moderate immunogenicity, which is comparable to the findings reported in studies of other new vaccine platforms, with an excellent safety profile. HCQ use seems to increase

immunogenicity whereas prednisone use and MMF use were identified as the most relevant factors to impair vaccine-induced antibody production. Disease activity was not associated with reduced response. For the ~25% unresponsive group, novel strategies to improve immunogenicity are urgently needed and may include having MMF temporarily withdrawn or a vaccine booster.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bonfa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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