Concise report

SARS-CoV-2 vaccine in patients with systemic sclerosis: impact of disease subtype and therapy

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Abstract

Objective. To analyse the safety, immunogenicity and factors affecting antibody response to Severe Acute Respiratory Syndrome–Coronavirus–2 (SARS-CoV-2) vaccination in patients with SSc.

Methods. This is a phase 4 prospective study within a larger trial of two doses of inactivated SARS-CoV-2 vaccine (CoronaVac) in 51 SSc patients compared with 153 controls. Anti-SARS-CoV-2-IgG and neutralizing antibodies (NAb) were assessed at each vaccine shot (D0/D28) and 6 weeks after the second dose(D69), only in individuals with negative baseline IgG/NAb and those who did not have coronavirus-19 (COVID19) during follow-up. Vaccine safety was also assessed in all participants.

Results. Patients and controls had comparable median ages [48 (38.5–57) vs 48 (38–57) years, \( P = 0.945 \)]. Patients had mostly diffuse SSc (68.6%) and the majority (74.5%) had interstitial lung disease. Most patients were under immunosuppressive therapy (72.5%), mainly MMF (52.9%). After full vaccination (D69), anti-SARS-CoV-2-IgG frequency (64.1% vs 94.2%, \( P < 0.001 \)) and NAb positivity (53.8% vs 76.9%; \( P = 0.006 \)) were moderate, although lower than controls. The first dose response (D28) was low and comparable for both seroconversion rates (SC) (\( P = 0.958 \)) and NAb positivity (\( P = 0.537 \)). SSc patients under MMF monotherapy vs other (no therapy/other DMARDs) had lower immunogenicity (SC: 31.3% vs 90%, \( P < 0.001 \)) and NAb (18.8% vs 85%, \( P < 0.001 \)). Multiple regression analysis confirmed that MMF use, but not disease subtype, is associated with insufficient seroconversion [odds ratio (OR) = 0.056 (95% CI: 0.009, 0.034), \( P = 0.002 \)] and NAb positivity [OR = 0.047 (95% CI: 0.007, 0.036), \( P = 0.002 \)]. No moderate/severe side-effects were observed.

Conclusion. CoronaVac has an excellent safety profile and moderate response to anti-SARS-CoV-2 vaccine in SSc. Vaccine antibody response is not influenced by disease subtype and is greatly affected by MMF, reinforcing the need for additional strategies to up-modulate vaccine response in this subgroup of patients.

Trial registration. ClinicalTrials.gov, https://clinicaltrials.gov, NCT04754698

Key words: systemic sclerosis, SARS-CoV-2, vaccine, immunogenicity, mycophenolate

Introduction

Severe Acute Respiratory Syndrome–Coronavirus–2 (SARS-CoV-2) has been considered the most important health emergency on our planet in this millennium. In a
major effort to develop immunization strategies that could refrain this coronavirus-19 (COVID-19) pandemic, several vaccines were developed in record time, but initially testing only healthy individuals. The non-inclusion of chronically immunosuppressed patients initially generated great apprehension in autoimmune rheumatic diseases (ARD) patients, as they usually have a lower response to vaccination and the use of immunosuppressants predisposes to infectious complications [1, 2].

In early 2021, strategies were developed to vaccinate ARD patients against COVID-19 worldwide [3–8]. Patients with SSc were especially concerned about the possible deterioration of interstitial lung disease (ILD) by COVID-19 infection [9], leading the World Scleroderma Foundation to recommend special care with COVID-19 transmission and the use of immunosuppressants in SSc patients [10]. Although some studies pointed rituximab, MTX and MMF as associated to reduced immunogenicity [3, 4, 7, 8], none of them focussed on SSc patients.

Brazil started mass vaccination of the adult population in January 2021 using an inactivated SARS-CoV-2 vaccine (CoronaVac), which was approved for emergency use in several countries based on phase 2 studies [11] and had its effectiveness confirmed in a phase 4 study for the prevention of hospitalization (87.5%), intensive care unit admission (90.3%) and COVID-19-related death (86.3%) [12]. Therefore, our aim was to specifically analyse the immunogenicity, safety and possible factors influencing CoronaVac response in SSc patients, focusing on disease subtype and drug treatment.

**Patients and methods**

**Study design and participants**

This study analysed the subgroup of SSc patients from an ongoing phase 4 prospective cohort of immunogenicity and safety of Sinovac-CoronaVac in ARD patients [8], carried out at the University of Sao Paulo, Brazil. The study had three face-to-face visits that occurred on 9–10 February (D0), 9–10 March (D28) and 19 April 2021 (D69), and consisted of two doses of Sinovac-CoronaVac, supplied by Instituto Butantan (Sao Paulo, Brazil), administered 28 days apart. This vaccine was the only one available in January 2021, at the beginning of the second wave of the pandemic in Brazil.

The protocol and the informed consent form were approved by the national (CONEP) and local (CAP PESQ-FC/FMUSP) ethics committee (CAAE: 42566621.0.0000.0068) and were registered at clinicaltrials.gov (#NCT04754698). Each participant provided a signed written informed consent prior to enrolment in the study.

**Inclusion criteria**

Consecutive patients from our SSc Outpatient Clinic were invited to participate in the study if they were ≥18 years of age and met the ACR/EULAR classification criteria for SSc [13]. Clinical symptoms, SSc subtypes, autoantibodies and medications were systematically evaluated. No medication was discontinued before or after vaccine doses.

Subsequently, a control group of individuals without autoimmune diseases, balanced for age (±five years) and sex using an Excel program (ratio 3 patients : 1 control) was invited to participate.

**Immunogenicity assessment**

Serum anti-SARS-CoV-2 S1/S2 IgG and SARS-CoV-2 neutralizing antibodies (NAb) were measured at baseline (D0), at the second visit (D28) and at the third visit (D69), only in subjects with baseline negative IgG and NAb. We also excluded participants with RT-PCR confirmed COVID-19 during follow-up. Antibody titre is expressed as geometric mean titres (GMT) with 95% CI. Seropositivity was defined as anti-SARS-CoV-2 (S1/S2) IgG ≥15.0 UA/ml. The factor increase in GMT(FI-GMT) was calculated at D28 and D69 by the ratio of the GMT after and before vaccination. Regarding NAb, results are expressed as positive or negative neutralizing antibodies, with a cut-off ≥30% inhibition.

**Safety assessment**

Follow-up by standardized diary was performed for longitudinal safety assessment, including the recording of local and systemic vaccine related adverse events (AE), which were carefully reviewed with each participant on face-to-face visits at D28 and D69.

**COVID-19 incident cases**

A standardized questionnaire was applied to all participants about COVID-19 infection prior to the first vaccination and at all visits. Incident cases were followed up from D0 to D39 (10 days after the second dose) and subsequently for the next 40 days (from D40 to D79). For more details on the protocol, see [8].

**Statistical analysis**

Categorical variables are presented in number (%). Continuous variables are presented as medians (inter-quartile ranges), except for anti-S1/S2 serology titres that were presented as geometric means (95% CI) and NAb as median (interquartile ranges). Statistical comparisons between groups included χ² or Fisher’s exact tests for categorical variables and Student’s t test or Mann–Whitney test for continuous variables. Anti-S1/S2 serology titres data were transformed in neperian logarithm (ln) prior to analysis. Comparisons of transformed anti-S1/S2 IgG titres between SSc and control were performed using generalized estimating equations (GEE) with normal marginal distribution and gamma distribution, respectively. Results were followed by Bonferroni multiple comparisons to identify differences between groups and timepoints. Statistical significance was considered as $P < 0.05$. 
Results

Demographic, clinical and therapeutic data

Fifty-one SSc patients and 153 age- and sex-balanced controls were included in this study (Table 1). Patients and controls had comparable median (interquartile range, IQR) ages [48 (38.5–57) vs 48 (38–57) years, $P = 0.945$]. The SSc group had a predominance of female sex (94.1%), Caucasian ethnicity (58.8%) and diffuse subtype (68.6%), with a median disease duration of 10 years.

The most frequent clinical manifestations were oesophageal dysmotility (80.4%) and ILD (74.5%), with positive anti-ScI70 in 60.8%. Immunosuppressants (IS) were currently being used in 72.5% of patients, mainly MMF in monotherapy (52.9%). Progressing ILD represented the main indication for treatment with MMF (52.2%).

Vaccine immunogenicity

Twelve patients and thirty-two controls were further excluded due to positive anti-SARS-CoV-2 serology at baseline [SSc ($n = 9$; 17.6%) vs controls ($n = 29$; 19%), $P = 0.836$] or COVID-19 after the first dose [SSc ($n = 3$; 5.9%) vs controls ($n = 3$; 2%), $P = 0.167$] (Table 2 and Supplementary Table S1, available at Rheumatology online). After the full vaccination, seroconversion rates (64.1% vs 94.2%; $P < 0.001$), GMT [26.4 (95% CI: 16.0, 43.6) vs 66.9 (95% CI: 58.6, 76.4); $P < 0.001$] and NAb positivity (53.8% vs 76.9%; $P = 0.006$) were moderate, but inferior to the observed in the control group. In contrast, the neutralizing activity among responders [80.6% (IQR 60.8–86.5) vs 62.5% (47.0–78.9); $P < 0.01$] was superior to the control group.

After the first dose, SC rates (35.9 vs 36.4; $P = 0.958$) and GMT [7.3 (95% CI: 4.9, 11.0) vs 10.9 (95% CI 8.7, 13.7); $P = 0.370$] were low and comparable in both groups. For NAb positivity, the first dose response was reduced and comparable for patients and controls (38.5 vs 33.1; $P = 0.537$), whereas for NAb activity a moderate and comparable response was obtained for both groups (46.5 vs 44.4; $P = 0.902$).

Analysis of demographic data, disease subtype/characteristics and current treatment revealed that MMF was the only variable associated with a significant reduction in the SC rates (20.0% vs 85.7%, $P < 0.001$) and in the number of patients with NAbs (14.3% vs 77.8%, $P < 0.001$), but without differences regarding median MMF dose [2 (2–3) vs 2 (2–2) g/day both for patients with IgG vs patients without IgG ($P = 0.310$) and for patients with NAb vs those without NAb ($P = 0.524$)] (Supplementary Table S1, available at Rheumatology online). Only three (7.7%) of these patients were under combined therapy with disease-modifying anti-rheumatic drugs (DMARDs), so we further compared SSc patients under MMF monotherapy vs no therapy/other drugs and observed that patients with MMF monotherapy had lower immunogenicity both regarding SC [5 (31.3%) vs 18 (90%), $P < 0.001$] and NAb positivity [3 (18.8%) vs 17 (85%), $P < 0.001$] after full vaccination.

Multiple regression analysis showed that current MMF use was significantly associated with insufficient SC [odds ratio (OR) = 0.056 (95% CI: 0.009, 0.034), $P = 0.002$] and production of NAbs [OR = 0.047 (95% CI: 0.007, 0.036), $P = 0.002$].

Incident cases

Three (5.9%) SSc patients vs three controls (2%, $P = 0.167$) had COVID-19 after being vaccinated, including one patient after the first shot and two after the second shot. All patients and controls recovered completely.

Vaccine safety

All SSc patients and controls were included for safety analyses, except one SSc patient in the second dose, due to missing data (Supplementary Table S2, available at Rheumatology online). Sinovac-CoronaVac was overall well tolerated by all participants, with only mild AEs. Among the local reactions, pain at injection site was the only AE referred by >10% of patients and controls. Systemic reactions were referred by 40% of the participants, being sore throat the only symptom that was more frequent in the SSc patients, after the first dose (13.7% vs 5.2%, $P = 0.044$).

Discussion

This study is the first to focus on SARS-CoV-2 vaccine in SSc patients and shows that CoronaVac is safe and induces moderate immunogenicity and further identified that MMF monotherapy has a major deleterious effect on the vaccine-induced antibody response. Adverse effects were mild, self-limiting and similar to controls, providing an important reassurance of this vaccine safety and supporting its recommendation for SSc.

The main advantage of this study was the inclusion of a representative sample of SSc patients with well-established classification criteria and the majority with ILD in use of immunosuppressive treatment, prospectively followed by a strict vaccine surveillance protocol. The well-balanced control group for age and sex prevented bias, as these parameters have a deleterious effect on immunogenicity [14]. Noteworthy, CG had compatible SC rate (94.2% vs 100%) and presence of NAb (76.9% vs 83.3%) to those found in healthy individuals in the phase I trial, despite the distinct laboratory methods and the older population evaluated herein [11]. The exclusion of SARS-CoV-2 pre-exposed individuals was also relevant, as previous reports have demonstrated a distinct dynamic of antibody production with a plateau response to the first vaccine dose in this population [15].

We also demonstrated that SSc presentation and main manifestations did not influence SARS-CoV-2 seroconversion rates. This finding is in accordance with our
This study provides new evidence that SSc patients were able to produce significant vaccine-induced antibodies after vaccination with CoronaVac, despite the high frequency of IS. However, MMF was the only factor associated with impaired response. Interestingly, no differences were observed after the first dose, neither for IgG nor NAb. In fact, the second dose is required to achieve the maximum response for patients and controls, as reported previously [8]. The small increment observed after the first dose was not significant, suggesting a threshold effect for the vaccine response in patients with SSc.

**TABLE 1** Demographic data, comorbidities and current treatments of SSc patients and controls at baseline of CoronaVac vaccination

|                      | SSc (n = 51) | Controls (n = 153) | P-value |
|----------------------|--------------|--------------------|---------|
| **Demographic data** |              |                    |         |
| Current age, years   | 48 (38.5–57) | 48 (38–57)         | 0.945   |
| Age at diagnosis, years | 35 (24.5–44.5) | — | — |
| Disease duration, years | 10 (6–16.5) | — | — |
| Female sex           | 48 (94.1)    | 144 (94.1)         | 1.000   |
| Caucasians           | 30 (58.8)    | 71 (46.4)          | 0.125   |
| **SSc subtype**      |              |                    |         |
| Diffuse SSc          | 35 (68.6)    | —                  | —       |
| Limited SSc          | 16 (31.4)    | —                  | —       |
| **Comorbidities**    |              |                    |         |
| Systemic arterial    | 9 (17.6)     | 45 (29.4)          | 0.099   |
| Hypertension         |              |                    |         |
| Diabetes mellitus    | 0 (0)        | 16 (10.5)          | 0.014   |
| Dyslipidaemia        | 5 (9.8)      | 13 (8.5)           | 0.776   |
| Obesity (BMI ≥30 kg/m²) | 11 (21.6)    | 48 (31.4)         | 0.158   |
| Chronic cardiomyopathy | 2 (3.9) | 3 (2.0) | 0.601 |
| Chronic renal disease | 1 (2.0) | 0 | 0.250 |
| Current smoking      | 3 (5.9)      | 10 (6.5)           | 1.000   |
| Asthma               | 2 (3.9)      | 6 (3.9)            | 1.000   |
| Cancer               | 5 (9.8)      | 0 (0)              | 0.001   |
| Stroke               | 1 (2.0)      | 0 (0)              | 0.250   |
| **Visceral/skin involvement** | | | |
| Telangiectasias      | 32 (62.7)    | —                  | —       |
| Pitting scars        | 36 (70.6)    | —                  | —       |
| Calciosis            | 8 (15.7)     | —                  | —       |
| Esophageal dysmotility | 41 (80.4) | — | — |
| Pulmonary involvement | 44 (86.3)    | —                  | —       |
| Interstitial lung disease | 38 (74.5) | — | — |
| Median FVC           | 66.5 (52.8–76.8) | — | — |
| **Autoantibodies**   |              |                    |         |
| Anti-ScI/70          | 30 (60.8)    | —                  | —       |
| Anticentromere       | 1 (2)        | —                  | —       |
| ANA—Nucleolar pattern | 8 (15.7)    | —                  | —       |
| **Current treatments** | | | |
| Hydroxychloroquine   | 3 (5.9)      | —                  | —       |
| Prednisone           | 6 (11.8)     | —                  | —       |
| Immunosuppressive/biologic drugs | 37 (72.5) | — | — |
| Monotherapy          | 33 (64.7)    | —                  | —       |
| >2 immunosuppressors | 4 (7.8)      | —                  | —       |
| MMF                  | 27 (52.9)    | —                  | —       |
| Median dose (g/day)  | 2 (2–3)      | —                  | —       |
| MTX                  | 5 (9.8)      | —                  | —       |
| AZA                  | 4 (7.8)      | —                  | —       |
| LEF                  | 2 (3.9)      | —                  | —       |
| Cyclophosphamide     | 0 (0)        | —                  | —       |
| Rituximab            | 1 (2.0)      | —                  | —       |

Results are expressed in median (interquartile range) and n (%); bold text indicates significance. ANA, antinuclear antibodies; FVC, forced vital capacity. Bold type indicates significance.
Data were compared using a two-sided Mann–Whitney U test for comparison between SSc patients and controls, after first and second doses, mean titres increased for SSc (P < 0.001). After first and second doses, mean titres increased for SSc (P < 0.001) and controls (P = 0.022). Results regarding neutralizing antibodies (NAb) were expressed in median (interquartile range) and n (%). Positivity for NAb was defined as a neutralizing activity ≥30% (cPass sVNT Kit, GenScript, Piscataway, NJ, USA). Data were compared using a two-sided Mann–Whitney U test for comparison between SSc patients and controls, after the first and second doses. Neutralizing activity was measured in positive cases, so longitudinal analyses were not performed. Bold type indicates significance.

**Table 2** Seroconversion rates (SC) and neutralizing antibodies (NAb) in SSc patients and controls

|                          | After first dose | After two doses |
|--------------------------|-----------------|-----------------|
|                          | SSc patients (n = 39) | Controls (n = 121) | P |
| Anti-S1/S2 IgG SC        | 14 (35.9)       | 44 (36.4)       | 0.958 | 25 (64.1)       | 114 (94.2) | <0.001 |
| Anti-S1/S2 IgG GMT       | 7.3 (4.9–11.0)  | 10.9 (8.7–13.7) | 0.370 | 26.4 (16.0–43.6) | 66.9 (58.6–76.4) | <0.001 |
| Anti-S1/S2 IgG FI-GMT    | 3.7 (2.4–5.5)   | 4.8 (4.0–5.9)   | 0.213 | 13.2 (7.9–22.1)  | 29.6 (25.6–34.2) | 0.022 |
| NAb Presence             | 15 (38.5)       | 33 (32.0)       | 0.185 | 21 (53.8)       | 93 (76.9)  | 0.006 |
| NAb Neutralizing activity| 46.5 (39.0–56.3) | 44.4 (35.3–71.7) | 0.902 | 80.6 (60.8–86.5) | 62.5 (47.0–78.9) | 0.038 |

Anti-SARS-CoV-2 S1/S2 IgG seroconversion rates (SC) and titles are expressed in n (%) and in geometric means (95% CI), respectively. FI-GMT, factor increase of geometric mean titres; GMT, geometric mean titres (AU/ml); SC, seroconversion (defined as post vaccination titre ≥15 AU/ml—Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Data regarding IgG titles were analysed using generalized estimating equations (GEE) with normal marginal distribution and gamma distribution, respectively and identity binding function assuming first order autoregressive correlation matrix between moments (D0, D28 and D69) in the comparison of the two groups (SSc vs controls), followed by Bonferroni’s multiple comparisons (Supplementary Table 1, available at Rheumatology online). The behavior of IgG titres was different for SSc and controls (P < 0.001). After first and second doses, mean titres increased for SSc (P = 0.001) and controls (P < 0.001). Presence and geometric means (95% CI) of excluding patients with negative NAb who were predominantly those under MMF. Nevertheless, the remaining patients had a robust NAb activity response and a similar phenomenon was also observed for H1N1 vaccine [16].

In conclusion, SSc had an excellent safety profile and a suboptimal response to SARS-CoV-2 vaccine. We further identified that MMF, and not disease subtype, was associate with a major deleterious impact on vaccine response. Novel strategies to improve the vaccine-induced antibody response, therefore, represent a relevant unmet need for the most vulnerable subgroups and particularly for patients with ARD, and include the possibility of a third dose and temporary suspension of therapies such as recently proposed by the ACR [20].

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**Disclosure statement:** The authors have declared no conflicts of interest.

**Data availability statement**

The data underlying this article will be shared on reasonable request to the corresponding author.

**Supplementary data**

Supplementary data are available at Rheumatology online.
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