RHEUMATOLOGY

Rheumatology 2021;00:1–6
https://doi.org/10.1093/rheumatology/keab886
Advance access publication 11 December 2021

Concise report

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

Percival Degrava Sampaio-Barros [1], Ana Cristina Medeiros-Ribeiro[1], Ana Paula Luppino-Assad[1], Renata Miossi[1], Henrique Carriço da Silva[1], Emily F. V. N. Yuki[1], Sandra G. Pasoto[1], Carla G. S. Saad[1], Clóvis A. Silva[1,2], Léonard V. K. Kupa[1], Giordano B. H. Deveza[1], Tatiana N. Pedrosa[1], Nádia E. Aikawa[1,2] and Eloisa Bonfá [1]

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 seroconvertion 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

CLINICAL SCIENCE

Rheumatology key messages

- Inactivated SARS-CoV-2 vaccine (CoronaVac) showed moderate response in SSc patients compared to age- and sex-balanced controls.
- Mycophenolate mofetil was the only factor associated with major deleterious impact in vaccine immunogenicity.
- Although the adverse effects were frequent, they were predominantly mild and self-limited.

[1]Division of Rheumatology and [2]Pediatric Rheumatology Unit, Childrens' Institute, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP, Brazil

Submitted 12 September 2021; accepted 18 November 2021

Correspondence to: Eloisa Bonfa, Av. Dr. Arnaldo, no 455, Sala 3190 - Cerqueira César, São Paulo, SP 01246-903, Brazil.
E-mail: eloisa.bonfa@hc.fm.usp.br

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-HC/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 $\geq$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 ($\pm$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 $\geq$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 $\geq$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 (interquartile ranges), except for anti-S1/S2 serology titres that were presented as geometric means (95% CI) and NAbs as median (interquartile ranges). Statistical comparisons between groups included χ^2 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 ln-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-Scl70 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

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	42 (82.4)	64 (41.8)	**<0.001**
Systemic arterial hypertension	9 (17.6)	45 (29.4)	0.099
Diabetes mellitus	0 (0)	16 (10.5)	**0.014**
Dyslipidaemia	5 (9.8)	13 (8.5)	0.776
Obesity (BMI $\geq$30 kg/m^2)	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	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)	—	
Calcinosis	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)	—	
Pulmonary hypertension	6 (11.8)	—	
Autoantibodies			
Anti-Scl70	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.

previous observation that non-adjuvanted influenza A H1N1 vaccine response was comparable in both subtypes [16].

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

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*	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**
GMT	7.3 (4.9–11.0)[1]	10.9 (8.7–13.7)[2]	0.370	26.4 (16.0–43.6)[3]	66.9 (58.6–76.4)[4]	**<0.001**
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**
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 titres 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 $\geq$15 AU/ml—Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Data regarding IgG titres were analysed using generalized estimating equations (GEE) with normal marginal distribution and gamma distribution, respectively and identity binding function assuming first order autoregressive correlation matrix between moments (D0, D28 and D69) in the comparison of the two groups (SSc *vs* controls), followed by Bonferroni's multiple comparisons (Supplementary Table 1, available at *Rheumatology* online). The behavior of IgG titres was different for SSc and controls ($P < 0.001$). After first and second doses, mean titres increased for SSc ([1,3] $P < 0.001$) and controls ([2,4] $P < 0.001$). Results regarding neutralizing antibodies (NAb) are expressed in median (interquartile range) and *n* (%). Positivity for NAb was defined as a neutralizing activity $\geq$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.

dose may have hampered the analysis of the deleterious effect of drugs observed after full vaccination.

In fact, MMF has already been associated with a significant reduction in immunogenicity to mRNA vaccine [3, 7, 17] and CoronaVac [8] in overall ARD patients with a heterogeneous analysis of several diseases with common use of MMF in combination with steroids [7, 8, 17] and other reports did not include SSc patients [3]. In this context, this is the first study to specifically evaluate the deleterious effect of MMF monotherapy in vaccine-induced antibody response in SSc patients [3]. MMF dose was uniformly high, and we could not establish a threshold of interference on vaccine immunogenicity. Of note, we did not discontinue medications because most patients under MMF had progressing ILD. Moreover, the first ACR guidelines were only available after the first vaccine dose [18].

This study also evaluated SARS-CoV-2 NAb, considered the most important parameter predictive of immune protection [19]. SSc patients had lower NAb positivity than controls, a pattern similar to that observed for IgG serology. Unexpectedly, NAb neutralizing activity was high and superior in SSc patients who had positive NAb compared with controls. The most likely explanation is the bias 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].

Limitations of this study included the relatively small representation of SSc subtypes and therapies other than MMF and the assessment of the influence of disease activity on the response to SARS-CoV-2 vaccine.

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].

Funding: This work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (#2015/03756–4 to S.G.P., C.A.S., N.E.A. and E.B., #2019/17272–0 to L.V.K.K.); Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq #304984/2020–5 to C.A.S., #305242/2019–9 to E.B.), B3 – Bolsa de Valores do Brasil to E.B., and Instituto Butantan supplied the study product and had no other role in the trial.

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.

References

1 Grainger R, Machado PM, Robinson PC. Novel coronavirus disease-2019 (COVID-19) in people with rheumatic disease: epidemiology and outcomes. Best Pract Res Clin Rheumatol 2021;35:101657.

2 Arnold J, Winthrop K, Emery P. COVID-19 vaccination and antirheumatic therapy. Rheumatology 2021;60: 3496–502.

3 Furer V, Eviatar T, Zisman D *et al.* Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis 2021;80:1330–8.

4 Simon D, Tascilar K, Fagni F *et al.* SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. Ann Rheum Dis 2021; 80:1312–6.

5 Geisen UM, Berner DK, Tran F *et al.* Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. Ann Rheum Dis 2021;80:1306–11.

6 Cherian S, Paul A, Ahmed S *et al.* Safety of the ChAdOx1 nCoV-19 and the BBV152 vaccines in 724 patients with rheumatic diseases: a post-vaccination cross-sectional survey. Rheumatol Int 2021;41: 1441–5.

7 Braun-Moscovici Y, Kaplan M, Braun M *et al.* Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2. Ann Rheum Dis 2021;80:1317–21.

8 Medeiros-Ribeiro AC, Aikawa NE, Saad CGS *et al.* Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial. Nat Med 2021;27:1744–51.

9 Orlandi M, Lepri G, Bruni C *et al.* The systemic sclerosis patient in the COVID-19 era: the challenging crossroad between immunosuppression, differential diagnosis and long-term psychological distress. Clin Rheumatol 2020; 39:2043–7.

10 Matucci-Cerinic M, Bruni C, Allanore Y *et al.* Systemic sclerosis and the COVID-19 pandemic: world Scleroderma Foundation preliminary advice for patient management. Ann Rheum Dis 2020;79:724–6.

11 Zhang Y, Zeng G, Pan H *et al.* Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21:181–92.

12 Jara A, Undurraga EA, González C *et al.* Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med 2021;385:875–84.

13 van den Hoogen F, Khanna D, Fransen J *et al.* 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 2013; 72:1747–55.

14 Palacios R, Batista AP, Albuquerque CSN *et al.* Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: the PROFISCOV Study. https://papers.ssrn.com/sol3/papers.cfm?abstract_id= 3822780, 2021, preprint: not peer reviewed.

15 Ebinger JE, Fert-Bober J, Printsev I *et al.* Antibody responses to the BNT162b2 mRNA vaccine in individuals previously infected with SARS-CoV-2. Nat Med 2021;27: 981–4.

16 Sampaio-Barros PD, Andrade DCO, Seguro LCP *et al.* Pandemic non-adjuvanted influenza A H1N1 vaccine in a cohort of patients with systemic sclerosis. Rheumatology 2018;57:1721–5.

17 Boyarsky BJ, Ruddy JA, Connolly CM *et al.* Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis 2021;80:1098–9.

18 Curtis JR, Johnson SR, Anthony DD *et al.* American College of Rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 1. Arthritis Rheumatol 2021;73:1093–107.

19 Khoury DS, Cromer D, Reynaldi A *et al.* Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27:1205–11.

20 Curtis JR, Johnson SR, Anthony DD *et al.* American College of Rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 3. Arthritis Rheumatol 2021;73:e60–e75.