RHEUMATOLOGY

Rheumatology 2021;00:1–11
https://doi.org/10.1093/rheumatology/keab773
Advance access publication 19 October 2021

Original article

Systemic autoimmune myopathies: a prospective phase 4 controlled trial of an inactivated virus vaccine against SARS-CoV-2

Samuel K. Shinjo[1], Fernando H. C. de Souza[1], Isabela B. P. Borges[1], Alexandre M. dos Santos[1], Renata Miossi[1], Rafael G. Misse[1], Ana C. Medeiros-Ribeiro[1], Carla G. S. Saad[1], Emily F. N. Yuki[1], Sandra G. Pasoto[1], Léonard V. K. Kupa[1], Carina Ceneviva[2], Júlia C. Seraphim[1], Tatiana N. Pedrosa[1], Margarete B. G. Vendramini[1], Clóvis A. Silva[3], Nádia E. Aikawa[1,3] and Eloisa Bonfá [1]

Abstract

Objectives. To evaluate immunogenicity and safety of an inactivated SARS-CoV-2 vaccine in systemic autoimmune myopathies (SAMs) and the possible influence of baseline disease parameters, comorbidities and therapy on immune response.

Methods. This prospective controlled study included 53 patients with SAMs and 106 non-immunocompromised control group (CTRL). All participants received two doses of the Sinovac-CoronaVac vaccine (28-day interval). Immunogenicity was assessed by anti-SARS-CoV-2 S1/S2 IgG seroconversion (SC), anti-S1/S2 IgG geometric mean titre (GMT), factor increase GMT (FI-GMT), neutralizing antibodies (NAb) positivity, and median neutralizing activity after each vaccine dose (D0 and D28) and six weeks after the second dose (D69). Participants with pre-vaccination positive IgG serology and/or NAb and those with RT-PCR confirmed COVID-19 during the protocol were excluded from immunogenicity analysis.

Results. Patients and CTRL had comparable sex ($P>0.99$) and age ($P=0.90$). Immunogenicity of 37 patients and 79 CTRL-naïve participants revealed at D69, a moderate but significantly lower SC (64.9% *vs* 91.1%, $P<0.001$), GMT [7.9 (95%CI 4.7–13.2) *vs* 24.7 (95%CI 30.0–30.5) UA/ml, $P<0.001$] and frequency of NAb (51.4% *vs* 77.2%, $P<0.001$) in SAMs compared with CTRL. Median neutralizing activity was comparable in both groups [57.2% (interquartile range (IQR) 43.4–83.4) *vs* 63.0% (IQR 40.3–80.7), $P=0.808$]. Immunosuppressives were less frequently used among NAb+ patients *vs* NAb- patients (73.7% *vs* 100%, $P=0.046$). Type of SAMs, disease status, other drugs or comorbidities did not influence immunogenicity. Vaccine-related adverse events were mild with similar frequencies in patients and CTRL ($P>0.05$).

Conclusion. Sinovac-CoronaVac is safe and has a moderate short-term immunogenicity in SAMs, but reduced compared with CTRL. We further identified that immunosuppression is associated with diminished NAb positivity.

Trial registration. COVID-19 CoronaVac in Patients With Autoimmune Rheumatic Diseases and HIV/AIDS (CoronavRheum), http://clinicaltrials.gov/ct2/show/NCT04754698

Key words: anti-SARS-CoV-2 vaccine, COVID-19, immunogenicity, myositis, neutralizing antibodies, safety

Rheumatology key messages

- Sinovac-CoronaVac is safe for patients with systemic autoimmune myopathies (SAMs).
- Anti-SARS-CoV-2 S1/S2 IgG seroconversion rates were of moderate effect.
- SAM patients have a moderate NAb response but it is reduced compared to the control group.

CLINICAL SCIENCE

[1]Division of Rheumatology, [2]Central Laboratory Division and [3]Pediatric Rheumatology Unit, Childrens' Institute, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, SP, Brazil (BR)

Submitted 24 July 2021; accepted 9 October 2021

Correspondence to: Samuel Katsuyuki Shinjo, Av. Dr. Arnaldo, 455, 3° andar, sala 3184, Cerqueira César, CEP 01246-903, Sao Paulo, SP, Brazil. E-mail: samuel.shinjo@usp.br

Introduction

Since the first case in Wuhan, China, in December 2019, the novel coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to more than four million deaths and ∼220 million confirmed cases worldwide up to August 2021 [1].

Several studies have identified risk factors associated with severe COVID-19, such as cardiovascular diseases and other comorbidities, male gender and age [2–4]. In addition, systemic autoimmune rheumatic diseases patients may have a worse COVID-19 associated prognosis [5, 6], due to the disease-associated immune dysregulation and immunosuppressive drugs.

Among these systemic autoimmune rheumatic diseases, idiopathic inflammatory myopathies or systemic autoimmune myopathies (SAMs) are a group of rare and heterogeneous diseases that affect primarily the striated skeletal muscles, including DM, PM, antisynthetase syndrome (ASSD), immune-mediated necrotizing myopathies (IMNM), inclusion body myositis, neoplasia-associated myositis and myositis-overlap syndromes [7–9]. Other tissues and systems may be also involved, such as skin, heart, joint, lung and gastrointestinal tract [7].

Gupta *et al.* [10] report challenges for SAMs patients in a large descriptive study during the COVID-19 pandemic, particularly health problems attributed to the pandemic, need to increase or facing of obstacles in the acquisition of medicines, hospitalization for disease-related complications, and reduction of physical exercises. More than a half of patients with SAMs had underlying cardiovascular risk factors and frequently required an increase in drug therapy due to worsening in health-related problems during the pandemic, resulting in a high risk for severe COVID-19 infection. Moreover, patients with SAMs are susceptible to general or opportunistic infections [11, 12]. The use of high doses of glucocorticoids and immunosuppressive drugs are potential risk factors associated with these complications [11]. Therefore, in the context of the COVID-19 pandemic, it becomes extremely important to establish strategic measures to protect these patients against SARS-CoV-2.

An extensive and intensive task force around the world has been combating and containing the SARS-CoV-2 through the development of COVID-19 vaccines. There are, however, few studies evaluating safety and immunogenicity after at least one vaccine dose or two shots of the messenger RNA (mRNA) (BioNTech/Pfizer, Moderna or BNT162b2) and Oxford/Astra- Zeneca/ChAdOx1 nCoV-19 anti-SARS-CoV-2 vaccines in systemic autoimmune rheumatic diseases populations, including <20 SAMs patients [13–19]. Our group has recently reported an overall adequate anti-SARS-CoV-2 IgG seroconversion rate (70.4%) with Sinovac-CoronaVac vaccine in 910 naïve adult autoimmune rheumatic diseases patients compared with 182 age and sex-matched subjects' frequencies showing a diminished frequency of COVID-19 incident cases after immunization [20]. However, none of these studies specifically assessed SAMs and its peculiar disease factors and treatment with an age- and sex-balanced population, in order to more accurately define vaccine response in this group of patients.

Therefore, the present study aimed to evaluate the safety and immunogenicity of Sinovac-CoronaVac vaccine in patients with SAMs compared with a control (CTRL) population, as well as to analyse the potential harmful effect of disease parameters, comorbidities and therapy on vaccine-induced antibody response.

Patients and method

Study design

This prospective phase 4 controlled study is within the protocol of a larger phase 4 trial (clinicaltrials.gov #NCT04754698) that assessed the immunogenicity and safety of the Sinovac-CoronaVac COVID-19 vaccine in a large sample of patients with systemic autoimmune rheumatic diseases [20]. The present study was conducted at a single tertiary centre in Sao Paulo (Brazil). The study had three in-person visits that occurred mostly on 9–10 February 2021 (D0—first vaccine dose), on 9–10 March 2021 (D28—second vaccine dose) and on 19 April 2021 (D69). For those unable to attend, we set a 15-day period for the recap.

The study was conducted according to the Declaration of Helsinki and local regulations and was approved by Comissão de Ética para Análise de Projetos de Pesquisa (CAPPesq) and Comissão Nacional de Ética em Pesquisa (CONEP) – the local and national ethical committees, respectively (CAAE: 42566621.0.0000.0068). Written informed consent was obtained from participants before enrolment.

Participants, inclusion and exclusion criteria

SAMs patients

Patients with SAMs from the Inflammatory Myopathy Outpatient Clinics were invited to participate in the study if they were 18 years or older, and if they fulfilled the EULAR/ACR2017 classification criteria for the inflammatory myopathies [8], and patients with ASSD fulfilled the criteria used by Behrens Pinto *et al.* (2020) [21]. All patients with ASSD had a positive anti-Jo-1 antibody.

Exclusion criteria

Exclusion criteria were history of anaphylactic response to vaccine components, acute febrile illness or symptoms compatible to COVID-19 at vaccination, Guillain–Barre syndrome, decompensated heart failure, demyelinating disease, previous vaccination with any SARS-CoV-2 vaccine, history of live virus vaccine up to four weeks before, history of inactivated virus vaccine up to two weeks before vaccination, history of having received blood products up to six months before vaccination,

cancer-associated myopathies, and inflammatory myopathies overlapping syndromes. Participants with pre-vaccination positive COVID-19 anti-S1/S2 IgG serology and/or SARS-CoV-2 cPass virus-neutralization antibodies (NAb) were excluded from immunogenicity analysis. Patients with RT-PCR confirmed COVID-19 infection after the first vaccine dose and during the protocol were excluded from the immunogenicity analysis.

Seventy SAMs patients were initially selected to participate after the review of the last 3-month medical records using an electronic database (Fig. 1). We preferentially selected patients with well-controlled disease to avoid hospitalizations or changes in therapy during the next three months of study. Selection of patients began within three weeks of the initial protocol, immediately after the emergency's approval of the vaccine in Brazil and invitations began after the ethics committee sanction of the trial. Among the invited patients, 17 patients were excluded due to refusal to participate ($n = 3$), hospitalization ($n = 1$), difficult coming to the hospital in the pre-established dates for vaccination ($n = 5$), scheduled to receive rituximab within short period of vaccination ($n = 3$) and disease activity ($n = 5$). SAMs patients and CTRL+ groups were balanced for age (up to ± 5 years' difference) and sex, using an Excel program for random selection of individuals in each category, with a 1 SAM : 2 CTRL ratio. Fifty-three patients comprised the study group, and 106 individuals with no autoimmune rheumatic disease or other immunosuppressive condition and without immunosuppressive therapy composed the CTRL group, who were recruited among healthcare workers from our centre. None of them had received the previous anti-SARS-CoV-2 vaccine.

Demographic data, comorbidities, disease activity parameters and treatments

The patients were clinically assessed, and a standardized interview was performed by physicians with expertise in SAMs. The following data were collected: current age, ethnicity, sex, type of SAMs, disease duration, comorbidities (e.g. systemic arterial hypertension, diabetes mellitus, dyslipidaemia, obesity, myocardial infarction, interstitial lung disease and stroke), habits (smoking) and current therapy (e.g. glucocorticoids, immunosuppressive and immunobiological drugs).

The disease status at D0 (first vaccine dose) was assessed using the International Myositis Assessment and Clinical Studies Groups (IMACS) core set measures, which included application of questionnaires based on scores of the Manual Muscle Testing-8 (MMT-8), Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT), HAQ, global assessment of the disease by the physician and by the patient using the Visual Analogue Scale (VAS) [22–24]. The serum levels of creatine phosphokinase (CPK, reference value: 26–192 U/l) were also tested only at the baseline of the protocol (D0).

Vaccination protocol

The vaccination protocol for patients with SAMs and CTRL consisted of a two-dose schedule of the COVID-19 vaccine. The first dose with blood collection was given mostly on 9–10 February 2021 (D0), the second dose with blood collection on 9–10 March 2021 (D28), and the last blood collection occurred on 19 April 2021 (D69). In case of incident COVID-19 between vaccine doses, the second dose was delayed four weeks after the beginning of symptoms. Ready-to-use syringes loaded with CoronaVac (Sinovac Life Sciences, Beijing, China, batch #20200412), that consists of 3 μg in 0.5 ml of β-propiolactone inactivated SARS-CoV-2 (derived from the CN02 strain of SARS-CoV-2 grown in African green monkey kidney cells – Vero 25 cells) with aluminum hydroxide as an adjuvant were administered intramuscularly in the deltoid area.

Immunogenicity evaluation

Primary immunogenicity evaluation included seroconversion rates of total anti-SARS-Cov-2 S1/S2 IgG and presence of NAb at D69. Secondarily, immunogenicity was assessed by anti-S1/S2 IgG seroconversion and presence of NAb at D28 (after vaccine first dose); geometric mean titres of anti-S1/S2 IgG and their factor-increase in GMT (FI-GMT) at D28 and D69; and median (interquartile range) neutralizing activity of NAb at D28 and D69. In order to assess these outcomes, blood samples (20 ml) from all participants were obtained at days D0 (baseline – immediately before first vaccine dose), D28 (immediately before the second dose) and D69 (six weeks after the second dose). Sera were stored in a −70°C freezer.

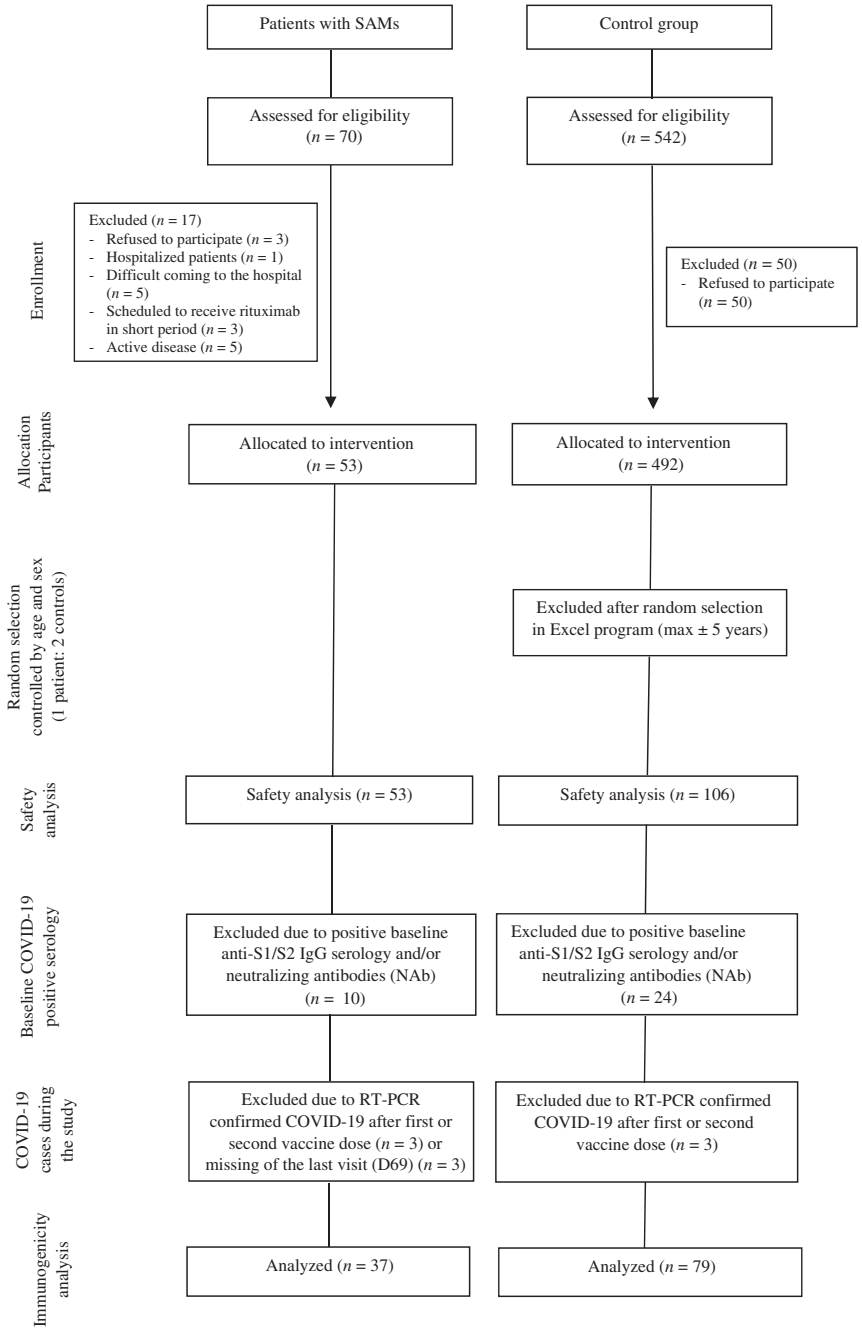
Anti-SARS-CoV-2 S1/S2 IgG antibodies

A chemiluminescent immunoassay was used to measure human IgG antibodies against the S1 and S2 proteins in the RBD (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Seroconversion rate (SC) was defined as positive serology (>15.0 UA/ml) post-vaccination, taking into consideration that only patients with pre-vaccination negative serology were included. Geometric mean titres (GMT) and 95% CI of these antibodies were also calculated at all time points, attributing the value of 1.9 UA/ml (half of the lower limit of quantification 3.8 UA/ml) to undetectable levels (<3.8 UA/ml). The factor increase in GMT (FI-GMT) is the ratio of the GMT after vaccination to the GMT before vaccination, showing the growth in titres. They are also presented and compared as geometric means and 95% CI.

NAb

The SARS-CoV-2 neutralizing antibodies analysis was performed according to manufacturer instructions using sVNT Kit (GenScript, Piscataway, NJ, USA). This analysis detects circulating neutralizing antibodies against SARS-CoV-2 that block the interaction between the receptor-binding domain of the viral spike glycoprotein with the angiotensin-converting enzyme 2 cell surface receptor. The tests were performed on the ETI-MAX-

Fig. 1 Flow chart of the present study



Nab: neutralization antibodies; SAMS: systemic autoimmune myopathies.

3000 equipment (DiaSorin, Italy). The samples were classified as either 'positive' (inhibition $\geq$30%) or 'negative' (inhibition $<$30%), as suggested by the manufacturer [25]. The frequency of positive samples was calculated at all time points. Median [interquartile range (IQR) 25th–75th] of the percentage of neutralizing activity only for positive samples were calculated at all time points.

Vaccine adverse events and incident cases of COVID-19

Patients and CTRL were advised to report any adverse events of the vaccine and they received on D0 (first dose) and on D28 (second dose) a standardized diary for local and systemic manifestations. Vaccine adverse event severity was defined according to World Health Organization (WHO) definition [1]. Additionally, all

patients and CTRL were instructed to communicate any manifestation associated or not with COVID-19 through telephone, smartphone instant messaging, or email. Independent vaccine experts monitored the study regarding anything adverse for data safety.

RT-PCR for SARS-CoV-2 incident cases

Clinical samples for SARS-CoV-2 RT-PCR consisted of naso- and oropharyngeal swabs, collected at our central laboratory [26] or another laboratory if the patient was unable to come to our hospital.

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the distribution of each parameter. The results were presented as mean (S.D.), median (IQR 25th–75th) for continuous variables, whereas the categorical variables were presented as frequency (%). Continuous variables were compared by *t*-Student or Mann–Whitney test for intergroup comparisons when applicable, whereas categorical variables were compared using the χ^2 or Fisher's exact tests when applicable. Specifically, continuous data regarding anti-S1/S2 IgG serology titres are presented as geometric means (95% CI) and compared with the same tests, but in neperian (ln) logarithm-transformed data. Comparisons of ln-transformed IgG titres between SAMs and CTRL in the three time points (D0, D28 and D69) were performed using generalized estimating equations (EEG) with normal marginal distribution and gamma distribution, respectively and identity binding function assuming first-order autoregressive correlation matrix between moments. Results were followed by Bonferroni multiple comparisons to identify differences between groups and time points. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences, version 20.0 (IBM-SPSS for Windows. 20.0, Chicago, IL, USA).

Results

Participants

Fifty-three patients with SAMs (25 with ASSD, 24 with DM and 4 with IMNM) with median disease duration of 6.0 (4.5–9.0) years, and 106 CTRL were prospectively assessed. SAMs and CTRL had comparable current age ($P = 0.925$), female sex ($P > 0.999$) and ethnicity distribution ($P = 0.312$) (Table 1). The disease duration was 6.0 (4.5–9.0) months. Seven (13.2%) patients with SAMs and seven (6.9%) CTRL ($P = 0.166$) were unable to attend on the defined days; therefore, they had up to 15 days for the recap.

Comorbidities were balanced in SAMs and CTRL, except for a higher prevalence of systemic arterial hypertension, dyslipidaemia and obesity in patients with SAMs compared with CTRL (Table 1). Interstitial lung disease occurs only in patients with SAMs, whereas one stroke case occurred in CTRL. There were no cases of arterial or venous thrombosis, chronic kidney disease, pulmonary hypertension, hemorrhage, liver disease, cancer, tuberculosis and HIV in both groups.

All patients had stable or low disease activity, based on the IMACS core set scores at baseline (Table 1). Concerning current treatment, 15 (28.3%) patients were under prednisone with current median dose of 6.3 (5.0–13.8) mg/day and the cumulative dose of the six previous months was 1.6 (1.1–4.8) g. In addition, 44 (83.0%) patients were using immunosuppressive drugs, six (11.3%) patients were under rituximab and one (1.9%) tofacitinib (Table 1). None of the immunosuppressive drugs, including CYC, rituximab and mycophenolate mofetil were discontinued in patients with SAMs.

Vaccine immunogenicity

Samples

For this assessment, 16 patients with SAMs were excluded: 10 patients had pre-vaccination positive COVID-19 IgG serology or NAb positivity, three patients had RT-PCR confirmed COVID-19 after the first dose of vaccine until D69, two patients who did not attend the final visit, and one patient deceased (not related to COVID-19). In the CTRL group, 24 individuals were excluded from immunogenicity analysis for positive anti-S1/S2 IgG and/or NAb at D0 and another three for RT-PCR confirmed COVID-19 during the protocol.

Anti-SARS-CoV-2 IgG antibodies

Humoral response to Sinovac-CoronaVac is shown in Table 2. Analysis of SARS-CoV-2 S1/S2 IgG response revealed that six weeks after vaccine second dose, SC rates were moderate but lower than CTRL (64.9% *vs* 91.1%, respectively; $P < 0.001$). GMT and FI-GMT were also significantly lower in patients with SAMs compared with CTRL ($P < 0.001$ and $P < 0.001$, respectively) (Table 2).

NAb

After complete vaccination, NAb positivity was also moderate but reduced when compared with CTRL (51.4% *vs* 77.2%, $P < 0.01$), whereas the median NAb was comparable in both groups after the first [39.2 (38.4–52.5) *vs* 46.6 (36.9–73.3), $P = 0.573$] and second dose [57.2 (43.4–83.4) *vs* 63.0 (40.3–80.7), $P = 0.808$] (Table 3).

Factors associated with seroconversion and NAb positivity among patients with SAMs

Patients with NAb positivity used less often immunosuppressive drugs than those without NAb (73.7% *vs* 100%, $P = 0.046$). Likewise, the median of patient global activity (VAS) was lower in the former group [1.0 (0.0–3.0) *vs* 2.0 (2.0–3.0), $P = 0.029$] (Table 4), although both groups were characterized by mild value alterations.

Vaccine tolerance and safety

Sinovac-CoronaVac vaccine tolerance and safety analysis is shown in Table 5. No moderate/severe adverse events were observed. The frequency of mild symptoms

Table 1 Baseline characteristics of patients with systemic autoimmune myopathies and controls

	SAMs ($n = 53$)	CTRL ($n = 106$)	*P*-value
Demographics			
Current age (years)	50.7 (11.1)	50.5 (10.6)	0.925
Disease duration (years)	6.0 (4.5–9.0)	—	—
Female sex	40 (75.5)	80 (75.5)	>0.999
White ethnicity	28 (52.8)	47 (44.3)	0.312
Comorbidities and habits			
Systemic arterial hypertension	28 (52.8)	38 (35.8)	0.041
Diabetes mellitus	10 (18.9)	18 (17.0)	0.768
Dyslipidaemia	14 (26.4)	7 (6.6)	0.001
BMI $\geq$30 kg/m^2	26 (49.1)	27 (25.5)	0.003
Myocardial infarction	2 (3.8)	2 (1.9)	0.601
Interstitial lung disease	19 (35.8)	0	—
Stroke	0	1 (0.9)	—
Current smoking	2 (3.8)	11 (10.4)	0.222
Type of diseases			
DM	24 (45.3)	—	—
Antisynthetase syndrome	25 (47.2)	—	—
IMNM	4 (7.5)	—	—
Disease status			
HAQ (0.0–3.0)	0.0 (0.0–0.0)		
Patients' EVA (0–10)	1.0 (0.0–3.0)		
Physician's EVA (0–10)	0.0 (0.0–1.0)		
MMT-8 (0–80)	80 (80–80)		
MYOACT (0–60)	0.0 (0.0–0.0)		
Creatine phosphokinase (U/l)	110 (78–174)		
Current therapy			
Prednisone (current use)	15 (28.3)	—	—
Dose (mg/day)	6.3 (5.0–13.8)		
Cumulative dose[a] (g)	1.6 (1.1–4.8)		
Immunosuppressive drugs	44 (83.0)	—	—
Mycophenolate mofetil	19 (35.8)	—	—
MTX	11 (20.8)	—	—
AZA	8 (15.1)	—	—
LEF	6 (11.3)	—	—
Ciclosporin	3 (5.7)	—	—
CYC	2 (3.8)	—	—
Rituximab	6 (11.3)	—	—
Tofacitinib	1 (1.9)	—	—

Results are expressed in mean (S.D.), median (interquartile range 25th–75th), and *n* (%). CTRL: control group; HAQ: Healthy Assessment Questionnaire; IMNM: immune-mediated necrotizing myopathies; MMT: manual muscle testing; MYOACT: Myositis Disease Activity Assessment Visual Analogue Scales; SAMs: systemic autoimmune myopathies; VAS: Visual Analogue Scale. [a]Last six months.

was comparable in patients with SAMs and CTRL, except for significantly higher prevalence of headache in patients with SAMs at the first vaccine dose (26.4% *vs* 8.5%, $P = 0.002$). No differences were observed in the frequencies of myalgia or muscle weakness among groups.

COVID-19 incident cases

A total of six incident symptomatic cases of COVID-19 confirmed by RT-PCR were identified among SAMs ($n = 3$) and CTRL ($n = 3$) throughout the study period. Three CTRL individuals and two patients with SAMs had COVID-19 between the first and second dose, whereas one patient had COVID-19 three weeks after the second dose. All participants had mild symptoms and none required hospitalization.

Discussion

To our knowledge, this is the largest study demonstrating a short-term disease safety and moderate immunogenicity of anti-SARS-CoV-2 inactivated vaccine in patients with SAMs but reduced compared with an age and sex-balanced non-immunocompromised control group. We further identified that immunosuppressive therapy reduces antibody response.

Table 2 Seroconversion rates and anti-SARS-CoV-2 S1/S2 IgG GMT in näive patients with myositis and control group

	Before vaccine	After vaccine			After vaccine		
	First dose	First dose (D28)			Second dose (D69)		
	GMT	SC	GMT	FI-GMT	SC	GMT	FI-GMT
SAMs ($n=37$)	2.1 (1.9–2.3)	3 (8.1)	3.3 (2.5–4.3)[a]	1.5 (1.2–2.0)[a]	24 (64.9)[a]	16.6 (9.7–28.3)[a,b]	7.9 (4.7–13.2)[a]
CTRL ($n=79$)	2.4 (2.1–2.7)	27 (34.2)	9.6 (7.2–12.9)	4.1 (3.2–5.1)	72 (91.1)	58.5 (48.4–70.8)[c,d]	24.7 (20.0–30.5)
P-value (SAMs *vs* CTRL)	0.630	0.005	<0.001	<0.001	<0.001	<0.001	<0.001

Results are expressed in mean (95% CI) or frequency (%). CTRL: control group; FI-GMT: factor increase of geometric mean titres; GMT: geometric mean titres (AU/ml); SAMs: systemic autoimmune myopathies; SC: seroconversion. Frequencies of SC are presented as number (%), and they were compared using two-sided χ^2 test between SAMs and CTRL at D28 and D69. Anti-S1/S2 IgG were expressed as geometric means (CI95%). Titers were compared between SAM and CTRL and between time points (D0, D28 and D69) using generalized estimating equations (EEG) with normal marginal distribution and gamma distribution, respectively. Results were followed by Bonferroni multiple comparisons to identify differences between groups and time points. [a]$P<0.001$ for longitudinal comparison of GMT in SAMs at D69 *vs* baseline. [b]$P<0.001$ for longitudinal comparison of GMT in SAMs at D69 *vs* D28. [c]$P<0.001$ for longitudinal comparison of GMT in controls at D28 and D69 *vs* baseline. [d]$P<0.001$ for longitudinal comparison of GMT in controls at D69 *vs* D28.

Table 3 Neutralizing antibodies and neutralizing activity in naïve patients with myositis in comparison to control group

	After vaccine first dose		After vaccine second dose	
	Subjects with positive NAb	Neutralizing activity (%)	Subjects with positive NAb	Neutralizing activity (%)
SAMs ($n=37$)	5 (13.5)[a]	39.2 (38.4–52.5)	19 (51.4)[a]	57.2 (43.4–83.4)
CTRL ($n=79$)	26 (32.9)	46.6 (36.9–73.3)	61 (77.2)	63.0 (40.3–80.7)

Results are expressed in median (25th–75th) or frequency (%). CTRL: control group; NAb: neutralizing antibodies; SAMs: systemic autoimmune myopathies. [a]$P<0.01$ in comparison to controls.

One advantage of the present study was the prospective analysis with a representative sample of patients with well-defined SAMs taking into consideration that they are a group of patients with rare conditions and the strict exclusion criteria applied herein. Another strength of the present study was that patients had comparable age and sex of the CTRL, as immunogenicity can vary according to these parameters [27, 28]. We also excluded cancer-associated myopathies and other associated autoimmune conditions in order to have a more homogeneous population [29]. A limitation of the present study is the inclusion of patients solely from a tertiary care centre who may not represent the full spectrum of SAMs and could result in an overestimation of the disease or drug complications in the context of a more severe disease.

All individuals were followed with three scheduled face-to-face appointments, telephone calls and smartphone instant messaging, which allowed a precise monitoring of vaccine-induced adverse effects in all phases of the study. The exclusion of pre-vaccination seropositive participants and those with RT-PCR confirmed COVID-19 during the study period were also relevant, allowing a more accurate evaluation of this vaccine response. The strict schedule for blood sample collection and vaccination in two days aimed to guarantee that most patients with SAMs and CTRL would be vaccinated in the same timeframe during the pandemic, precluding the possible confounding nonlinear relationship between the elapsed time and immune response.

Currently, most studies on the immunogenicity and safety of the anti-SARS-CoV-2 vaccines in patients with systemic autoimmune rheumatic diseases evaluated distinct vaccines, mainly mRNA or vector-borne vaccines [13–19]. Regarding safety, all those studies related acceptable rates of adverse events [13–20], without apparent impact on disease activity. However, specifically for SAMs, the number of patients was small [14–19], and they were not evaluated with specific and validated instruments for SAMs. The current study adds data about the safety of the inactivated vaccine in well-controlled patients with SAMs, using specific and validated instruments at baseline [22–24]. Importantly,

TABLE 4 Baseline characteristics of patients regarding to seroconversion for anti-SARS-CoV-2 S1/S2 IgG, and neutralizing antibodies positivity

	Patients with SC ($n = 24$)	Patients without SC ($n = 13$)	*P*-value	Patients with Nab ($n = 19$)	Patients without Nab ($n = 18$)	*P*-value
Demographic data						
Current age (years)	50.0 (11.7)	55.0 (8.9)	0.187	48.8 (11.6)	54.9 (9.4)	0.090
Current age >60 years	3 (12.5)	2 (15.4)	>0.999	2 (10.5)	3 (16.7)	0.660
Female sex	16 (66.7)	12 (92.3)	0.119	13 (68.4)	15 (83.3)	0.447
White ethnicity	14 (58.3)	6 (46.2)	0.478	11 (57.9)	9 (50)	0.630
Diseases						
DM	11 (45.8)	6 (46.2)	>0.999	7 (36.8)	10 (55.6)	0.330
Antisynthetase syndrome	11 (45.8)	6 (46.2)	>0.999	10 (52.6)	7 (38.9)	0.515
IMNM	2 (8.4)	1 (7.6)	>0.999	2 (10.6)	1 (5.5)	>0.999
Disease parameters						
HAQ (0.0–3.0)	0.0 (0.0–1.2)	0.0 (0.0–0.0)	0.537	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.746
Patients' EVA (0–10)	1.0 (0.0–2.8)	3.0 (2.0–3.0)	0.058	1.0 (0.0–3.0)	2.0 (2.0–3.0)	**0.029**
Physician's EVA (0–10)	0.0 (0.0–0.0)	0.0 (0.0–3.0)	0.387	0.0 (0.0–0.0)	0.0 (0.0–3.0)	0.221
MMT-8 (0–80)	80 (80–80)	80 (79–80)	0.353	80 (80–80)	80 (80–80)	0.558
MYOACT (0–60)	0.0 (0.0–10.0)	0.0 (0.0–3.5)	0.479	0.0 (0.0–1.0)	0.0 (0.0–0.8)	0.940
Creatine phosphokinase (U/l)	121 (89–183)	99 (74–189)	0.460	124 (81–181)	111 (74–189)	0.663
Prednisone						
Current use	6 (25)	7 (53.8)	0.096	5 (26.3)	8 (44.4)	0.298
Dose (mg/day)	6.3 (2.5–20.0)	5 (2.5–30.0)	0.945	10.0 (7.3)	9.1 (8.9)	0.847
Dose >10 mg/day	2 (8.3)	3 (23.1)	0.321	2 (10.5)	3 (16.7)	0.660
Immunosuppressive drugs	19 (79.2)	13 (100)	0.140	14 (73.7)	18 (100)	**0.046**
Mycophenolate mofetil	7 (29.2)	8 (61.5)	0.056	6 (31.5)	9 (50)	0.254
MTX	7 (29.2)	1 (7.7)	0.216	5 (26.3)	3 (16.7)	0.693
AZA	4 (16.7)	2 (15.4)	1.000	3 (15.7)	3 (16.7)	>0.999
LEF	3 (12.5)	0 0	0.538	2 (10.5)	1 (5.6)	>0.999
Ciclosporin	0	2 (15.4)	–	0	2 (11.1)	–
CYC	1 (4.2)	1 (7.7)	1.000	1 (5.3)	1 (5.6)	1.000
Rituximab	3 (12.5)	3 (23.1)	0.643	2 (10.5)	4 (22.2)	0.405

Results are expressed in mean (S.D.), median (interquartile range 25th–75th) and frequency (%). Bold text indicates significance. IMNM: immune-mediated necrotizing myopathies; Nab: neutralization antibodies; SAMs: systemic autoimmune myopathies; SC: seroconversion.

vaccine safety was demonstrated by the absence of severe or moderate adverse events related to vaccination with only mild and self-limiting side effects.

We observed that patients with SAMs had a moderate immune response to this vaccine and within the standards established by Food and Drugs Administration (FDA) and European Medicine Agency for Emergency Use Authorization of pandemic vaccines [30, 31]. In addition, the WHO recently approved the Sinovac-CoronaVac COVID-19 vaccine for emergency use [32]. However, after complete vaccination, the immunogenicity was lower compared with CTRL, but with SC rates comparable to the 64% reported for the pandemic influenza A H1N1 inactivated vaccine in a study of 1,600 autoimmune rheumatic disease patients [33]. Our findings with Sinovac-CoronaVac vaccine confirm and extends Furer *et al.*'s study [19] which assessed serum IgG antibody levels against SARS-CoV-2 proteins after the second dose of BNT162b2 mRNA COVID-19 vaccine and showed significantly reduced vaccine-induced immunogenicity in a small SAMs population ($n = 19$). We further demonstrated that NAb rates, now recognized as one of the major predictors of SARS-CoV-2 immune protection [34] were also moderate but lower than CTRL.

In contrast, after the first dose there was a negligible vaccine response (SC and NAb positivity) reinforcing the importance of the second dose for these patients. However, among patients who develop NAb, NAb activity was comparable for both groups after the first and second dose.

Further analysis of possible interference of clinical and laboratory parameters, comorbidities and type of SAMs in vaccine immunogenicity revealed that solely immunosuppressive drugs hampered the NAb positivity. This finding is in line with the reported reduced vaccine response in patients under mycophenolate mofetil therapy [17, 19, 20], rituximab [17–20], MTX [19, 20] and abatacept [19, 20] after different kinds of vaccines and their schedules [13–20]. Accordingly, in the present study, >80% of patients were under immunosuppressive drugs, especially mycophenolate mofetil in one third of

TABLE 5 Adverse events of Sinovac-CoronaVac vaccination in patients with systemic autoimmune myopathies and control group

	After vaccine first dose			After vaccine second dose		
	SAMs	CTRL	*P*-value	SAMs	CTRL	*P*-value
	(*n* = 53)	(*n* = 106)		(*n* = 50)	(*n* = 106)	
No symptoms	27 (50.9)	66 (62.3)	0.172	27 (54.0)	63 (59.4)	0.431
Local reactions[a]	11 (20.8)	18 (17.0)	0.561	11 (22.0)	19 (17.9)	0.579
Pain	9 (17.0)	15 (14.2)	0.638	11 (22.0)	17 (16.0)	0.390
Erythema	0	1 (0.9)	—	3 (6.0)	3 (2.8)	0.390
Swelling	0	4 (3.8)	—	4 (8.0)	6 (5.7)	0.728
Bruise	0	4 (3.8)	—	1 (2.0)	2 (1.9)	>0.999
Pruritus	2 (3.8)	1 (0.9)	0.258	2 (4.0)	6 (5.7)	>0.999
Induration	2 (3.8)	1 (0.9)	0.258	2 (4.0)	4 (3.8)	>0.999
Systemic reactions	23 (43.4)	34 (32.1)	0.161	16 (32.0)	31 (29.3)	0.775
Fever	2 (3.8)	0	—	0	3 (2.8)	—
Malaise	5 (9.4)	3 (2.8)	0.118	3 (6.0)	9 (8.5)	0.752
Somnolence	8 (15.1)	11 (10.4)	0.387	6 (12.0)	12 (11.3)	0.931
Lack of appetite	2 (3.8)	3 (2.8)	>0.999	1 (2.0)	5 (4.7)	0.664
Nausea	1 (1.9)	1 (0.9)	>0.999	1 (2.0)	10 (9.4)	0.104
Vomiting	0	0	—	0	1 (0.9)	—
Diarrhea	2 (3.8)	7 (6.6)	0.719	1 (2.0)	6 (5.7)	0.428
Abdominal pain	2 (3.8)	4 (3.8)	>0.999	2 (4.0)	5 (4.7)	>0.999
Vertigo	5 (9.4)	5 (4.7)	0.248	2 (4.0)	6 (5.7)	>0.999
Tremor	0	0	—	0	0	—
Headache	14 (26.4)	9 (8.5)	**0.002**	8 (16.0)	19 (17.9)	0.731
Fatigue	6 (11.3)	8 (7.5)	0.429	5 (10.0)	15 (14.1)	0.445
Sweating	2 (3.8)	3 (2.8)	>0.999	3 (6.0)	1 (0.9)	0.100
Myalgia	5 (9.4)	5 (4.7)	0.248	5 (10.0)	9 (8.5)	0.783
Muscle weakness	3 (5.7)	2 (1.9)	0.334	4 (8.0)	7 (6.6)	0.748
Arthralgia	4 (7.5)	6 (5.7)	0.732	5 (10.0)	8 (7.5)	0.627
Back pain	5 (9.4)	6 (5.7)	0.377	1 (2.0)	9 (8.5)	0.168
Cough	4 (7.5)	7 (6.6)	>0.999	3 (6.0)	7 (6.6)	>0.999
Sneezing	2 (3.8)	6 (5.7)	0.720	1 (2.0)	11 (10.4)	0.104
Coryza	1 (1.9)	10 (9.4)	0.101	3 (6.0)	8 (7.5)	>0.999
Stuffy nose	0 0	3 (2.8)	0.551	2 (4.0)	6 (5.7)	>0.999
Sore throat	3 (5.7)	5 (4.7)	>0.999	1 (2.0)	7 (6.6)	0.438
Shortness of breath	0	2 (1.9)	—	1 (2.0)	3 (2.8)	>0.999
Conjunctivitis	0	0	—	0	1 (0.9)	—
Pruritus	1 (1.9)	3 (2.8)	>0.999	1 (2.0)	5 (4.7)	0.664
Skin rash	1 (1.9)	2 (1.9)	>0.999	1 (2.0)	2 (1.9)	>0.999

Results are presented in frequency (%). Bold text indicates significance. [a]At the injection site. CTRL: control group; SAMs: systemic autoimmune myopathies.

patients, but also, at lower frequencies, MTX and rituximab. Although we could not show any specific drug effect due to the limited sample size, probably pooled analysis of these drugs was responsible for the interference in NAb positivity. In contrast to Furer *et al.* [19], that found a deleterious effect of glucocorticoids even at low dose [6.7 (6.3) mg/day of prednisone], we failed to show such interference with a very similar dose, also probably due to sample size.

Our patients had stable or low disease activity, according to inclusion criteria and IMACS core set measures at baseline and precluded any interpretation regarding the effect of disease activity in vaccine response, in spite of an association between mild elevated VAS of patient global activity and reduced frequency of NAb positivity. Therefore, further studies of SARS-CoV-2 vaccines with a large population of SAMs, including analysis of effect of individual immunosuppressive drugs, disease activity and different subtypes of SAMs will be necessary.

Patients with systemic autoimmune rheumatic diseases, including SAMs, may be at a higher risk for COVID-19 infection. Preliminary ACR guidelines recommended that patients with rheumatic and musculoskeletal diseases should be promptly vaccinated for COVID-19 [35]. Recent reports have also suggested that immunosuppressive drugs should be suspended for patients after COVID-19 vaccinations, particularly for

those under mycophenolate mofetil, MTX, CYC and rituximab to improve immunogenicity [36, 37]. Although our patients were in low disease activity, we choose not to withdraw medications due to the risk of reactivation and lack of definitive findings about each drug suspension at this specific population. Moreover, the current recommendations were not available during the study design.

There are limitations in the present study. First, inclusion of patients with different SAMs subtypes and from only one tertiary care centre, who may not represent the full spectrum of SAMs and could result in an overestimation of the disease activity or drug complications in the context of a more severe disease. Second, the sample size was not calculated because we used a convenience sample. Third, the FI-GMT and GMT values were not assessed for individual immunosuppressive drugs because of the small representation of each medication.

In conclusion, our data demonstrated that Sinovac-CoronaVac inactivated vaccine is safe and has a moderate short-term immunogenicity in inactive or low disease activity SAMs patients, although inferior compared with the CTRL. We further confirmed that immunosuppressive drugs have a deleterious effect on vaccine-induced antibody production, affecting in particular NAb positivity rates. These findings support the recommendation of SARS-CoV-2 vaccination for SAMs patients.

Acknowledgements

We thank the contribution of the Central Laboratory Division, Registry Division, Security Division, IT Division, Superintendence, Pharmacy Division and Vaccination Center (CRIE) for their technical support. We also thank the volunteers for handling the biological material and those responsible for the medical follow-up of all participants.

Funding: This work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (#2015/03756–4 to N.E.A., S.G.P., C.A.S. and E.B., #2019/17272–0 to L.V.K.K., #2019/21211–6 to J.C.S.; #2019/11776-6 to S.K.S.); Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq #305242/2019–9 to E.B., #304984/2020–5 to C.A.S., #303379/2018–9 to S.K.S.), B3 - Bolsa de Valores do Brasil to E.B., and Faculdade de Medicina da USP—SP to S.K.S. 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 cannot be shared publicly due to the privacy of individuals that participated in the study. Anonymised data are available on request from the corresponding author.

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