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ORIGINAL ARTICLE

Inactivated SARS-CoV-2 vaccine in primary Sjögren's syndrome: humoral response, safety, and effects on disease activity

Sandra Gofinet Pasoto[1] · Ari Stiel Radu Halpern[1] · Lissiane Karine Noronha Guedes[1] · Ana Cristina Medeiros Ribeiro[1] · Emily Neves Figueiredo Yuki[1] · Carla Gonçalves Schahin Saad[1] · Clovis Artur Almeida da Silva[1] · Léonard de Vinci Kanda Kupa[1] · Lorena Elizabeth Betancourt Villamarín[1] · Victor Adriano de Oliveira Martins[1] · Carolina Campagnoli Machado Freire Martins[1] · Giordano Bruno Henriques Deveza[1] · Elaine Pires Leon[1] · Cleonice Bueno[1] · Tatiana Nascimento Pedrosa[1] · Roseli Eliana Beseggio Santos[2] · Renata Soares[1] · Nádia Emi Aikawa[1] · Eloisa Bonfa[1]

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Abstract

Introduction There is no study specifically focused on SARS-CoV-2 vaccine in primary Sjögren's syndrome (pSS).

Objectives To assess the immunogenicity, safety, possible effects on disease activity, and autoantibody profile of the Sinovac-CoronaVac vaccine in pSS.

Methods Fifty-one pSS patients and 102 sex- and age-balanced controls without autoimmune diseases were included in a prospective phase 4 trial of the Sinovac-CoronaVac vaccine (two doses 28 days apart, D0/D28). Participants were assessed in three face-to-face visits (D0/D28 and six weeks after the 2nd dose (D69)) regarding adverse effects; clinical EULAR Sjögren's Syndrome Disease Activity Index (clinESSDAI); anti-SARS-CoV-2 S1/S2 IgG (seroconversion (SC) and geometric mean titers (GMT)); neutralizing antibodies (NAb); and pSS autoantibody profile.

Results Patients and controls had comparable female sex frequency (98.0% vs. 98.0%, $p=1.000$) and mean age (53.5 ± 11.7 vs. 53.4 ± 11.4 years, $p=0.924$), respectively. On D69, pSS patients presented moderate SC (67.5% vs. 93.0%, $p<0.001$) and GMT (22.5 (95% CI 14.6–34.5) vs. 59.6 (95% CI 51.1–69.4) AU/mL, $p<0.001$) of anti-SARS-CoV-2 S1/S2 IgG but lower than controls, and also, moderate NAb frequency (52.5% vs. 73.3%, $p=0.021$) but lower than controls. Median neutralizing activity on D69 was comparable in pSS (58.6% (IQR 43.7–63.6)) and controls (64% (IQR 46.4–81.1)) ($p=0.219$). Adverse events were mild. clinESSDAI and anti-Ro(SS-A)/anti-La(SS-B) levels were stable throughout the study ($p>0.05$).

Conclusion Sinovac-CoronaVac vaccine is safe in pSS, without a deleterious impact on disease activity, and has a moderate short-term humoral response, though lower than controls. Thus, a booster dose needs to be studied in these patients.

Trial registration ClinicalTrials.gov Identifier: NCT04754698.

Key Points

- *Sinovac-CoronaVac vaccine is safe in pSS, without a detrimental effect on systemic disease activity, and has a moderate short-term humoral response*
- *A booster dose should be considered in these patients*

Keywords COVID-19 · Immunogenicity · Safety · SARS-CoV-2 · Sjögren's syndrome · Vaccine

✉ Sandra Gofinet Pasoto
sandra.pasoto@hc.fm.usp.br

[1] Rheumatology Division, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, Av. Dr. Arnaldo, 455, 3º andar, sala 3190, Sao Paulo, SP 01246-903, Brazil

[2] Central Laboratory Division, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

Introduction

Primary Sjögren's syndrome (pSS) is a chronic inflammatory rheumatic illness categorized mainly by the immune-mediated injury to the lacrimal and salivary glands. Additionally, pSS has a wide spectrum of organic involvements [1]. pSS prevalence is around 60.82 (95% CI 43.69–77.94)/100,000 population and varies among different regions of the globe [2]. This disease predominantly affects Caucasian women aged 40–60 years [2–4].

Infections, especially pulmonary, are significant mortality causes in pSS, probably due to treatment with glucocorticoids and immunosuppressive drugs, as well as the older age of the patients [5–7].

Concerning coronavirus disease 2019 (COVID-19), there is some evidence of risk factors for disfavored results in systemic autoimmune rheumatic disorder (ARD) patients [8–11]. In pSS, it was recently shown that the presence of comorbidities is associated with a 6 times higher risk of hospitalization and poor outcomes for COVID-19 [12].

However, there are few data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunization in pSS. In this aspect, a recent trial including 264 overall ARD patients not excluding pre-exposed individuals showed that 86% of them developed a significant humoral response afterwards two doses of the messenger mRNA vaccine against SARS-CoV-2 (Pfizer), and the adverse effects were mild [13]. Nevertheless, only two pSS patients were included in this cohort [13].

The inactivated vaccine for SARS-CoV-2 (Sinovac-CoronaVac) is the most extensively used globally [14], and a recent study that evaluated a very large cohort of the Chilean population showed that it reduces hospitalization rate for COVID-19 by 87.5%, admission to intensive care unit by 90.3%, and deaths by 86.3% [15].

Our group assessed the immunogenicity and safety of the Sinovac-CoronaVac vaccine in a newly published clinical trial that enrolled 910 ARD patients (41 of them with pSS) and 182 age- and sex-balanced controls [16]. The vaccine had an adequate safety profile. Six weeks after the second dose, a moderate seroconversion rate was observed in ARD patients, but it was lower than that in the control group (70.4% vs. 95.5%, $p < 0.001$). However, a specific analysis of pSS patients was not performed [16, 17]. This is an important point, since pSS usually affects older individuals, which is a known deleterious factor for inactivated [16] and mRNA COVID-19 vaccine immunogenicity [18, 19]. Furthermore, the possible impact of the vaccine on the systemic activity of pSS and on the autoantibody profile has not been evaluated. In this context, we have described an increase in anti-Ro(SS-A) and anti-La(SS-B) serum concentrations after immunization against influenza A H1N1 in pSS [20].

Therefore, this study aims to assess the safety, humoral response, and the possible impact of the Sinovac-CoronaVac vaccine on the systemic disease activity and autoantibody profile in pSS.

Materials and methods

Study design

This was a prospective controlled trial within a larger phase 4 study [16] evaluating specifically 51 pSS patients and 102 sex- and age-balanced controls who received two doses of the Sinovac-CoronaVac vaccine 28 days apart (CoronavRheum, clinicaltrials.gov #NCT04754698).

Ethical approval and consent

The study followed the local regulations and the Declaration of Helsinki and its amendments, and it was approved by the institutional and national ethics committees (Comissão Nacional de Ética em Pesquisa – CONEP) (CAAE 42566621.0.0000.0068). In addition, all pSS patients and control individuals signed an informed consent form before inclusion in the trial.

Participants, inclusion and exclusion criteria, and data collection

pSS patients Fifty-seven consecutive adult (18 years of age or older) pSS patients fulfilling the classification criteria of the American-European Consensus Group (2002) [21] and regularly followed at the Sjögren's Syndrome Outpatient Clinic of the Rheumatology Division of the Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo (Sao Paulo, SP, Brazil), were invited to participate in the study.

Control individuals The control group (2 control individuals: 1 patient) consisted of hospital administrative and maintenance employees and their relatives, without history of autoimmune diseases, HIV infection, or immunosuppression, and balanced for sex and age (with differences of up to ± 5 years). The control individuals were randomly selected from the parental study participants [16] using an Excel program (2 control individuals: 1 patient), with comparable sex frequency and age (≤ 5-year difference).

Exclusion criteria Exclusion criteria for pSS patients and controls were as follows: presence of infectious symptoms or fever at study entry; heart failure (class III or IV); diagnosis

of demyelinating diseases (such as Guillain-Barré syndrome); previous history of anaphylaxis to vaccines; prior immunization with any SARS-CoV-2 vaccine; immunization with any attenuated live virus vaccine in the last 28 days before the study or with inactivated virus vaccines in the last 14 days; blood transfusion in the last 6 months; hospitalized patients; and not agreeing to participate in the study as per the signed informed consent form.

Participants with pre-vaccination positive anti-SARS-CoV-2 S1/S2 IgG and/or NAb, as well as those with RT-PCR (reverse transcription-polymerase chain reaction)-confirmed COVID-19 throughout the study, were excluded for the immunogenicity analysis.

Final samples Of the 57 pSS patients invited, four refused to participate in the study, and two were excluded because they were hospitalized at the time of inclusion. Thus, 51 pSS patients and 102 sex- and age-balanced controls were included.

Of the 51 pSS patients, 8 had positive anti-SARS-CoV-2 S1/S2 IgG and/or NAb prior to vaccination (D0), 1 patient did not collect peripheral blood samples, and 2 had RT-PCR-confirmed COVID-19 throughout the study. In the control group, 14 had positive anti-SARS-CoV-2 S1/S2 IgG and/or NAb before vaccination and 2 had RT-PCR-confirmed COVID-19 during the study period. These patients and controls were excluded from the analysis of the humoral response to the vaccine. Thus, 40 pSS patients and 86 control individuals were included in the immunogenicity analysis.

Data collection All data were collected on REDCap web-platform (Vanderbilt University, Nashville, TN, USA) [22].

Immunization protocol

Patients and controls received intramuscularly two doses of Sinovac-CoronaVac vaccine (Sinovac Life Sciences, Beijing, China, lot #20200412) 28 days apart (D0 and D28, respectively). The first dose of the vaccine was administered on February 9–10, 2021 (D0), and the second dose, on March 9–10, 2021 (D28).

Vaccine adverse events and incident cases of COVID-19

Adverse effects (AE) and symptoms of COVID-19 were monitored through a symptom diary, which was provided to patients and control individuals on the D0 and D28. In addition, all participants were advised to contact the investigators by telephone, WhatsApp, and e-mail in case of AE or symptoms of COVID-19 appear. In cases of suspected COVID-19, RT-PCR was carried out. Furthermore, a team of physicians provided participants with appropriate recommendations and medications for each case, including the indication of hospitalization if necessary. Vaccine AE severity was defined according to the World Health Organization (WHO) [23]. Additionally, an independent Data Safety Monitoring Board reviewed and assessed the study protocol. Local AE comprised pain, pruritus, erythema, swelling, induration, and bruise at the vaccination site. Systemic AE included fever, fatigue, malaise, headache, coryza, sneezing, sore throat, stuffy nose, conjunctivitis, cough, shortness of breath, myalgia, arthralgia, muscle weakness, back pain, inappetence, abdominal pain, nausea, vomit, diarrhea, pruritus, skin rash, somnolence, vertigo, and tremor.

Clinical evaluation of the systemic activity of the pSS

The degree of systemic disease activity was assessed in face-to-face visits on D0, D28, and 6 weeks after the second dose (D69) using the clinical European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Index (clinESSDAI) [24]. Medications in use at study entry and their respective doses were recorded: prednisone, hydroxychloroquine, immunosuppressants (methotrexate, leflunomide, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, cyclophosphamide), and biological agents. In addition, electronic medical records were extensively reviewed for checking the fulfillment of the pSS classification criteria [21], as well as previous glandular and extraglandular involvements. Of note, no strategy of temporary discontinuation of medications for vaccination was adopted in the present study.

Evaluation of the humoral response to Sinovac-CoronaVac vaccine

Serum samples Peripheral blood samples were obtained from patients and control individuals immediately before the administration of each vaccine dose (on D0 and D28) and also on D69. Serum samples were then separated and stored at − 70 °C until use.

Humoral response For immunogenicity analysis, the serum responses of anti-SARS-CoV-2 S1/S2 IgG and neutralizing antibodies (NAb) were assessed. Participants with pre-vaccination positive anti-SARS-CoV-2 S1/S2 IgG and/or NAb, as well as those with RT-PCR-confirmed COVID-19 throughout the study, were excluded from this analysis (see above).

Anti-SARS-CoV-2 S1/S2 IgG antibodies Circulating anti-SARS-CoV-2 IgG antibodies directed to the S1/S2 proteins in the receptor-binding domain (RBD) were determined by a chemiluminescent immunoassay (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy). Seroconversion (SC) was defined as a positive (≥ 15.0 UA/mL)

anti-SARS-CoV-2 S1/S2 IgG test after the immunization [16]. Geometric mean titers (GMT) of anti-SARS-CoV-2 S1/S2 IgG were calculated on D0, D28, and D69, ascribing the value of 1.9 UA/mL (half of the inferior quantification limit, 3.8 UA/mL) to untraceable antibody concentrations (< 3.8 UA/mL) [16]. Factor increase in GMT (FI-GMT) is the relation of the GMT after immunization to the GMT previous to the immunization, thus quantifying the increase of GMT [16].

Neutralizing antibodies (NAb) Serum NAb against SARS-CoV-2 were measured by SARS-CoV-2 sVNT Kit (GenScript, Piscataway, NJ, USA) that detects inhibitor antibodies of the linkage of the RBD (of the viral spike glycoprotein) to the angiotensin-converting enzyme 2 (ACE2) cell surface receptor [16]. The NAb positivity was defined as inhibition ≥ 30% according to the manufacturer's instructions [25]. Frequencies of positive NAb samples were calculated on D0, D28, and D69, and the percentages of neutralizing activity were calculated for positive samples on the same days.

Autoantibody profile

The three serum samples from each patient/control (collected on D0, D28, and D69) were assayed for antinuclear antibodies (ANA) by indirect immunofluorescence on HEp-2 cells (INOVA Diagnostics Inc., San Diego, USA), anti-Ro(SS-A), and anti-La(SS-B) (INOVA Diagnostics Inc., San Diego, USA), following the recommendations of the manufacturer.

Statistical analysis

Statistical analyses were performed through the Statistical Package for the Social Sciences, version 22.0 (IBM-SPSS for Windows 22.0, Chicago, IL, USA). Categorical parameters were presented as number (%), and they were analyzed by the chi-square or Fisher's exact tests, as indicated. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile intervals or minimum–maximum). For these variables, the hypothesis of normality was appraised through the Kolmogorov–Smirnov test, and the Mann–Whitney *U* test, Student's *t* test, or the Friedman repeated measures analysis of variance on ranks were used, when recommended. Frequencies of SC of anti-SARS-CoV-2 S1/S2 IgG were expressed as number (%), and they were compared through two-sided chi-square test between pSS and controls on D28 and D69. Anti-SARS-CoV-2 S1/S2 IgG concentrations were expressed as GMT (95% CI), and neperian logarithm (ln)-transformed titers were compared between pSS and controls and between timepoints (D0, D28, and D69) by means of generalized estimating equations (EEG) with normal marginal distribution and gamma distribution, respectively. Then, these results were analyzed by Bonferroni's multiple comparisons to recognize differences between the groups and timepoints. Only two-tailed tests were used. The level of significance adopted was $p < 0.05$. The population of pSS patients was selected among ARD patients of the overall parental study [16] and was a convenience sample. The post hoc power analysis considering the SC rate of anti-SARS-Cov-2 S1/S2 IgG in pSS patients and controls after the second dose of the vaccine was 93.7%, and based on positive NAb frequency, it was 63.2%. Based on the general ARD population from the parental study [16] and considering the SC (defined as post vaccination titer > 15 AU/mL—Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy) rate observed after the 2nd dose (D69) in ARD patients (70.4%) and in the control group (95.5%), with an enrollment ratio of 1 patient: 2 controls, the sample size would be 23 patients and 46 controls, with an alpha of 0.05 and a power of 80%. On the other hand, considering the frequency of positive NAb (defined as a neutralizing activity ≥ 30%; cPass sVNT Kit, GenScript, Piscataway, USA) observed after the 2nd dose (D69) in ARD patients (56.3%) and in control individuals (79.3%), with an enrollment ratio of 1 patient: 2 controls, the sample size would be 46 patients and 92 controls, with an alpha of 0.05 and a power of 80%.

Results

Fifty-one pSS patients and 102 age-balanced control individuals were included. pSS patients and control individuals were comparable regarding mean age (53.5 ± 11.7 vs. 53.4 ± 11.4 years, $p = 0.924$), female sex (50 (98.0%) vs. 100 (98.0%), $p = 1.000$), and White race (30 (58.8%) vs. 49 (48.0%), $p = 0.208$) predominance.

Mean age at pSS diagnosis was 42.4 ± 12.2 years, and disease duration was 11.1 ± 8.0 years. Previous clinical manifestations and pSS organic involvements included dry eye (48 (94.1%)), dry mouth (48 (94.1%)), parotitis (20 (39.2%)), arthralgia (24 (47.1%)), arthritis (16 (31.4%)), purpura of the lower limbs (10 (19.6%)), Raynaud's phenomenon (10 (19.6%)), interstitial pneumonitis and/or bronchiolitis (14 (27.5%)), renal tubular acidosis (3 (6%)), glomerulonephritis (1 (2.0%)), peripheral neuropathy (1 (2.0%)), central nervous system impairment (1 (2.0%)), and myositis (1 (2.0%)).

Table 1 shows the main comorbidities in the pSS and control groups.

At study inclusion, current therapies in the pSS group were as follows: hydroxychloroquine 31 (60.8%), prednisone 14 (27.5%) (median dose: 10 mg/day (range: 5–30 mg/day)), immunosuppressive drugs 22 (43.1%) (azathioprine 11 (21.6%), mycophenolate mofetil 7 (13.7%), methotrexate 4 (7.8%), leflunomide 1 (2.0%)), biologic agents 2 (3.9%) (abatacept 1 (2.0%) and ustekinumab 1 (2.0%)).

Table 1 Demographic characteristics and comorbidities of pSS patients and controls

	pSS ($n=51$)	Controls ($n=102$)	p-value
Demographic characteristics			
Current age, years	53.5 ± 11.7	53.4 ± 11.4	0.924
Female sex	50 (98.0)	100 (98.0)	1.000
White race	30 (58.8)	49 (48.0)	0.208
Comorbidities	30 (58.8)	53 (52.0)	0.492
Systemic arterial hypertension	14 (27.5)	39 (38.2)	0.186
Diabetes mellitus	1 (2.0)	17 (16.7)	0.007
Dyslipidemia	8 (15.7)	13 (12.7)	0.618
Obesity (BMI ≥ 30 kg/m^2)	14 (27.5)	30 (30.3)	0.716
Chronic cardiomyopathy	2 (3.9)	0 (0)	0.110
Chronic renal disease	3 (5.9)	0 (0)	0.036
Current smoking	2 (3.9)	10 (9.8)	0.339
Chronic obstructive pulmonary disease	0 (0)	0 (0)	-
Asthma	4 (7.8)	3 (2.9)	0.223
Lung disease	14 (27.5%)	0 (0)	< 0.001
Hematologic disease	0 (0)	0 (0)	-
Hepatic disease	1 (2.0)	0 (0)	0.333
Current cancer	0 (0)	0 (0)	-
Stroke	2 (3.9)	0 (0)	0.110
Current tuberculosis	0 (0)	0 (0)	-
HIV	0 (0)	0 (0)	-

Results are expressed as mean ± standard deviation or *n* (%)

pSS, primary Sjögren's syndrome; *BMI*, body mass index

Vaccine-related adverse events were mild, with higher frequencies of vomiting, muscle weakness, arthralgia, and back pain in pSS patients than in control individuals ($p<0.05$) (Table 2).

The clinESSDAI median values persisted unchanged during the study: D0 (0 (minimum 0–maximum 14)), D28 (0 (0–15)), and D69 (0 (0–12)) ($p=0.162$). In addition, the frequencies of pSS patients with clinESSDAI ≥ 5 (6%, 13.6%, and 13.6%; $p=0.400$) or ≥ 13 (2%, 2.3%, and 0%; $p=1.000$) were also comparable on D0, D28, and D69, respectively.

Forty pSS patients and 86 control individuals were included in the immunogenicity analysis. After the second dose of the vaccine (D69), pSS patients presented moderate but lower SC (67.5% vs. 93.0%, $p<0.001$), GMT (22.5 (95% CI 14.6–34.5) vs. 59.6 (95% CI 51.1–69.4) AU/mL, $p<0.001$), and FI-GMT (8.9 (95% CI 5.6–14.0) vs. 27.4 (95% CI 22.9–32.7), $p<0.001$) of anti-SARS-CoV-2 S1/S2 IgG than control individuals (Table 3). Importantly, there was a longitudinal increase in GMT of anti-SARS-CoV-2 S1/S2 IgG from D0 and D28 vs. D69 ($p<0.001$) in both groups (Table 3).

On D69, pSS patients also had a moderate but lower frequency of NAb (52.5% vs. 73.3%, $p=0.021$) than controls. Median neutralizing activity at D69 was comparable in both groups (58.6% (IQR 43.7–63.6) vs. 64% (IQR 46.4–81.1), $p=0.219$) (Table 4).

Of note, frequency of current methotrexate use was lower in pSS patients with SC of anti-SARS-CoV-2 S1/S2 IgG compared to non-seroconverters (0 (0%) vs. 3 (23.1%), $p=0.029$) (Table 5). Disease activity, assessed by clinESSDAI, had no impact on the humoral response to the vaccine (Table 5).

In the pSS group, only 5/51 (9.8%) patients were negative for anti-Ro(SS-A) on D0 and remained negative on D28 and D69. Similarly, 21/51 (41.2%) of pSS patients were negative for anti-La(SS-B) on D0 and persisted negative on D28 and D69. Nine of 51 pSS patients (17.7%) had negative ANA on D0 and only one of them (11.1%) developed positive ANA on D69, with nuclear fine speckled pattern (AC-4). Serum levels of anti-Ro(SS-A) (D0: 91.5 (IQR 82.0–97.0), D28: 92.0 (IQR 80.0–97.0), and D69: 92.0 (IQR 79.8–96, 0) U, $p=0.921$) and anti-La(SS-B) (D0: 58.0 (IQR 37.8–74.8), D28: 59.0 (IQR 38.3–73.0), and D69: 59.5 (IQR 38.0–74.0) U, $p=0.555$) in the pSS patients positive for this reactivity remained stable throughout the study.

Regarding the control individuals, 2/102 (2%) of them presented positive anti-Ro(SS-A) on D0 and remained positive on D28 and D69. Concerning anti-La(SS-B), 1/102 controls (1%) was positive on D0 and continued positive on D28 and D69. Eighteen of 102 controls (17.7%) had positive ANA on D0 and remained positive on D28 and D69, with the same fluorescence pattern (which was nuclear fine speckled

Table 2 Adverse events of CoronaVac vaccination in pSS patients and controls

	After vaccine 1st dose			After vaccine 2nd dose		
	pSS ($n=51$)	Controls ($n=102$)	p-value	pSS ($n=51$)	Controls ($n=102$)	p-value
No symptoms	26 (51)	62 (60.8)	0.247	27 (52.9)	61 (61.6)	0.307
Local reactions (at the injection site)	11 (21.6)	20 (19.6)	0.776	9 (17.6)	20 (20.2)	0.707
Pain	9 (17.6)	14 (13.7)	0.552	6 (11.8)	19 (19.2)	0.248
Erythema	1 (2.0)	3 (2.9)	1.000	1 (2.0)	1 (1.0)	1.000
Swelling	2 (3.9)	9 (8.8)	0.338	2 (3.9)	5 (5.1)	1.000
Bruise	1 (2.0)	4 (3.9)	0.665	3 (5.9)	1 (1.0)	0.114
Pruritus	1 (2.0)	1 (1.0)	1.000	1 (2.0)	5 (5.1)	0.664
Induration	4 (7.8)	4 (3.9)	0.442	4 (7.8)	5 (5.1)	0.490
Systemic reactions	19 (39.6)	34 (33.3)	0.455	22 (43.1)	30 (30.3)	0.118
Fever	3 (5.9)	3 (2.9)	0.401	2 (3.9)	1 (1.0)	0.267
Malaise	5 (9.8)	7 (6.9)	0.524	8 (15.7)	9 (9.1)	0.227
Somnolence	8 (15.7)	11 (10.8)	0.386	6 (11.8)	9 (9.1)	0.605
Lack of appetite	1 (2.0)	3 (2.9)	1.000	2 (3.9)	2 (2.0)	0.605
Nausea	6 (11.8)	5 (4.9)	0.121	6 (11.8)	6 (6.1)	0.223
Vomiting	4 (7.8)	0 (0)	0.011	0 (0)	2 (2.0)	0.548
Diarrhea	2 (3.9)	6 (5.9)	0.719	4 (7.8)	7 (7.1)	0.864
Abdominal pain	2 (3.9)	3 (2.9)	1.000	4 (7.8)	6 (6.1)	0.735
Vertigo	6 (11.8)	4 (3.9)	0.085	8 (15.7)	6 (6.1)	0.055
Tremor	3 (5.9)	1 (1.0)	0.108	2 (3.9)	0 (0)	0.114
Headache	12 (23.5)	13 (12.7)	0.089	11 (21.6)	17 (17.2)	0.513
Fatigue	7 (13.7)	6 (5.9)	0.101	8 (15.7)	14 (14.1)	0.800
Sweating	3 (5.9)	3 (2.9)	0.401	3 (5.9)	1 (1.0)	0.114
Myalgia	6 (11.8)	3 (2.9)	0.061	9 (17.6)	12 (12.1)	0.356
Muscle weakness	8 (15.7)	4 (3.9)	0.021	8 (15.7)	5 (5.1)	0.028
Arthralgia	10 (19.6)	5 (4.9)	0.004	11 (21.6)	10 (10.1)	0.055
Back pain	11 (21.6)	7 (6.9)	0.008	7 (13.7)	12 (12.1)	0.780
Cough	3 (5.9)	6 (5.9)	1.000	3 (5.9)	9 (9.1)	0.752
Sneezing	3 (5.9)	6 (5.9)	1.000	9 (17.6)	11 (11.1)	0.265
Coryza	2 (3.9)	9 (8.8)	0.338	7 (13.7)	11 (11.1)	0.641
Stuffy nose	1 (2.0)	6 (5.9)	0.425	6 (11.8)	5 (5.1)	0.135
Sore throat	1 (2.0)	7 (6.9)	0.270	6 (11.8)	5 (5.1)	0.135
Shortness of breath	3 (5.9)	3 (2.9)	0.401	2 (3.9)	5 (5.1)	1.000
Conjunctivitis	1 (2.0)	0 (0)	0.333	2 (3.9)	1 (1.0)	0.267
Pruritus	3 (5.9)	2 (2.0)	0.334	5 (9.8)	4 (4.0)	0.274
Skin rash	1 (2.0)	0 (0)	0.333	2 (3.9)	0 (0)	0.114

Results are presented as *n* (%). *pSS*, primary Sjögren's syndrome

(AC-4)) in the majority of controls. Of note, 2/84 (2.4%) controls with negative ANA on D0 developed positive ANA after vaccination, one with nuclear homogeneous pattern (AC-1) and the other with multiple nuclear dots (AC-6).

During the study, there were 2/51 (3.9%) incident cases of RT-PCR confirmed COVID-19 in the pSS and 2/102 (2%) in the control groups ($p=0.601$), only one of them after the immune response time (after 10 days of the

Table 3 Seroconversion rates and anti-SARS-CoV-2 S1/S2 IgG titers before and after the first and second doses of CoronaVac vaccination in pSS patients and controls

	Before 1st dose (D0)	After 1st dose (D28)			After 2nd dose (D69)			
	GMT	SC	GMT	FI-GMT	SC	GMT	FI-GMT
pSS, $n=40$	2.5 (2.1–3.0)	5 (12.5)	4.9 (3.6–6.8)[c]	1.9 (1.4–2.7)	27 (67.5)	22.5 (14.6–34.5)[c]	8.9 (5.6–14.0)
Controls, $n=86$	2.1 (2.0–2.3)	24 (27.9)	9.0 (6.8–11.8)[d]	4.2 (3.3–5.4)	80 (93.0)	59.6 (51.1–69.4)[d]	27.4 (22.9–32.7)
p-value(pSS vs. controls)[a,b]	> 0.999	0.056	0.009	< 0.001	< 0.001	< 0.001	< 0.001

Results are expressed as mean (95% CI) or *n* (%)

pSS, primary Sjögren's syndrome; *SC*, seroconversion (defined as post vaccination titer ≥ 15 AU/mL—Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy); *GMT*, geometric mean titers (AU/mL); *FI-GMT*, factor increase of geometric mean titers; *CI*, confidence interval

[a]Frequencies of SC of anti-SARS-CoV-2 S1/S2 IgG were expressed as number (%), and they were compared through two-sided chi-square test between pSS and controls on D28 and D69

[b]Anti-SARS-CoV-2 S1/S2 IgG concentrations were expressed as GMT (95% CI), and neperian logarithm (ln)-transformed titers were compared between pSS and controls and between time-points (D0, D28, and D69) by means of generalized estimating equations (EEG) with normal marginal distribution and gamma distribution, respectively. Then, these results were analyzed by Bonferroni's multiple comparisons to recognize differences between the groups and timepoints

[c]$p < 0.001$ for longitudinal comparisons of GMT in pSS patients on D28 and D69 vs. D0

[d]$p < 0.001$ for longitudinal comparison of GMT in controls on D28 and D69 vs. D0

2nd dose). The other cases occurred before or 2 days after the 2nd dose. All of them had mild COVID-19, with no need for hospitalization.

Discussion

To our knowledge, this is the first prospective phase 4 controlled study of a COVID-19 vaccine specifically focused on pSS patients. The present trial evaluated an inactivated virus vaccine, Sinovac-CoronaVac, and revealed that it had an excellent safety profile and a moderate humoral response in pSS, albeit diminished compared to age- and sex-balanced controls. It was also observed that the current treatment with methotrexate negatively influenced the humoral response to vaccine. In contrast, disease activity showed no deleterious effect on the humoral response to the vaccine. Furthermore, it was shown that the clinical systemic activity index (clinESSDAI) and the anti-Ro(SS-A)/anti-La(SS-B) levels did not change after vaccination in a short-term analysis.

The present study has the advantage of including a balanced control group for age and sex, which are known factors that may affect vaccinal response in general [26] and also of mRNA vaccines for COVID-19 [18, 19]. Furthermore, serum samples for anti-SARS-Cov-2 IgG and NAb immunoassays were obtained at the same time for all pSS patients and controls, enabling a similar interval for production of vaccine-induced antibodies, which is a parameter that affects the SC rate [19]. The detection of NAb was also important, as recent studies have suggested that the neutralization levels are associated with protection against COVID-19 [27, 28]. Additionally, the prospective nature of the study, with three face-to-face visits; the use of a symptom diary; and the uninterrupted availability of communication with the responsible investigators by phone, WhatsApp, and e-mail allowed a rigorous analysis of adverse effects. In this regard, the possibility of activation of the underlying disease was also considered, and it was objectively assessed by an accepted index in the literature, clinESSDAI [29, 30].

A limitation of the present study is the convenience sample. In this aspect, the post hoc power analysis considering the SC rate of anti-SARS-Cov-2 S1/S2 IgG in pSS patients and controls after the 2nd dose of the vaccine was 93.7%, although based on positive NAb frequency, it was 63.2%.

The vaccine humoral response of pSS patients observed here was moderate, although significantly lower than age- and sex-balanced control participants. Importantly, the detailed analysis of the influence of current therapies on vaccine immunogenicity, including prednisone, different immunosuppressive drugs, and biological agents,

Table 4 Frequency of neutralizing antibodies (NAb) and median percentage of neutralizing activity in positive cases, after the first and second doses of CoronaVac vaccination in pSS patients in comparison to controls

	After 1st dose (D28)		After 2nd dose (D69)	
	Subjects with positive NAb *n* (%)	Neutralizing activity (%) Median (interquartile range)	Subjects with positive NAb *n* (%)	Neutralizing activity (%) Median (interquartile range)
pSS, $n=40$	4 (10)	35.1 (31.8–54.5)	21 (52.5)	58.6 (43.7–63.6)
Controls, $n=86$	26 (30.2)	46.9 (37.7–59.8)	63 (73.3)	64 (46.4–81.1)
p-value(pSS vs. controls)	0.014	0.190	0.021	0.219

Results are expressed as median (interquartile range) or *n* (%)

pSS, primary Sjögren's syndrome

Positivity for NAb defined as a neutralizing activity ≥ 30% (cPass sVNT Kit, GenScript, Piscataway, USA)

Table 5 Baseline (D0) characteristics of pSS patients with and without seroconversion (SC) for anti-SARS-CoV-2 S1/S2 IgG antibodies and with and without neutralizing antibodies (NAb) after two doses of CoronaVac vaccination

	pSS with SC ($n=27$)	pSS without SC ($n=13$)	*p*-value	pSS with NAbs ($n=21$)	pSS without NAbs ($n=19$)	*p*-value
Demographic characteristics						
Current age, years	53.8 ± 10.6	55.3 ± 11.0	0.683	53.8 ± 10.7	54.8 ± 10.8	0.763
Current age > 60 years	8 (29.6)	5 (38.5)	0.576	6 (28.6)	7 (36.8)	0.577
Female sex	27 (100)	12 (92.3)	0.325	21 (100)	18 (94.7)	0.475
White race	16 (59.3)	7 (53.8)	0.746	11 (52.4)	12 (63.2)	0.491
clinESSDAI	0 (0–14)	0 (0–8)	0.643	0 (0–14)	0 (0–8)	0.756
Current therapies						
Hydroxychloroquine	16 (59.3)	9 (69.2)	0.542	12 (57.1)	13 (68.4)	0.462
Prednisone	6 (22.2)	5 (38.5)	0.281	6 (28.6)	5 (26.3)	0.873
Prednisone dose, mg	10.0 ± 5.5	13.0 ± 10.4	0.552	10.0 ± 5.5	13.0 ± 10.4	0.552
Prednisone ≥ 10 mg/day	4 (14.8)	3 (23.1)	0.662	4 (19.0)	3 (15.8)	1.000
Immunosuppressive drugs	9 (33.3)	8 (61.5)	0.091	7 (33.3)	10 (52.6)	0.218
Azathioprine	5 (18.5)	3 (23.1)	1.000	3 (14.3)	5 (26.3)	0.442
Mycophenolate mofetil	3 (11.1)	3 (23.1)	0.370	3 (14.3)	3 (15.8)	1.000
Methotrexate	0 (0)	3 (23.1)	0.029	0 (0)	3 (15.8)	0.098
Leflunomide	1 (3.7)	0 (0)	1.000	1 (4.8)	0 (0)	1.000
Abatacept	1 (3.7)	0 (0)	1.000	1 (4.8)	0 (0)	1.000
Ustekinumab	0 (0)	1 (7.7)	0.325	0 (0)	1 (5.3)	0.475

Results are expressed as mean ± standard deviation, median (minimum and maximum values), or *n* (%)

pSS, primary Sjögren's syndrome; *clinESSDAI*, clinical European League Against Rheumatism (EULAR) Disease Activity Index

SC, seroconversion (defined as a positive anti-SARS-CoV-2 S1/S2 IgG test (≥ 15 AU/mL) after vaccination (Indirect ELISA, LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy))

Positivity for Nabs defined as a neutralizing activity ≥ 30% (cPass sVNT Kit, GenScript, Piscataway, USA)

showed that the current methotrexate usage was significantly associated with reduced SC rate of anti-IgG SARS-CoV-2 S1/S2 antibodies. Nevertheless, the small sample size precludes a definitive conclusion. In line with this possibility, methotrexate has been related to decreased humoral response to pneumococcal vaccine [31, 32] and may impair influenza vaccine immunogenicity [31] in rheumatoid arthritis (RA) patients. In this regard, the temporary discontinuation of this medication before and/or after influenza vaccination improved the immunogenicity in RA patients [33, 34]. Thus, it is possible that the temporary discontinuation of methotrexate (if the patient has a good control of the underlying disease) may also be a valid strategy in pSS for immunization against COVID-19, as recently suggested by the updated recommendations of the American College of Rheumatology (ACR) [35].

Of note, several medications used to treat ARD patients (such as prednisone, methotrexate, mycophenolate mofetil,

anti-TNF, abatacept, and rituximab) have been related to diminished humoral response to the Sinovac-CoronaVac vaccine [16] and also to the mRNA vaccine (Pfizer) (mycophenolate of mofetil, abatacept, and anti-CD20) [13]. Such studies evaluated larger cohorts with patients affected by different ARD [13, 16]. As a result of the small sample size of the present study specifically addressed to pSS, not all of these immunosuppressant drugs and biological agents are represented with an adequate number for analysis.

clinESSDAI values did not seem to influence the humoral response to vaccine. Similar findings were observed for systemic lupus erythematosus (SLE) patients evaluated using the SLEDAI (SLE Disease Activity Index) after mRNA and adenovirus vaccines [36].

With regard to adverse effects, despite higher frequencies of vomiting, muscle weakness, arthralgia, and back pain in pSS patients than in control individuals, vaccine-related adverse events were mild. Therefore, the vaccine had an excellent safety profile, as previously shown for the Sinovac-CoronaVac vaccine [16] and for the mRNA vaccines [13, 19, 36–39] in patients with rheumatic diseases.

The present study added an important analysis to the safety profile in pSS not evaluated in previous studies, that is, the systemic activity of the disease prospectively evaluated through an objective index (clinESSDAI). In this respect, no changes in this score were observed after vaccination, which expands the notion of vaccine safety.

Moreover, the present study assessed whether vaccine antigens could induce the production of autoantibodies, mainly anti-Ro(SS-A) and anti-La(SS-B). This issue is interesting, as it was recently demonstrated through post-mortem biopsies of patients with COVID-19 that this virus can infect the epithelial cells of the major salivary glands [40]. Thus, some authors postulate the hypothesis that SARS-CoV-2 infection could mimic or trigger pSS [41]. After immunization with Sinovac-CoronaVac vaccine, there was no induction of anti-Ro(SS-A) and anti-La(SS-B) antibodies in the pSS patients or control individuals, and low percentages of pSS patients and controls developed positive ANA.

In conclusion, Sinovac-CoronaVac is safe in pSS patients, without deleterious impact on disease activity, and has a moderate short-term humoral response, though lower than controls. Therefore, the strategy of a booster dose needs to be studied in these patients.

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Data availability All relevant data were included in the manuscript and tables, and the raw data will be supplied to interested investigators when requested. The protocol was registered in Clinicaltrials.gov (#NCT04754698).

Declarations

Ethics approval and consent This study was approved by the institutional and national ethics committees (Comissão Nacional de Ética em Pesquisa – CONEP) (CAAE 42566621.0.0000.0068). In addition, all participants signed an informed consent form before inclusion in the study.

Disclosures None.

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