Safety and efficacy of SARS-CoV-2 vaccination in 1237 patients with primary Sjögren syndrome

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Abstract

Objective

To investigate the safety and efficacy of SARS-Cov-2 vaccination in patients with primary Sjögren syndrome (pSS) due to scarcity of data in this population.

Methods

By the first week of May 2021, all Big Data SS Consortium centres patients who had received at least one dose of any SARS-CoV-2 vaccine were included in the study. The in-charge physician asked patients about local and systemic reactogenicity to collect SARS-CoV-2 vaccination data.

Results

The vaccination data of 1237 patients were received. A total of 835 patients (67%) reported any adverse events (AEs), including local (53%) and systemic (50%) AEs. Subjective symptoms (63%) were the most common local AEs, followed by objective signs at the injection site (16%), and general symptoms were the most commonly reported systemic AEs (46%), followed by musculoskeletal (25%), gastrointestinal (9%), cardiopulmonary (3%), and neurological (2%). In addition, 141 (11%) patients reported a significant worsening/exacerbation of their pre-vaccination sicca symptoms and fifteen (1.2%) patients reported active involvement in the glandular (n=7), articular (n=7), cutaneous (n=6), pulmonary (n=2), and peripheral nervous system (n=1) domains due to post-vaccination SS flares. In terms of vaccination efficacy, breakthrough SARS-CoV-2 infection was confirmed after vaccination in three (0.24 %) patients, and positive anti-SARS-Cov-2 antibodies were detected in approximately 95% of vaccinated SS patients, according to data available.

Conclusion

Our data suggest that patients with pSS develop adequate humoral response and no severe AEs after SARS-CoV-2 vaccination and therefore raise no concerns about the vaccine's efficacy or safety profile in this population.

Key words

primary Sjögren syndrome, SARS-CoV-2 vaccination, Sjögren Big Data Consortium, adverse events, disease flare

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Introduction

Primary Sjögren syndrome (pSS) is a systemic autoimmune disease overwhelmingly diagnosed in women (>95%) between 30 and 60 years of age (around 70%) (1). The key clinical feature is the dryness of mucosal surfaces reported by more than 95% of patients and accompanied by a wide variety of systemic manifestations, including the immune-mediated damage of internal organs in a significant number of cases (2). The pathogenesis of the disease is not yet fully elucidated, and there is a wide list of genetic and environmental factors potentially involved (3). Among environmental factors, immunisation and vaccination have been proposed as potential triggers of an autoimmune response against epithelial molecules that share structural similarities with microbial epitopes (molecular mimicry) (4). However, there are only 4 reported cases of SS/SS-like diagnosed after receiving H1N1, HBV, BCG and COVID-19 vaccination, respectively (5, 6).

In the pandemic scenario related to SARS-CoV-2 infection, COVID-19 vaccination played a game-changing role with an unprecedent worldwide immunisation programme. More than 65% of the world population received at least one dose of a COVID-19 vaccine at the end of April 2022 (7). Twenty-four vaccines are currently in use [COVID-19 vaccine tracker. Available from https://www.covid-19vaccinetracker.org. Accessed on April, 27 2022] based on different technology platforms (inactivated or weakened virus, protein-based, viral vector and RNA and DNA vaccines) and 11.438.720.838 vaccine doses have been administrated worldwide. People with systemic autoimmune diseases are considered at-risk for severe COVID-19 considering their underlying abnormal immune response and the frequent use of immunosuppressive drugs (8), and therefore were excluded from the pivotal prospective RCTs testing COVID-19 vaccines. However, except for patients with high disease activity, studies with a small number of patients with systemic autoimmune diseases show no increased risk of contracting SARS-CoV-2 or a worse prognosis of COVID-19 than individuals without RMDs, possibly explaining the increased risk seen for glucocorticoid use (9, 10). Recent large studies (Supplementary Table S1) have evaluated the safety and efficacy of COVID-19 vaccines in patients with immune-mediated diseases (11-18), but specific information in patients with SS is limited to single-centre, small-size cohorts of patients (19, 20). The objective of this study was to analyse the safety and efficacy of SARS-Cov-2 vaccination in a large international cohort of patients with SS.

Methods

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry designed in 2014 to take a worldwide picture of the main features of pSS using through a data-sharing cooperative merging of databases from leading centres in clinical research in SS from the five continents (3, 21). The centres share a harmonised data infrastructure and conduct cooperative online efforts in order to refine already-collected data and update prospective data in each centre. Inclusion criteria are the fulfilment of the 2002 classification criteria (22) and/or 2016 ACR/EULAR criteria (23). Exclusion criteria for considering SS as a primary disease included chronic HCV/HIV infection and associated systemic autoimmune diseases other than SS. The Registry was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Design and variables collected

By the first week of May 2021, all centres included in the Big Data Project were contacted via email by MRC asking for patients included in the Registry who received SARS-CoV-2 vaccination. Patients were eligible for inclusion if they have received at least one dose of any vaccine against SARS-CoV-2. The physician in charge asked the patients for local and systemic reactogenicity through a pre-defined electronic questionnaire including the following information: age at the time of first dose of vaccine; number of doses; previous

SARS-CoV-2 infection; type of vaccine; pre-vaccine modification of SS treatments; post-vaccination local side effects (signs and symptoms); duration of post-vaccination local side effects (days); post-vaccination systemic side effects (organ-specific classification)**;** duration of post-vaccination systemic side effects (days); specific management of side effects; post-vaccination worsening of sicca symptoms; post-vaccination systemic flare measured according to the EULAR Sjögren's syndrome disease activity index (ESSDAI) classification**;** efficacy of the vaccine (data of post-vaccination COVID-19 infection confirmed by polymerase chain reaction).

Adverse events

Local adverse events (AEs) were defined as those reported by the patient at the site of injection within 7 days from vaccination (reactogenicity), classified as local symptoms (pain, tenderness, parestesia and/or dysaesthesia) and signs (oedema, induration, swelling, erythema, rash, ecchymosis and/or haematoma at site infection, enlargement of regional lymph nodes). Systemic AEs were classified as generalised (fever, chills, dizziness, drowsiness, fatigue), musculoskeletal (arthralgia and/or myalgia), gastrointestinal (nausea, diarrhoea, decreased appetite and/or abdominal pain), cardiopulmonary (dyspnoea, palpitation, tachycardia, blood pressure changes, and/or chest pain), neurological (headache, confusion, lethargy, paraesthesia, dysesthesia, somnolence and/or tingling) and allergic (oedema in the face, arm and/or groin) symptoms. Post-vaccination AEs of special interest related to SS (SS flares) were classified as sicca-related (worsening of sicca features after vaccination) and systemic flares (development of organ-specific systemic activity fulfilling the corresponding ESSDAI definitions) (24). Severity of AEs was graded as mild (not requiring hospitalisation nor systemic medications), moderate (not requiring hospitalisation, but requiring systemic medications) and severe (resulting in hospitalisation, prolongation of existing hospitalisation, or death).

Table I. The main features of the 1237 patients with primary SS who received the SARS-CoV-2 vaccine.

Variables	N (%)
Epidemiological data	
Continent (n=1237)	
Europe	959 (77.6)
America	237 (19,2)
Others	41 (3.2)
Ethnicity (n=1172)	
White	1005 (85.8)
Hispanic	109 (9.3)
African American	34 (2.9)
Asian	24 (2)
Sex (n=1237)	
Women	1170 (94.6)
Men	67 (5.4)
Age (n=1235)	
Age at the time of first dose of vaccine (mean, SD)	60.3 ± 12.7
Age decades	
18-30	11 (1)
30-40	42 (4)
40-50	160 (14)
50-60	315 (26)
60-70	358 (30)
70-80	255 (21)
>80	48 (4)
COVID-19 Vaccination data	
Previous SARS-CoV-2 infection	83/1166 (7.1)
COVID-19 vaccine	
BNT162b2	679 (54.9)
ChAdOx1 nCov-19	240 (19.4)
Coronavac	135 (10.9)
CX-024414	132 (10.7)
Others	51 (4.1)
COVID-19 vaccine regimens	
Complete	1143 (92)
Incomplete	94 (8)
COVID-19 vaccination side effects	
Patients reporting side effects	835 (67)
Patients reporting local side effects	662 (53)
Number of local side effects (n=778)	
Pain/tenderness/paresthesia/dysaesthesia	491 (63)
Axillary lymph node swelling	13 (2)
Erythema/rash/echymosis/haematoma	57 (7)
Oedema/induration/swelling	70 (9)
Not specified	147 (19)
Duration of post-vaccination local side effects (n=886)	2.3 ± 4.8
Patients reporting systemic side effects	620 (50)
Number of systemic side effects (n=871)	
General (fever, diziness)	401 (46)
Musculoskeletal (body and joint pain, irritation, burning sensation)	214 (25)
Gastrointestinal (nausea, diarrhoea, decreased appetite)	78 (9)
Cardiopulmonary (dyspnoea, palpitation, tachycardia, blood pressure changes, monodor's disease, chest pain)	25 (3)
Neurological symptoms	18 (2)
Allergic reaction	2 (0.2)
Not specified	133 (15)
Duration of post-vaccination systemic side effects (n=907)	3.1 ± 7.0
Specific management of side effects (n=1648)	
Symptomatic treatment (analgesics, NSAIDs)	195 (12)
Systemic therapies (corticosteroids)	5 (0.3)
Topical therapies	5 (0.3)

Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. Univariate logistic regression analyses were performed to study the main features related to COVID-19 vaccination according to the following dichotomic variables: local side effects, systemic side effects, sicca worsening and systemic flares. Logistic multivariate regression models were constructed to analyse independent factors associated with side effects, sicca worsening and systemic flares. Variables with a $p<0.05$ in the univariate analyses were included in the models. Odds ratios (OR) and their 95% confidence intervals (95%CI) obtained in the logistic regression analysis were calculated. Forest plots were used to represent OR and 95%CI. To handle missing data due to non-evaluated features, "available case analysis" was assumed. All significance tests were two-tailed and values of $p<0.05$ were considered significant. All analyses were conducted using the R v. 3.6.1 for Windows statistical software package (https://www.R-project.org/).

Results

The email requesting for patients with pSS with COVID-19 vaccination was answered by 19 centres. By October 2021, we received vaccination data about 1237 patients (1170 women, mean age at diagnosis of pSS of 50.5±13.2). The frequencies of the main SS-related features were 92.2% for dry eye, 91.7% for dry mouth, 81.5% for abnormal ocular tests, 87.7% for abnormal oral diagnostic tests, 87.5% for positive minor salivary gland biopsy, 72.6% for anti-Ro antibodies and 40.5% for anti-La antibodies. The mean total ESSDAI score was 7.5 (range 0–48). Systemic involvements with the highest frequencies of active patients included the articular (27.4%), biological (24.5%), haematological (11%) and glandular (8.5%) ESSDAI domains at the time of the last visit before vaccination (Supplementary Table S2).

Table I summarises the main features of the 1237 patients with pSS who received at least one dose of any vaccine against SARS-CoV-2 (55% received the BNT162b2 vaccine, 19% the ChAdOx1 nCov-19 vaccine, 11% the CoronoVac, inactivated virus Covid-19 vaccine and 11% the mRNA-1273, CX-024414 COVID-19 mRNA vaccine). Any AEs was reported by 835 (67%) patients, including local (53%) and systemic (50%) AEs. The most common local AEs included subjective symptoms (63%), followed by objective signs at the injection site (16%). Thirteen vaccine recipients (2%) reported axillary lymph node swelling. Mean duration of post-vaccination local side effects was 2.3±4.8 days. With respect to systemic AEs, general symptoms were the most reported systemic AEs (46%), followed by musculoskeletal (25%), gastrointestinal (9%), cardiopulmonary (3%) and neurological (2%) symptoms. Only 2 (0.2%) patients complained about allergic reaction (oedema in the face, arm and/or groin). The mean duration of post-vaccination systemic AEs was 3.1±7.0 days. Symptomatic treatment with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) was required in 195 (12%) patients, and only 10 patients required topical (n=5) or systemic (n=5) glucocorticoids.

Table II shows the association between features at the time of vaccination and the risk of developing AEs. A significant difference for a higher odd of developing AEs after vaccination was identified in people aged 60 years or below (OR 2.48, CI 95% 1.89-3.27), with low systemic SS activity (OR 1.62, CI 95% 1.22-2.15) and having received mRNA vaccines (OR 1.57, CI 95% 1.12-2.18) in the multivariate analysis (Fig. 1). The same features were related to a higher odd of developing local AEs (Table III, Fig. 1), while the odd for developing systemic AEs was also higher in women (OR 2.85, CI 95% 1.60-5.34), White people (OR 1.73, CI 95% 1.14-2.65), and those who are only receiving one dose despite the fact that the scheme includes two (OR 1.78, CI 95% 1.12-2.88) (Table IV, Fig. 1). Supplementary Figure S1 summarises the distribution of AEs (only local, systemic, and none) stratified according to the ESSDAI activity at the time of the first shot (no activity, low, moderate, and high).

With respect to post-vaccination SS flares, 141 (11%) patients reported a significant worsening/exacerbation of their pre-vaccination sicca symptoms. Multivariate analysis identified that patients showing SS-related autoantibodies were at lower risk of developing a post-vaccination exacerbation of sicca features (OR 0.58, CI 95% 0.40-0.86) (Suppl. Table S3). Post-vaccination systemic SS flares in clinical ESSDAI domains were reported in 15 (1.2%) patients (13 women, mean age at vaccination of 41.9 years), including active involvement in the glandular (n=6), articular (n=5), cutaneous (n=5) (Fig. 2), pulmonary (n=1) and peripheral nervous system (n=1) domains (Suppl. Table S4). Among the 18 reported episodes of flares, 11 (65%) consisted of an exacerbation of an already-diagnosed systemic involvement and 7 (35%) were new systemic involvements. The vaccines related to systemic flares included the

Table II. The relationship between SS patient characteristics at vaccination and the risk of developing adverse events.

Variables	Adverse events (total)			
	No (n=385)	Yes (n=835)	OR [95% CI]	Multivariate OR [95% CI]
Mean age at vaccination	64.5 ± 12.7	58.5 ± 12.2	**0.96 [0.95-0.97]**	
Age (<60 years)	120/384 (31.2)	433/834 (51.9)	**2.38 [1.84-3.07]**	**2.48 [1.89-3.27]**
Sex (women)	359 (93.2)	794 (95.1)	1.40 [0.84-2.31]	
Ethnicity (white)	308/369 (83.5)	692/786 (88.0)	**1.46 [1.02-2.06]**	1.21 [0.76-1.92]
Country (Europe)	280 (72.7)	677 (81.1)	**1.61 [1.21-2.13]**	1.16 [0.75-1.79]
Anti-Ro/La (+)	290 (75.3)	611 (73.2)	0.89 [0.67-1.18]	
Mean ESSDAI at vaccination	3.8 ± 4.7	2.9 ± 4.4	**0.96 [0.93-0.98]**	
Disease activity state (low)	246/369 (66.7)	634/818 (77.5)	**1.72 [1.31-2.26]**	**1.62 [1.22-2.15]**
Previous SARS CoV2 infection	23/331 (6.9)	58/818 (7.1)	1.02 [0.63-1.72]	
Vaccine type (RNA)	221 (57.4)	584 (69.9)	**1.73 [1.34-2.22]**	**1.57 [1.12-2.18]**
Vaccine regimen (incomplete)	28 (7.3)	64 (7.7)	0.94 [0.59-1.48]	

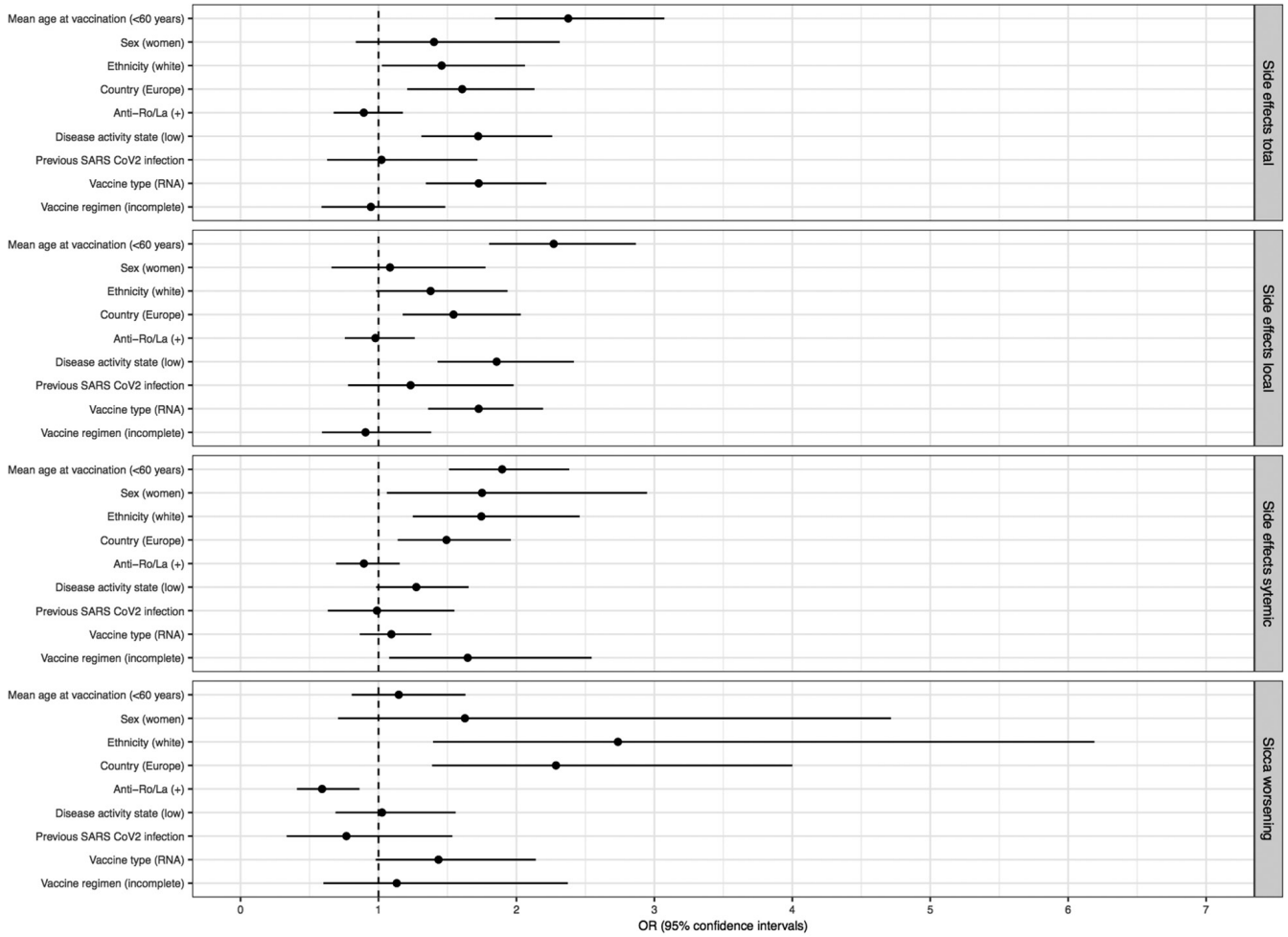

Fig. 1. Prognostic factors for adverse events (total, local, systemic and sicca worsening) after COVID-19 vaccination in 1237 patients with pSS.

BNT162b2 (n=10), ChAdOx1 nCoV-19 (n=3) and CoronaVac (n=2) vaccines; flares were reported after the first shot in 8 patients, in 6 after the second shot, and in one patient with both shots. ESSDAI severity of systemic flares was categorised as low in 7 cases, moderate in 7 and high in the remaining 3 flares. Therapeutic management of systemic flares included symptomatic therapy (n=6) and glucocorticoids (n=12) not requiring hospital admission, and all flares resolved after 1–3 weeks with no significant sequelae or death.

Postvaccination breakthrough SARS-CoV-2 infection was confirmed in 3 (0.24%) patients. In the first case, the patient developed symptomatic infection 4 days after the first dose of BNT162b2 vaccine, requiring hospitalisation and being discharged after recovering from infection. The second case developed symptoms on the 13 days after the first shot of SinoVac vaccine and fully recovered without requiring hospitalisation. The third case presented with symptomatic infection 3 days after the first dose of ChAdOx1 nCoV-19 vaccine and fully recovered without requiring hospitalisation. Information about post-vaccine anti-SARS-CoV-2 antibody level was available in 258 patients, with 241 (93%) being positive. Other post-vaccination outcomes that were reported were considered unrelated to SS, including one patient diagnosed with lung cancer 8 weeks after completing vaccination, two patients diagnosed with new onset type II diabetes mellitus, and one patient who developed herpes zoster. No deaths were reported among vaccine recipients during the post-vaccination follow-up.

Discussion

Vaccination campaigns are a key public health strategy whose immediate goal is preventing the dissemination of an infectious disease in individuals and populations, with the ultimate goal to achieve the eradication of the disease in humans (25). Active vaccination provides a safer "artificial" contact with the pathogen in replacement of the natural primary infection, not producing the disease yet providing a pathogen-related immunogen able to induce a long-lasting protection (26). Administration of vaccines, like all other prescription drugs, may be followed by adverse events, defined as any unfavourable or unintended sign, including the development of abnormal laboratory findings, symptoms or diseases. The safety of vaccines is a priority, particularly in worldwide preventive programmes, and the general public worldwide has great concerns about adverse reactions, especially about severe vaccine-associated AEs, leading to a widespread lack of trust in the evidence-based benefit-risk considerations in vaccination programmes (27).

Table III. The relationship between SS patient characteristics at vaccination and the risk of developing local adverse events.

Variables	Adverse events (local)			
	No (n=561)	Yes (n=662)	OR [95% CI]	Multivariate OR [95% CI]
Mean age at vaccination	63.3 ± 12.6	57.8 ± 12.1	**0.96 [0.95-0.97]**	
Age (<60 years)	194/559 (34.7)	362 (54.7)	**2.27 [1.80-2.87]**	**2.26 [1.78-2.88]**
Sex (women)	529 (94.3)	627 (94.7)	1.08 [0.66-1.78]	
Ethnicity (white)	453/536 (84.5)	549/622 (88.3)	1.38 [0.98-1.94]	
Country (Europe)	417 (74.3)	541 (81.7)	**1.54 [1.18-2.03]**	1.15 [0.80-1.66]
Anti-Ro/La (+)	416 (74.2)	488 (73.7)	0.98 [0.76-1.26]	
Mean ESSDAI at vaccination	3.7 ± 4.5	2.8 ± 4.5	**0.96 [0.93-0.98]**	
Disease activity state (low)	365/539 (67.7)	518/651 (79.6)	**1.86 [1.43-2.42]**	**1.77 [1.35-2.32]**
Previous SARS CoV2 infection	31/495 (6.3)	50/657 (7.6)	1.23 [0.78-1.98]	
Vaccine type (RNA)	333 (59.4)	474 (71.6)	**1.73 [1.36-2.19]**	**1.55 [1.14-2.11]**
Vaccine regimen (incomplete)	41 (7.3)	53 (8.0)	0.91 [0.59-1.38]	

Table IV. The relationship between SS patient characteristics at vaccination and the risk of developing systemic adverse events.

Variables	Adverse events (systemic)			
	No (n=613)	Yes (n=620)	OR [95% CI]	Multivariate OR [95% CI]
Mean age at vaccination	62.9 ± 12.4	57.9 ± 12.4	**0.97 [0.96-0.98]**	
Age (<60 years))	230/612 (37.6)	330/619 (53.3)	**1.90 [1.51-2.38]**	**2.10 [1.65-2.68]**
Sex (women)	571 (93.1)	595 (96.0)	**1.75 [1.06-2.95]**	**2.85 [1.60-5.34]**
Ethnicity (white)	491/595 (82.5)	511/573 (89.2)	**1.75 [1.25-2.46]**	**1.73 [1.14-2.65]**
Country (Europe)	455 (74.2)	503 (81.1)	**1.49 [1.14-1.96]**	1.09 [0.77-1.55]
Anti-Ro/La (+)	461 (75.2)	453 (73.1)	0.89 [0.69-1.15]	
Mean ESSDAI at vaccination	3.4 ± 4.6	3.0 ± 4.4	0.98 [0.96-1.01]	
Disease activity state (low)	425/590 (72.0)	466/608 (76.6)	1.27 [0.98-1.65]	
Previous SARS CoV2 infection	40/557 (7.2)	43/605 (7.1)	0.99 [0.63-1.55]	
Vaccine type (RNA)	396 (64.6)	413 (66.6)	1.09 [0.86-1.38]	
Vaccine regimen (incomplete)	58 (9.5)	37 (6.0)	**1.65 [1.08-2.55]**	**1.78 [1.12-2.88]**

COVID-19 vaccination programme is the greatest example of worldwide immunisation until now. Various studies have been focused in the analysis of safety and efficacy of COVID-19 vaccines in people with various immune-mediated inflammatory diseases (Suppl. Table S1) (11-18). In all these studies, inflammatory arthritis represented more than 50% of people included, with SS representing only 5-15% of cases. Two case-control studies focused on SS evaluating around 50 patients each have been recently published reporting no specific safety signals (19, 20).

This is one of the largest reported series of vaccinated patients affected by a specific systemic autoimmune disease, with very few studies evaluating until now more than 1000 patients to date (28). Our data showed that pSS patients frequently experienced reactions following vaccination including mainly pain and other local reactogenicity (63%), fever and other general symptoms (46%), and arthralgias/myalgias (25%). The frequency of total AEs in IMID patients ranges widely in the different studies from 41% to 87% (Supplementary Table S1), and we found a frequency of 67.5%, that is in the mid of this interval. Regarding local and systemic AEs both the profile and frequency of AEs were similar with respect to other studies evaluating IMID patients. The other factor related to a higher odd of developing AEs in our study was having an age at vaccination <60 years, while women and people with a White ethnicity had a higher odd of developing systemic AEs. With respect to the frequency and type of AEs among vaccine types, we found that mRNA recipients had a higher odd of developing AEs due to the 1.5-fold high odd of developing local AEs, a feature previously reported in other studies (13). The higher frequencies of general and musculoskeletal symptoms post-vaccination have also been reported in vaccinated patients with systemic lupus erythematosus and rheumatoid arthritis, and some studies have suggested that since all these symptoms are common to the underlying autoimmune disease, patients could be more prone to report these symptoms following vaccination (29), as recently also reported in patients with pSS (19). Despite the higher figures of reactogenicity, only 12% of our vaccinated patients required symptomatic treatment, and only 0.3% systemic therapies.

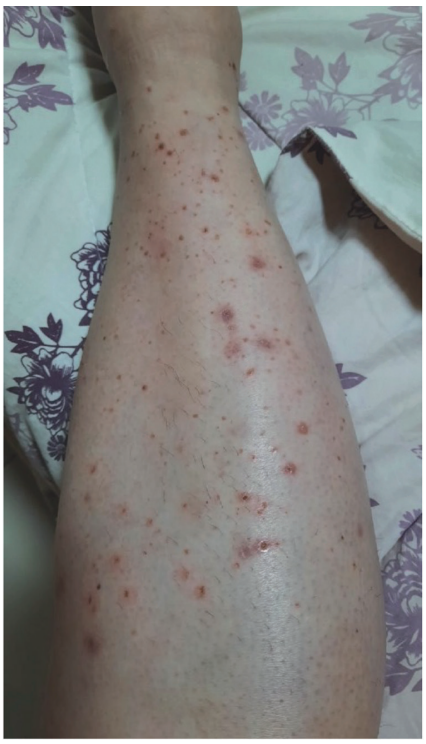

Fig. 2. Diffuse purpura in a 39-year-old woman with pSS 7 days after receiving the first shot of ChAdOx1 nCoV-19 vaccine.

With respect to SS-related features, a positive result in Ro/La autoantibodies did not influence the safety rates of vaccination, while systemic activity at the time of vaccination was inversely related to the risk of AEs, especially for local AEs. There are no previous studies focused on investigating a potential association between disease activity at the time of vaccination and rates of AEs. It has been postulated that vaccination could induce a polyclonal B-cell activation that might favour a higher frequency of side effects, or even an increase in baseline disease activity after vaccination in pSS (19). However, Verstappen *et al*. (19) reported

that both the median baseline EULAR Sjögren's syndrome patient reported index (ESSPRI) and ESSDAI scores did not change after vaccination, and no significant changes were observed for serum IgG or anti-Ro52/Ro60 antibody levels. In fact, we found a rate of post-vaccination flares of 11%, which is comparable to that reported in other immune mediated inflammatory diseases (ranging from 3.4% to 15.9%) (Suppl. Table S1). In pSS, flares were overwhelmingly related to a worsening of sicca features, with systemic flares rarely occurring and being more frequently related to an exacerbation of previous systemic activity (overwhelmingly in the glandular, articular and cutaneous ESSDAI domains). In line with other post-vaccination studies, no patient with systemic flare required hospitalisation or intense immunosuppression, as has been reported in other post-vaccination studies (30). Interestingly we did not find any severe haematological flare consisting of haemolytic anaemia or immune thrombocytopenia, considering the reported case of a subclinical SS that becomes clinically apparent after severe immune thrombocytopenic purpura following administration of the first COVID-19 vaccine dose, that could be act as a trigger in an asymptomatic carrier of anti-Ro antibodies (6).

While the primary aim of our study was to collect safety data among pSS patients receiving vaccines against SARS-CoV-2, we also collected information about efficacy. Among patients with available data about anti-SARS-Cov-2 antibodies, we detected a positive result in nearly 95% of patients, confirming the results recently reported by Verstappen *et al*. (19), that also reported that the increase in spike-specific IFN-γ producing SFCs from pre-vaccination to postvaccination was comparable between SS patients and controls. With respect to breakthrough infections, we found a frequency of 0.2%, a figure in line of that reported in the largest reported series of IMID patients by Machado *et al*. (1%) (11) who found that more than half of fully vaccinated individuals with breakthrough infections requiring hospitalisation were on mycophenolate or B-cell depleting agents (31).

In summary, we retrospectively evaluated the post-vaccination data of 1237 patients with pSS who received SARS-CoV-2 vaccinations and no major safety concerns emerged. Local and systemic reactions were common, but these were consistent with expected vaccine reactogenicity. Eleven percent of participants reported flares of their underlying disease, overwhelmingly related to a worsening of underlying sicca symptoms, with systemic flares being reported in 1% of patients (mostly were reactivations of already-diagnosed systemic involvements). There were no reports of severe disease flare, and no patient required intravenous therapy or hospitalisation. Therefore, COVID-19 vaccination should be considered safe in pSS following previous data that reported an adequate response and no safety signals with other vaccines (32-34). There are no findings that warranted any specific concern about the safety of SARS-CoV-2 vaccination in patients with pSS.

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