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ORIGINAL ARTICLE

An Argentinean cohort of patients with rheumatic and immune-mediated diseases vaccinated for SARS-CoV-2: the SAR-CoVAC Registry—protocol and preliminary data

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Abstract

Background/objective To evaluate the efficacy and safety of SARS-CoV-2 vaccine in patients with rheumatic and immune-mediated inflammatory diseases (IMIDs) in Argentina: the SAR-CoVAC registry.

Methods SAR-CoVAC is a national, multicenter, and observational registry. Adult patients with rheumatic or IMIDs vaccinated for SARS-CoV-2 were consecutively included between June 1 and September 17, 2021. Sociodemographic data, comorbidities, underlying rheumatic or IMIDs, treatments received, their modification prior to vaccination, and history of SARS-CoV-2 infection were recorded. In addition, date and place of vaccination, type of vaccine applied, scheme, adverse events (AE), disease flares, and new immune-mediated manifestations related to the vaccine were analyzed.

Results A total of 1234 patients were included, 79% were female, with a mean age of 57.8 (SD 14.1) years. The most frequent diseases were rheumatoid arthritis (41.2%), osteoarthritis (14.5%), psoriasis (12.7%), and spondyloarthritis (12.3%). Most of them were in remission (28.5%) or low disease activity (41.4%). At the time of vaccination, 21% were receiving glucocorticoid treatment, 35.7% methotrexate, 29.7% biological (b) disease modifying anti-rheumatic drugs (DMARD), and 5.4% JAK inhibitors. In total, 16.9% had SARS-CoV-2 infection before the first vaccine dose. Most patients (51.1%) received Gam-COVID-Vac as the first vaccine dose, followed by ChAdOx1 nCoV-19 (32.8%) and BBIBP-CorV (14.5%). Half of them (48.8%) were fully vaccinated with 2 doses; 12.5% received combined schemes, being the most frequent Gam-COVID-Vac/mRAN-1273. The median time between doses was 51 days (IQR 53). After the first dose, 25.9% of the patients reported at least one AE and 15.9% after the second, being flu-like syndrome and local hypersensitivity the most frequent manifestations. There was one case of anaphylaxis. Regarding efficacy, 63 events of SARS-CoV-2 infection were reported after vaccination, 19% occurred during the first 14 days post-vaccination, 57.1% after the first dose, and 23.8% after the second. Most cases (85.9%) were asymptomatic or mild and 2 died due to COVID-19.

Conclusions In this national cohort of patients, the most common vaccines used were Gam-COVID-Vac and ChAdOx1 nCoV-19. A quarter of the patients presented an AE and 5.1% presented SARS-CoV-2 infection after vaccination, in most cases mild.

Study registration This study has been registered in ClinicalTrials.gov under the number: NCT04845997.

Extended author information available on the last page of the article

Key Points
- *This study shows real-world data about efficacy and safety of SARS-CoV-2 vaccination in patients with rheumatic and immune-mediated inflammatory diseases. Interestingly, different types of vaccines were used including vector-based, mRNA, and inactivated vaccines, and mixed regimens were enabled.*
- *A quarter of the patients presented an adverse event. The incidence of adverse events was significantly higher in those receiving mRAN-1273 and ChAdOx1 nCoV-19.*
- *In this cohort, 5.1% presented SARS-CoV-2 infection after vaccination, in most cases mild.*

Keywords Argentina · COVID-19 · SARS-CoV-2 · Rheumatic diseases · Vaccines

Introduction

After the SARS-CoV-2 infection outbreak in 2019 [1], multiple research groups have focused their work in designing and developing vaccines, which are now one of the most important tools to decrease viral dissemination and avoid severe forms of COVID-19 [2].

In Argentina, the vaccination campaign against COVID-19 is voluntary and it is performed according to the Strategic Plan for COVID-19 Vaccination provided by the Ministry of Health, which sets out staggered priorities for identifying the target population based on exposure risk, risk of serious illness, and vulnerability [3, 4]. It started in December 2020 and as of October 2021, more than 32 million people were vaccinated with the first dose and 25 million with the second one [5]. At first, three vaccines were approved in our country: Gam-COVID-Vac, ChAdOx1 nCoV-19, and BBIBP-CorV. Afterwards, mRAN-1273, BNT162b2, and Ad5-nCoV were also authorized and are now available [6].

Patients with immune-mediated diseases are a special population, as they have been associated with increased risk of viral infections both related to the intrinsic risk associated with their disease and secondly to the treatments used [7, 8]. Another interesting point is the role of immunosuppressive and immunomodulatory drugs on the efficacy and safety of vaccines. Although no controlled and randomized trials were published, real-world data has shown lower seropositivity rates in patients with immune-mediated diseases compared to healthy controls, particularly those treated with glucocorticoids, rituximab, mycophenolate mofetil, abatacept, and methotrexate [9, 10].

Even though at first vaccination of patients with immune-mediated diseases in our country was contraindicated due to the lack of evidence, the Ministry of Health issued a statement in June 2021 authorizing the vaccination of pregnant and breastfeeding women, immunosuppressed patients, or those with rheumatic diseases [11]. This new strategy led to an increase in medical consultations to decide the benefit-risk balance of vaccination for each individual case. However, there is scarce information on the efficacy and safety of vaccination in our patients with immune-mediated diseases and/or under immunosuppressive treatment, particularly in relation to the vaccines applied in our country. For this reason, the Argentine Society of Rheumatology (SAR) in collaboration with the Argentine Society of Psoriasis (SOARPSO) set out to develop a national register of patients with rheumatic and immune-mediated inflammatory diseases (IMIDs) who received a SARS-CoV-2 vaccine (SAR-CoVAC) in order to assess their efficacy and safety.

We report baseline characteristics, safety profile, and efficacy of the COVID-19 vaccines in Argentina among patients with IMIDs included in the SAR-CoVAC registry.

Methods

Study design

SAR-CoVAC is a national, multicenter, observational, longitudinal registry of consecutive patients with rheumatic or IMIDs who have been vaccinated for SARS-CoV-2 in Argentina or any other country. All the included patients are followed for a period of 12 months. Baseline evaluation took place after the SARS-CoV-2 vaccine application (full scheme or partial scheme if there were any contraindications or difficulties in completing it). Sociodemographic data, characteristics, and severity of rheumatic or IMID, treatments received, and their modification prior to vaccination and history of SARS-CoV-2 infection were recorded. In addition, the date and place of vaccination, type of vaccine applied, scheme, and indication were registered. Finally, adverse events, disease flares, and new immune-mediated manifestations related to the vaccine were taken into consideration. The second evaluation will be performed after 12 months (±90 days) of the application of the last dose of the vaccine and will aim to detect adverse events, development of new long-term immune-mediated manifestations, rate, and severity of SARS-CoV-2 infection.

The inclusion phase started on June 1, 2021. For this analysis, the data from the baseline visit collected until September 17, 2021, was used. This trial was registered at ClinicalTrials.gov (NCT04845997) in May 2021.

Center selection

An invitation to participate in this registry was sent to all rheumatologists affiliated to SAR and dermatologists affiliated to SOARPSO. This information was delivered through the usual information channels including e-mail, website, and scientific events.

Currently, 68 researchers have registered to collaborate with the project and over 1200 patients have been included.

Participants and eligibility criteria

Criteria for inclusion were adult patients (age 18 or older) with a prior diagnosis of immune-mediated or rheumatic disease, according to the American College of Rheumatology (ACR) or European League against Rheumatism (EULAR) criteria (Supplementary Table 1). Patients were included regardless of their therapy in order to assure inclusion of patients with immunomodulatory and/or immunosuppressive drugs (Supplementary Table 2). All patients received at least one dose of a SARS-CoV-2 vaccine (Supplementary Table 3) in Argentina or in any other country. All patients gave written informed consent.

This is a non-probability sampling study with enrollment of consecutive patients who met the selection criteria.

Study variables

During the first phase of this registry, sociodemographic data was collected, including age, sex, city of residence, socioeconomic level according to the Graffar scale [12], years of scholarship, occupation, and health insurance, categorized into four different groups: private health plus social security, private health, social security, and public health. Ethnicity was defined according to the parents' and all 4 grandparents' self-reported ethnicity as follows: Caucasian: individuals with all white European ancestors; Mestizo: individuals born in Latin America who had both Amerindian and white ancestors; African-Latin Americans: individuals born in Latin America with at least one African ancestor irrespective of whether other ancestors were white or Amerindian; and others. Moreover, the presence of comorbidities, like hypertension, diabetes, obesity, dyslipidemia, pulmonary, cardiovascular, cerebrovascular, neurologic, hepatic and renal chronic diseases, malignant neoplasm, organ transplant, immunodeficiency, and psychiatric disorders, was documented. In relation to the underlying immune-mediated disease, diagnosis date and treatment (glucocorticoids, immunosuppressive, and/or immunomodulatory drugs taken for at least three months) (Supplementary Table 2) were registered, as well as treatment suspension or dose reduction before and after vaccination. Disease activity at vaccine application was evaluated using patient and physician global assessments, by a numerical visual scale (0–10 cm) and according to physician criteria reported as remission, low, moderate, or high disease activity. History of SARS-CoV-2 infection previous vaccination and severity (WHO Ordinal Scale for Clinical Improvement [13]) were registered.

Regarding SARS-CoV-2 vaccination, date, place, vaccine type (Supplementary Table 3), prescription (rheumatologist, dermatologist, general physician, other specialty or patient's decision), and causes of incomplete scheme when applicable were recorded.

AE were registered during the medical appointment, either on-site or virtual, at the baseline visit. Development of AE after the first and second doses, date, characteristics, and severity were described. They were classified as follows: local hypersensitivity (pain, warm, swelling at the injection site), flu-like syndrome (chills, fever, arthralgia, myalgia, asthenia, malaise, headache), systemic symptoms (hypersensitivity, seizures, anaphylaxis, or other). Furthermore, disease flares and new immune-mediated manifestation after vaccination were considered. In all cases, the Naranjo scale [14] was used to determine the possible association of the event with vaccination. Finally, SARS-CoV-2 infection after vaccination, date, diagnostic method, and severity (WHO Ordinal Scale for Clinical Improvement [13]) were documented.

Data management and monitoring

All variables were collected through patient interrogation either face-to-face, virtual, or by telephone and the review of medical records, according to availability, with the authorization of the patient once having signed the informed consent. The data was entered into the ARTHROS eCRF (online application designed ad hoc), which in turn facilitated the generation of queries and the statistical analysis.

A Data Control Committee (DCC) was created to guarantee quality information and to avoid potential data loss. A person specifically hired and trained to detect inconsistencies generated queries to the investigators at each participating center in case of the presence of missing or incorrect data. In addition, ARTHROS eCRF has filters that prevent the entry of unreliable data.

Ethical considerations

The study protocol and its corresponding informed consent form were approved by an independent ethics committee. All patients signed the informed consent before data collection.

This study was conducted in accordance with Good Clinical Practice (GCP) guidelines, the International Conference on Harmonization (ICH), the ethical principles established in the Declaration of Helsinki, the law 3301/09, and the guidelines of the local ethics committee. Personal identification data was kept anonymous and protected according to international and national regulations in order to guarantee confidentiality, in accordance with the Law on Protection of Personal Data No. 25.326/2000.

For the purposes of this project, only medical researchers had access to patients' medical records in order to obtain the data required for the investigation, thus ensuring their confidentiality. The data extracted from medical records was downloaded into a database where the patient's anonymity was guaranteed using an identification number.

Statistical analysis

Descriptive analysis of sociodemographic and clinical data was carried out. Continuous variables are expressed as mean and standard deviation when the distribution was considered normal, or as median and interquartile range otherwise. Categorical variables are presented as frequencies and percentages.

The incidence of AE for the most used vaccines is described as the number of events/1000 doses applied. To compare the incidence of AE and the types of AE between vaccines, Chi [2] test was used.

Efficacy was evaluated according to the number of SARS-CoV-2 infections events after vaccination and its severity. They were classified as follows: (A) events without protection: between 0 and 14 days after the first dose; (B) events after the first dose: > 14 days after the first dose and before the second dose; (C) events after the second dose: after the second dose application. The association between events B and C with sociodemographic and clinical variables was analyzed using Chi [2] or Fisher's exact test, as appropriate. A $p < 0.05$ was considered significant. All statistical analyses and model development were performed with R version 4.0.0 (Free Software Foundation, Inc., Boston, USA).

Results

A total of 1234 patients were included; 79% were female, with a mean age of 57.8 (SD 14.1) years old. Most of them were Caucasian (56.6%) with medium socioeconomic status (53.2%) and 87.1% had social security and/or private health insurance. Median years of schooling was 12 (IQR 7). The most frequent immune-mediated diseases were rheumatoid arthritis (41.2%), psoriasis (12.7%), and spondyloarthritis (12.3%). Additionally, 14.5% presented osteoarthritis. Most of them were in remission (28.5%) or low disease activity (41.4%). At the time of vaccination, 21% were receiving glucocorticoid treatment, 35.7% methotrexate, 29.7% biological (b) disease-modifying anti-rheumatic drugs (DMARD), and 5.4% JAK inhibitors. Half of them (51.2%) had comorbidities, the most frequent arterial hypertension, dyslipidemia, and obesity (Table 1). Before vaccine application, 16.9% had a previous SARS-CoV-2 infection.

Regarding the first dose of the vaccine, the majority (51.1%) received Gam-COVID-Vac vaccine, followed by

Table 1 Baseline characteristics of 1234 patients from the SAR-CoVAC registry

Variables	Patients ($n = 1234$)
Female sex, *n* (%)	975 (79)
Age (years), *X* (DE)	57.8 (14.1)
Ethnicity	
Caucasian, *n* (%)	698 (56.6)
Mestizo, *n* (%)	494 (40)
Others, *n* (%)	15 (1.2)
Unknown, *n* (%)	27 (2.2)
Socioeconomic level	
High, *n* (%)	35 (2.8)
Medium–high, *n* (%)	239 (19.4)
Medium, *n* (%)	656 (53.2)
Medium–low, *n* (%)	223 (18.1)
Low, *n* (%)	54 (4.4)
Unknown, *n* (%)	27 (2.1)
Education (years), *m* (Q1,Q3)	12.0 (10, 17)
Health insurance	
Social security, *n* (%)	643 (52.1)
Private health, *n* (%)	372 (30.1)
Private health + social security, *n* (%)	61 (4.9)
Public health, *n* (%)	144 (11.7)
Unknown, *n* (%)	14 (1.2)
Rheumatic disease	
Rheumatoid arthritis, *n* (%)	508 (41.2)
Psoriasis, *n* (%)	158 (12.7)
Spondyloarthritis, *n* (%)	152 (12.3)
Systemic lupus erythematosus, *n* (%)	113 (9.2)
Sjögren syndrome, *n* (%)	45 (3.7)
Systemic sclerosis, *n* (%)	36 (2.9)
Vasculitis, *n* (%)	16 (1.3)
Antiphospholipid syndrome, *n* (%)	14 (1.1)
Inflammatory myopathy, *n* (%)	13 (1.1)
Osteoarthritis, *n* (%)	179 (14.5)
Fibromyalgia, *n* (%)	39 (3.2)
Disease duration (years), *m* (Q1,Q3)	8 (4.16)
Disease activity	
Remission, *n* (%)	352 (28.5)
Low disease activity, *n* (%)	511 (41.4)
Moderate disease activity, *n* (%)	229 (18.6)
High disease activity, *n* (%)	39 (3.2)
Unknown/not applicable, *n* (%)	103 (8.3)
Treatment	
Glucocorticoids, *n* (%)	256 (21)
Glucocorticoids dose (mg equivalent to prednisone), *m* (Q1,Q3)	5 (5,5)
Topical treatment for psoriasis	
Glucocorticoid, *n* (%)	24 (1.9)
Calcipotriol/calcitriol, *n* (%)	4 (0.3)
Calcipotriol/calcitriol + glucocorticoid, *n* (%)	3 (0.2)

Table 1 (continued)

Variables	Patients ($n=1234$)
Coaltar, *n* (%)	2 (0.2)
Salicylic acid, *n* (%)	5 (0.4)
Salicylic acid + glucocorticoid, *n* (%)	1 (0.1)
Tazarotene, *n* (%)	0 (0)
Tacrolimus/pimecrolimus, *n* (%)	0 (0)
Phototherapy, *n* (%)	2 (0.2)
Immunosuppressor/immunomodulator	
Methotrexate, *n* (%)	440 (35.7)
Antimalarials, *n* (%)	168 (13.6)
Leflunomide, *n* (%)	93 (7.5)
Mycophenolate mofetil/mycophenolic acid, *n* (%)	37 (3)
Azathioprine, *n* (%)	30 (2.4)
Sulfasalazine, *n* (%)	8 (0.6)
Acitretine, *n* (%)	7 (0.6)
Cyclosporine, *n* (%)	0 (0)
Cyclophosphamide, *n* (%)	3 (0.2)
Tacrolimus, *n* (%)	2 (0.2)
Antifibrotics, *n* (%)	13 (1.1)
TNF α inhibitors, *n* (%)	210 (17)
IL-17 inhibitors, *n* (%)	54 (4.4)
IL-6 inhibitors, *n* (%)	30 (2.4)
IL-23 or IL-12/23 inhibitors, *n* (%)	26 (2.1)
Abatacept, *n* (%)	28 (2.3)
Rituximab, *n* (%)	15 (1.2)
Belimumab, *n* (%)	3 (0.2)
IL-1 inhibitors, *n* (%)	0 (0)
JAK inhibitors, *n* (%)	67 (5.4)
Apremilast, *n* (%)	7 (0.6)
Denosumab, *n* (%)	17 (1.4)
Comorbidities, *n* (%)	617 (51.2)
Arterial hypertension, *n* (%)	345 (27.9)
Dyslipidemia, *n* (%)	201 (16.3)
Obesity, *n* (%)	149 (12.1)
Diabetes, *n* (%)	113 (20.8)
Lung disease, *n* (%)	108 (8.7)
Cardiovascular or cerebrovascular disease, *n* (%)	46 (3.7)
Cancer, *n* (%)	28 (5.3)
Chronic kidney failure, *n* (%)	7 (1.3)
Smoking status	
Active, *n* (%)	89 (7.2)
Former smoker, *n* (%)	247 (20)
Never, *n* (%)	814 (65.9)
Unknown, *n* (%)	84 (6.8)

n, number; *X*, mean; *SD*, standard deviation; *m*, median; *Q*, quartile

ChAdOx1 nCoV-19 (32.8%) and BBIBP-CorV (14.5%) and to a lesser extent Comirnaty (0.6%), Janssen (0.2%), and SinoVac (0.2%). In 51.8%, vaccination was indicated by the rheumatologist or dermatologist and in 40.9% it was the patient's decision. Almost half of them (48.9%) completed the scheme at the time of this analysis, and most of them with homologous scheme (Gam-COVID-Vac 73.3%, ChAdOx1 nCoV-19 98.3%, BBIBP-CorV and Comirnaty 100%). Only 12.5% received combined schemes, being the most frequent Gam-COVID-Vac/mRAN-1273 (Fig. 1). The median time between doses was 51 days (IQR 53). A total of 630 patients did not complete the scheme at the time of inclusion in the registry, mostly (78.4%) since the recommended interval between doses had not yet passed at the time of the baseline visit. Nonetheless, three patients did not receive the second dose due to AE; pure red cell aplasia, anaphylaxis, and one case of concomitant enanthem and bullous exanthema; all had received Gam-COVID-Vac.

A quarter (25.9%) of the patients reported at least one AE after the first dose and 15.9% after the second. Flu-like syndrome and local hypersensitivity were the most frequent manifestations (Fig. 2A and B). All of them were mild or moderate and no patient was hospitalized. There was one case of anaphylaxis in a patient who received one dose of Gam-COVID-Vac. The event was mild/moderate and did not require hospitalization. Only 10 from all AE were also reported in the vaccination security platform from the National Health Ministry. Altogether, the incidence of AE was significantly lower for BBIBP-CorV (118.5 events/1000 doses) compared to Gam-COVID-Vac (195.4 events/1000 doses), ChAdOx1 nCoV-19 (359 events/1000 doses), and mRAN-1273 (522.4 events/1000 doses), $p<0.001$ in all cases (Table 2). Additionally, 14.4% of patients who had an AE after the first dose also reported an AE after the second one.

A total of 26 patients (2.1%) reported a disease flare after vaccination, in most cases arthritis or arthralgia. According to the Naranjo scale, only two of them were definitively associated with vaccination and in seven cases it was probable. Sixteen had rheumatoid arthritis, 6 psoriatic disease, and the remaining four rhupus, idiopathic juvenile arthritis, primary Sjögren sindrome, and other inflammatory arthritis. Ten patients with rheumatoid arthritis suspended treatment, mostly methotrexate, after vaccination. No new immune-mediated manifestations were reported.

Regarding efficacy, 63 (5.1%) SARS-CoV-2 infections were reported after vaccination; 19% occurred during the first 14 days post-vaccination, 57.1% after the first dose, and 23.8% after the second. In most cases (85.9%), the infection was asymptomatic with no requirement of hospitalization and 2 (3.2%) died due to COVID-19. One of them, a woman with rheumatoid arthritis, treated with tofacitinib, who also had arterial hypertension, cardiovascular disease, atrial fibrillation, and pulmonary hypertension, died 49 days after the first dose of ChAdOx1 nCoV-19. The other one, a man with IgG4-related disease in remission, treated with

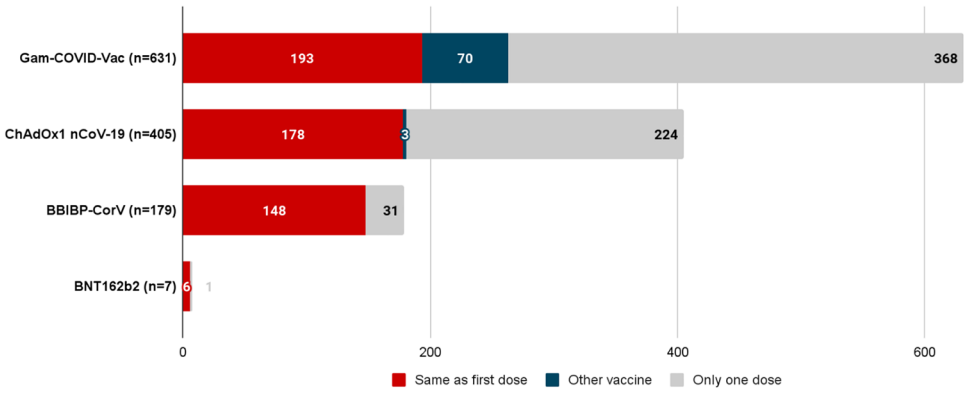

Fig. 1 SARS-CoV-2 vaccine scheme according to the first dose

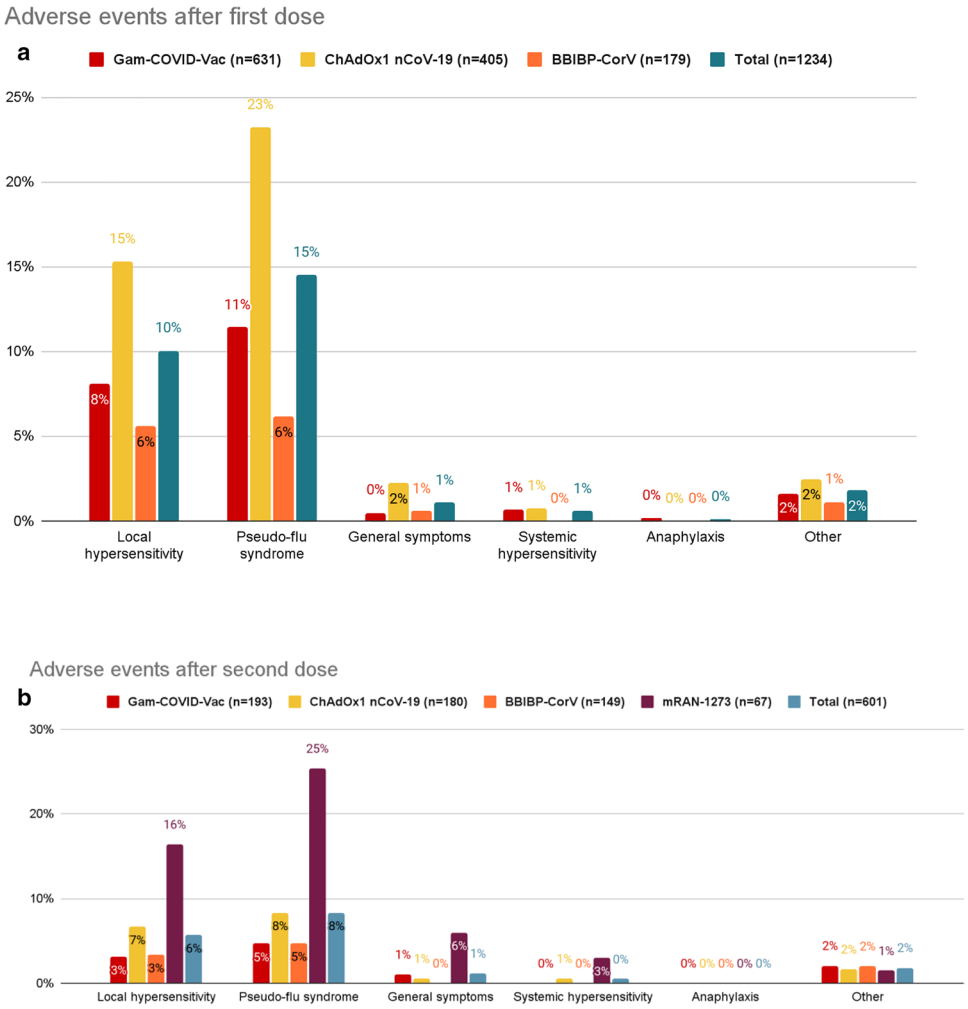

Fig. 2 Description of adverse events after the first and second doses

prednisone 5 mg/day and methotrexate, former smoker, had personal history of chronic obstructive pulmonary disease (COPD), diabetes, obesity, and chronic kidney disease, died 133 days after the second dose of Gam-COVID-Vac. With reference to the 51 events that occurred 14 days after vaccination, 57.9% received Gam-COVID-Vac as the first dose, 25.4% ChAdOx1 nCoV-19, and 15.7% BBIBP-CorV. The 15 patients with infection after two doses received homologous schemes (Table 3). Although the frequency of infection was numerically higher after the first dose in comparison to the second one (36/1234, 2.9% vs. 15/600, 2.5%), it did not reach statistical significance ($p = 0.719$). No differences were found when comparing the rate of AE among patients with IMID and other rheumatic conditions like fibromyalgia

Table 2 Incidence of AE according to the SARS-CoV-2 vaccine applied and comparison among them

	Gam-COVID-Vac	ChAdOx1 nCoV- 19	BBIBP-CorV	mRAN-1273
Number of doses	824	585	329	67
Number of AE	161	210	39	35
Incidence of AE (every 1000 doses, 95% CI)	**195.4 (168.3–222.5)**	**359.0 (320.1–397.9)**	**118.5 (83.6–153.5)**	**522.4 (402.8–642.0)**
Gam-COVID-Vac		**< 0.001**	**0.0025**	**< 0.001**
ChAdOx1 nCoV-19			**< 0.001**	**0.0130**
BBIBP-CorV				**< 0.001**
mRAN-1273				

AE, adverse events; *CI*, confidence interval

The incidence of AE was calculated according to the number of doses and to the number of AE reported for each of the most frequent types of vaccines. The last four rows show the *p*-value of the comparison of the incidence of AE between types of vaccines

or osteoarthritis (4.9% vs 6.8%, $p = 0.111$). Additionally, no association between infection and disease treatment at vaccination time was observed.

Discussion

We present the protocol and first baseline characteristics of the SAR-CoVAC registry including over 1200 patients with rheumatic and IMIDs. The SARS-CoV-2 vaccines used are according to availability in our country, being the most frequent Gam-COVID-Vac, ChAdOx1 nCoV-19, and BBIBP-CorV. mRNA vaccines were introduced later in our country and were used in most of the cases as second doses in mixed regimens.

In this cohort, a total of 413 patients reported at least one AE after a vaccine dose, which represents 22.5% of the totality of doses administered. All of them were mild or moderate and none required hospitalization. This prevalence is higher than that reported by the Argentine Ministry of Health on August 31, 2021, which was 0.12% [15], probably related to the fact that AE documentation is not mandatory but voluntary. Moreover, there is a higher proportion of BBIBP-CorV vaccine use in the general population which was associated with fewer AE. Only 10 from all AE from our cohort were also reported in the vaccination security platform, which represents 2.4% of all AE. If only these AE were taken into consideration, the prevalence would have been 0.5%.

On the other hand, the frequency of AE was lower than the one shown in clinical trials, being 65–70% for Gam-COVID-Vac [16] and ChAdOx1 nCoV-19 [17, 18], and 29% for BBIBP-CorV [19]. It is likely that some patients underestimated or did not report AE given the fact that most of them were mild. Similarly to what clinical trials have shown, BBIBP-CorV vaccine was associated with significantly lower incidence of AE in comparison to ChAdOx1 nCoV-19, mRAN-1273, and Gam-COVID-Vac. However, the characteristics of the AE were similar between vaccines and no new immune-mediated manifestation was reported among these patients.

Regarding the efficacy, we reported 63 events of SARS-CoV-2 infection after vaccination. Since 19% occurred between 1 and 14 days after first dose, only 51 were considered as events in patients fully or partially protected. Over 85% were asymptomatic or had mild disease, but two patients died during follow-up. It should be noted that no patient with a heterologous scheme presented SARS-CoV-2 infection after vaccination. Although this should be studied in the future, the combination of vaccines with different platforms could produce greater protection in these patients.

The type of vaccines and the schemes used in our country differ from other countries, making it difficult to compare them with other cohorts, where mRNA and ChAdOx1 nCoV-19 vaccines predominate. Data from the two biggest international registries, COVID-19 Global Rheumatology Alliance vaccine survey 20 and EULAR Coronavirus Vaccine (COVAX) physician-reported registry 21, showed a frequency of AE after vaccination between 37 and 48% and about 4% of the patients developed a flare of the rheumatic disease. Additionally, 1.1% of the European fully vaccinated patients reported SARS-CoV-2 infection. In our cohort, we observed lower frequency of AE (25%) and flares (2.1%) and higher frequency of SARS-CoV-2 infection in patients who received two vaccine doses (2.5%). These differences could be partially explained by the use of Gam-COVID-Vac and BBIBP-CorV in Argentina, which have shown a better safety profile; however, the inactivated vaccine was associated with lower efficacy [19].

This is the biggest cohort of patients with immune-mediated diseases and SARS-CoV-2 vaccination in our country. Unlike other registries from other parts of the world with data from only one vaccine platform, mostly mRNA, we included all types of vaccines: viral platform, mRNA and inactivated, and also combined schemes. This is also

Table 3 Characteristics of 51 patients with SARS-CoV-2 infection after vaccination

Variables	After the first dose $n=36$	After the second dose $n=15$
Vaccine		
Gam-COVID-Vac, *n* (%)	21 (58.3)	9 (60.0)
ChAdOx1 nCoV-19, *n* (%)	11 (30.6)	2 (13.3)
Sinopharm, *n* (%)	4 (11.1)	4 (26.7)
Scheme		
Both doses with the same vaccine, *n* (%)	-	15 (100)
Second dose with a different vaccine, *n* (%)	-	0 (0)
Infection severity		
Asymptomatic, *n* (%)	2 (5.6)	0 (0)
Ambulatory, *n* (%)	29 (80.6)	13 (86.6)
Hospitalized without O2, *n* (%)	0 (0)	0 (0)
Hospitalized, O2 by mask or nasal prongs, *n* (%)	3 (8.2)	0 (0)
Hospitalized, high flow O2 or NIMV, *n* (%)	0 (0)	1 (6.7)
Hospitalized, IMV or ECMO, *n* (%)	1 (2.8)	0 (0)
Death, *n* (%)	1 (2.8)	1 (6.7)
History of SARS-CoV-2 infection, *n* (%)	10 (28.6)	1 (6.7)
Rheumatic disease		
Rheumatoid arthritis, *n* (%)	18 (50)	7 (46.7)
Osteoarthritis, *n* (%)	8 (22.2)	1 (6.7)
Fibromyalgia, *n* (%)	4 (11.1)	0 (0)
Systemic lupus erythematosus, *n* (%)	3 (8.3)	2 (13.3)
Psoriasis, *n* (%)	3 (8.3)	1 (6.7)
Psoriatic arthritis, *n* (%)	3 (8.3)	1 (6.7)
Sjögren syndrome, *n* (%)	1 (2.8)	1 (6.7)
Systemic sclerosis, *n* (%)	1 (2.8)	1 (6.7)
Antiphospholipid syndrome, *n* (%)	1 (2.8)	1 (6.7)
Polymyalgia rheumatica, *n* (%)	1 (2.8)	0 (0)
IgG4 related disease, *n* (%)	0 (0)	1 (6.7)
Sarcoidosis, *n* (%)	1 (2.8)	0 (0)
Treatment		
Glucocorticoids, *n* (%)	9 (25)	2 (13.3)
Conventional DMARDs, *n* (%)	23 (63.9)	9 (60)
Immunosuppressors, *n* (%)	1 (2.8)	2 (13.3)
Biologic DMARDs, *n* (%)	10 (27.8)	4 (26.7)
JAK inhibitors, *n* (%)	2 (5.6)	2 (13.3)

n, number; *O2*, oxygen; *NIMV*, non-invasive mechanical ventilation; *IMV*, invasive mechanical ventilation; *ECMO*, extracorporeal membrane oxygenation; *DMARDs*, disease-modifying rheumatic drugs; *JAK*, Janus Kinase

a representative sample of patients with different immune-mediated diseases who regularly attend rheumatology and dermatology clinics, with diverse sociodemographic characteristics and from almost all Argentine provinces, particularly the most populated cities like the metropolitan area (36.2%), Córdoba (27.5%), Buenos Aires (20.3%), and Santa Fe (5.8%). However, this registry has some limitations. Firstly, it is voluntary and for this reason, patients' inclusion depends on the investigator's motivation. Despite this, investigators from almost all regions of our country, including both private and public consultation, were actively working. Secondly, because the AE report is made by the patient sometime after the vaccine application, a forgetfulness bias may be present. Nonetheless, there is a great awareness of the SARS-CoV-2 virus in our society and physicians trained patients to pay close attention to events that may appear after the intervention. Third, due to the design of this study, no blood samples were collected to assess the

humoral or cellular immune response to the vaccine. For this reason, we studied the clinical efficacy of the vaccines by evaluating SARS-CoV-2 infection after vaccination. It is important to highlight that the infection and the development of symptoms depend not only on vaccination, but also on other sociodemographic characteristics like occupation and clinical factors. In addition, the infection was informed by the patients, which could have led to a smaller number of cases reported. Fourth, the severity and treatment after a disease flare were not registered.

To conclude, in this large national cohort of patients with rheumatic conditions and IMIDs from Argentina, the most common vaccines used were Gam-COVID-Vac and ChAdOx1 nCoV-19. A quarter of the patients presented an AE and 5.1% presented SARS-CoV-2 infection after vaccination, in most cases mild.

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Data availability All data and materials generated and analyzed during the current study belong to the SAR-CoVAC registry, the Argentine Society of Rheumatology, and the Argentine Society of Psoriasis. They are available from the corresponding author on reasonable request. The authors declare that all relevant data are included in the article and its supplementary information files. More information about the registry is available in https://www.unisar.reumatologia.org.ar/registros_sarcovac.php.

Declarations

Disclosures None.

Ethics approval This study was conducted in accordance with Good Clinical Practice (GCP) guidelines, the International Conference on Harmonization (ICH), and with the ethical principles established in the Declaration of Helsinki, the law 3301/09, and local guidelines. Personal identification data was kept anonymous. An independent ethics committee has approved the protocol and the informed consent form.

Consent to participate All patients signed the corresponding informed consent form to participate in this registry.

Consent for publication Individuals provided signed consent for the publication of their data.

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