Title

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Journal

JCR Journal of Clinical Rheumatology, 29(2)

ISSN

1076-1608

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Publication Date

2023-03-01

DOI

10.1097/rhu.0000000000001903

Peer reviewed

Does the Use of Immunosuppressive Drugs Impact on SARS-CoV-2 Infection Outcome? Data From A National Cohort of Patients With Immune-Mediated Inflammatory Diseases (SAR-COVID Registry)

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Funding: The SAR-COVID, a strategic registry from the Argentine Society of Rheumatology, has received unrestricted research grants to carry out this project from Pfizer, Abbvie, and Elea Phoenix. In addition, 2 International League of Associations of Rheumatology grants have been obtained. He authors disclosed receiving financial support for the publication of this article.

Conflicts of interest: The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SAR-COVID is a multisponsor registry, where Pfizer, Abbvie, and Elea Phoenix had provided unrestricted grants. None of them has participated or influenced the development of the project, data collection, analysis, and interpretation, or the drafting of this report. They do not have access to the information collected in the database.

Availability of data and material: All data and materials generated and analyzed during the current study belong to the SAR-COVID registry of the Argentine Society of Rheumatology. They are available from the corresponding author upon 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 at https://www.unisar.reumatologia.org.ar/registros_sarcovid.php.

Authors' contributions: All authors listed in this manuscript were involved in drafting or revising this manuscript critically for important intellectual content, and all authors approved the final version to be published. A list of all the SAR-COVID registry subinvestigators is included in Appendix I, http://links.lww.com/RHU/A496.

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Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.jclinrheum.com).

ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000001903

Background/Objective: This study describes the impact of immunomodulatory and/or immunosuppressive (IM/IS) drugs in the outcomes of COVID-19 infection in a cohort of patients with immune-mediated inflammatory diseases (IMIDs).

Methods: Adult patients with IMIDs with a confirmed SARS-CoV-2 infection were included. Data were reported by the treating physician between August 13, 2020 and July 31, 2021. Sociodemographic data, comorbidities, and DMARDs, as well as clinical characteristics, complications, and treatment of the SARS-CoV-2 infection, were recorded. Descriptive analysis and multivariable logistic regression models were carried out.

Results: A total of 1672 patients with IMIDs were included, of whom 1402 were treated with IM/IS drugs. The most frequent diseases were rheumatoid arthritis (47.7%) and systemic lupus erythematosus (18.4%). COVID-19 symptoms were present in 95.2% of the patients. A total of 461 (27.6%) patients were hospitalized, 8.2% were admitted to the intensive care unit, and 4.4% died due to COVID-19.

Patients without IM/IS treatment used glucocorticoids less frequently but at higher doses, had higher levels of disease activity, were significantly older, were more frequently hospitalized, admitted to the intensive care unit, and died due to COVID-19. After adjusting for these factors, treatment with IM/IS drugs was not associated with a worse COVID-19 outcome (World Health Organization–Ordinal Scale ≥5) (odds ratio, 1.24; 95% confidence interval, 0.73–2.06).

Conclusions: SAR-COVID is the first multicenter Argentine registry collecting data from patients with rheumatic diseases and SARS-CoV-2 infection. After adjusting for relevant covariates, treatment with IM/IS drugs was not associated with severe COVID-19 in patients with IMIDs.

Study Registration: This study has been registered in ClinicalTrials.gov under the number NCT04568421.

Key Words: SARS-CoV-2, COVID-19, rheumatic diseases, Argentina

(*J Clin Rheumatol* 2023;29: 68–77)

On March 11, 2020, the World Health Organization (WHO) declared SARS-CoV-2 to be a pandemic.[1,2] In Argentina, the first COVID-19 case was reported on March 3, 2020; as of January 31, 2022, almost 8 million people (17.5% of the population) have developed the infection and 120,000 have died from it.[3]

Among the rheumatic diseases, systemic autoimmune diseases are usually associated with a greater predisposition to viral infections, due to the intrinsic risk of the preexisting disease and the iatrogenic effect of immunomodulatory/immunosuppressive (IM/IS) drugs used for their treatments.[4,5] Furthermore, older age, the presence of comorbidities, and moderate/high disease activity have been associated with poor COVID-19 outcomes.[6,7] However, there is a growing optimism regarding the potential beneficial effect of different IM/IS drugs, commonly used in these diseases, in the treatment of hyperinflammation, acute respiratory distress syndrome (ARDS), endothelial dysfunction, and disseminated intravascular coagulation related to COVID-19.[8,9] On the other hand, some treatments, including glucocorticoids, rituximab, sulfasalazine, azathioprine, and cyclophosphamide, have been associated with poor COVID-19 outcomes.[10,11]

Most of the information available regarding COVID-19 in patients with rheumatic diseases has been published from cohorts/registries from the United States, China, and Europe. These data might not necessarily reflect the Argentine population, which exhibits significant sociodemographic diversity, unequal access to health care system, and rheumatic treatments, particularly to biologics and small molecules. In addition, the health system, primarily intensive care units (ICUs), was overwhelmed during the early phases of the pandemic, with limited personnel and protective elements, which affected the management and outcomes of COVID-19.

Inspired by the COVID-19 Global Rheumatology Alliance (GRA),[12,13] the Argentine Society of Rheumatology decided to develop a national registry of COVID-19 in patients with rheumatic diseases (National Registry of Patients With Rheumatic Diseases and COVID-19; SAR-COVID), while also collaborating with the international database.

The primary objective of this national registry is to evaluate COVID-19 characteristics, course, and outcomes, mortality included, of SARS-CoV-2 infection in patients with rheumatic diseases. This substudy addresses the impact of IM/IS treatment in COVID-19 outcomes in patients with immune-mediated inflammatory diseases (IMIDs).

METHODS

Registry Design

SAR-COVID is a national, multicenter, observational, physician-reported registry of consecutive adult patients with a diagnosis of a rheumatic disease (Supplementary Table 1, http://links.lww.com/RHU/A492) and confirmed SARS-CoV-2 infection. Patients were classified according to disease diagnosis in those having an IMIDs and those not having one. They were later divided according to whether or not they received IM/IS drugs (Supplementary Table 2, http://links.lww.com/RHU/A493) during at least 3 months before the SARS-CoV-2 infection. For the purpose of this report, only patients with IMIDs have been included.

This registry has 2 different data collection phases. During the first phase, sociodemographic data, comorbidities, rheumatic disease activity and treatment, symptoms, and outcomes regarding SARS-CoV-2 infection were recorded. The second phase is taking place 12 months after enrollment to the registry and will record the long-term complications related to SARS-CoV-2 infection, the impact of the infection on the rheumatic disease including disease flares, and the onset of new associated autoimmune manifestations, as well as the efficacy and safety of SARS-CoV-2 vaccination (Fig. 1). The initial phase started on August 13, 2020, and concluded on July 31, 2021. Only data from the first phase are being included in this report. This study was registered at ClinicalTrials.gov (NCT04568421) on September 29, 2020.

Center Selection

An invitation to participate in this registry was sent to all SAR-affiliated rheumatologists. Those interested in participating registered as SAR-COVID investigators. Currently, 158 researchers, from all 23 Argentine provinces, have registered to collaborate and over 1800 patients have been included (Supplementary Fig. 1, http://links.lww.com/RHU/A494).

Participants and Eligibility Criteria

Eligible patients were those aged ≥18 years with a prior diagnosis of a rheumatic disease, according to the American College of Rheumatology or European League Against Rheumatism criteria or according to the clinical diagnosis of the primary rheumatologist (Supplementary Table 1, http://links.lww.com/RHU/A492). Patients were included whether or not they were being treated with IM/IS drugs (Supplementary Table 2, http://links.lww.com/RHU/A493).

Past or present confirmed SARS-CoV-2 infection relied on a positive test for SARS-CoV-2 virus from nasopharyngeal or oropharyngeal swab specimens (reverse transcriptase–polymerase chain reaction assay [RT-PCR]) or by serology, independently of symptoms. Before inclusion, all patients provided signed consent.

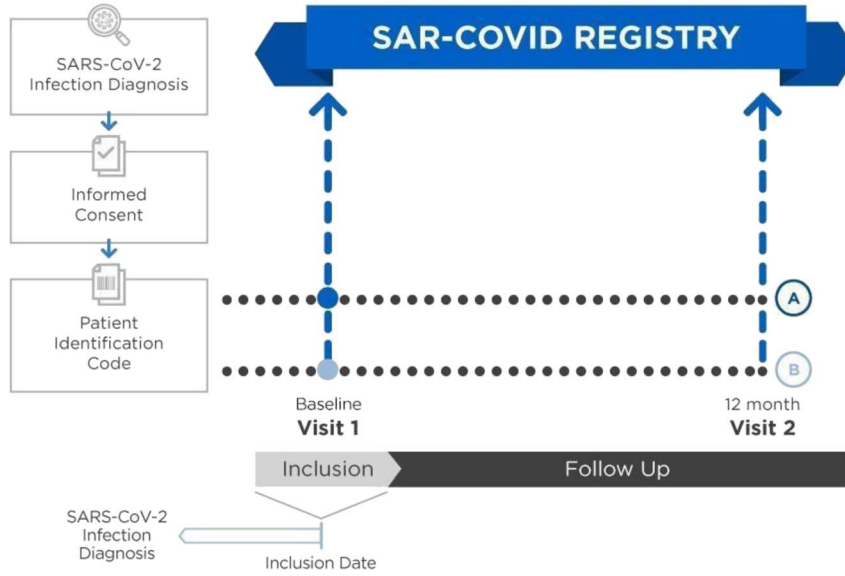

FIGURE 1. SAR-COVID study design. A, Patients with IMIDs; B, Patients with no IMIDs.

Study Variables

During the first phase of this registry, sociodemographic data (including age, sex, city and province of residence), socioeconomic level according to the Graffar scale,[14] formal education as a continuous variable in years, and occupation and health insurance (categorized into 4 different groups: private health plus social security, private health only, social security only, and public health only) were recorded. Ethnicity was reported by the patients according to their parents' and all 4 grandparents as follows: White (individuals with all White European ancestors); Mestizo (individuals born in Latin America who had both Amerindian and European ancestors); African–Latin American (individuals born in Latin America with at least 1 African ancestor irrespective of whether other ancestors were White or Amerindian); and other. Moreover, in accordance with the data collected by COVID-19 GRA, the presence of comorbidities including hypertension, diabetes, obesity, dyslipidemia, pulmonary, cardiovascular, cerebrovascular, neurologic, hepatic and renal chronic diseases, malignant neoplasm, organ transplantation, immunodeficiency, and psychiatric disorders was documented. In relation to the underlying rheumatic disease, date of diagnosis and treatment with glucocorticoids or IM/IS drugs during at least 3 months (Supplementary Table 2, http://links.lww.com/RHU/A493) before theSARS-CoV-2 infection were recorded. Global disease activity was ascertained by patients and physicians using a numerical visual analog scale (0–10 cm). In addition, disease activity was categorized according to the treating physician in remission, low, moderate, or high disease activity.

Regarding SARS-CoV-2 infection, date, place, diagnostic method, symptoms, laboratory changes, pharmacological treatments, outcomes (including hospitalization), admission to the ICU, mechanical ventilation, and complications (such as ARDS, cytokine storm,[15] sepsis, cardiovascular manifestations according to the treating physician, and secondary infections) were recorded. The highest level of care required by hospitalized patients was registered and categorized as follow: no supplemental oxygen required; supplemental oxygen by mask or nasal prongs; noninvasive mechanical ventilation or high-flow oxygen devices; invasive mechanical ventilation; extracorporeal membrane oxygenation; required ventilation, but type unknown; unknown interventions. In addition, SARS-CoV-2 infection severity was categorized according to the WHO Ordinal Scale for Clinical Improvement: ambulatory; hospitalized with mild disease (hospitalized with no oxygen therapy or with oxygen mask or nasal prongs); hospitalized with severe disease (hospitalized with high-flow oxygen or noninvasive mechanical ventilation or invasive mechanical ventilation or extracorporeal membrane oxygenation); or death.[16]

Patients will complete a second visit by their rheumatologists at 12 months from enrollment to record, long-term complications, COVID-19 vaccination,[17] and new SARS-CoV-2 infections. The patients' quality of life and functional capacity were assessed at enrollment and during the second formal assessment using the EuroQoL (EQ-5D-3L Spanish version)[18] and the Health Assessment Questionnaire (HAQ-DI).[19]

Up to the onset of the second phase, patients were categorized as follows: (1) total recovery—those who resolved all COVID-19 symptoms; (2) recovery with sequela—patients who developed long-term effects of COVID-19, such as fatigue, anosmia, headache, cough, dyspnea, joint and muscle pain, and so on,[20] and those who experienced hospitalization complications, such as chronic polyneuropathy; (3) not recovered—patients with persistent COVID-19 symptoms (only at the first time point); (4) death due to COVID-19—those who died because of COVID-19 manifestations or complications; and (5) death from another cause.

Data Management and Monitoring

All variables have been collected from medical records and interviews with the patients by their rheumatologists during the patient's hospitalizations due to COVID-19, or at the patients' regular virtual or face-to-face visits performed after SARS-CoV-2 infection, or with a family member depending on availability. The data were entered into the ARTHROS Electronic Case Report Form, an ad hoc designed online application.

A Data Control Committee was constituted to guarantee the quality of the information and to avoid potential data loss. An assistant specifically trained to detect inconsistencies and to generate queries for the investigators about missing or incorrect data was hired. In addition, ARTHROS Electronic Case Report Form has filters that limit the entry of unreliable data (data outside the allowed range, etc).

TABLE 1. Baseline Characteristics of the 1672 Patients With IMIDs and SARS-CoV-2 Infection From the SAR-COVID Registry

Variables	Patients on IM/IS Drugs (n = 1402)	Patients on No IM/IS Drugs (n = 270)	*p* value	All Patients (n = 1672)
Female sex, n (%)	1131 (80.7)	211 (78.1)	0.384	1342 (80.3)
Age, mean (SD), y	**49.8 (13.6)**	**52.8 (15.6)**	**0.004**	50.3 (14.0)
Ethnicity			0.055	
White, n (%)	671 (47.9)	117 (43.3)		788 (47.1)
Mestizo, n (%)	640 (45.6)	125 (46.3)		765 (45.8)
Others, n (%)	91 (6.5)	28 (10.4)		119 (7.1)
Socioeconomic level			0.756	
High or medium-high, n (%)	258 (18.4)	53 (19.6)		311 (18.6)
Medium, n (%)	697 (49.7)	140 (51.9)		837 (50.1)
Low or medium-low, n (%)	398 (28.4)	72 (26.7)		470 (28.1)
Unknown, n (%)	49 (3.5)	5 (1.8)		54 (3.2)
Education, mean (SD), y	13.3 (3.7)	13.1 (3.7)	0.360	13.3 (3.7)
Employed, n (%)	762 (54.4)	145 (53.7)	0.898	907 (54.2)
Health insurance			0.196	
Social security, n (%)	677 (48.3)	124 (45.9)		801 (47.9)
Private health, n (%)	320 (22.8)	79 (29.3)		399 (23.9)
Private health + social security, n (%)	76 (5.4)	10 (3.7)		86 (5.1)
Public health, n (%)	311 (22.2)	54 (20.0)		365 (21.8)
Unknown, n (%)	18 (1.3)	3 (1.1)		21 (1.3)
Rheumatic disease				
Rheumatoid arthritis, n (%)	**725 (51.7)**	**73 (27.0)**	**<0.001**	798 (47.7)
Systemic lupus erythematosus, n (%)	264 (18.8)	43 (15.9)	0.297	307 (18.4)
Spondyloarthritis, n (%)	162 (11.6)	24 (8.9)	0.242	186 (11.1)
Sjögren syndrome, n (%)	84 (6.0)	17 (6.3)	0.958	101 (6.0)
Systemic sclerosis, n (%)	**49 (3.5)**	**32 (11.9)**	**<0.001**	81 (4.3)
Vasculitis, n (%)	**47 (3.4)**	**18 (6.7)**	**0.016**	65 (3.9)
Antiphospholipid syndrome, n (%)	**30 (2.1)**	**18 (6.7)**	**<0.001**	48 (2.9)
Inflammatory myopathy, n (%)	41 (2.9)	10 (3.7)	0.625	51 (3.1)
Disease duration, mean (SD), y	**9.1 (7.7)**	**7.9 (7.9)**	**<0.001**	8.9 (7.8)
Disease activity			**<0.001**	
Remission, n (%)	**485 (34.6)**	**112 (41.5)**		597 (35.7)
Low disease activity, n (%)	**591 (42.2)**	**68 (25.2)**		659 (39.4)
Moderate disease activity, n (%)	**234 (16.7)**	**55 (20.4)**		289 (17.3)
High disease activity, n (%)	**44 (3.1)**	**14 (5.2)**		58 (3.5)
Unknown/not applicable, n (%)	**48 (3.4)**	**21 (7.8)**		69 (4.1)
Treatment				
Glucocorticoids, n (%)	**576 (41.1)**	**84 (31.1)**	**0.003**	660 (39.5)
Glucocorticoids dose (as prednisone or equivalent)			**<0.001**	
<10 mg/d, n (%)	**418 (29.8)**	**48 (17.8)**		466 (27.9)
≥10 mg/d, n (%)	**158 (11.3)**	**36 (13.3)**		194 (11.6)
Immunosuppressor/immunomodulator				
Methotrexate, n (%)	714 (50.9)	—	—	714 (50.9)
Antimalarials, n (%)	361 (25.7)	—	—	361 (25.7)
Leflunomide, n (%)	148 (10.6)	—	—	148 (10.6)
Mycophenolate mofetil, n (%)	94 (6.7)	—	—	94 (6.7)
Azathioprine, n (%)	79 (5.6)	—	—	79 (5.6)
Sulfasalazine, n (%)	15 (1.1)	—	—	15 (1.1)
Cyclosporine n (%)	1 (0.1)	—	—	1 (0.1)
Cyclophosphamide, n (%)	6 (0.4)	—	—	6 (0.4)
TNF-α inhibitors, n (%)	204 (14.6)	—	—	204 (14.6)
CD20 inhibitors, n (%)	38 (2.7)	—	—	38 (2.7)
IL-6 inhibitors, n (%)	24 (1.7)	—	—	24 (1.7)
Abatacept, n (%)	24 (1.7)	—	—	24 (1.7)

Continued next page

TABLE 1. *(Continued)*

Variables	Patients on IM/IS Drugs (n = 1402)	Patients on No IM/IS Drugs (n = 270)	*p* value	All Patients (n = 1672)
IL-17 inhibitors, n (%)	24 (1.7)	—	—	24 (1.7)
Belimumab, n (%)	7 (0.5)	—	—	7 (0.5)
IL-23 o IL-12/23 inhibitors, n (%)	8 (0.6)	—	—	8 (0.6)
JAK inhibitors, n (%)	84 (6.0)	—	—	84 (6.0)
Apremilast, n (%)	2 (0.1)	—	—	2 (0.1)
Comorbidities			0.107	
One comorbidity, n (%)	214 (15.3)	54 (20.0)		268 (16.0)
Two or more comorbidities, n (%)	399 (28.5)	79 (29.3)		478 (28.6)
Comorbidities				
Arterial hypertension, n (%)	**311 (22.2)**	**79 (29.3)**	**0.025**	390 (23.3)
Obesity, n (%)	193 (13.8)	31 (11.5)	0.305	224 (13.4)
Dyslipidemia, n (%)	172 (12.3)	31 (11.5)	0.763	203 (12.1)
Lung disease, n (%)	141 (10.1)	30 (11.1)	0.737	171 (10.2)
Diabetes, n (%)	100 (7.1)	23 (8.5)	0.559	123 (7.4)
Cardiovascular disease, n (%)	39 (2.8)	12 (4.4)	0.237	51 (3.1)
Chronic kidney failure, n (%)	28 (2.0)	5 (1.9)	1	33 (2.0)
Cancer, n (%)	26 (1.9)	6 (2.2)	0.913	32 (1.9)
Cerebrovascular disease, n (%)	**7 (0.5)**	**7 (2.6)**	**0.004**	14 (0.8)
Smoking status			0.846	
Active, n (%)	82 (5.8)	17 (6.3)		99 (5.9)
Past smoker, n (%)	291 (20.7)	54 (20.0)		345 (20.6)
Never, n (%)	884 (63.1)	157 (58.1)		1041 (62.3)
Unknown, n (%)	145 (10.7)	42 (15.5)		187 (11.2)

Psoriatic arthritis, axial spondyloarthritis (including ankylosing spondylitis), and other spondyloarthritis (including reactive arthritis) were grouped as spondyloarthritis; similarly, ANCA-associated vasculitis (eg, GPA, EGPA, MPA), giant cell arteritis, and other vasculitis including Kawasaki disease were grouped as vasculitis; lung disease included interstitial, obstructive (COPD/asthma), and other lung diseases; cardiovascular disease, coronary artery disease, and congestive heart failure.

COPD, Chronic obstructive pulmonary disease; EGPA, Eosinophilic granulomatosis with polyangiitis; GPA, Granulomatosis with polyangiitis; MPA, Microscopic polyangiitis; n, number; SD, standard deviation.

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 the Good Clinical Practice guidelines, the International Conference on Harmonization, and with the ethical principles established in the Declaration of Helsinki, the law 3301/09, and the guidelines of the local ethics committee. Personal identification data were kept anonymous and protected according to the 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 purpose of this project, only SAR-COVID medical researchers had access to the patients' medical records, thus ensuring confidentiality. The data extracted from medical records were uploaded into a database where the patient's identity was omitted and anonymized using an identification number.

Statistical Analysis

Data from the initial phase of the study were collected during the first year of the SAR-COVID registry between August 13, 2020 and July 31, 2021.

Descriptive statistical analysis of sociodemographic, clinical characteristics, laboratory, and COVID-19 outcomes data were performed. Continuous variables are presented as mean and standard deviation if their distribution was considered normal, or median and interquartile range, otherwise. Categorical variables are summarized as frequencies and percentages.

To compare the associations between groups and different sociodemographic and clinical variables, as well as SARS-CoV-2 infection outcomes, Student's *t* or χ^2 tests were used; if assumptions were not fulfilled, categories were grouped, and Fisher exact test was applied. Multivariable logistic regression models, using hospitalization with severe disease and death due to COVID-19 (WHO Ordinal Scale ≥5)[16] as the dependent variable, were performed to establish if the use of IM/IS drugs at the time of SARS-CoV-2 infection was independently associated with poor outcomes. These models were adjusted for sex, age, ethnicity, health insurance, socioeconomic level, the presence of comorbidities, rheumatic disease diagnosis, disease activity, and glucocorticoids dose. In addition, propensity score analyses were performed to adjust for confounding by indication.

All statistical analyses and model development were performed using R version 4.0.0 (Free Software Foundation, Inc, Boston, MA).

RESULTS

At the time of this analysis, there were 1898 patients in the SAR-COVID registry, 1672 had IMIDs, of whom 1402 (83.9%) received IM/IS drugs. Most of the patients were female (80.3%), with a mean age of 50.3 years (SD 14). The predominant ethnic groups were White and Mestizo, 47.1% and 45.8%, respectively.

Approximately half of the patients were employed (54.2%) and 79.6% had private health and/or social security insurance. Regarding socioeconomic level, 50.1% were classified as middle class; the mean years of schooling was 13.3 years (SD, 3.7) (Table 1).

The most frequently registered IMID was rheumatoid arthritis (47.7%), followed by systemic lupus erythematosus (18.4%) and spondyloarthritis (11.1%). At the time of the SARS-CoV-2 infection, 39.5% of the patients were receiving glucocorticoids and 75.1% were considered to be in remission or low disease activity. At least 1 comorbidity was reported by 44.6% of the patients (Table 1).

Patients taking IM/IS drugs at the time of SARS-CoV-2 infection were younger (mean, 49.8; SD, 13.6 years vs 52.8; SD, 15.6 years, $p = 0.004$), had more frequently rheumatoid arthritis (51.7% vs 27%, $p < 0.001$), and less frequently systemic sclerosis (3.5% vs 11.9%, $p < 0.001$), vasculitis (3.4% vs 6.7%, $p = 0.016$), or antiphospholipid syndrome (2.1% vs 6.7%, $p < 0.001$). Patient not receiving IM/IS had higher disease activity (moderate/high disease activity 25.6% vs 19.8%, $p = 0.015$), and although the frequency of glucocorticoid use was significantly lower (31.1% vs 41.1%, $p = 0.003$), the dose used in this group was higher (mean, prednisone, or prednisone equivalent, 12.5; SD, 13.4 mg/d vs 8.2; SD, 8.5 mg/d, $p = 0.002$) (Table 1).

Close contact with confirmed or probable cases of SARS-CoV-2 infection was the most frequent method of contagion. In 88% of the cases, the diagnosis was made with RT-PCR test; during an outpatient evaluation in 45.3% of the patients, in the emergency

TABLE 2. Epidemiological and Clinical Characteristics of SARS-CoV-2 Infection of Patients With IMIDs Taking or Not IM/IS Drugs

Variables	Patients on IM/IS Drugs (n = 1402)	Patients on No IM/IS Drugs (n = 270)	*p* value	All Patients (n = 1672)
SARS-CoV-2 diagnostic method				
RT-PCR, n (%)	**1220 (87.0)**	**251 (93)**	**0.008**	1483 (88.0)
Serology, n (%)	**196 (14.0)**	**23 (8.5)**	**0.019**	222 (13.2)
SARS-CoV-2 diagnostic place				
Outpatient facility, n (%)	644 (45.9)	111 (41.1)	0.164	763 (45.3)
Emergency department, n (%)	473 (33.7)	95 (35.2)	0.697	568 (33.7)
Inpatient/hospital, n (%)	**95 (6.8)**	**42 (15.6)**	**<0.001**	139 (8.3)
Home/community detection, n (%)	191 (13.6)	26 (9.6)	0.316	217 (13.0)
Nursing home or assisted living facility, n (%)	4 (0.3)	1 (0.4)	0.586	5 (0.3)
Unknown, n (%)	3 (0.2)	0 (0)	1	3 (0.2)
Symptoms, n (%)	1335 (95.2)	257 (95.2)	1	1592 (95.2)
Fever, n (%)	782 (55.8)	153 (56.7)	0.839	941 (55.8)
Headache, n (%)	616 (43.9)	103 (38.1)	0.091	719 (42.7)
Cough, n (%)	600 (42.8)	117 (43.3)	0.923	722 (42.8)
Myalgia, n (%)	**551 (39.3)**	**88 (32.6)**	**0.045**	641 (38.0)
General discomfort, n (%)	518 (36.9)	113 (41.9)	0.146	632 (37.5)
Anosmia, n (%)	486 (34.7)	79 (29.3)	0.099	565 (33.5)
Odynophagia, n (%)	424 (30.2)	71 (26.3)	0.219	497 (29.5)
Dysgeusia, n (%)	351 (25.0)	52 (19.3)	0.099	403 (23.9)
Dyspnea, n (%)	319 (22.8)	65 (24.1)	0.694	389 (23.1)
Arthralgia, n (%)	306 (21.8)	50 (18.5)	0.257	356 (21.1)
Symptoms duration, median (IQR), d	15.0 (11.0–21.0)	15.0 (11.0–21.0)	0.820	15.0 (11.0–21.0)
Pharmacological treatment				
Dexamethasone, n (%)	252 (18.0)	62 (23.0)	0.066	317 (18.8)
Azithromycin, n (%)	214 (15.3)	38 (14.1)	0.684	253 (15.0)
Anticoagulation, n (%)	94 (6.7)	22 (8.2)	0.469	116 (6.9)
Oral glucocorticoids, n (%)	105 (7.5)	16 (5.9)	0.436	121 (7.2)
Plasma from recovered patients, n (%)	41 (2.9)	8 (3.0)	1	49 (2.9)
Antimalarial, n (%)	17 (1.2)	4 (1.5)	0.764	21 (1.3)
Ivermectin, n (%)	24 (1.7)	4 (1.5)	1	28 (1.7)
Complications, n (%)	**117 (8.5)**	**37 (14.0)**	**0.007**	154 (9.4)
ARDS, n (%)	83 (5.9)	20 (7.4)	0.428	103 (6.2)
Sepsis, n (%)	26 (1.9)	7 (2.6)	0.576	33 (2.0)
Cytokine storm, n (%)	9 (0.6)	2 (0.7)	0.695	11 (0.7)
SARS-CoV-2 severity (WHO-OS)			**<0.001**	
Ambulatory, n (%)	**1047 (74.7)**	**167 (61.9)**		1214 (72.6)
Hospitalized mild disease, n (%)	**262 (18.7)**	**74 (27.4)**		336 (20.1)
Hospitalized severe disease, n (%)	**38 (2.7)**	**10 (3.7)**		48 (2.9)
Death, n (%)	**55 (3.4)**	**19 (7.0)**		74 (4.4)

ARDS, acute respiratory distress syndrome; IQR, interquartile range; n, number; SD, standard deviation; WHO-OS, World Health Organization-Ordinal Scale.

department in 33.7%, and during hospitalization in 8.3%. Most of the patients (95.2%) reported symptoms associated with the infection, the most frequent were fever (55.8%), cough (42.8%), and headache (42.7%). The median duration of symptoms was 15 days (interquartile range [IQR], 11–21) (Table 2). During the SARS-CoV-2 infection, 461 (27.6%) patients had to be hospitalized. The median length of hospital stay was 7 days (IQR, 4–11). Because the severity of the symptoms, 8.2% of them were admitted to the ICU (stay: median, 8 days; IQR, 5–16). Patients not receiving IM/IS drugs were more frequently hospitalized (38.15% vs 25.6%, $p < 0.001$) and admitted into the ICU (13% vs 7.3%, $p = 0.003$). No differences were observed in relation to oxygen requirement according to IM/IS treatment (Fig. 2).

A third (31.1%) of the patients received some treatment other than analgesic or nonsteroidal anti-inflammatory drugs for the management of the infection; the most commonly used drugs were as follows: dexamethasone (18.8%), azithromycin (15%), and anticoagulants (6.9%). Patients not on IM/IS drugs were more frequently diagnosed during hospitalization (15.6% vs 6.8%, $p < 0.001$) and received more frequently dexamethasone (23% vs 18%, $p = 0.066$) and anticoagulants (8.2% vs 6.7%, $p = 0.469$), but neither comparison reached statistical significance. In addition, these patients presented complications more frequently (14% vs 8.5%, $p = 0.007$) (Table 2).

The large majority of the patients recovered completely (82.6%), whereas 10.3% had some sequelae. The most frequently reported sequelae were as follows: hyposmia/anosmia, asthenia, arthromyalgia, and dyspnea. In addition, 22 patients reported interstitial lung damage or progression of previous injury, 3 had critical illness polyneuropathy, and 1 had postviral myositis. A total of 74 (4.4%) patients died due to COVID-19, 55 (3.4%) in the group with IM/IS treatment, and 19 (7%) in those without it ($p < 0.001$).

In the multivariate analysis, considering severe COVID-19 or death as the dependent variable, male sex, older age (per year), having 2 or more comorbidities, diabetes, chronic renal disease, having high disease, and the use of glucocorticoids (as prednisone or equivalent) were associated with poor outcome. Treatment with IM/IS drugs, however, was not found to be associated with severe disease and death due to COVID-19 (odds ratio [OR], 1.24; 95% confidence interval [CI], 0.73–2.06) (Table 3). Alternative analyses using propensity score approach were performed with similar results; IM/IS drugs did not affect COVID-19 outcomes (OR, 1.34; 95% CI, 0.77–2.41) (Supplementary Table 3, http://links.lww.com/RHU/A495).

DISCUSSION

We present the protocol and preliminary baseline data of the SAR-COVID registry. We are particularly reporting the sociodemographic, clinical, and outcome characteristics of SARS-CoV-2 infection of over 1600 patients with IMIDs included in this registry.

Patients with IMIDs not taking IM/IS at the time of SARS-CoV-2 infection diagnosis were more frequently hospitalized and admitted to the ICU, received dexamethasone more frequently, and had more complications, although the intake of IM/IS per se did not seem to contribute to worse COVID-19 outcomes as shown in the multivariate main model and in the analyses. These patients were older and more frequently diagnosed with vasculitis, systemic sclerosis, and antiphospholipid syndrome, and used higher doses of glucocorticoids. All these factors could explain the higher hospitalization and mortality rate in this group of patients. Similar results were seen in the National COVID Cohort Collaboration from the United States, where over 220,000 patients were studied. In this case, immunosuppression was associated with a reduced risk of invasive mechanical ventilation, whereas rheumatic patients under rituximab treatment presented higher risk of in-hospital death.[21] The effect generated by the different IM/IS drugs is probably different. Although some of them have shown a beneficial effect in managing the inflammation driven by the infection, such as IL-6 inhibitors, JAK inhibitors, IL-1 inhibitors, and TNF-α inhibitors,[22] others, including rituximab, azathioprine, and cyclophosphamide, have been associated with poorer outcomes in patients with IMIDs.[10,11,23–26]

Similarly, data from the ReumaCoV Brazil registry,[27,28] which includes patients with IMIDs infected with SARS-CoV-2, showed comparable frequency of hospitalization, admission to the ICU, requirement of invasive mechanical ventilation, and death to our population, 33%, 15%, 10.5%, and 8.4%, respectively. In this Brazilian cohort, the use of oral glucocorticoids, pulse therapy with methylprednisolone, or cyclophosphamide for IMIDs treatment was associated with ICU admission, and particularly these last 2 were also associated with increased risk of death. On the other hand, patients with IMIDs from Latin America included in the international GRA registry[29] presented a higher frequency of hospitalization (61%),

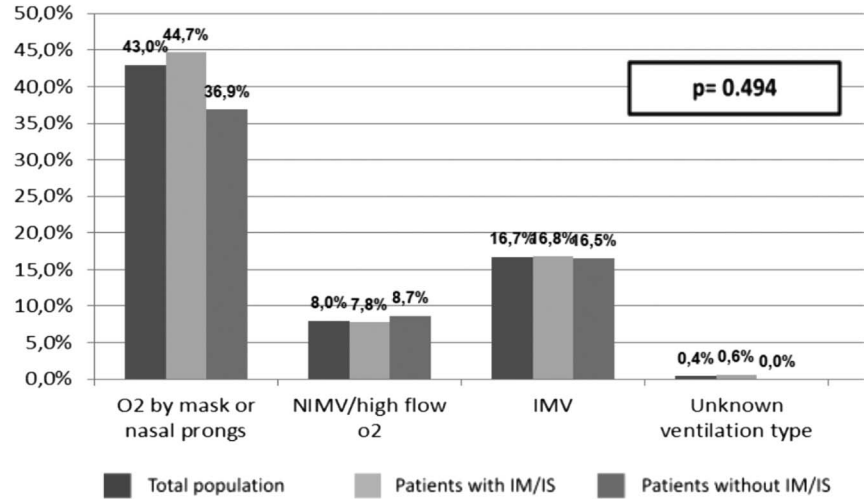

FIGURE 2. Oxygen requirements during hospitalization in patients with SARS-CoV-2 infection and IMIDs. Difference between groups, $p = 0.143$. NIMV, noninvasive mechanical ventilation; IMV, invasive mechanical ventilation.

TABLE 3. Sociodemographic and Clinical Variables Associated With Severe COVID-19 (WHO Ordinal Scale ≥5) in Patients With IMIDs

	Unadjusted Analysis		Adjusted Analysis	
	OR	**95% CI**	**OR**	**95% CI**
Sex (ref. female)				
Male	1.78	1.17–2.66	1.95	1.21–3.09
Age (per year)	1.06	1.04–1.08	1.05	1.04–1.07
Ethnicity (ref. White)				
Mestizo	0.99	0.66, 1.48	—	—
Other	2.47	1.36, 4.31	—	—
Socioeconomic level (ref. high and medium-high)				
Low and medium-low	1.80	1.03–3.30	—	—
Medium	1.22	0.71–2.20	—	—
Health insurance (ref. social security and/or private health)				
Public health	1.02	0.64–1.57	—	—
No. comorbidities (ref. no comorbidities)				
One	1.52	0.78–2.84	0.97	0.47–1.9
Two or more	5.23	3.44–8.13	1.97	1.12–3.46
Comorbidities				
Arterial hypertension	0.33	0.22–0.48	—	—
Diabetes	4.54	2.77–7.14	2.34	1.32–4.12
Cardio/cerebrovascular disease	4.67	2.45–8.48	—	—
Lung disease	2.90	1.81–4.53	—	—
Chronic renal disease	7.69	3.57–16.67	4.10	1.68–9.8
Obesity	2.47	1.58–3.77	—	—
Dyslipidemia	2.44	1.51–3.85	—	—
IMID				
Rheumatoid arthritis	1.03	0.71–1.49	—	—
Systemic lupus erythematosus	0.61	0.34–1.03	—	—
Spondyloarthritis	0.69	0.33–1.28	—	—
Sjögren syndrome	0.24	0.04–0.78	—	—
Systemic sclerosis	1.01	0.39–2.19	—	—
Vasculitis	6.00	3.32–10.5	—	—
Antiphospholipid syndrome	0.84	0.20–2.34	—	—
Inflammatory myopathy	1.39	0.47–3.25	—	—
Glucocorticoid dose (ref. prednisone 0 mg/d)				
<10 mg/d	1.91	1.16–3.11	1.80	1.11–2.91
≥10 mg/d	0.47	0.31–0.72	2.32	1.25–4.23
Disease activity (ref. remission)				
Low disease activity	1.65	1.01–2.77	1.44	0.83–2.54
Moderate disease activity	2.17	1.22–3.86	1.58	0.81–3.07
High disease activity	9.49	4.69–18.92	7.85	3.36–18.33
IM/IS treatment	1.68	1.07–2.58	1.24	0.73–2.06

CI, Confidence interval; OR, Odds Ratio; ref, reference 4.

complications (38%), requirement of invasive mechanical ventilation (20%), and mortality (12%). It should be noted that the frequency of glucocorticoid use was higher in this group (51% vs 39.5%), which was associated in our cohort with poorer outcomes.

Currently data confirming that COVID-19 severity in patients with IMIDs depends on well-known risk factors also described in the general population, including male sex, older age, and the presence of comorbidities, such as diabetes, obesity, renal, and pulmonary diseases.[7,10,11,28,30] During the pandemic, treatment with IM/IS in high-risk patients has been challenging to determine the best standard of care for SAR-CoV-2 infection. In general, IM/IS seem not to affect COVID-19 course[7,30]; however, if analyzed individually, some of them could have a beneficial effect, whereas others may be associated with ICU admission and death.[10,11,28]

Given the observational design of this registry, it has some important limitations. First, we anticipate inclusion bias, because the reporting of data by rheumatologists was voluntary. Marketing campaigns are constantly carried out to promote patient inclusion, and now nearly 15% of SAR members are participating in this project. On the other hand, most of these rheumatologists are from the metropolitan areas of Buenos Aires, Córdoba, and Santa Fe, which simply reflects the distribution of the population in our country, where also the highest incidence of SARS-CoV-2 infection cases have been reported.[3] There is a possibility that some

outcomes or covariates may have been misclassified, because in some cases, the information has been collected from available records or by interview of family members. Because of the study design, we also anticipate that there may be some missing data; however, after data monitoring, only 4.6% of the patients had some missing data, which was considered minor; that is, it did not prevent the proposed analysis from being carried out. In addition, because few patients were treated with some of the drugs, no individual drug analysis was possible. Furthermore, drugs were categorized into conventional DMARDs, biological DMARDs, immunosuppressants, and targeted synthetic DMARDs, but this analysis did not show any significant differences between groups. We expect in the near future, with a higher number of patients, to perform a specific analysis of each drug.

Furthermore, as most of the baseline data were collected during the implementation of mandatory preventive isolation, there might have been some under ascertainment of asymptomatic or mild cases, as well as of very severe cases that resulted in death before the patient could be evaluated in the health care system, resulting in what is called an immortal bias.[31] We believe, nevertheless, that rheumatologists are almost always consulted by other practitioners about the management of hospitalized patients with rheumatic diseases, which should have allowed the detection of most of the cases. In addition, to increase the specificity of our cohort, we decided to include only patients with confirmed SARS-CoV-2 infection by the detection of viral particles or serological tests.

To conclude, this is the largest registry of patients with IMIDs and SARS-CoV-2 infection from Argentina. We are confident that this project will shed light on some of the questions that persist around the management of this population, and we expect to help rheumatologists make the evidence-based decisions regarding the management of COVID-19 in their clinical practice, not only in Argentina but also in the Latin American region. Moreover, we are completing the baseline and 12-month phase, which will allow us in the near future to enlarge the number of patients enrolled and identify long-term complications related to SARS-CoV-2 infection, vaccination strategies, and the impact of COVID-19 in patients with IMIDs.

ACKNOWLEDGMENT

The authors would like to acknowledge all the investigators for their participation and all the data collectors across the country for their ongoing support to the registry. The authors are deeply grateful to Leonardo Grasso for providing expert assistance with the ARTHROS web software and Leandro Cino for his contribution in the registry management tasks. The authors also gratefully acknowledge Graciela S. Alarcón, MD, MPH, for her most helpful comments to an earlier version of this manuscript.

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