Impact of the Treatment with Immunomodulatory and Immunosuppressive Drugs in Patients with Rheumatic Diseases and COVID-19

Unidad de Investigación de la Sociedad Argentina de Reumatología (UNISAR)
(Research Unit of the Argentine Society of Rheumatology)

STUDY PROTOCOL
Version 3.0

Principal Investigator: Guillermo J. Pons-Estel.

Scientific Committee: Enrique R. Soriano, María Celina de la Vega, Bernardo A. Pons-Estel, Karen Roberts and Rosana Quintana.

Argentine Rheumatology Society representative: Cesar Graf, President.

TABLE OF CONTENTS

INTRODUCTION

COVID-19 (Corona Virus Disease-2019) is an infectious disease produced by a novel strain of a beta-coronavirus RNA, called SARS-CoV-2 according to the International Committee on virus taxonomy; the name was given due to the similarities between this virus and the one that causes severe acute respiratory syndrome (SARS) (1). In December 2019, the first outbreak of cases of severe pneumonia caused by this coronavirus emerged in Wuhan, a city in the Hubei province of China (2). After an increasing number of cases and a rapid geographical spread worldwide, the World Health Organization (WHO) declared it to be a pandemic on March 11, 2020 (3).

Person-to-person transmission of the virus occurs through droplets that are spread by coughing, sneezing, or talking and can be breathed in, or contaminate surfaces that people touch. The virus usually enters through the airways, mouth or conjunctiva and replicates in the epithelial cells of the upper and lower respiratory tract (4). The spread is fast and each contaminated person usually infects around 2 to 4 people (5).

Approximately 80% of the people who become infected suffer a mild form of the disease, 15% a severe form that will require hospitalization, and about 5% develop the most severe form (6). All people are susceptible to infection, however those with pre-existing comorbidities such as hypertension, obesity, chronic lung disease, diabetes and/or cardiovascular disease and those with a weakened immune system appear to be more vulnerable to develop a more aggressive and fatal disease (7, 8). Rheumatic diseases, including systemic autoimmune diseases, are usually associated with a greater predisposition to viral infections, due to the intrinsic risk of the pre-existing disease and the iatrogenic effect of the immunosuppressive drugs used for their treatments (9, 10). Nevertheless, there is growing optimism, although still with a low level of scientific evidence, about the role that different immunomodulatory and immunosuppressive drugs used to treat rheumatic diseases, may have a beneficial effect in the treatment of acute respiratory distress syndrome (ARDS) associated with a cytokine storm, with endothelial dysfunction and disseminated intravascular coagulation (11-13). These treatments include antimalarials (14), colchicine (15), corticosteroids (16,

17), janus kinase inhibitors (18, 19) and biologic drugs such as anti-IL-1, anti-IL-6, (20, 21), anti-IL-6r (22), and anti-TNFα (23), among others (24-26).

Internationally, a rheumatologist consortium or alliance has recently emerged with the aim of creating a global registry of patients with rheumatic diseases and COVID-19 (Global Rheum-COVID Registry - https://www.rheum-covid.org) (27).

At the local level, and due to the lack of information, the Argentine Society of Rheumatology (Sociedad Argentina de Reumatología - SAR) proposes to carry out a national registry of COVID-19 in patients with rheumatic diseases (SAR-COVID) that aims to study the socio-demographic, clinical characteristics and outcomes of COVID-19 in this group of patients, and to compare them with the data obtained by the Global Rheum-COVID Registry.

JUSTIFICATION OF THE STUDY

The COVID-19 pandemic is a matter of great concern to rheumatologists because the majority of patients with rheumatic diseases, especially those with systemic autoimmune diseases, have abnormalities of the underlying immune system and are commonly treated with immunosuppressive therapies that may increase the risk of serious infections. However, at present, there is insufficient information to support this claim, and the extrapolation of these data to SARS-CoV-2 infection is at least ambiguous due to the potentially protective role of immunomodulatory and immunosuppressive drugs in the control of a severe inflammatory response to infection.

In the short time that we have been navigating this uncharted pandemic, its evolution over time is still unknown, therefore it is a priority to get real life information. A rheumatology COVID-19 registry to be made throughout Argentina and led by the SAR, who considers this project strategic, will enable the rapid collection of case information from physicians who treat patients with rheumatic diseases. This registry is designed to answer at least three important questions: a) what are the COVID-19 outcomes among patients with rheumatic diseases, particularly those with systemic autoimmune diseases treated with immunomodulatory and/or immunosuppressive therapies, in terms of harms or benefits?; b) what is the impact of genetic (ethnicity), sociodemographic (e.g.

socioeconomic status, level of education) and environmental factors (geographical areas) on the severity of patients affected by COVID-19?; c) what will be the interaction between coronavirus, systemic autoimmune diseases and immunomodulatory and/or immunosuppressive treatment in the short and longer term?.

Finally, this real life registry will help the scientific community and entities that generate and finance health policies, to develop better strategies for the benefit of all patients with rheumatic diseases.

HYPOTHESIS OF THE INVESTIGATION

Patients with rheumatic diseases who are under chronic treatment with immunomodulatory and/or immunosuppressive drugs more frequently have an asymptomatic infection, a milder COVID-19 and lower mortality than patients with rheumatic diseases without immunomodulatory and/or immunosuppressive treatments.

OBJECTIVES

PRIMARY OBJETIVE

- Evaluate through a national registry of patients with rheumatic diseases, chronically treated or not with immunomodulatory and/or immunosuppressive drugs, the course (disease presentation, evolution and mortality) of the SARS-CoV-2 infection.

SECONDARY OBJECTIVES

- Assess the protective effect of chronic treatment (three months or longer) with immunomodulatory and/or immunosuppressive drugs on the development of COVID-19.
- Measure the impact of chronic treatment with immunomodulatory and/or immunosuppressive drugs on the development of severe forms of COVID-19 (admission in intensive care unit -ICU, use of invasive mechanical ventilation) and mortality.

- Describe the impact of sociodemographic conditions on the COVID-19 outcomes.
- Assess the impact of coronavirus infection on the appearance of unusual or atypical manifestations of rheumatic disease, and on the development of a new associated autoimmune disease.
- Evaluate the recovery rate of COVID-19 in patients with rheumatic diseases treated chronically with immunomodulatory and/or immunosuppressive drugs.
- Assess the impact of coronavirus infection on the quality of life of patients with rheumatic diseases.
- Evaluate the burden of both diseases (rheumatic diseases and COVID-19) on the health system.
- Contribute to the best international knowledge of COVID-19 through collaboration with the Global International Alliance Rheum-COVID Registry -https://www.rheum-covid.org

ETHICAL ASPECTS

This study will be conducted in accordance with the 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 the guidelines of the local ethics committee. Personal identification data will be 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.

The protocol, any amendment that arises and the informed consent of the patients, must be approved by the Research Ethics Committee “Dr. Claude Barnard”, from Rosario, Argentina, Argentina, prior to the initiation of the study.

For the purposes of this project, only medical researchers will access patients' medical records in order to obtain the data required for the investigation, thus ensuring their confidentiality. The data extracted from the medical records will be downloaded into a database where the patient's first and last name will not appear, but their data will be anonymized with an identification number, sex and date of birth.

ADVERSE EVENT (AE), PREGNANCY EXPOSURE, AND INCIDENT REPORTING

During the study all adverse events will be collected. The Investigators will assess information on adverse events, pregnancies and special situations at each patient visit during the course of the study and report them to the sponsor when one of the sponsor's drugs is involved.

The investigators will:

- Transfer to the sponsors in an ongoing manner reports of serious AEs, drug misuse or abuse and reports of drug exposure during pregnancy.
- Transfer to the sponsor any other information that may suggest a change in the benefit-risk profile for the sponsor's drug, and where required, copies of Investigator Notifications for suspected unexpected serious adverse events (SUSAR) and copies of the Development Safety Update Report.

The following is a list of events will be reported to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious AEs
- Adverse events of Special Interest (AESIs)
- Pregnancies

The investigators will report new significant follow-up information for these events to the sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event’s outcome, including recovery.
- Additional narrative information on the clinical course of the event.
- Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

METHODOLOGY

DESIGN

SAR-COVID is a national, multicenter, prospective, observational longitudinal study (registry) of consecutive patients with diagnosis of rheumatic diseases (see appendix 1) treated or not with immunomodulatory and/or immunosuppressive drugs (see appendix 2) and SARS-CoV-2 infection (asymptomatic or COVID-19).

TARGET POPULATION

Patients ≥ 18 years of age with any rheumatic disease.

ELIGIBILITY CRITERIA

Inclusion Criteria

- Age ≥ 18 years.
- Patients with diagnosis of rheumatic diseases (treated or not with immunomodulatory and/or immunosuppressive drugs).
- Patients with diagnosis of SARS-CoV-2 infection (past or present) with positive test for the virus SARS-CoV-2 from analysis of nasopharyngeal or oropharyngeal swab specimens (reverse transcriptase–polymerase-chain-reaction assay) or by serology, independently of symptoms.

Exclusion Criteria

- Patients who do not wish to participate or are unable to give informed consent.

SAMPLE SIZE CALCULATION

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

It is expected that 3,000 patients with COVID-19 and some rheumatic disease, who are cared for by rheumatologists in any of the 23 provinces of Argentina, will be enrolled in the SAR-COVID registry during the period from July 1 to December 31, 2020. Twelve-month extension of the recruitment period will be applied if the expected number of patients is not achieved by the end of the inclusion date.

Two cohorts will be included: the first will enroll 1,500 patients treated with immunomodulatory and/or immunosuppressive drugs, and the second will enroll 1,500 patients without immunomodulatory and/or immunosuppressive drugs.

In Argentina, there are currently 31,000,000 inhabitants 18 years of age or older. Assuming, conservatively, that the SARS-CoV-2 infection rate will progressively increase to 0.5% of the population, it is expected that during the enrollment period of this registry 155,000 persons will develop SARS-CoV-2 infection. Considering a prevalence of 3% of patients with systemic autoimmune diseases who are mostly expected to be chronically treated with immunomodulatory and/or immunosuppressive drugs, and 17% with rheumatic diseases without immunomodulatory and/or immunosuppressive drugs (28), it is expected that around 4,650 and 26,350 patients, respectively, will develop SARS-CoV-2 infection during the recruitment period. In the event that before December 31, 2020 the expected numbers are not completed, the registration period will be extended until the targeted number is achieved.

Being mortality the primary outcome and considering that currently the mortality rate of COVID 19 in our country is 5.2%, with an expected reduction of 50% for those patients taking immunosuppressive drugs, with 80% power and alpha=0.05, we would need 796 patients per group.

RECRUITMENT

Center selection process and patient recruitment (Figure 1):

1. All rheumatologists, members of the Argentine Society of Rheumatology will be invited to participate in the registry.
2. The information about this project will be delivered through the usual SAR's information channels: a) NotiSAR (flyers), b) SAR-website (for professionals and patients), c) Argentine Journal of Rheumatology, and d) Scientific events (National Congress of Rheumatology, Fall Symposium, Visiting Professor, and others).
3. All rheumatologists will have personal interviews with a methodologist from the SAR Research Unit to solve doubts and acquire skills for the use of the survey, database and different indexes that will be performed.
4. Enrolment period will take place from July to December 2020.

5. All consecutive patients who meet the inclusion criteria and who have signed the informed consent will be included
6. To guarantee the homogeneity and quality of the information, each variable of the registry will have standardized definitions.
7. The rheumatologist will obtain the information in a face-to-face visit and through an exhaustive review of the patient's medical records. This day will be defined as baseline visit or index day (T0).
8. Follow-up visits will be made by the rheumatologist at 12 months.

VARIABLES AND DEFINITIONS

Variables and definitions are described in detailed in Appendix 3.

DATA COLLECTION

All variables will be collected by self-report, clinical and laboratory examination and/or medical records review, performed by the rheumatologist during patient hospitalization due to COVID-19, or at the patient control visit performed after SARS-CoV-2 infection.

The data will be entered into the ARTHROS eCRF (online application designed ad hoc), which in turn will facilitate generating queries and perform the statistical analysis.

CODING

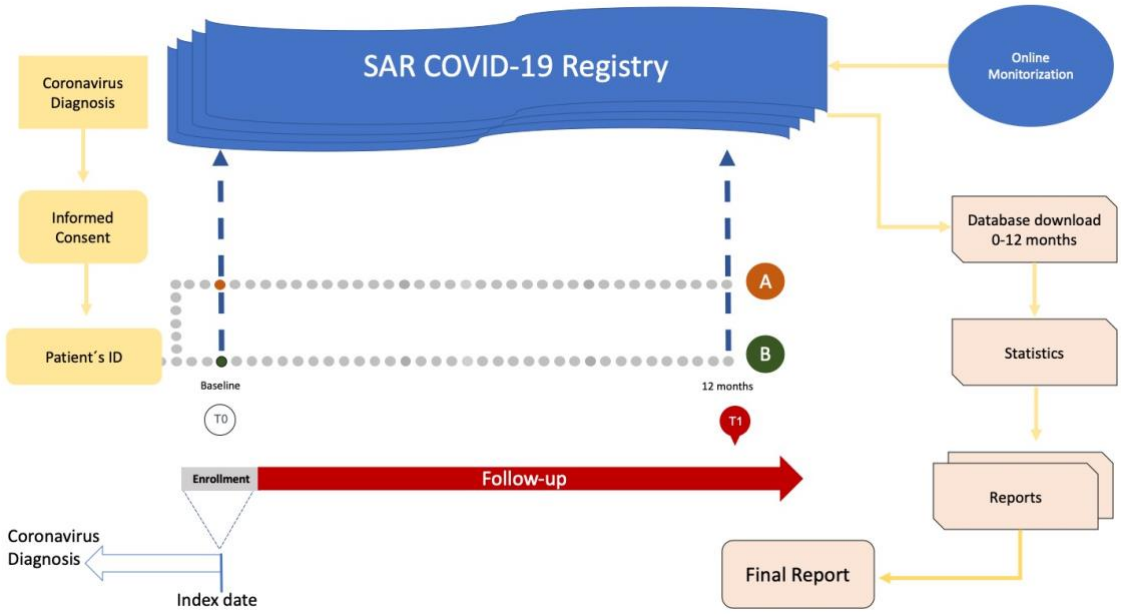
Each patient will receive a unique, unchangeable numerical code, even if the patient changes locations. If this happens, the rheumatologist in charge will notify to the study monitor in order to avoid data duplication.

QUALITY CONTROL

A Data Control Committee (DCC) will be created to guarantee quality information and to avoid potential data loss.

To guarantee the quality of the information, the entire process will be monitored by a person specifically hired and trained to detect inconsistencies and to generate queries to the investigators at each participating center.

ARTHROS eCRF will have filters that limit the entry of unreliable data (data outside the allowed range, etc.).



(A) 1,500 patients with rheumatic diseases treated with immunomodulatory and/or immunosuppressive drugs.
(B) 1,500 patients with rheumatic diseases without treatment with immunomodulatory and/or immunosuppressive drugs.

Figure 1. Flow chart showing the information process in the SAR-COVID registry.

PERIODIC REPORTS

Reports will be made at the end of every study visits, including the following information:

- Number of participants.
- Gender.
- Diagnoses of the rheumatic diseases.
- Age at diagnosis of the rheumatic disease.
- Age at diagnosis of the SARS-CoV-2 infection.
- Duration of the rheumatic disease at the diagnosis of SARS-CoV-2 infection.
- Immunomodulatory and/or immunosuppressive treatments received prior to SARS-CoV-2 infection.
- Immunomodulatory and/or immunosuppressive treatment interruptions at SARS-CoV-2 infection.

- COVID-19 clinical and laboratory characteristics.
- Treatments received for COVID-19.
- Use of ICU and invasive mechanical ventilation.
- Mortality.

These reports will be uploaded to the SAR-COVID website. Other fast communication channels could be used if necessary.

STATISTICAL CONSIDERATIONS

Overall comparisons of the general cohort and of both subgroup (patients stratified according to be chronically treated or not with immunomodulatory and/or immunosuppressive drugs) will be performed using a descriptive statistical analysis of sociodemographic, clinical characteristics, laboratory and mortality data.

Continuous variables will be presented as mean and standard deviation when distribution is considered normal, or median and interquartile range otherwise. To decide whether distribution can be considered as normal the following information will be used: boxplot, histogram visual inspection and Shapiro-Wilk test. Categorical variables will be summarized as frequencies and percentages.

To compare associations between treatments used and final result of COVID-19 infection (recovered or deceased), Chi-square test will be used, and if assumptions are not fulfilled, categories will be grouped to apply Fisher exact test.

Two multivariable logistic regression models will be performed, the first to evaluate COVID-19 as the outcome variable and the use of immunomodulatory and/or immunosuppressive drugs as independent variables adjusting for confounding variables; and the second to evaluate the influence of sociodemographic conditions and treatment status on the outcomes (admission in ICU, use of invasive mechanical ventilation and mortality).

To compare recovery rate of COVID-19 in patients with rheumatic diseases treated chronically or not with immunomodulatory and/or immunosuppressive drugs, the Z test will be used to show proportions.

Nonparametric Wilcoxon signed-rank test for comparison between baseline and follow-up visits between the different treatment groups (immunomodulatory

and/or immunosuppressive drugs) and age and sex matched population with rheumatic diseases without immunomodulatory and/or immunosuppressive drugs for HAQ and EuroQol components.

All statistical analyses and model development will be performed using R version 3.6.2.

NAMES AND CONTACT DETAILS

Sociedad Argentina de Reumatología

Unidad de Investigación (Research Unit)
Contact person: Guillermo J. Pons-Estel.
Callao 384 Piso 2 Dto 6.
Ciudad Autónoma de Buenos Aires.
Tel/Fax: (+54 11) 4371-1759/1643
E-mail: unisar@reumatologia.org.ar

Unidad de Gestión (Management Unit)
Contact person: Leandro Cino.
Callao 384 Piso 2 Dto 6.
Ciudad Autónoma de Buenos Aires.
Tel/Fax: (+54 11) 4371-1759/1643
E-mail: gerencia@reumatologia.org.ar

TIMETABLE

Milestones	**Duration of the project - From July 2020 to July 2022**					
	Time 0	July 2020	December 2020	July 2021	December 2021	July 2022
Protocol approval						
Local IRB approval						
Official launch of the project: July, 2020						
Baseline visit (T0)						
Data analysis of T0 visits						
Dissemination of results (T0)*						
Follow-up visit - 12 months (T1)						
Data analysis of all visits from T0-T1						
Dissemination of results*						

*****abstracts and manuscript preparation and publication

BIBLIOGRAPHY

1. Guan WJ, Zhong NS. Clinical Characteristics of Covid-19 in China. Reply. The New England journal of medicine. 2020;382.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. The New England journal of medicine. 2020.
3. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
4. Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. The Lancet Infectious diseases. 2018;18(8):e217-e27.
5. Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2020;92:214-7.
6. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. Jama. 2020.
7. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. Jama. 2020.
8. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74.
9. Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Seminars in arthritis and rheumatism. 2010;39(5):327-46.
10. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmunity reviews. 2020:102523.
11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
12. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clinical and experimental rheumatology. 2020;38(2):337-42.
13. Zhai Z, Li C, Chen Y, Gerotziafas G, Zhang Z, Wan J, et al. Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. Thromb Haemost. 2020.
14. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bioscience trends. 2020;14(1):72-3.
15. Deftereos SG, Siasos G, Giannopoulos G, Vrachatis DA, Angelidis C, Giotaki SG, et al. The GReek study in the Effects of Colchicine in COvid-19 complications prevention (GRECCO-19 study): rationale and study design. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese. 2020.

16. Rubin EJ, Baden LR, Morrissey S. Audio Interview: New Research on Possible Treatments for Covid-19. The New England journal of medicine. 2020;382(12):e30.
17. Zhao JP, Hu Y, Du RH, Chen ZS, Jin Y, Zhou M, et al. [Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases. 2020;43(0):E007.
18. Favalli EG, Biggioggero M, Maioli G, Caporali R. Baricitinib for COVID-19: a suitable treatment? The Lancet Infectious diseases. 2020.
19. .
20. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. Journal of biological regulators and homeostatic agents. 2020;34(2).
21. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. International journal of antimicrobial agents. 2020:105954.
22. Available from: https://clinicaltrials.gov/ct2/show/NCT04315298.
23. Haga S, Yamamoto N, Nakai-Murakami C, Osawa Y, Tokunaga K, Sata T, et al. Modulation of TNF-alpha-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-alpha production and facilitates viral entry. Proc Natl Acad Sci U S A. 2008;105(22):7809-14.
24. Lu CC, Chen MY, Chang YL. Potential therapeutic agents against COVID-19: What we know so far. Journal of the Chinese Medical Association : JCMA. 2020.
25. Rosenbaum L. Facing Covid-19 in Italy - Ethics, Logistics, and Therapeutics on the Epidemic's Front Line. The New England journal of medicine. 2020.
26. Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience. 2020;14:1022.
27. Robinson PC, Yazdany J. The COVID-19 Global Rheumatology Alliance: collecting data in a pandemic. Nature reviews Rheumatology. 2020.
28. Alvarez-Nemegyei J, Pelaez-Ballestas I, Sanin LH, Cardiel MH, Ramirez-Angulo A, Goycochea-Robles MV. Prevalence of musculoskeletal pain and rheumatic diseases in the southeastern region of Mexico. A COPCORD-based community survey. J Rheumatol Suppl. 2011;86:21-5.

APPENDIX 1. RHEUMATIC DISEASES.

- ANCA-associated vasculitis (e.g., GPA, EGPA, PAN, MPA)
- Other vasculitis including Kawasaki disease
- Antiphospholipid syndrome
- Autoinflammatory syndrome (including TRAPS, CAPS, FMF, HIDS)
- Axial spondyloarthritis (including ankylosing spondylitis)
- Other spondyloarthritis (including reactive arthritis)
- Behcet's
- Chondrocalcinosis
- Chronic recurrent multifocal osteomyelitis
- Fibromyalgia
- Giant cell arteritis
- Gout
- IgG4-related disease
- Inflammatory myopathy (e.g. dermatomyositis, polymyositis)
- Juvenile idiopathic arthritis, not systemic
- Juvenile idiopathic arthritis, systemic
- Mixed connective tissue disease
- Myofascial pain syndrome
- Ocular inflammation
- Polymyalgia rheumatica
- Psoriatic arthritis
- Rheumatoid arthritis
- Other inflammatory arthritis
- Osteoarthritis
- Osteopenia / Osteoporosis
- Sarcoidosis
- Sjogren's syndrome
- Stills disease, adult onset
- Systemic lupus erythematosus
- Systemic sclerosis
- Undifferentiated connective tissue disease

GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; PAN: Polyarteritis nodosa, MPA: Microscopic poyangiitis; TRAPS: Tumor necrosis factor receptor-associated periodic syndrome; CAPS: Cryopyrin-associated periodic syndrome; FMF: Familial Mediterranean fever; HIDS: Hyperimmunoglobulinemia D *syndrome*.

APPENDIX 2. IMMUNOMODULATORY AND/OR IMMUNOSUPPRESSIVE CHRONIC TREATMENTS.

Disease-modifying Antirheumatic Drugs (DMARDs) and other Non-Biologics treatments.

- Azathioprine
- Chloroquine/hydroxychloroquine
- Cyclosporine
- Cyclophosphamide
- Leflunomide
- Methotrexate
- Minocycline
- Mycophenolate mofetil / mycophenolic acid
- Prednisone
- Sulfasalazine
- Tacrolimus
- Thalidomide

Biologics and small molecules.

- Actemra (Tocilizumab)
- Amgevita (Adalimumab)
- Abrilada (Adalimumab)
- Benlysta (Belimumab)
- Cimzia (Certolizumab pegol)
- Cosentyx (Secukinumab)
- Enbrel (Etanercept)
- Enerceptan (Etanercept)
- Humira (Adalimumab)
- Ilaris (Canakinumab)
- Inflectra (Infliximab)
- Ixifi (Infliximab)
- Kevzara (Sarilumab)
- Kineret (Anakinra)
- Mabthera (Rituximab)
- Novex (Rituximab)
- Nucala (Mepolizumab)
- Ocrelizumab
- Olumiant (Baricitinib)
- Orencia (Abatacept)
- Otezla (Apremilast)
- Ofev (Nintedanib)
- Pirfenidona
- Prolia (Denosumab)
- Rinvoq (Upadacitinib)
- Remicade (Infliximab)
- Remsima (Infliximab)

- Skyrizi (Risankizumab)
- Simponi (Golimumab)
- Stelara (Ustekinumab)
- Taltz (Ixekizumab)
- Tremfya (Guselkumab)
- Xeljanz (Tofacitinib)

APPENDIX 3. VARIABLES.

All variables will be collected at INDEX DATE by self-report, clinical and laboratory examination and/or medical records review.

I. Socio Demographic Variables

Variable	Codification
Physician ID number	Number
Unique Patient Identifier	Number
Date enrolment	Number
City, Province	Descriptive
Date of birth	Number
Gender	Male / Female
Race/ethnicity	Caucasian / Mestizo / African-Latin American / Other
Years of formal education	Number (0-20)
Medical coverage	Partial / Full / No
Socioeconomic status	Graffar method
Residence	Rural / Urban

II. COVID-19 Variables

Variable	Codification
COVID-19 Diagnosis: Date	Number
COVID-19 Diagnosis: Location	• Home or standalone • Nursing home or assisted living facility • Outpatient facility • Emergency department • Inpatient/hospital • Unknown • Other
COVID-19 Diagnosis Method	• Presumptive diagnosis based on symptoms only • PCR • Antibody • Metagenomic testing • CT scan • Laboratory assay, type unknown • Unknown • Other
Previous symptoms COVID	Yes / No
COVID-19: Treatment	• No treatment except supportive care • Remdesivir • Lopinavir/ritonavir • Antimalarials • IL-6 and IL-6r inhibitors • IL-1 inhibitors • Bevacizumb • JAK inhibitors • Serpin inhibitors

	• Ciclesonide • Glucocorticoids • Anti-TNF • IVIG • Plasma from recovered patients • Anti-coagulation • Other
Complications	• No known complications • Acute Respiratory Distress Syndrome (ARDS) • Macrophagic activation syndrome (MAS) • Thrombosis • Sepsis • Myocarditis or new heart failure • Concomitant or secondary infection (e.g. Influenza) • Other serious complication
Infection Acquisition: In the 14 days before onset of illness did the patient have any of the following?	• History of travel to an area with documented cases of COVID-19 infection • Close contact with a confirmed or probable case of COVID-19 infection • Presence in a healthcare facility where COVID-19 infections have been managed • None of the above (community acquired) • Unknown • Other
Abnormal Laboratory test result	• Anemia: Yes / No / Not assessed • D-Dimer abnormal: Yes / No / Not assessed • Ferritin > 2000ng/ml: Yes / No / Not assessed • IL-6 Levels > UNL: Yes / No / Not assessed • sIL2R > UNL: Yes / No / Not assessed • Fibrinogen < 250 mg/dL: Yes / No / Not assessed

	• Leukopenia (WBC < 5000/mm3) : Yes / No / Not assessed • AST or ALT (GOT OR GPT) > UNL: Yes / No / Not assessed • Absolut Lymphocyte Count < 1,500/mm3: Yes / No / Not assessed • Platelets < 110,000/mm3: Yes / No / Not assessed • Triglyceride > 133 mg/dL: Yes / No / Not assessed • Known splenomegaly or hepatomegaly: Yes / No / Not assessed
Pathogen Tests	• Influenza A: Yes / No / Not assessed • Influenza B: Yes / No / Not assessed • NON COVID-19 Coronavirus: Yes / No / Not assessed • RSV: Yes / No / Not assessed • Adenovirus: Yes / No / Not assessed • Bacteria: Yes / No / Not assessed • Other Respiratory Infection (e.g. fungal): Yes / No / Not assessed
Develop Interstitial Lung disease	Yes / No / Unknown • Idiopathic pulmonary fibrosis • Connective tissue disease, specify CTD:_____ • Hypersensitivity pneumonitis • Sarcoidosis • Unknown • Other ILD:_____
	•

III. Rheumatic Disease Variables

Variable	Codification
Year rheumatic disease diagnosis	Number
Primary rheumatic/autoimmune diagnosis(es)	• ANCA-associated vasculitis (e.g., GPA, EGPA, PAN, MPA) • Other vasculitis including Kawasaki disease • Antiphospholipid syndrome • Autoinflammatory syndrome (including TRAPS, CAPS, FMF, HIDS) • Axial spondyloarthritis (including ankylosing spondylitis) • Other spondyloarthritis (including reactive arthritis) • Behcet's • Chondrocalcinosis • Chronic recurrent multifocal osteomyelitis • Fibromyalgia • Giant cell arteritis • Gout • IgG4-related disease • Inflammatory myopathy (e.g. dermatomyositis, polymyositis) • Juvenile idiopathic arthritis, not systemic • Juvenile idiopathic arthritis, systemic • Mixed connective tissue disease • Myofascial pain syndrome • Ocular inflammation • Polymyalgia rheumatica • Psoriatic arthritis • Rheumatoid arthritis • Other inflammatory arthritis • Osteoarthritis • Osteopenia / Osteoporosis

	• Sarcoidosis • Sjogren's syndrome • Stills disease, adult onset • Systemic lupus erythematosus • Systemic sclerosis • Undifferentiated connective tissue disease
Rheumatic disease activity at the time of COVID-19 symptom onset or at COVID-19 diagnosis if asymptomatic	• Remission • Minimal or low disease activity • Moderate disease activity • Severe or high disease activity • Unknown
Physician Global Assessment	Number
Patient Global Assessment	Number
Glucocorticoids (including prednisone, methylprednisolone) at time of COVID-19 symptom onset (or at COVID-19 diagnosis if asymptomatic):	Yes / No / Unknown
Immune modulating medications immediately prior to the time of COVID-19 symptom onset (or at COVID-19 diagnosis if asymptomatic): Medication 1-5	Stopped / Continued / Unknown
Immune modulating medications immediately prior to the time of COVID-19 symptom onset (or at COVID-19 diagnosis if asymptomatic):	• None • Azathioprine • Chloroquine/hydroxychloroquine • Cyclosporine • Cyclophosphamide • Leflunomide • Methotrexate • Minocycline

	• Mycophenolate mofetil / mycophenolic acid • Prednisone • Sulfasalazine • Tacrolimus • Thalidomide • Actemra (Tocilizumab) • Amgevita (Adalimumab) • Abrilada (Adalimumab) • Benlysta (Belimumab) • Cimzia (Certolizumab pegol) • Cosentyx (Secukinumab) • Enbrel (Etanercept) • Enerceptan (Etanercept) • Humira (Adalimumab) • Ilaris (Canakinumab) • Inflectra (Infliximab) • Ixifi (Infliximab) • Kevzara (Sarilumab) • Kineret (Anakinra) • Mabthera (Rituximab) • Novex (Rituximab) • Nucala (Mepolizumab) • Ocrelizumab • Olumiant (Baricitinib) • Orencia (Abatacept) • Otezla (Apremilast) • Ofev (Nintedanib) • Pirfenidona • Prolia (Denosumab)

	• Rinvoq (Upadacitinib) • Remicade (Infliximab) • Remsima (Infliximab) • Skyrizi (Risankizumab) • Simponi (Golimumab) • Stelara (Ustekinumab) • Taltz (Ixekizumab) • Tremfya (Guselkumab) • Xeljanz (Tofacitinib)
At the time of COVID-19 symptom onset (or diagnosis if asymptomatic), was the patient taking any of the following medications?	
ACE inhibitor	Yes and medication continued / Yes and medication stopped / No / Unknown
Angiotensin receptor blocker	Yes and medication continued / Yes and medication stopped / No / Unknown
Nonsteroidal anti-inflammatory (NSAID)	Yes and medication continued / Yes and medication stopped / No / Unknown
PD5 inhibitor (e.g., sildenafil)	Yes and medication continued / Yes and medication stopped / No / Unknown
Comorbidity and Pregnancy	• None • Interstitial lung disease (e.g. NSIP, UIP, IPF) • Obstructive lung disease (COPD/asthma) • Other lung disease • Diabetes • Morbid obesity (BMI 40+) • Hypertension • Cardiovascular disease (coronary artery disease, congestive heart failure) • Pulmonary hypertension • Chronic renal insufficiency or end stage renal disease • Cancer • Organ transplant recipient • Immunodeficiency

	• Inflammatory bowel disease • Liver disease • Chronic neurological or neuromuscular disease • Trisomy 21 • Psychiatric condition (e.g., schizophrenia, bipolar disorder) • Pregnancy • Post-partum (< 6 weeks) • Unknown
Smoking Status	Current smoker / Former smoker / Never smoked / Unknown smoking status

IV. Outcome Variables

Variable	Codification
Health Assessment Questionnaire (HAQ-DI)	Questionnaire
EuroQoL	Questionnaire
Global Burden Disease-GBD	Questionnaire
Hospitalization	Yes / No
Internal medicine hospitalization days	Number
UCI hospitalization days	Number
Requirement of conventional ventilatory support	Yes / No
Conventional ventilatory support days	Number
Computed tomography scan	Yes / No
Number of computed tomography scan performed	Number
Deceased	Yes / No
Cause of dead	Descriptive