ReumaCoV Brasil Registry: Brazilian Study of Patients with Immuno-mediated Chronic Inflammatory Diseases Infected by SARS-CoV-2

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Method Article

Keywords: COVID-19, SARS-CoV-2, prospective cohort, Immune-mediated rheumatic diseases, registry

DOI: https://doi.org/10.21203/rs.3.pex-1104/v1

Abstract

Patients with immune-mediated rheumatic diseases (IMRD) are at increased risk of infections, including significant morbidity and high mortality. Considering the potential for unfavorable outcomes of SARS-CoV-2 infection in patients with IMRD, a huge number of questions were released regarding the impact of COVID-19 in the beginning of the pandemic. Seeking to better understand this complex interaction, this study was developed to evaluate prospectively patients with IMRD and a suspected or confirmed COVID-19 diagnosis, according to the Ministry of Health of Brazil's definitions. The primary outcomes will be the IMRD disease activity changes after COVID-19, at four time points: (1) At baseline and prior 6 months; (2) The first rheumatic evaluation after known infection by SARS-CoV-2 (4-6 weeks); (3) 3 months after the inclusion (±15 days); (4) 6 months after inclusion (±15 days). The secondary outcomes will be the progression rate to severe forms of COVID-19, need for intensive care unit admission and mechanical ventilation, death and therapeutic changes related to the IMRD. Two outcomes are of particular interest considering the COVID-19 in IMRD patients, namely pulmonary and the thromboembolic events, and they will be monitored with more attention and details (clinical, lab, function tests and imaging). This protocol was approved by the Brazilian Committee of Ethics in Human Research (CONEP) on April 5th, 2020 (CAAE 30186820.2.1001.8807; Number: 3.933.204) and registered on the Brazilian Registry of Clinical Trials – REBEC (RBR-33YTQC) in June, 1st 2020. We believe this study will provide many clinically relevant data on the general impact of COVID-19 on IMRD patients.

Introduction

The Coronavirus Disease (COVID-19) was declared as pandemic in March, 11th, 2020 by World Health Organization (WHO) [1] and Brazil was the first Latin American country to have a confirmed case of COVID-19 in February 26th, 2020[2]. Heretofore, almost 3 millions of cases and more than 90,000 deaths have been confirmed in our country by July, 31th 2020 [3].

Patients with immune-mediated rheumatic diseases (IMRD) are at increased risk of infections, including significant morbidity and high mortality[4]. It is worthy emphasizing this is a complex binomial with many factors involved, such as disease activity, age, comorbidities and drugs, such as glucocorticoids (GCs), conventional synthetic, specific target or biological disease-modifying anti-rheumatic drugs (csDMARD, stDMARD or bioDMARD, respectively) and immunosuppressants [5]. Considering a possibly poorer evolution of SARS-CoV-2 infection in patients with IMRD, a large amount of questions have been posed regarding the impact of COVID-19 in the beginning of the pandemic, including withdrawal or spacing of medications, hospitalization, need of mechanical ventilation and mortality rate [6-8].

With the evidences moving forward, some Italian, American, French and Chinese databases have started to demonstrate that the risk of bad/poor outcome is quite similar to general population and could be more related to comorbidities and aging than IMRD itself [9-11]. However, there are controversial data, especially regarding the mortality rates [12].

Considering Brazil as a continental country and with relevant regional and socioeconomic differences, as well as discrepancies concerning basic sanitation and access to the public and private health care systems, it is important to address the incidence, peculiarities related to disease activity and drug management, and survival curve in IMRD patients with COVID-19.

Reagents

Equipment

Procedure

This paper shows details of the protocol design for the Brazilian Registry of Patients with Immuno-mediated Chronic Inflammatory Diseases Infected by Sars-Cov-2 (ReumaCoV-Brasil) (Brazilian Register of Clinical Trials – RBR-33YTQC, registered on June, 1st, 2020).

1. Data collection began in May 2020, using a convenience sampling strategy.

2. The data will be collected at three distinct periods: inclusion, 3 months, and 6 months. Participating centers were selected based on their expressed interest after a collective invitation had been sent to all rheumatologists affiliated to the Brazilian Society of Rheumatology. Most of them are public reference centers involved in teaching and forming fellows in rheumatology, but some have focus in private care.

3. Regardless COVID-19 diagnosis, the eligible patients include those aged 18 years or over with prior diagnosis of IMRD, according to the American College of Rheumatology (ACR) or European League against Rheumatism (EULAR) criteria, including rheumatoid arthritis (RA)[14, 15], systemic lupus erythematosus (SLE)[16, 17], Sjögren's syndrome (SS)[18], systemic sclerosis (ES)[19], inflammatory myopathies[20], axial spondyloarthritis[21-23], enteropathic arthritis[24], psoriatic arthritis[25] sarcoidosis[26], antiphospholipid syndrome (APS)[27], Behçet disease [28], mixed connective tissue disease[29], Takayasu arteritis[30, 31], giant cell arteritis[32], ANCA-associated vasculitides[33-36] and juvenile idiopathic arthritis at adult age [37].

4. The exclusion criteria were other immunodeficiency diseases, past organ or bone marrow transplantation, neoplasms within the last five years, current chemotherapy, HIV diagnosis and thymus diseases. The controls (not exposed) will be patients with IMRD without suggestive symptoms or diagnosis of COVID-19, matched for sex, age and IMRD, respecting the same exclusion criteria.

5. Cases (exposed) and controls (non exposed) will be enrolled after reading and signing the informed consent (ICF – Appendix A).

6. The clinical form (Appendix B) will be filled at baseline and 3- and 6-month follow-up using the REDCAp platform.

7. A total of 14 mL of blood will be collected for further lab exams, according to the protocol described at figure 3.

8. The blood will be centrifuged at 3000 rpm with serum being separated and stored at -20ºC in each participating center and it will be sent to the Hermes Pardini Laboratory posteriorly in a one-way shipping.

9. The anti-SARS-CoV-2 antibodies (IgM and IgG) will be evaluated by ELISA (Euroimmun®), using plasma aliquots, according to the manufacturer's recommendations. Rheumatoid factor, anti-CCP, ANA, anticardiolipin (IgG and IgM) and immunoglobulins (IgM, IgG and IgA) will be tested using serum aliquots, using pre-established protocols.

10. The total blood and another one tube that the RNAlater was added will be shipped to the LIKA (Keizo Asami Immunopathology Laboratory), located at Federal University of Pernambuco (UFPE) and maintained at -80oC until the genetic and epigenetics evaluation.

11. The primary outcomes will be the IMRD disease activity changes after COVID-19, at four time points: (1) At baseline or recording data in the last 6 months; (2) The first rheumatic evaluation after COVID-19 (4-6 weeks); (3) 3 months after the inclusion (±15 days); (4) 6 months after inclusion (±15 days) (Table 2).

12. Details about previous lab exams will also be recorded, such as ESR, CRP, rheumatoid factor, anti-CCP, ANA, anti-ENA, anti-double-stranded-DNA, HLA-B27, complement, anticardiolipin IgG and IgM, ANCA and cryoglobulins.

Troubleshooting

Time Taken

Anticipated Results

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Acknowledgements

We thank the researchers involved in the 43 centers participating in the protocol.

Figures

Figure 1

Mapping of 43 centers spread in five geographic regions of the country

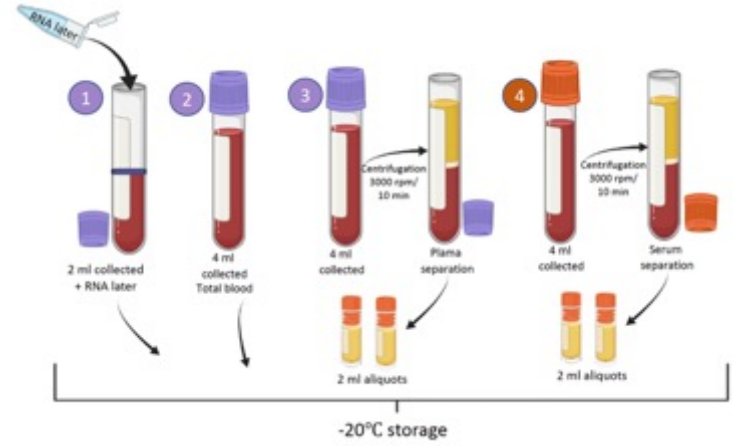

Figure 2

Blood collection and storage protocol The blood from the peripheral vein will be collected in a total of 16 ml: 3 EDTA tubes, one with 2 ml and two with 4 ml and 1 dry tube with separating gel. To the first EDTA tube, where 2 ml of blood was collected, 2 ml of RNAlater will be added for later storage. The second EDTA tube will be stored with total blood. The third EDTA tube will be centrifuged for plasma separation, along with the dry tube, for serum separation. Serum and plasma will be divided into 2 ml aliquots and frozen at -20ºC, together with the tube where RNAlater was added, and the EDTA tube containing whole blood.

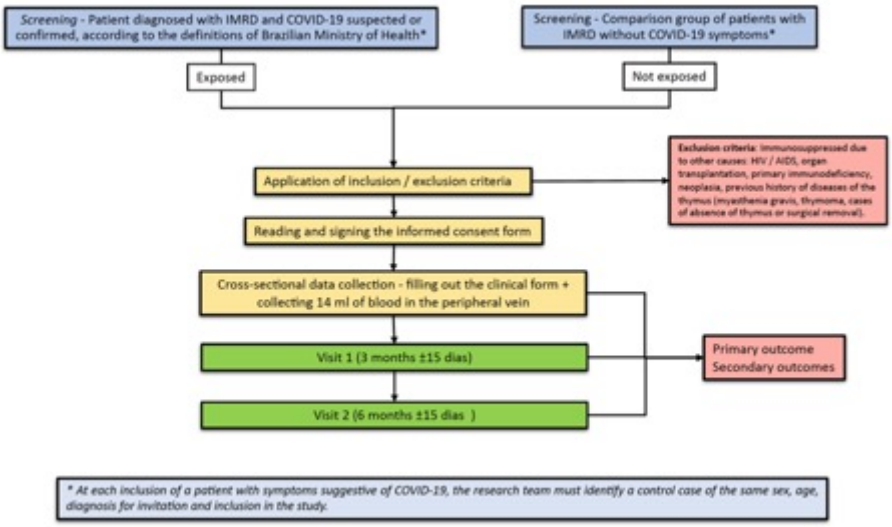

Figure 3

Study flowchart