CLINICAL RESEARCH PROTOCOL

Observational study to evaluate the potential effects of biological, biosimilar, and targeted synthetic disease-modifying antirheumatic drugs in the appearance of symptoms compatible with COVID-19 infection

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1. SUMMARY

Title	Observational study to evaluate the potential effects of biological, biosimilar, and targeted synthetic disease-modifying antirheumatic drugs in the appearance of symptoms compatible with COVID-19 infection
Study Description	Observational, retrospective study to compare the cumulative incidence of symptoms compatible with COVID19 infection during the period 1st to 29th March 2020 between patients receiving disease-modifying anti-rheumatic drugs (DMARDs; including biologic gents [bDMARDs], biosimilar agents [bsDMARDs], and targeted synthetic drugs [tsDMARDs) and patients with other rheumatic diseases not treated with these drugs
Objectives	**Primary objective** • To study the cumulative incidence of symptoms compatible with coronavirus infection in patients treated with bDMARDs, bsDMARDs, and tsDMARDs compared to a similar population of patients not treated with DMARDs. **Secondary objectives** • To investigate whether there is an immunosuppressive /immunomodulatory treatment with a protective effect on symptoms compatible with coronavirus infection • To study the association between ACEi (angiotensin converting enzyme inhibitors) and AIIAs (angiotensin II AT1 receptor antagonists) and the development of symptoms compatible with coronavirus infection • In the case of corticosteroids, to study the possible effect of the dose used • To study the possible differential effects of these drugs depending on the patient's gender and age • To investigate which comorbidities and treatments or combinations of treatments may be associated with a lower or higher risk of showing symptoms compatible with coronavirus infection or influence the severity of the disease • To investigate the demographic and clinical characteristics of patients with confirmed or strong suspicion of coronavirus infection in order to find associations that can help in the management of the disease and to identify patients with greater or lesser risk of infection
Inclusion and exclusion criteria	<u>Inclusion criteria for both groups:</u> • Adults >18 years of age • Referred from any of the primary care centres (PPCs) of

	the area of influence of the Hospital del Mar • With data in the medical history of the Hospital del Mar available for at least 80% of the values of the variables under study Study population: • Patients receiving bDMARDs, bsDMARDs, or tsDMARDs at the time of their inclusion in the study and prescribed for at least three months before inclusion • Patients whose adherence to treatment was good or otherwise not recorded in the patient's medical history Control group: • Patients with rheumatologic diseases not treated with bDMARDs, bsDMARDs, or tsDMARDs • Visited during the last 6 months at the Rheumatology service of Hospital del Mar Exclusion criteria for both groups: • No access to clinical courses from the family and community medicine specialist • Alive before the 29th March 2020 • Having a negative result in the SARS-VOC-2 detection test
Variables	**Main variables** • Treatment with bDMARDs, bsDMARDs, or tsDMARDs • Treatment with cMARDs • Treatment with corticosteroids • Consulted for symptoms of COVID-19 infection **Secondary variables** • Result issued for the test for SARS-COV-2 detection • Home isolation • Discharged from any CatSalut emergency service • Hospitalisation related with coronavirus infection • Death from confirmed SARS-COV-2 virus infection • Treated with ACEIs • Treated with AIIAs • Gender • Smoking status • Baseline disease (study population) • Other comorbidities
Population and number of subjects	The medical history of 2,551 patients will be reviewed: 1,701 adult patients treated with bDMARDs, bsDMARDs, or tsDMARDs, and 850 similar patients not treated with these drugs
Participating centres	Hospital del Mar, Parc de Salut Mar Primary care centres in the area of influence of Hospital del Mar - *PCC Vila Olímpica* - *PCC Barceloneta*

	- *PCC Besòs* - *PCC La Mina* - *PCC El Clot* - *PCC CAP Sant Martí 2* - *PCC Drassanes* - *PCC Raval Nord* - *PCC Poble Nou* - *PCC Ramón Turró* - *PCC Gòtic* - *PCC Casc Antic* - *PCC La Pau*
Overall duration of the study	12 days (from 20th April to 1st May 2020)

2. ABBREVIATIONS

AIIAs	Angiotensin II AT1 receptor antagonists
ACEI	Angiotensin converting enzyme inhibitors
bDMARDs	Biologic disease-modifying anti-rheumatic drugs
bsDMARDs	Biosimilar disease-modifying anti-rheumatic drugs
cDMARD	Conventional disease-modifying anti-rheumatic drugs
COVID-19	Coronavirus infection
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
DM	Diabetes Mellitus
DMARDs	Disease-modifying anti-rheumatic drugs
GCP	Good clinical practice
HT	Arterial hypertension
ICH	International Conference on Harmonization
IL	Interleukin
OSAS	Obstructive sleep apnoea syndrome
PCC	Primary care centre
SAD	Systemic autoimmune disease
SARS-COV-2	Severe acute respiratory syndrome due to Coronavirus 2
SARS	Severe acute respiratory syndrome
TNF	Tumour necrosis factor
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drugs

3. HISTORY OF VERSIONS

Version	Date	Description of the change	Brief justification
1.0	13/04/2020	NA	NA

4. THEORETICAL FRAMEWORK

Background and rationale of the proposed study

Since December 2019, cases of coronavirus infection (COVID-19) responsible for severe acute respiratory syndromes (SARS-CoV-2) have been reported in China. Coronaviruses are important pathogens for humans that appear to be of animal origin like other zoonoses. COVID-19 infection causes a respiratory infection with a clinical presentation that ranges between mild to serious (1, 2).

Severe forms develop in approximately 15% of the patients who have been diagnosed with COVID-19 infection (3). However, it is possible that, at the present time, this is not accurate if we consider the possibility of underrecognized infections for the calculations. Among severe forms, pneumonia is one of the most frequent presentation that can also evolve into severe acute respiratory syndromes (SARS) (4). The pathophysiological mechanisms of these pneumonic conditions seem related to an abnormal and massive activation of the inflammatory response of the organism itself. The most severe forms of COVID-19 infection require the patient's hospitalization and it is associated with a mortality that currently ranges between 7.2% in Italy (5, 6) and 0.9% in South Korea (7).

Evidence suggests that the hyperactivation of the immune response is of paramount importance in COVID-19 infection. The natural history of the infection has typical clinical and analytical characteristics. A rapid clinical deterioration has been described in the literature between 7 and 15 days after the onset of symptoms (8, 9). It is characterized by a worsening of the respiratory function in which infiltrates of monocytic and macrophage cells are observed, as well as multiorgan failures secondary to hypercoagulability and vasculitis processes (4). This systemic inflammation state of has been compared to that also occurring in two systemic autoimmune diseases (SAD): macrophage activation syndrome and antiphospholipid syndrome.

This pathologically exacerbated immune response can, in severe cases, trigger a cytokine storm. The cytokine storm is an abnormal and excessive inflammatory response mediated by pro-inflammatory cytokines that usually originates from multiple causes, among which are infectious processes and autoimmune diseases (4). At the clinical level, it manifests as elevated inflammatory parameters in peripheral blood, multi-organ failure, and systemic inflammation. In the case of COVID-19 infection, it is presumed that the high viral replication level in the lungs, pulmonary inflammatory infiltrates, and the secondary cytokine storm, are responsible for both the acute serious respiratory syndrome (SARS-COV-2) and the multiorgan failure that can lead to the death of some patients (10, 11).

The increasing knowledge on the pathophysiology of this disease points to different molecules that are part of the main inflammatory pathways in its etiopathogeny. We currently have specific treatments used in the routine management of various SADs that inhibit some of these pathways. The clearest example is interleukin-6, which contribution to the development of severe forms of the disease is not only known, but its inhibition is one of the main available resources in patients with torpid evolution (4). Other examples of involved molecules which inhibition represents a potential therapeutic alternative are tumour

necrosis factor (TNF)-alpha and interleukin 1, which respective inhibitory drugs are anti-TNF-alpha and anakinra / canakinumab / rilonacept (4).

Another sign of the importance of this immune hyperactivation is the efficacy of hydroxychloroquine in the treatment of the disease (12, 13). Of note, hydroxychloroquine is the mainstay immunomodulatory therapy for certain SADs such as systemic lupus erythematosus.

Given the progressive increase in the pandemic in relation to the available health resources, it is critical to find new effective treatments, especially when everything indicates that a rapid shortage of the stock of some of the existing treatments is likely. In these circumstances, any drug with a potential protective effect against the exacerbation of symptoms would be a valuable tool to prevent serious manifestations of the disease, future deaths, and ultimately the collapse of the health system.

Hypothesis

- bDMARDs, bsDMARDs, or tsDMARDs decrease the risk of developing symptoms compatible with coronavirus

5. OBJETIVES

Primary objective

• To study the cumulative incidence of symptoms compatible with coronavirus infection in patients treated with bDMARDs, bsDMARDs, and tsDMARDs compared with a similar population of patients not treated with DMARDs.

Secondary objectives

- To investigate whether there is an immunosuppressive /immunomodulatory treatment with a protective effect on symptoms compatible with coronavirus infection
- To study the association between ACEi (angiotensin converting enzyme inhibitors) and AIIAs (angiotensin II AT1 receptor antagonists) and the development of symptoms compatible with coronavirus infection
- In the case of corticosteroids, to study the possible effect of the dose used
- To study the possible differential effects of these drugs depending on the patient's gender and age
- To investigate which comorbidities and treatments or combinations of treatments may be associated with a lower or higher risk of showing symptoms compatible with coronavirus infection or influence the severity of the disease
- To investigate the demographic and clinical characteristics of patients with confirmed or strong suspicion of coronavirus infection in order to find associations that can help in the management of the disease and to identify patients with greater or lesser risk of infection

6. METHODOLOGY

6.1. Study design

Observational, retrospective study to compare the cumulative incidence of symptoms compatible with COVID19 infection during the period 1st to 29th March 2020 between

patients receiving bDMARDs, bsDMARDs, and tsDMARDs and patients with other rheumatic diseases not treated with these drugs

6.2. Study population, inclusion / exclusion criteria, and criteria for subject's withdrawal

Inclusion criteria for both groups:

- Adults >18 years of age
- Referred from any of the primary care centres (PPCs) of the area of influence of the Hospital del Mar
- With data in the medical history of the Hospital del Mar available for at least 80% of the values of the variables under study

Inclusion criteria for the study population:

- Patients receiving bDMARDs, bsDMARDs, or tsDMARDs at the time of their inclusion in the study and prescribed for at least three months
- Patients whose adherence to treatment was good or otherwise not recorded in the patient's medical history

Inclusion criteria for the control group:

- Patients with rheumatologic diseases not treated with bDMARDs, bsDMARDs, or tsDMARDs
- Visited during the last 6 months at the Rheumatology service of Hospital del Mar

Exclusion criteria for both groups:

- No access to clinical courses from the family and community medicine specialist
- Alive before the 29th March 2020
- Having a negative result in the SARS-VOC-2 detection test

6.3. Definition of the study variables

6.3.1. Main variables

- Treatment with bDMARDs, bsDMARDs, or tsDMARDs. The patient will be considered to be in treatment when this is stated in his/her updated hospital prescription and regularly picks the treatment from the pharmacy
- Treatment with bDMARDs and bsDMARDs:
    - Anti-TNF (Etanercept, Infliximab, Adalimumab, Golimumab, and Certolizumab)
    - Anti-IL6 (Sarilumab and Tocilizumab)
    - Anti-other ILs (Ustekinumab, Brodalumab, Guselkumab, Secukinumab, Ixeizumab, and Anakinra)
    - Anti-T lymphocytes (Abatacept)
    - Anti-B lymphocytes (Rituximab and Belimumab)

- Others: Vedolizumab

- Treatment with tsDMARDs (Tofacitinib, Baricitinib, and Upadacitinib)

- Treatment with cDMARDs. The patient will be considered to be in treatment when this is stated in his/her updated electronic prescription and his/her doctor does not record in the clinical course that the patient does not take them.

    - Leflunomide
    - Sulfasalazine
    - Methotrexate
    - Tacrolimus
    - Azathioprine
    - Cyclosporine
    - Mycophenolate / mycophenolic acid
    - Hydroxychloroquine / Chloroquine
    - Apremilast

- Treatment with corticosteroids. The patient will be considered to be in treatment when it is stated in his/her updated electronic prescription and his doctor does not record in the clinical course that the patient does not take them. The different corticosteroids will be adjusted to the equivalent dose of prednisone.

- Consultation for symptoms of COVID-19 infection. Consultations from the 1st to the 29th March 2020 in patients with the following symptoms will be considered as positive:

    - Body temperature above 37ºC plus asthenia and / or dry cough. In the absence of asthenia and / or dry cough, those with two or more of the following symptoms: anosmia, ageusia, rhinorrhoea, diarrhoea of one week of duration, pharyngitis, or odynophagia and arthromyalgia.

6.3.2. Secondary variables

- Positive result of the SARS-COV-2 detection test by any of the accredited reference laboratories in Catalonia between the 1st and the 29th March 2020.
- Home isolation indicated by a doctor and related to symptoms compatible with COVID-19 infection manifested between the 1st and the 29th March 2020.
- Discharge from any CatSalut emergency service that did not require hospitalisation between the 1st and the 29th March 2020.
- Hospitalisation related with coronavirus infection in any hospital accessed via the HC3 between the 1st and the 29th March 2020.

- Death from confirmed SARS-COV-2 virus infection when certified by a doctor.
- Treatment with ACEIs if specified in the updated electronic prescription
- Treatment with AIIAs if specified in the updated electronic prescription
- Gender
    - Man
    - Woman
- Smoking: it will be recorded whether the subject is or not a smoker, the years that he/her has been smoking or not smoking (in the case of ex-smokers) and the number of cigarettes / day
- Base diseases in the study population: SAD diagnosed by an accredited doctor and stated in the patient's medical history.
    - Rheumatoid arthritis
    - Psoriatic arthritis
    - Spondyloarthritis
    - Ulcerative colitis
    - Crohn's disease
    - Psoriasis
    - Behçet disease
    - Lupus
    - Pyoderma gangrenosum
    - Still's disease
    - Amyloidosis
    - Polyarteritis nodosa
    - Eosinophilic fasciitis
    - Juvenile idiopathic arthritis
    - Autoinflammatory disease
    - Uveitis
    - Hidradenitis
    - Sjögren syndrome
- Other comorbidities. The clinical diagnoses from the hospital clinical history, from the PCC, and from all available reports will be reviewed. The following comorbidities of interest will be recorded:
    - Diagnosed with hypertension (HT) in medical treatment

- Lung disease (asthma, chronic obstructive pulmonary disease [COPD], obstructive sleep apnoea syndrome [OSAS], interstitial lung disease, cystic fibrosis, and others)
- Need for home oxygen
- Diagnosed with cardiovascular disease
- Diagnosed with chronic kidney disease
- Diabetes mellitus (DM): we will register whether the patient has been diagnosed with DM and if he/she is being treated with oral antidiabetics or insulin
- Transplant: The presence of transplanted organs and / or tissues will be recorded
- Cancer and / or active treatment until 29th March. In those patients with a history of cancer that show cure criteria documented by an oncologist, cancer will not be considered as a comorbidity.

No criteria for withdrawal of subjects will be considered; the data of all patients who meet all the inclusion criteria will be analysed

7. STUDY PROCEDURES

To obtain study the population, a list of all patients being treated with bDMARDs, bsDMARDs, or tsDMARDs, will be requested to the PCCs of the area of reference of the Hospital del Mar and the CatSalut.

To obtain the control group, the records from the 1st September 2019 to the 29th February 2020 of the monographic medical dispensaries of the Rheumatology service of Hospital del Mar will be reviewed.

A database or case report form (CRF) will be designed with the Access® software, and will include all the variables under study. Five researchers will review the clinical history of the potential patients to be included in both cohorts. Only those who meet all the inclusion criteria and none of the exclusion criteria will be included for further analysis. In accordance with the General Data Protection Regulation 2016/679 and the Organic Law 3/2018 of the 5th December on Protection of Personal Data and Guarantee of Digital Rights, a unique code will be assigned to each patient and will not include any personal data that could make the subject of the study identifiable. The patient identification code will consist of a number assigned to each investigator, followed by a number assigned to patients in order of entry into the database. As an example, patient number 234 included by researcher number 3 will be assigned the number 3-234.

All the data that include the described variables, available and updated as of 29th March, will be recorded, so that no new treatments, diagnoses or symptoms will be recorded from that date onwards.

This observational study does not include other additional tests or procedures that may pose additional risks for the patient.

8. PERIOD OF STUDY

The collection of data in the electronic CRF will take place from the 20th to the 26th April 2020. The data will be analysed and discussed from the 27th to the 28th April 2020, and it is estimated that they will be ready for publication before the 1st May 2020.

9. STATISTICAL METHODS

9.1. Calculation and / or justification of the sample size

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, 1,701 subjects are required in the exposed group and 850 in unexposed group to detect a minimum relative risk of 1.3 and if the rate of patients in the unexposed group is 0.15. It has been estimated the follow-up loss rate will be 0%. For these calculations, the POISSON approximation was used.

9.2. Statistical analyses

An exhaustive descriptive analysis of all the variables of interest will be carried out. The analyses will include measures of central tendency and dispersion for numerical variables, as well as absolute and relative frequencies for categorical variables. The number of missing data will be reported in each case. To evaluate the associations between the different treatments and the appearance of symptoms of COVID-19, Poisson regression models with robust estimation of variance will be used to estimate incidence rates and 95% confidence intervals, excluding those individuals with negative confirmation in the test of the SARS-COV-2.

10. ETHICAL ASPECTS

The study will be conducted in accordance with the ethical principles derived from the Declaration of Helsinki (Fortaleza, Brazil, October 2013). In addition, the study will be conducted in accordance with protocol, the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP), and the regulatory requirements for the participating institutions.

The study will be carried out according to a protocol reviewed by qualified personnel from an Ethics Committee. The benefits of the study are considered to be in proportion to the risks and the rights and well-being of the subjects will be respected.

Due to the nature of the study (all the data will be completely anonymous), the importance of immediate results, and their implication for the treatment of the SARS-CV-2 pandemic, it is not planned to obtain informed consent from the participants.

11. CONFIDENTIALITY OF DATA

This study will be conducted in accordance with the General Data Protection Regulation (RGPD) No 2016/679 of the European Parliament and of the Council of 27 April 2016 and the Organic Law 3/2018, of 5 December, of Protection of Personal Data and Guarantee of Digital Rights. A unique code will be assigned to each patient and no personal data or data that could make the study subject identifiable will be included (pseudo-anonymised data). The patient identification code will consist of a number assigned to each investigator, followed by a number assigned to patients in order of entry into the database.

The 5 researchers who will have access to the clinical history of the patients to be included in the study are hospital doctors who have personal codes for their routine

clinical practice and will ensure the protection of all personal data. No other research staff will have access the patient's history or will be able to consult any data that is not included in the CRF, always appropriately and completely pseudo-anonymised.

The study data will be verifiable against the source data, all the original records, laboratory reports, and subject records will remain in the corresponding hospital medical documentation and on the HC3 portal. The confidentiality of the data and the identity of the patients will be maintained during the study and after its completion. Only the Principal Investigator and authorized study staff will have access to these confidential records. All original data will be in the IMASIS and the HC3 shared history. The Principal Investigator is responsible for ensuring that no paper copy will be kept.

No data used in the analysis and subsequent dissemination of the study results will contain any identifiable reference regarding the names of the patients.

Once the study is completed, the results will be communicated to the competent authorities in a convenient manner and in accordance with the local legislation.

It is anticipated that the results will be published in indexed scientific journals and the study will be registered in ClinicalTrials.gov.

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