TITLE: Effect of drug consumption before and during the SARS-COV-2 infection on the evolution of patients with COVID-19. A population-based study. (COVIDrug)

Protocol Version 1.2

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Funded by ISCIII in the Extraordinary Call for COVID-19 projects (2020). Scope of action: Point H of the call; artificial intelligence and massive integrated data analysis aimed at the epidemiological control of the COVID-19 disease.

Applicant entity: Foundation of the Santiago Biomedical Research Institute (IDIS).

1. BACKGROUND

COVID-19 in Galicia

As of March 21, 2020, Galicia doubled the number of COVID-19 cases by 2.9 days, one of the worst in Spain, compared to other communities such as Madrid, with 4.8. At the beginning of June, the number of total accumulated cases in Galicia was over 11,000 cases. Therefore, the number of COVID-19 cases that can become part of the study will be high, which will allow sufficient statistical power to be able to combat the existing misinformation, and the lack of scientific evidence on COVID-19. In this way, the information offered on COVID-19 and possible treatments to the scientific community and the population will improve.

The opportunities

The Autonomous Community of Galicia, through its Galician Public Health System, covers some 2.5 million people. In 2007, the Single Electronic Health Record (IANUS) was implemented in all the centers dependent on the Galician Public Health System (both at the hospital level and in the field of Primary Care), as well as a unique electronic prescription system that includes to all community pharmacies in the Autonomous Community of Galicia. Therefore, health information in our area meets the criteria of uniqueness and homogeneity, which offers a unique opportunity for massive data analysis and the extraction of reliable conclusions.

On the other hand, one of the pillars in the fight against the pandemic, as established by the WHO is “Pillar 2: Risk communication and community engagement” (COVID-19: Operational planning Guidelines and COVID-19 Partners Platform to Support Countries Preparedness and Response). In the aforementioned pillar, the WHO establishes as a priority action the implementation of systems to detect and respond to rumors and errors in the information related to the pandemic.

The drugs

Since the beginning of the COVID-19 pandemic, numerous contradictory information has emerged regarding different treatments that can positively or negatively affect the evolution of the disease. These have focused mainly on ACEI and/or ARBs and non-steroidal anti-inflammatory drugs (NSAIDs). There is also no clear evidence on the effectiveness of drugs that have been used empirically for the treatment of COVID-19 (chloroquine, hydroxychloroquine ...).

After the description of the pathogenic mechanism of the SARS-CoV-2 virus in humans (1), in which the virus uses an angiotensin-converting enzyme (ACEs) as a receptor to penetrate cells, it was hypothesized that patients treated with drugs that increase the level of expression of these receptors (ACEIs, ARB, ibuprofen ...) could increase their susceptibility to COVID-19 (2).

ACEI / ARB

Some publications suggest that treatment with ACE inhibitors and/or AIIRAs could be a risk factor for severity (and even mortality) for hospitalized patients infected with COVID-19. However, most studies do not adequately control the clinical and demographic characteristics of the patients (3-5). In one of the few case-control studies carried out, no evidence was found that treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II AT1 receptor antagonists (ARBs) will affect the risk of COVID -19 (6). Despite everything, the potential association between the use of ACE inhibitors or ARBs and the risk of COVID-19 has not yet been studied in-depth and the level of evidence is not sufficient to change the recommendations, as stated by the Spanish Agency of Medicines and Health Products (AEMPS).

NSAIDs

There is also a lack of evidence regarding the possible relationship between ibuprofen or ketoprofen treatment and exacerbation of infection. Thus, the AEMPS and the Food and Drug Administration (FDA) indicate that there is insufficient evidence to advise against the use of ibuprofen and ketoprofen, while the WHO and the French drug agency recommend using paracetamol, and not ibuprofen, at the same time. Time to self-medicate for COVID-19 symptoms.

Even though until now there is no scientific evidence that contradicts the use of NSAIDs in patients with COVID-19, various institutions continue to recommend using these drugs with caution, pending the completion of new studies, since in various studies their use has been associated with the use with higher rates of complications after respiratory infections (7-9).

Medicines used empirically for the treatment of SARS CoV2 infection

Empirically, since the beginning of the pandemic, different drugs authorized for other indications have been used as a treatment for SARS CoV2 infection. The drugs included in the list available in the AEMPS information note "Available treatments subject to special access conditions for

the management of respiratory infection by SARS-CoV-2" (latest update available 05/28/2020) include chloroquine, lopinavir-ritonavir, tocilizumab, remdesivir, sarilumab, baricitinib, anakinra, Interferon, ruxolitinib (10).

Many of these therapeutic strategies are in different phases of clinical trials (more than 1500 to date), but there is no evidence to recommend a specific treatment against SARS-CoV-2. To date, there is only partial, preliminary, and often contradictory data.

The existing evidence at the time of preparing this proposal is detailed below:

HYDROXYCHLOROQUINE / AZITROMYCIN. Initially, a study was published (11) that claimed that by combining hydroxychloroquine with the macrolide antibiotic azithromycin, 100% of the treated patients had been cured. However, this study had only 20 participants and had no control subjects. On May 22, The Lancet magazine published the results of a large study (12) that analyzed the efficacy of hydroxychloroquine as a potential treatment for COVID-19, concluding that it decreased survival and increased arrhythmias in patients, but on June 2, the same journal launched an "expression of concern" about the study because it had generated many doubts in the scientific community and finally withdrew the study on June 4 due to the dubious veracity of its data.

REMDESIVIR. A nucleotide analog that interferes with the polymerization of virus RNA. It was initially developed as a treatment for Ebola virus disease, also exhibiting in vitro activity against this and other viruses, including coronavirus. An open study was recently published with the first patients who received compassionate use treatment (13) in which it was associated with an improvement in the need for oxygen therapy in 68%.

LOPINAVIR / RITONAVIR. HIV protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV. It has been the treatment recommended by the Chinese health authorities during the crisis in this country. A randomized, controlled and open-label clinical trial results in hospitalized adult patients with confirmed SARS-CoV-2 infection and respiratory disease indicate that a beneficial effect of the treatment is not observed (14) without ruling out that the beneficial effect could be demonstrated. in other studies

TOCILIZUMAB. Immunosuppressive agent, IL-6 inhibitor, authorized for the treatment of rheumatoid arthritis. Around 500 SARS-CoV-2 patients have been treated with tocilizumab in Wuhan. However, it has not received health authority approval for this indication in any country, and at present, there is no solid clinical evidence regarding the safety and efficacy of SARS-CoV-2 treatment.

SARILUMAB. Immunosuppressive agent, IL-6 inhibitor, authorized for the treatment of rheumatoid arthritis. Currently, there are no data on the use of Sarilumab in patients with SARS-CoV-2 respiratory infection, although there are ongoing clinical trials in Spain and the European Union.

RUXOLITINIB. Immunosuppressive agent, selective inhibitor of Janus associated kinases (JAK) JAK1 and JAK2. The use of Ruxolitinib could reduce the inflammatory cytokine release storm by inhibiting the jak1 / jak2 pathway. There are currently two independent clinical trials underway, in China and Spain, although there are no published data for any of them to date.

SILTUXIMAB. Immunosuppressive agent, IL-6 inhibitor. Currently, several ongoing clinical trials are evaluating the efficacy of this treatment.

BARCITINIB. Immunosuppressive agent licensed for rheumatoid arthritis in adults, selective and reversible inhibitor of Janus-associated kinases (JAK), JAK1, and JAK2. There are currently several ongoing clinical trials that evaluate the efficacy and safety of Barcitinib in patients with COVID-19 pneumonia.

ANAKINRA. IL receptor antagonist licensed for the treatment of Rheumatoid Arthritis. It could have potential use to reduce systemic inflammation and lung damage caused by SARS-CoV2 without this being demonstrated in clinical trials to date.

INTERFERON BETA-1B (IFNB) AND INTERFERON ALPHA-2B. Immune system modulators. Some authors have postulated that in vitro interferon can increase the expression of the ACE2 receptor in human epithelial cells, which is why it could favor COVID-19 infection (15, 16).

CORTICOIDS. The use of corticosteroids for the treatment of critical patients with COVID-19 remains in question. The main reason for its use is to modulate the destruction caused by inflammation of the immune response. There is great controversy regarding the use of corticosteroids. Corticosteroids were widely used during the SARS and MERS outbreaks and have also been used in patients with Covid-19. On the one hand, they can reduce lung inflammation, but at the same time also immunity. In a meta-analysis on the use of corticosteroids in SARS patients, only four studies provided conclusive data, and they were a detrimental effect (17). A review of treatments for acute respiratory distress syndrome of any cause, based on six studies with a total of 574 patients, concluded that there is insufficient evidence to recommend corticosteroid treatment (18).

As can be seen, there is currently little conclusive data on their efficacy and safety and the few existing data are unreliable or in need of replication. On the other hand, the exponential increase in the publication of studies without peer review on the preprint servers and the echo of many

of them in the media has led to situations of misinformation in the population about the efficacy of new treatments to study.

2. THEORETICAL MODEL

In summary, the information that has emerged about different medications and their possible negative or positive effects on COVID-19, many of them with a lack of evidence, favor rumors and errors in the information that can negatively affect Health Public, either because they stop prescribing and/or consuming indicated and safe drugs, or because they are consuming drugs that have safer therapeutic alternatives. This project aims to generate knowledge from a population-based cohort study to improve the scientific evidence on different therapeutic groups.

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4. OBJECTIVES

General objectives

1. A) Assess whether prior consumption of certain medications (ACEIs, ARBs, ibuprofen…) conditions a greater susceptibility to infection by SARS-COV-2.

1. B) Identify which factors in patients with COVID+ are associated with greater severity (hospital admission).

Specific

1.1. Assess whether there are differences in the risk of developing COVID-19 by active ingredient within each therapeutic group (NSAIDs, ARA2, ACEI).

1.2. Determine if there is a dose-response effect between exposure to the drug and the risk of suffering from COVID-19.

1.3. Assess the influence of the previous duration of the treatments.

1.4. Identify possible interactions (synergism, antagonism) with individual and clinical variables (sex, body mass index, clinical history).

1.5. Identify the factors of patients with COVID + that condition their evolution towards more serious stages (hospital admission) compared to COVID + who do not enter.

5. METHODS

Study design

A population-based retrospective cohort study (Autonomous Community of Galicia) will be carried out, which will involve the 2.5 million subjects covered by the Galician Public Health System.

Study period

The study period will be as follows:

- Start six months before the first declared case of COVID-19 in the C.A of Galicia.

- Completion: Last declared case of COVID-19 in the C.A of Galicia. In case of not declaring the end of the pandemic in Galicia before 12/31/2020, this date will be taken as a reference for data extraction.

Data sources

The database of Electronic Health Record in Galicia (IANUS) and the databases of prescription and dispensing of medicines of the Galician CA will be used, as well as other sources of data available in the Public Health System of Galicia.

The information extraction will be carried out in an automated way by an independent information technology services company based on the Complex Information and Analysis Systems (SIAC) of the Servizo Galego de Saude (SERGAS). SIAC is a data warehouse that stores information for the organization of different systems (Sanitary Card, Electronic prescription dispensing (DISEL), Hospital pharmacy administration/dispensing (SILICON), Hospital admission information system (SIHGA), Minimum Set Basic Data (CMBD), Statistical Bulletin of Death, Personnel and payroll, Laboratory of clinical analysis, EHR Analysis and Administration of medication in ICU / REA).

In addition, the platform will be used for the exploitation of clinical and epidemiological data HEXIN, which the Galician Health Service (SERGAS) has recently implemented, and which has been designed with a charge of European funds (INNOVASAÚDE Project). HEXIN can obtain clinical data for epidemiological research at a low cost due to its computational capacity and for its reuse in different use cases. In addition, from unstructured information, it can generate records automatically, something that was not possible until its implementation.

Some of the possible applications that HEXIN offers relevant to this proposal are:

1. The characterization of the population through the definition of specific areas (disease, case study, areas ...), to know the total number of people who present certain symptoms or the incidence and prevalence of diseases, suspected effects adverse and risk factors.

2. It allows evaluating the efficacy and efficiency of treatments by comparing similar patients and/or being able to measure comorbidity (presence of one or more disorders or diseases in addition to the primary disease or disorder).

In short, it is a Big Data platform that allows the exploitation of the clinical information available in the electronic medical record (IANUS) and others, to generate databases that can be analyzed using advanced epidemiological tools.

https://www.sergas.es/Hospital-2050---Innova-Saude/IS-HEXIN?print=1

Participants and study groups

A nested case-control study will be designed in this population-based retrospective cohort. All patients diagnosed with COVID-19 in the C.A. of Galicia during the study period will be considered as cases. Two groups will be used as controls; a sample from the rest of the cohort (objective G1.A) and the COVID + patients by PCR not admitted (objective G1.B).

Case definition: Patients diagnosed with COVID-19 by PCR, identified by their respective ICD 10 and ICD 11 codes. All incident cases diagnosed with COVID-19 during the period studied will be included.

Definition of CONTROL 1 (objectives E1.1 to E1.4): Subjects with a health card that are part of the population served by the Galician Public Health System. Up to 20 controls will be selected for each case, matched by health area (to guarantee the same opportunity for geographic exposure to SARS-COV-2), sex, and age.

Definition of CONTROL 2 (objective E1.5): COVID + patients by PCR not admitted. All patients in the database who meet this criterion will be included.

Those in which the registered data are not of sufficient quality to be processed will be excluded.

Variables

Exposure variables. Exposure variables will be considered for all drugs prescribed to cases and controls in the cohort, during the study period. They will be defined as drugs prescribed by a doctor from the Galician Public Health System and at the same time dispensed (defined as drugs withdrawn in the Hospital Pharmacy Service or the Pharmacy Office) such as Ibuprofen, ACE inhibitors, NSAIDs ... These drugs will go away updating as new suspicions arise, proceeding to a review in the database generated of the associated risks.

To assess the exposure to the drug or therapeutic group under study, the index day will be considered as the 10 days before the diagnosis of the disease.

The consumption of these drugs in the 6 months before the index day will be assessed. From the prescription data, the mean number of Defined Daily Dose (DDD) consumed per day by each patient will be calculated. This approach makes it easy to compare different active ingredients and considers adherence to treatment.

Effect variables: the case or control condition.

Covariates: Age, sex, comorbidities (diabetes mellitus, obesity, history of active neoplasms, chronic obstructive pulmonary disease (COPD), asthma, hypertension, ischemic heart disease) identified through ICD-10 codes for subjects admitted to hospital and Classification International Primary Care (CIAP) in the rest.

Statistical analysis.

We will express qualitative variables as frequencies and percentages and quantitative variables as mean and standard deviation. The between-group relative difference in clinical features and drug exposures will be used for comparing case patients and controls. Differences in means will be assessed using the Student's t-test and differences in percentages were assessed using the $\chi 2$ test.

Multilevel logistic regression analysis will be performed, considering each stratum (a case and the controls with the matching variables) as an aggregation unit to estimate the odds ratio, and its 95% confidence interval (CI) for the risk of Covid- 19 associated with exposures of interest. Adjustments will be made for the above-reported covariates. Odds ratio trends will be tested, when feasible, according to the statistical significance of the regression coefficient of the recoded variable obtained by scoring the corresponding categories.

Crude and adjusted estimates will be obtained for the effect of different therapies dispensed compared with the absence of any drug therapy.

All analyzes were performed using the R software (version 4.1.2). Statistical significance will be set at the 0.05 level.

6. ETHICAL AND LEGAL ASPECTS

With the platform, data can be obtained in a pseudonymized way and, therefore, guaranteeing the requirements established in terms of data protection in the General Data Protection Regulation and in the Seventeenth Additional Provision of Organic Law 3/2018, of December 5, Protection of Personal Data and Guarantee of Digital Rights.

The evaluation and report of the Galician Drug Research Ethics Committee (CEIm G) and the classification of the Spanish Agency for Medicines and Health Products (AEMPS) were obtained.

A data treatment contract will be signed following the applicable data protection regulations, ensuring that the data will be processed only for the purpose provided in this research protocol. Once the project is finished, the data will be deleted or returned to the person responsible for the treatment under the provisions of the treatment contract.

7. LIMITATIONS

● Underdiagnosis of COVID-19 by: (1) Patients who have died without diagnosis and (2) Patients who have suffered from the disease almost asymptomatically and who have not been diagnosed. This bias will underestimate the effect, so it will not be relevant if effects are found in the study.

● Confusion by indication. It occurs when the choice of one or the other treatment is affected by the specific baseline characteristics of the patients. To avoid this, a match will be made by Propensity scores if necessary.

● Consumption of non-prescription drugs (especially important in the case of NSAIDs).

8. EXPECTED IMPACT OF THE PROJECT:

This project aims to generate a population-based data set that allows testing alerts on new drugs that may act positively or negatively in the clinical evolution of the COVID-19 disease. The final objective will be to provide consistent evidence to the National Health System about these alerts and which, in turn, can help decision-making at the national and international level to fight the

pandemic. This goal is in line with the report published by the European Medicines Agency (EMA) and the heads of the Medicines Agency (HMA) recommending making the most of the use of Big data in healthcare: (https://www.aemps.gob.es/informa/notasinformativas/laaemps/2020-laaemps/recomendaciones-para-desarrollar-el-potencial-del-big-data-para-la-salud-publica-en-la-ue/).

The research group plans to apply the knowledge and experience accumulated in recent years in the field of pharmacoepidemiology and the massive analysis of clinical data (extracted from the different data sources of the Galician Public Health System). The results will be applied to the current health emergency due to COVID-19, to combat the misinformation and, therefore, improve the evidence offered to the scientific community and the population.

9. SCHEDULE AND TASKS

The study is expected to last 1 year (duration allowed in the Extraordinary Call for COVID 19 projects), which will be distributed in the following tasks:

• Definition of terms for the selection of subjects and variables. The research team (two months)

• Data extraction through the HEXIN platform and debugging (three-four months)

• Data analysis and reporting by drugs / therapeutic groups. The research team (five months)

• Preparation of final report. The research team (one month).

10. BUDGET

This project has been funded by the ISCIII through the extraordinary call for COVID 19 projects. 71,000 euros were awarded to the IDIS Foundation, distributed in the following concepts:

● ICT company for data extraction

● Personnel for database debugging

● Dissemination of results: Submission to OPEN ACCESS journals of the manuscripts derived from the study.