Project plan:

EULAR-COVID-19 Datenbank

Paul Studenic[1], Helga Lechner-Radner[2], Michael Bonelli[3], Daniel Aletaha[4]

Division of Rheumatology, Department of Internal Medicine 3, Medical University Vienna

1: Regional Lead of the EULAR-COVID Global Alliance

2: Associate Professor and international database expert

3: Associate Professor and translational scientist expert

4: Professor of Rheumatology, division head and EULAR treasurer

CONTENT

1. BACKGROUND

The outbreak of the new coronavirus infections COVID-19 in December 2019 in China has quickly become a global health emergency. Given the lack of specific anti-viral therapies, the current management of severe acute respiratory syndrome coronaviruses (SARS-CoV-2) is mainly supportive, even though several compounds are now under investigation for the treatment of this life-threatening disease. Sars-CoV2 / COVID-19 is a novel coronavirus which has caused a WHO-declared pandemic in 2020. Patients with underlying chronic health conditions and who are taking immunomodulatory medications are thought to be at increased risk of poor outcomes. Collecting information about COVID-19 outcomes among patients with rheumatic diseases and on immunosuppressive medications will allow clinicians to provide advice and improve the care of such patients. The current situation poses a need to develop strategies to protect people at high risk of infection or more severe courses of disease. Theories exist that people with hypertension and diabetes mellitus are at increased risk of infection. On the one hand since several studies outline that these morbidities were highly prevalent among COVID-19 positive tested individuals and those admitted to intensive care units, and on the other hand, since COVID binds via angiotensin converting enzyme (ACE) 2 to their target cells. ACE2 expression is increased in people with diabetes mellitus and treatment with ACE-inhibitors results in an upregulation of ACE2. Both statements might add to the discussion of increased risk for these groups of people. There is no literature on the risk of people with rheumatic diseases on disease modifying anti-rheumatic drugs (DMARDs) concerning infection and course of disease. However, some groups have argued that certain DMARDs are helpful in treatment of (severe) COVID. Baricitinib a JAK1/2-inhibitor also inhibits AP2-associated protein kinase 1 (AAK1), which promotes endocytosis and binds the cyclin G-associated kinase, also a mediator of endocytosis. This effect might make baricitinib a useful drug to target viral transmission in the host. One of the most popular drugs in current COVID trials is hydroxychloroquine (HCQ). HCQ, an old anti-malarial and used in treating various rheumatic conditions has demonstrated its ability to interfere with virus spreading in vitro. More than 20 clinical trials are running in China and interims analyses have indicated superiority of HCQ compared to standard treatment in COVID patients in an ICU setting. The first recently published letter of the COVID alliance has reviewed the values of HCQ critically.

The EULAR-COVID-19 Database (https://www.eular.org/eular_covid19_database.cfm) is a European paediatric and adult database designed to monitor and report on outcomes of COVID-19 occurring in patients with RMDs. The first description of the database and preliminary crude analyses have been published in Lancet Rheumatology.

2. OBJECTIVES

This internet-based register-survey will capture information about COVID-19 cases among rheumatology patients. Data will be used in quality improvement/surveillance efforts to inform efforts aimed at improving treatment of these patients, including:

- Management of rheumatic diseases in light of the COVID-19 epidemic,
- Prevention and treatment of COVID-19 in patients on immunomodulatory medications

3. PATIENTS AND METHODS

Eligible patients will be informed in detail about the procedures of the study. Patients who are willing to participate will have to give oral and written informed consent according to the Declaration of Helsinki. People who are in a critical medical state of an ICU setting will only be entered into the database after their recovery, when being able to provide informed consent. Eligible patients that pass away on the sequelae of COVID19 before being able to provide informed consent will be included without. The register is designed for patient data entry of all age groups and was approved by the Pediatric Rheumatology European Society (PReS). We will include patients starting with the age of 18 years. The database has been pre-reviewed by several IRBs in the USA. The IRB of the US-host at the University of California San Francisco has exempted the Global Rheumatology Alliance (GRA) register survey (https://rheum-covid.org/about/) from further IRB investigation. The UK Health Research Authority has likewise exempt the EULAR COVID-19 database from formal approval. There was no requirement for informed patient consent.

4. DATA COLLECTION AND STUDY VARIABLES

Only data obtained during routine clinical care will be collected and entered in the register. All variables and definitions are listed in the separate file “codebook”. The crf is also submitted as an extra file.

Data is entered by the respective physician only once into the register survey. An automated number for each entry will be generated. Data on name, birthdate will not be entered in the survey. For data extraction and analyses, all data is pseudonymized. The data is being stored on the RedCap database, hosted by the University of Manchester in the United Kingdom. The European League against Rheumatism (EULAR) is in control of the data. Both the data-host

and controller are under GDPR. The server might we relocated into a European Union member state until the end of the year. However there will be additional contracts in place most likely. The European Union has stated on this matter: “The COVID-19 pandemic has disrupted the negotiations on the future relationship between the EU and UK, with the two sides unable to meet since 5 March 2020, and no clear plan in place for the negotiations to resume. The increasingly uncertain circumstances have led to calls for an extension to the transition period, as provided for in the Withdrawal Agreement, which is currently due to expire on 31 December 2020." More detailed SOPs are currently being developed for data access, however any person submitting data should have access to the data they submitted, and similarly any institution/society/regional lead would also have access to the data submitted by their institution/society/region. For getting access to the entire dataset a transparent process will be implemented that will include peer-review processes involving the EULAR COVID-19 Steering group and access should then be provided if the project is of scientific interest and in line with EULAR/Global Rheumatology alliance objectives. Anonymised patient data will also be shared with the global database which is based in the United States. All data items except for reporter data (name, hospital, etc) will be shared with the GRA. The data shared with the US group GRA will be stored in MyResearch, a secure data hosting service for researchers at UCSF. MyResearch provides research teams with a professionally managed, secure, web-based, collaborative environment in which to manage files containing data. MyResearch also provides remote desktop capability with application and database services that allow investigators to view, manipulate, and save their data entirely in a protected environment without requiring files to be stored on their own computers. Applications such as SAS, STATA, Excel and many others run on MyResearch servers in our secure data center but they appear on the user’s own screen as if they were running locally on the user’s computer. Only 5 UCSF members of the analytical team will access data from this secure environment, and all of them will access data using secure, encrypted computers in a private setting.

5. STATISTICAL ANALYSES

Data will be pseudonymized for analyses. To understand if morbidity and mortality of COVID is associated with different rheumatic conditions, patients will be subdivided according to their underlying rheumatic disease and outcomes such as severity of COVID-19 infection (e.g. presence acute respiratory distress syndrome, sepsis, myocarditis or death) will be compared across subgroups

Data analyses will be carried out using SPSS®, Version 26 (SPSS, Chicago, IL, USA) and SAS (SAS Institute Inc., Cary, NC, USA), and SAS® (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA) and STATA (StataCorp. 2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC)

.

6. RISK-BENEFIT EVALUATION

Incorporated patients do not gain any benefit out of the study nor will there be any risks, as all variables will be collected during routine clinical care. Analyses of routine care data is a necessity to quickly generate knowledge on a population that is considered as high risk in a pandemic. Results from such analyses, particularly that relating to health and disease outcomes may facilitate the more harmonized understanding of mutual management of inflammatory arthritis & connective tissue diseases. As with any online register survey, there is a risk of data breach. Systems that are used by RedCap (server for storage of data) assure to the best of possible a secure web connection with authentication of data logging.

6 REFERENCES

1. Kim AHJ, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-García A, et al. A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19. Annals of Internal Medicine. 2020 doi:10.7326/m20-1223.
2. 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? Clin Exp Rheumatol. 2020 Mar-Apr; 38(2):337-342
3. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases. 2020 doi:10.1093/cid/ciaa237.
4. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. International Journal of Antimicrobial Agents. 2020 2020/03/04/:105932 doi:https://doi.org/10.1016/j.ijantimicag.2020.105932.
5. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020 Feb 15; 395(10223):e30-e31 doi:10.1016/s0140-6736(20)30304-4.
6. Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? The Lancet. 2020 doi:10.1016/S0140-6736(20)30691-7.
7. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. The Lancet Infectious Diseases. 2020 doi:10.1016/S1473-3099(20)30243-7.
8. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? The Lancet Respiratory medicine. 2020 Mar 11 doi:10.1016/s2213-2600(20)30116-8.
9. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virology journal. 2005 Aug 22; 2:69 doi:10.1186/1743-422x-2-69.
10. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Annals of the Rheumatic Diseases. 2020:annrheumdis-2020-217424 doi:10.1136/annrheumdis-2020-217424.
11. Spinelli FR, Ceccarelli F, Di Franco M, Conti F. To consider or not antimalarials as a prophylactic intervention in the SARS-CoV-2 (Covid-19) pandemic. Annals of the Rheumatic Diseases. 2020:annrheumdis-2020-217367 doi:10.1136/annrheumdis-2020-217367.
12 Gianfrancesco MA, Hyrich KL, Gossec L, Strangfeld A, Carmona L, Mateus EF, et al. Rheumatic disease and COVID-19: initial data from the COVID-19 Global Rheumatology Alliance provider registries. The Lancet Rheumatology. doi:10.1016/S2665-9913(20)30095-3.