NYU RORY MEYERS COLLEGE OF NURSING

COVID-19 and Rheumatological Conditions: An Observation, Correlational Study

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Introduction

In 2009, the H1N1 influenza A spread far and wide, earning the distinction of a pandemic (Centers for Disease Control, 2020). While many other infections deemed outbreaks occurred in the past decade, no other infectious disease has earned the distinction of pandemic until COVID-19 originated in 2019. A mainstay of rheumatic diseases' is treatment with disease modifying anti-rheumatic drugs (DMARDs) and biologics. These therapeutics have an increased immunomodulating effect, thereby, increasing the risk of infections at baseline (American College of Physicians [ACP], 2017). There is a paucity of knowledge related to COVID-19 in the general and rheumatological patient population. This descriptive correlation study will aim to increase knowledge and recommendations for adult rheumatological patient care in the setting of the COVID-19 pandemic via the presentation and summary of provider data submitted to the COVID-19 Global Rheumatology Alliance (GRA) Database and the European League Against Rheumatism (EULAR) COVID-19 Database.

Methods

Upon the classification of COVID-19 as a pandemic, the COVID-19 Global Rheumatology Alliance was formed in mid-March 2020. Composed of community and academic rheumatologists from around the world, the committee gained to gather and disseminate rapid, accurate, and evidence-based information to the rheumatology community (GRA, 2020). The study was determined to be exempt by the Institutional Review Board at Boston Children's Hospital (GRA, 2020).

The Alliance electronically collected data using Qualtrics from rheumatology providers and patients around the world using standardized surveys: rheumatology providers The provider survey consists of 37 questions, including questions specific to COVID-19 infections relating to signs and symptoms, diagnosis, treatment, and outcomes. Autoimmune and rheumatology specific questions relating to primary disease, comorbidities, and treatment for such conditions prior to COVID-19 are assessed. Additional questions regarding medication use for other non-autoimmune, rheumatological disease states are also assessed. Data relating to age, gender, race, and ethnic origin was also gathered. The Alliance recommended to providers to wait seven days from COVID-19 symptom onset to complete the survey to observe disease course; however, a follow-up email was also sent for follow-up on each case. To date (May 26, 2020), providers have submitted information on 874 patients.

The Global Alliance did not accept survey results from countries that are part of EULAR. In collaboration with the Pediatric Rheumatology European Society (PReS), EULAR created a separate database and further directed providers from EULAR countries (Italy, Portugal, Germany, and Sweden) to separate databases to minimize repetition of data, yet included this data in the EULAR Database. Providers were instructed to report cases that were confirmed or strongly suggested after a minimum of 14 days, as outcomes could not be updated, in contrast to the Alliance. The data collection and reporting was performed using REDCap (EULAR, 2020). The EULAR provider survey can be seen in Appendix B.

Providers completed a survey assessing age, gender, COVID-19 diagnosis details, signs and symptoms, treatment, and outcome of COVID-19, including the need for hospitalization or associated complications primary rheumatological or autoimmune diagnosis (maximum of three), current disease activity and treatment, as well as assessment of continuation or discontinuation in the setting of COVID-19 diagnosis. Pregnancy and comorbidities were also surveyed, as well as administration of the influenza vaccination for the 2019-2020 season. The EULAR survey also included reporting of significantly abnormal laboratory findings: anemia, elevations in d-Dimer, ferritin, IL-6, sIL2R, fibrinogen, leukopenia, thrombocytopenia, decreased ALC, triglycerides, and CRP, as well as splenomegaly and hepatomegaly. Additionally, the survey allowed for open responses regarding lessons learned or survey feedback. These additional findings were not publicly available. To date (March 7, 2020 through May 26, 2020), over 900 cases reported (N=985).

The data from this registry is stored at the University of California, San Francisco. The EULAR – COVID-19 data will be stored at The University of Manchester in the United Kingdom (Alliance, 2020). Data analysis included aggregation of the publicly available domains shared by these two registries using Microsoft Excel Spreadsheet. Aggregation included combining categories in terms of age, gender, primary rheumatological disease, comorbidities, and pre-COVID-19 rheumatology pharmacological management.

Results

The two registries present data from mid-March thru May 26, 2020 of 1859 rheumatology patients with COVID-19. Of these patients, the majority were female: 67% among the combined registry, with 74.9% from the GRA registry and 61.6% from the EULAR registry.. The GRA and EULAR registries used unique age groupings in their data. This data was aggregated using a histogram, revealing the GRA registry had the greatest number of cases among patients aged 30-65 (n=612), compared to EULAR's highest number of reported cases among those aged 61 and up (478). Both registries had the lowest cases among those less than 30 years of age (Figure 1).

- **Hospitalization & Fatality:** A combined 939 patients required hospitalization: 583 (59%) from EULAR, and 356 (40.7%) from the Global Registry (Figure 3). Of the 1859 cases, the Global Registry reported 63 deaths with a case fatality rate of 7.2%; EULAR 146 deaths and case fatality rate of 14.8%; combined registries with 209 death, 1.1% case fatality.

- **Primary Diagnosis (Figure 2):**
  - Rheumatoid arthritis was most: 711 patients (38%); 337 (38%) in the GRA registry and 374 (38%) in the EULAR registry.
  - Psoriatic arthritis: 226 reported cases comprising a total of 12.15% of cases: GRA reporting 88 (10%) and EULAR 138 (14%)
  - SLE also had a high incidence of COVID-19 cases, 225 (12.1%) with 156 reported by GRA (17.85%) and 69 (7%) reported by EULAR
  - Spondylarthritis patients had 159 total cases (8.5%) with 60 cases reported by GRA to 99 reported by EULAR.
  - Gout patients had 68 total reported cases (3.65%) with 19 in the GRA registry compared to 49 in the EULAR registry.
  - The EULAR registry limited reporting to top five reported primary rheumatological conditions; GRA reported 12 total, including: vasculitis (58 cases), Sjogren's syndrome (31 cases), inflammatory myopathy (31), systemic sclerosis (27), sarcoidosis (20), undifferentiated connective tissue disease (17), and other inflammatory arthritis (32).

- **Comorbidities:** Among COVID-19 positive rheumatology patients, hypertension was the most prevalent comorbidity with a total of 683 cases (36.7%) with 335 patients reported through GRA and 348 from EULAR. Lung disease, consisting of chronic obstructive pulmonary disease (COPD), asthma, emphysema, interstitial lung disease (ILD), and others was present in 396 patients (21%) with 187 in GRA, 209 in EULAR. Diabetes was prevalent in 15% (285 cases: 153 in GRA and 132 in EULAR). Cardiovascular disease was present in 229 total cases (12.3% combined cases); 85 reported via GRA and 144 in EULAR. EULAR reports 13% of cases without comorbidities (244). GRA also reports comorbidities of morbid obesity in 64 cases, chronic renal insufficiency (62), and cancer (56). See Figure 3.

- **Pharmacotherapy:** The registries also reported pharmacological management of rheumatological conditions. Many reported patient cases report the use of a convention disease modifying anti-rheumatic drug (DMARD), at 1167 or 62.7%, split evenly between the GRA (n= 572) and EULAR (n= 595) registries. Biologic DMARDs was the second most frequent therapeutic reported, with 619 or 33.2% of COVID-19 positive cases; again, with an equal distribution between GRA (295) and EULAR (324) registries. The final reported therapeutic is a targeted synthetic DMARD in the EULAR registry, listed as a JAK inhibitor in the GRA registry. Of the reported cases, 3.87% (n=72) patients use this therapy. The GRA registry also reports the use of antimalarials (n 240), glucocorticoids (284), and NSAIDs (197).

Figure 1: Age

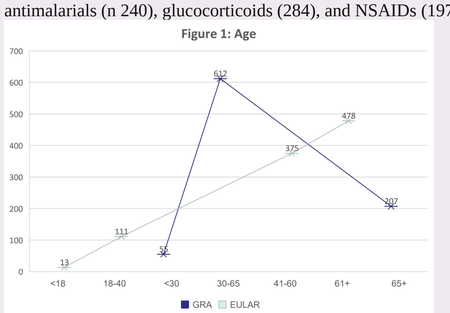


Figure 2: Primary Rheumatic Disease: Combined GRA & EULAR Registries

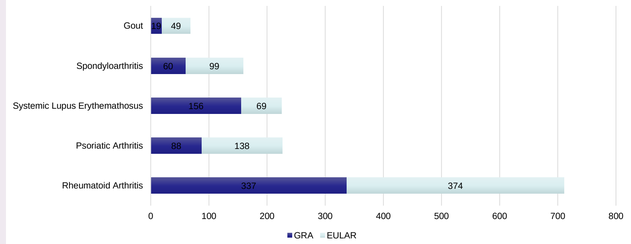


Figure 3: Comorbidities Among COVID-19 Positive Rheumatological Patients Combined GRA and EULAR Registries

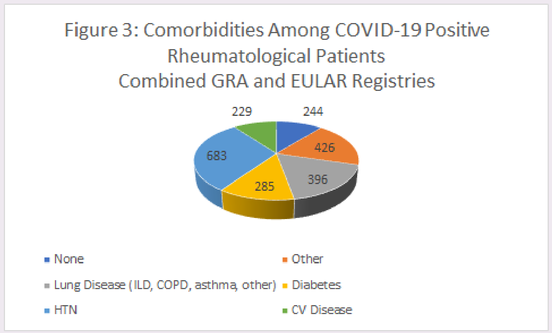
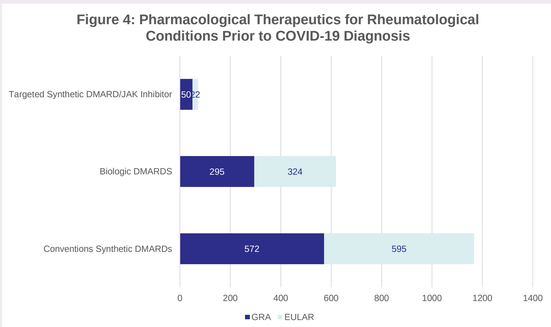


Figure 4: Pharmacological Therapeutics for Rheumatological Conditions Prior to COVID-19 Diagnosis



Discussion

The preliminary data presented by the Global Alliance for Rheumatology and European League Against Rheumatism illustrates COVID-19 to have a great presence among female patients over the age of 30 with diagnoses of inflammatory arthritis (rheumatoid, psoriatic, and gout) of systemic lupus erythematosus (SLE). This pattern is consistent with general disease prevalence as RA affects 1% of worldwide population with two to three times greater incidence in females than males; psoriatic arthritis also affecting an estimated 1% worldwide population with equal incidence across genders (ACP, 2017). Gout prevalence increases with age, consistent with reported cases evaluated in this study (ACP, 2017). This does not account for the likely underdiagnosis of rheumatic diseases or patients with multiple rheumatic diseases. Furthermore, the comorbidities of lung disease, hypertension, and diabetes reported to these registries are consistent with preliminary reports indicating higher risk for COVID-19 infection and poor outcomes among the general population (CDC, 2020).

Data shows higher incidence of COVID among patients taking conventional synthetic DMARDs in comparison with biologic or targeted synthetic DMARDs. Conventional synthetic DMARDs include antimalarials, azathioprine, leflunomide, cyclophosphamide, cyclosporine, methotrexate (MTX), mycophenolate mofetil, sulfasalazine, tacrolimus (GRA, 2020). Biologic DMARDs included abatacept, belimumab, CD-20 inhibitors, IL-1 inhibitors, IL-6 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, TNF-inhibitors (GRA, 2020). Targeted synthetic DMARDs include JAK inhibitors. Does not specify dual use of biologics and MTX. Furthermore, the use of these medications correlates with the increased risk of infections from the immunosuppressive properties associated with DMARDs (ACP, 2017).

This study has a multitude of limitations. An observational, correlational design study is a lower level of evidence (DiCenso, et al., 2005). Furthermore, the data comprising this study is aggregated from two registries' summaries; the complete database was not publicly available, limiting more conclusive summaries and controlling for confounding. Additionally, both GRA and EULAR registries used different data collection tools with variation in questions.

The amassed data is from cases both suspected from symptoms and confirmed via testing. A positive test was not required for submission, thereby increasing the risk of potential false positives; conversely, COVID testing capacity has had noted limitations which may have also excluded submissions in the setting of false negatives. It has been projected there is a 1 in 5 chance in having a false negative test using the COVID-19 rapid test polymerase chain reaction (PCR) test (Kucirka, et al., 2020). Furthermore, providers submitting case data in the GRA registry had the opportunity to submit with follow-up emails sent later; the EULAR registry required submission after 14 days from symptoms onset, without follow-up emails. This may significantly limit the data related to hospitalization, death, and recovery. For example, the GRA registry had 63 cases ending in death compared to EULAR's 146.

Additionally, the EULAR registry did not report demographic data relating to race or ethnicity and limited the amount of reported primary rheumatological diagnoses and comorbidities. Although COVID-19 is still under significant study, there is early evidence linking infection with poor outcomes to gender, race, and comorbidities: hypertension, diabetes, and morbid obesity. As of April 2020, analysis of the COVID-Net registry of hospitalized, COVID-19 patients revealed half of the patients hospitalized had hypertension and nearly half (48%) were obese. Prevalence of these underlying conditions mirror those of hospitalized influenza patients per the FluSurv-NET during influenza seasons 2014-2019 (Garg, et al., 2020). Furthermore, a complete dataset could help assess if the comorbidities are associated with an increased incidence with or without rheumatic disease, helping to further stratify risks. Currently, recommendations among rheumatologists and dermatologists reflect these findings, as recommendations to consider withholding treatment is noted among older adults (age 65 and greater), poorly controlled underlying condition, and relative stability and mild symptoms of rheumatological condition (Gelfand, 2020).

Lastly, this study presents an analysis of incomplete data. As COVID-19 continues to have a pandemic presence, it is anticipated more cases will continue to be reported within the rheumatological community.

Conclusion

Early data from the Global Rheumatology Alliance and European League Against Rheumatism (EULAR) illustrate that rheumatology patients are at risk for COVID-19 infections, including hospitalization and death. While the data does not permit extensive correlation or attribution for confounding, high rates of COVID-19 as associated with underlying conditions and the use of therapeutics. Therefore, continued employment of social distancing, use of personal protective equipment, and consideration for therapeutic discontinuation should continue among rheumatological patients, particularly those with increased age and comorbidities. Further review of EULAR and GRA data is warranted.

Works Cited and Follow-Up Contact: michac03@nyu.edu