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COVID-19 in Rheumatic Diseases: A Research Agenda

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Although only a few months have passed since the coronavirus disease 2019 (COVID-19) pandemic began, we have learned a lot about the infection and outcomes in people with rheumatic diseases. Below I summarize recent findings as well as remaining gaps in knowledge about the epidemiology and outcomes of COVID-19 in rheumatic diseases. I also outline a clinical research agenda for the coming months.

Current Knowledge. *People with rheumatic diseases are not significantly more susceptible to initial infection with SARS coronavirus-2 (SARS-Cov-2) compared to the general population***.** Much of the research informing this issue has come from European cities heavily impacted early on in the pandemic. Researchers quickly mobilized to systematically survey entire clinic populations or disease cohorts, identifying COVID-19 cases and their outcomes. Across the over 3000 people in these studies, the prevalence of COVID-19 was very low and no deaths were recorded.[1] In several

cohorts, including one nationwide inflammatory bowel disease cohort of TNFi and thiopurine users, the prevalence of COVID-19 was similar to that in the general population.[2,3] The survey reported by Favalli and colleagues in this issue of the journal provides further reassurance.[4] The researchers contacted 955 individuals with inflammatory conditions seen in a biologics clinic in Pavia, Italy, achieving a remarkably high response rate of 98% over a short period. They found that <1% of patients had been diagnosed with COVID-19, and no patient required mechanical ventilation or died. A recent study from China examined 42 families of people with rheumatic diseases in whom at least one person had COVID-19. Matching people with rheumatic disease to family members, they found a higher susceptibility to infection among those with rheumatic diseases. However, this was a small study so no definitive conclusions can be drawn.[5] Taken together, these studies suggest that the risk for acquiring COVID-19 is either similar or only slightly increased for people with rheumatic diseases. Indeed, the extremely high attack rates in vulnerable populations, such as prison inmates, homeless individuals, and nursing home residents illustrate that initial infection is most strongly associated with high-risk exposures rather than underlying conditions or immunosuppression.

*The risk of severe outcomes in patients with rheumatic diseases is closely tied to age and comorbidities, similar to the general population***.** Population-based studies and large case series in people with rheumatic diseases have shown that older age and the presence of comorbidities such as diabetes or cardiovascular, kidney and lung disease increase the risk for hospitalization, mechanical ventilation, and death.[1,6] Comorbidities occur at higher rates in people with rheumatic disease, either as a result of organ-manifestations of the underlying disease (e.g. lupus nephritis, interstitial lung disease) or as a complication of treatment (e.g. glucocorticoid-induced diabetes). This puts many of our patients in a high-risk group for severe COVID-19 outcomes like respiratory failure, although overall mortality has been low. Moreover, COVID-19 mortality in rheumatic diseases has been lower than in populations with cancer or organ transplants.[1]

Most immunosuppressive drug regimens are not associated with a significantly increased risk of severe COVID-19 outcomes. Although more data is needed to look at specific drug categories, available studies provide some reassurance. For example, data from 600 patients in the COVID-19 Global Rheumatology Alliance (GRA) registry, a case-reporting registry for rheumatologists, shows that most immunosuppressive drugs, including biologics and targeted synthetic agents, are not associated with a significantly higher risk of hospitalization.[6] A case series of 86 patients with autoimmunity hospitalized for COVID-19 in New York had similar findings.[7] Studies using age- and

sex- matched-control designs also suggest comparable risks of hospitalization and mortality regardless of exposure to most immunosuppressive medications.[8]

Interestingly, moderate to high dose glucocorticoids are the one class of medication associated with a higher risk of hospitalization and severe outcomes in both the GRA and SECURE-Inflammatory Bowel Disease registries.[6,9] Whether this represents a biological effect of glucocorticoids in reducing host-defenses to initial viral infection and replication, or confounding by factors such as social determinants of health (i.e. poor access to care), remains to be determined. If substantiated, these data suggest that glucocorticoids early in infection are harmful, even if trials like RECOVERY suggest a significant benefit later during the disease.[10] Although more research is needed to examine specific drug classes and drug-disease-comorbidity interactions, there is now good evidence that patients with rheumatic diseases should not discontinue immunosuppressive drugs. And while reducing glucocorticoid exposure is always important, it may be especially important to minimize exposure during the pandemic.

Knowledge gaps. Despite the significant progress noted above, several significant gaps in our knowledge remain. We know very little about the spectrum of symptom severity in people with rheumatic diseases or those on immunosuppression. Are similar proportions of patients asymptomatic and are clinical presentations similar compared to the general population? There are theoretical concerns that some immunosuppressive drugs may prolong viral shedding by dampening the innate immune response, but no studies to date have addressed this question. In addition, many questions remain about whether SARS-Cov-2 antibody and T-cell responses confer protection against future infection, and it remains unclear if these responses are reduced in those receiving immunosuppression.

We also know very little about the long-term outcomes of people with rheumatic diseases who have recovered from COVID-19. In the general population, neurological sequelae (e.g. permanent anosmia, cognitive fogging), respiratory problems, and other organ damage (e.g. renal damage, Type 1 diabetes mellitus) have all been described. Whether these sequelae are more prevalent or severe in those with pre-existing autoimmunity or organ damage from their rheumatic disease remains to be determined.

Finally, the pandemic has again highlighted the profound impact of social determinants of health on outcomes. In rheumatology, health disparities are pervasive, and our most vulnerable patients are already suffering disproportionately during the pandemic. Racial/ethnic minorities, those living in poverty and experiencing housing and food insecurity, and those who are unable to reduce SARS-Cov-2 exposures because of work-related duties are more likely to acquire the infection, and multi-morbidity and inadequate access to health care result in more severe outcomes. Indeed, in the GRA registry, U.S. patients who are racial/ethnic minorities are significantly more likely to have severe COVID-19 outcomes. Ensuring that vulnerable groups retain or gain access to rheumatology care is important to ensure that morbidity from rheumatic diseases does not increase during the pandemic.

Research Agenda for the Coming Year. As the pandemic has evolved, clinical research studies will also need to evolve (**Figure**). The early phases of the pandemic were marked by an information vacuum, with virtually no data available on how people with rheumatic diseases or on immunosuppression would fare if infected. Case series, small case-control studies, and rapidly-deployed patient surveys can be assembled quickly and were appropriate to fill information needs during this phase. Now several months into the pandemic, larger case series with clearly defined denominators (i.e. a health system, hospital, or region) and larger case-control studies and patient surveys add precision to early estimates. Large registries still also have an important role in examining rare diseases or less commonly used immunosuppressive drugs. Over the coming months, investigators should increasingly shift towards conducting studies in which the denominators (populations at risk) are larger and more precise, the numerators (COVID-19 infection) are accurately captured, and control populations are available to calculate risks attributable to rheumatic diseases and immunosuppressive drugs.

In the **Supplemental Table**, I list a research agenda for the next phase of clinical studies in COVID-19 and rheumatic diseases. To answer the many remaining questions about the spectrum of COVID-19 illness severity in immunosuppressed patients, we need studies that systematically perform viral RNA and serologic screening on well-defined populations of patients with rheumatic diseases. Longitudinal comparisons of the duration of viral shedding and spectrum of symptoms and severity compared to matched control populations will help us gain a more nuanced picture of infection in immunocompromised hosts.

To more clearly define the risk of severe COVID-19 outcomes attributable to specific rheumatic diseases and drugs, large population-based studies are needed. The integration of multiple data sources, including those that capture social determinants of health, will be important in identifying patients at highest risk and developing population-based public health interventions to mitigate these risks.

Globally, case reporting registries such as the GRA will continue to play an important role since population-based studies with multi-source national data are sometimes unavailable in low and middle-income countries. Moving toward the systematic collection and entry of cases by rheumatologists from health systems or regions in these countries will be key to understanding the outcomes of COVID-19 in rheumatic disease populations globally. This information is likely to have a significant international impact as policy makers and physicians use local data to make important decisions about issues such as which high-risk groups to prioritize for treatment or vaccination.

Individuals with rheumatic diseases and COVID-19, particularly those with severe infection, may have long-term physical and psychological sequelae. Quantifying long-term consequences through cohort studies will help rheumatologists appropriately screen for these sequelae, manage symptoms, and refer patients to appropriate services. Similar longitudinal cohorts in the general population will also help define possible autoimmune or musculoskeletal syndromes resulting from COVID-19.

Although sample sizes will likely preclude randomized controlled trials of anti-viral or immunomodulating therapies in those with rheumatic diseases, subgroup analyses of large, well-done randomized trials may be possible to examine differential treatment responses and guide therapeutic approaches in people with autoimmunity or those who are immunocompromised. Similarly, although it is unlikely that primary vaccine efficacy studies will be performed in patients with rheumatic diseases, randomized controlled trials examining immune responses and safety in immunocompromised people are feasible and should be conducted to inform clinical decision-making.

Finally, it is inevitable that the COVID-19 pandemic will have far-reaching consequences on rheumatology care and the outcomes of people with rheumatic diseases. Treatment interruptions, disruptions in access to both ambulatory and inpatient care, less frequent laboratory monitoring, and

the rapid and somewhat chaotic deployment of telehealth have the potential to increase morbidity and mortality, particularly among vulnerable populations with rheumatic diseases. Using national data sources such as registries linked to other sources such as administrative claims, census information, and the national death index will eventually help us understand the true impact of the pandemic on people with rheumatic diseases. Although this information may not come in time to improve outcomes during the current pandemic, we have a moral obligation to use the lessons learned to improve the clinical care and outcomes of future patients with rheumatic disease.

Figure. Clinical and Observational Research Timeline for COVID-19 and Rheumatic Diseases

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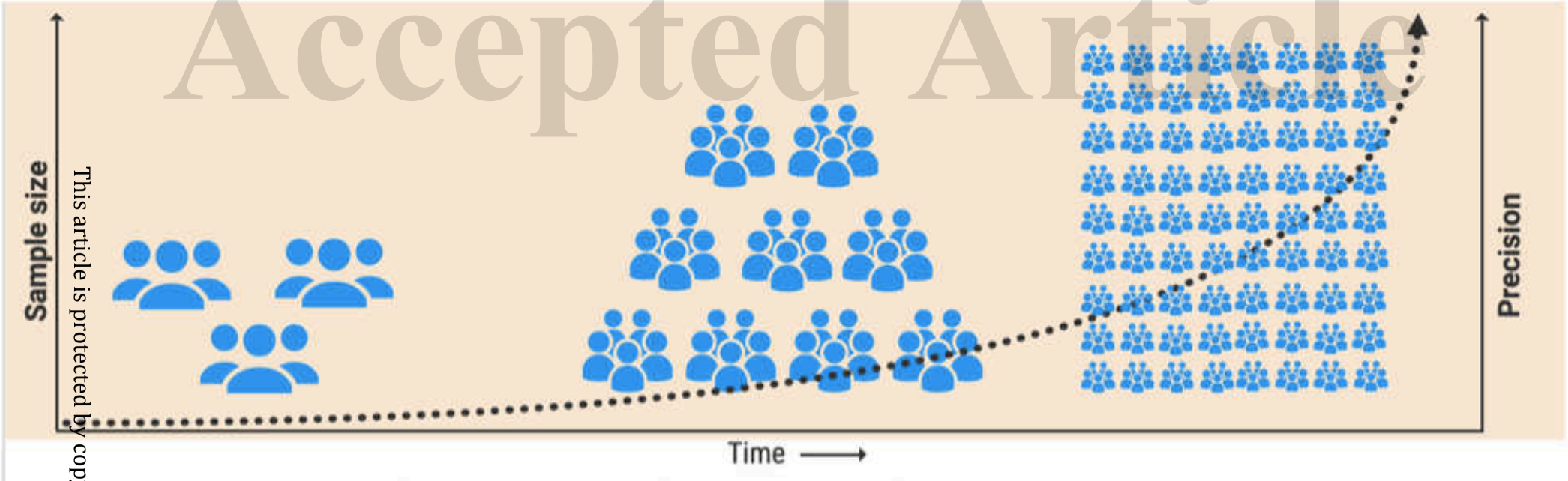

Early Pandemic:

Small sample sizes

- Case series
- Small case-control studies
- Patient surveys

Mid-Pandemic

Larger sample sizes

- Large case series and registries
- Large case-control studies
- Larger, systematic patient surveys

Late Pandemic

Population-based studies, longitudinal cohorts and trials

- Population-based registry and administrative data studies
- Large, systematic case series with defined denominator
- Subgroup analyses of randomized treatment trials
- Randomized trials of vaccine response in immunosuppressed people
- Cohort studies of long-term health outcomes