



Are patients with rheumatologic diseases on chronic immunosuppressive therapy at lower risk of developing severe symptoms when infected with COVID-19?

Kiana Vakil-Gilani¹ · Kenneth O'Rourke¹

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Individuals susceptible to infection with coronavirus 2019 (COVID-19) represent heterogeneous populations presenting a large risk spectrum. Risk stratification is critical to define clinically relevant subpopulations to more accurately target screening, prevention, and therapeutic interventions and allocate resources. Patients over age of 65 and those with comorbidities including obesity, cardiovascular disease, chronic pulmonary disease, and diabetes mellitus are at higher risk for severe COVID-19 disease [1]. Various common viral agents including influenza and adenovirus are associated with an increased risk of a severe disease course and respiratory complications in immunocompromised patients; however, this has not been the case with coronaviruses [2]. It is unclear at this time whether rheumatic disease patients on chronic immunosuppressive therapy are at higher risk of developing a more severe disease course when infected with COVID-19 as data regarding this topic are limited and conflicting.

One small study conducted in Italy, involving thirteen patients—four patients with confirmed COVID-19 identification through nasopharyngeal swab, four with symptoms highly suggestive of COVID-19, and five asymptomatic patients with a known exposure to COVID-19—treated with a biologic DMARD, a targeted synthetic DMARD, or a combination of the two, showed no increase risk of developing severe symptoms [3]. None of the thirteen patients developed severe

respiratory complications, and only one patient (age 65) required short-term hospitalization [3]. All patients in this study had a diagnosis of rheumatoid arthritis (RA) or spondyloarthritis (SpA) [3]. In a recent larger cohort in New York City of 86 patients with immune-mediated diseases and either confirmed or highly suspected COVID-19 symptomatic infection studied prospectively, the incidence of hospitalization among patients with immune-mediated inflammatory disease was consistent with that among patients with COVID-19 in the general population, suggesting that the baseline use of biologics is not associated with worse COVID-19 outcomes [4].

Another report, however, suggests that systemic lupus erythematosus (SLE) patients may be prone to severe COVID-19 disease independent of their immunosuppression from lupus treatment. Hypomethylation and overexpression of angiotensin-converting enzyme-2 (ACE-2) in lupus patients may facilitate viral entry into the cells [5].

Recent data indicates that a small fraction of patients infected with COVID-19 develop rheumatic disease symptoms including arthralgia, interstitial pneumonia, myocarditis, leucopenia, thrombocytopenia, and coagulopathy with anti-phospholipid antibodies [6, 7]. Significant efforts to assess the efficacy of anti-rheumatic drugs in COVID-19 patients are currently underway. All coronaviruses express a surface glycoprotein termed a “spike” which binds to the host receptor for entry [8]. This receptor has been identified as the ACE-2 which is expressed in mature lung epithelial cells, enterocytes, kidney proximal tubular cells, and endothelial cells [8]. This distribution of ACE-2 would explain the risk for multiorgan involvement of this viral infection. When the lysosomal proteases cleave the spike protein, it releases signal peptide that facilitates viral entry into the cells [8]. Low synthesis of antiviral cytokines, including interferon alpha and beta, and increased pro-inflammatory cytokines, including IL-1 and IL-6,

✉ Kiana Vakil-Gilani
KVakilGila@mmc.org

Kenneth O'Rourke
korheum@gmail.com

¹ Department of Rheumatology, Maine Medical Center, Portland, ME, USA

play a significant role in the pathogenesis of COVID-19 [8]. Tocilizumab, an anti-IL-6 receptor antibody used in rheumatoid arthritis (RA) patients, leads to recovery and disappearance of lung opacities in 90% of twenty-one patients in China with severe respiratory syndrome related to COVID-19 [8]. Baricitinib, a JAK 1 and 2 inhibitor used in RA, is also under evaluation for use in COVID-19 patients with the hypothesis that it can reduce both viral entry and inflammation by blocking receptor-mediated endocytosis and the downstream signaling of interferon alpha and beta [8, 9]. Lastly, checkpoint inhibitors such as anti-CD200-CD200R1 have been found to prevent an excessive inflammatory response and downregulate macrophage activation in a mouse model [8].

Current recommendations for patients with rheumatologic diseases are to continue their immunosuppressive therapy unless infected with COVID-19, with the exception of hydroxychloroquine and tocilizumab in select circumstances [6, 10]. Limited and conflicting data warrant closer surveillance of patients with autoimmune diseases on chronic immunosuppressive therapy. This will assist with risk stratification and promote evidence-based recommendations to our patients.

One proposed study would be to retrospectively collect comprehensive data from all hospitalized COVID-19 patients who were on immunosuppressive therapy prior to hospital admission. This data would include the following: age, sex, BMI, race, ethnicity, history of tobacco and e-cigarette use, co-morbidities, pregnancy status, date of diagnosis, symptoms, radiologic findings, laboratory findings, treatment method during hospitalization, severity of illness using American Thoracic Society guidelines for CAP, infection complications, outcomes, diagnosis of baseline autoimmune disease, disease activity of baseline autoimmune disease, type of immunosuppressive therapy prior to hospitalization, length of immunosuppressive therapy prior to admission, half-life of immunosuppressive therapy, whether baseline therapy was held on admission, and list of all other medications prior to admission. One can use a multivariate regression analysis to extrapolate which immunosuppressive therapies were associated with the best patient outcomes with the theory that those with a longer half-life and ability to best suppress a cytokine storm would be superior.

The COVID-19 Global Rheumatology Alliance created a global registry during the COVID-19 pandemic that captures the majority of the data listed above [11] and would be an appropriate source of data for conducting various studies related to immunosuppressive therapy and COVID-19 infection severity. We recommend collection of additional data in the current registry in order to conduct the study described above. This data includes the following: BMI, stratification of COVID-19 illness severity using a well-described severity score calculator such as the CURB-65 or PSI for those with pulmonary manifestations, indices used to assess disease

activity of various autoimmune diseases, length of immunosuppressive therapy use prior to COVID-19 diagnosis, and half-life of immunosuppressive therapies used.

Compliance with ethical standards

Disclosures None.

References

- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al (2020) Epidemiology and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395:497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- Antiga A (2020) Coronaviruses and immunosuppressed patients. The facts during the third epidemic. *Liver Transplant*. <https://doi.org/10.1002/lt.25756>
- Monti S, Balduzzi A, Paolo D, Bellis E, Quadrelli VS, Montecucco C (2020) Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis* 79:667–668. <https://doi.org/10.1136/annrheumdis-2020-217424>
- Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, Neimann A, Adhikari S, Hudesman D, Scher JU (2020) Covid-19 in immune-mediated inflammatory diseases — case series from New York. *N Engl J Med* <https://www.nejm.org/doi/full/10.1056/NEJMc2009567>
- Sawalha AH, Zhao M, Coit P, Lu Q (2020) Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. *Clin Immunol* 215:108410. <https://doi.org/10.1016/j.clim.2020.108410>
- Misra DP, Agarwal V, Gasparyan AY, Zimba O (2020) Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. *Clin Rheum*. <https://doi.org/10.1007/s10067-020-05073-9>
- Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y, Zhang S (2020) Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med* 382:e38. <https://doi.org/10.1056/NEJMc2007575>
- Ceribelli A, Motta F, De Santis M, Ansari AA, Ridgway WM (2020) Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy. *J Autoimmun* 109:102442. <https://doi.org/10.1016/j.jaut.2020.102442>
- Favalli EG, Biggioggero M, Maioli G, Caporali R (2020) Baricitinib for COVID-19: a suitable treatment? *Lancet Infect Dis*. [https://doi.org/10.1016/S1473-3099\(20\)30262-0](https://doi.org/10.1016/S1473-3099(20)30262-0)
- ACR COVID-19 Clinical Guidance Task Force: ACR COVID-19 clinical guidance for adult patients with rheumatic diseases; <https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-Patients-with-Rheumatic-Diseases.pdf>; accessed 16 Apr 2020
- Robinson P, Yazdany J (2020) The COVID-19 Global Rheumatology Alliance: collecting data in a pandemic. *Nat Rev Rheumatol*. <https://doi.org/10.1038/s41584-0>

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