Biologics in systemic autoimmune diseases during COVID-19 pandemic

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Dear Editor,

Over the past two decades, multiple biologic agents have been approved for treating systemic autoimmune diseases targeting a wide range of cytokines. In the current era of COVID-19 pandemic, there is concern of iatrogenic immunosuppression increasing the risk of symptomatic COVID-19 in these patients. However, at the same time “cytokine storm” has been proposed as the predominant cause of adverse outcomes in COVID-19 patients, patients with autoimmune diseases on biologics present a unique challenge. Understanding the relationship of COVID-19 infection in patients on immunosuppressive medications can help provide guidance in managing these patients. Using data from a large de-identified database, we try to address the knowledge gap in the management of autoimmune conditions requiring immunosuppressive medications.

We used TriNetX, a global health research platform that collects electronic medical records from their network of health care organizations. We included patients with six most

common chronic autoimmune diseases in our analysis—rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, and ulcerative colitis based on ICD-10 coding for period starting 6 months before January 20, 2020 (first reported case of COVID-19 in the USA). We examined the rates of COVID-19 infection, hospitalizations, need for critical care services, intubations, and death among these patients. Patients were divided into two groups based on whether they are taking or not taking any one of the following classes of immunosuppressive medications—TNF inhibitors, IL-6 inhibitors, kinase inhibitors, IL-17inhibitors, IL-12/23 inhibitors, and T cell co-stimulation blockade drugs. Detailed methodology for data collection and study protocol have been described in the supplement and have previously been reported [1–3].

To compare the mean age difference between the two groups, we used pooled variance *t* test, as the variance in mean age in both groups are similar. The odds of acquiring COVID-19 disease and clinical outcomes were compared between the two groups using chi-square or Fischer’s exact test wherever applicable (Table 1). Alpha of 0.05 was considered significant, and we used Benjamini-Hochberg correction to control for multiple correction using a false discovery rate of 0.1.

The odds of acquiring COVID-19 are not significantly different between the study groups. Among the patients that had COVID-19, there was no significant difference in mean age of patients between the two groups. Interestingly, the group on immunosuppressive medications had significantly lower odds of hospitalizations and intensive care unit (ICU) admissions than the group not on immunosuppressive medications (Table 1).

Hyper inflammatory markers such as elevated interleukins IL-2 and IL-7, TNF-alpha, macrophage inflammatory protein 1-alpha, monocyte chemo attract protein 1-alpha, granulocyte colony-stimulating factor, and interferon-gamma have been associated with severity of COVID-19 [4]. Mehta et al. proposed that COVID-19 patients identified as high risk based on

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Key Points • *Continuation of immunosuppressive medications during COVID-19 seems to be safe as suggested by the ACRTF.*

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Table 1 Baseline demographics and clinical outcomes of COVID-19 with and without biologics

COVID-19-positive patients	With biologics	Without biologics	<i>p</i> value
Number of patients	93/26671 (0.35%)	353/105730 (0.33%)	0.7 ($\chi^2 = 0.14$)**
Age (years) $\pm$ SD	48.3 $\pm$ 16.2	57.9 $\pm$ 16.9	0.1*
Woman	67(72.0%)	251 (71.1%)	0.52 ($\chi^2 = 0.4$)**
Race			
White	55 (59.1%)	205 (58.1%)	0.84 ($\chi^2 = 0.04$)**
African-American	25 (26.9%)	88 (24.9%)	0.87 ($\chi^2 = 0.35$)**
Hispanic (ethnicity)	5 (5.4%)	24 (6.8%)	0.5 ($\chi^2 = 0.45$)**
Clinical outcomes			
Hospitalization, <i>n</i> (%)	13 (13.9%)	107 (30.3%)	0.01 ($\chi^2 = 6.24$)**
ICU, <i>n</i> (%)	2 (2.2%)	34 (9.6%)	0.01 ^ψ
Intubation, <i>n</i> (%)	3 (3.2%)	18 (5.1%)	0.5 ^ψ
Death, <i>n</i> (%)	4 (4.3%)	25 (7.1%)	0.36 ^ψ

ICU, intensive care unit; SD, standard deviation

*Pooled variance *t* test

**Chi-square

^ψ Fisher's exact test

HScore and other inflammatory markers should be targeted for immunosuppression [5]. Prior studies showed an increased risk of bacterial and opportunistic infections with patients on biologics but data regarding risk of viral infections is sparse [6]. On the contrary, stopping biologics increase the risk of flares of the underlying autoimmune condition, which itself is an increased risk factor for infections [7]. American College of Rheumatology task force (ACR TF) recommended continuing biologics in stable rheumatological patients during the pandemic, in the absence of COVID-19 infection (<https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-Patients-with-Rheumatic-Diseases.pdf>). Despite the inherent limitations of a large retrospective database study and inability to adjust for underlying comorbidities, our data re-enforces the guidelines issued by the ACR TF.

Our analysis suggests that even though the risk of COVID-19 infection remains the same between the two groups, the risk of hospitalizations and need for critical care services appear to be low in patients on the immunosuppressive medications. Additional longitudinal registry—based data is needed to confirm these findings.

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Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were

performed by Krishna Nalleballe, Sanjeeva Reddy Onteddu, and Rohan Sharma. The first draft of the manuscript was written by Suman Siddamreddy, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The data that supports the findings of this study are available from the corresponding author (K.N.), upon reasonable request.

Compliance with ethical standards

Disclosures None.

Ethics approval The University of Arkansas Institutional Review Board (IRB) deemed this study to be “not human subject research” (global de-identified COVID-19 Research Network data), and this study received an exempt status. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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