**Adverse Effects of Tocilizumab versus Baricitinib in Severe COVID-19**

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We read with interest the article by Peterson *et al.* (1). In this retrospective cohort study involving 956 adults hospitalized with severe COVID-19 at 11 Georgia hospitals (June to October, 2021), the frequency of “adverse effects” – secondary infection, venous thromboembolism (VTE), acute liver injury, and acute kidney injury (AKI) – was compared between 291 tocilizumab- and 291 baricitinib-treated patients. The authors concluded that tocilizumab-treated patients had higher frequencies of secondary infection (32% vs. 22%), VTE (24% vs. 16%), and liver injury (8% vs. 3%) compared to baricitinib.

The investigators are to be commended for seeking to fill an important and timely evidence gap. However, key methodological considerations may limit the utility of the findings. As a backdrop, both tocilizumab and baricitinib have been demonstrated in multiple, large randomized clinical trials (RCTs), involving thousands of patients with COVID-19, to have well-established efficacy and safety profiles. Although transaminitis has been infrequently reported with tocilizumab, the other “adverse effects” are not supported as attributable to either agent in RCTs. Rather, these are sick patients at risk for adverse events regardless of (or despite) receipt of tocilizumab or baricitinib.

This is particularly important in an observational study, where treatment decisions were not randomized. Physicians clearly prescribed tocilizumab to sicker patients than baricitinib (Supplemental Table S1). It is therefore unsurprising that tocilizumab-treated patients subsequently experienced more adverse events. The authors address this by using propensity matching, but this is limited to only eight variables, and necessitated excluding many more baricitinib-treated patients than were initially included. There is therefore a strong possibility of residual confounding despite attempts to balance the groups. For instance, baricitinib is contraindicated in patients with low glomerular filtration rate, yet no comparison of serum creatinine between groups is provided to ensure this important variable is balanced.

No data are presented on the nature of secondary infections, nor their likelihood of being treatment-related, and reported incidences of 32% and 22% in the tocilizumab- and baricitinib-treated groups are misleading without a reference control group. For example, in over 4,000 critically ill adults in the multicenter STOP-COVID cohort, the frequency of secondary infection was similar among tocilizumab-treated and untreated patients (32.3% vs. 31.1%), as was the frequency of thrombotic complications (10.6% vs. 9.8%) (2). A meta-analysis including 10,930 patients from 27 RCTs observed similar rates of secondary infection comparing patients treated with or without IL-6 antagonists (primarily tocilizumab) (21.9% vs. 17.6%) (3).

Similarly, the notion that thrombotic events and AKI are adverse effects of tocilizumab or baricitinib runs counter to existing data. In the RECOVERY trial, which randomly assigned over 4,000 hospitalized adults to tocilizumab vs. usual care, there was no difference in the frequency of thrombotic events between groups, while the incidence of AKI treated with kidney replacement therapy was *reduced* with tocilizumab (120/1994 [6%] vs. 172/2065 [8%]; P=0.005) (4). In the COV-BARRIER study, which randomized 1525 patients to baricitinib or placebo, serious infection (9% vs. 10%) and VTE (3% vs. 3%) occurred similarly between groups (5).

Accordingly, we are unsure that these results should influence clinical practice.

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**CONFLICT OF INTEREST STATEMENT**

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