Response to Correspondence: Baricitinib – Impact on COVID-19 Coagulopathy?

Jorgensen et al.

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Dear Editor,

We read with interest the correspondence by Jorgensen et al. in response to our recent publication in Clinical Infectious Diseases (CID) on the use of baricitinib for treatment of patients with moderate to severe COVID-19. The authors raise concerns on the potential impact of JAK-inhibitors on COVID-19 coagulopathy, citing data on tofacitinib and baricitinib from the WHO Vigibase1. Several small cohort studies including cumulatively over 100 patients have reported on the use of the JAK1/2 inhibitors baricitinib and ruxolitinib for the treatment of patients with COVID-192-8. Treatment duration in these studies ranged from 1-14 days, with no short-term toxicities reported with ruxolitinib dosing of 10-15 mg/day4-6 and baricitinib dosing up to 8 mg/day2. The largest of these studies, a prospective longitudinal study in which 20 patients with COVID-19 received 4 mg baricitinib twice daily for 2 days followed by 4 mg daily for 7 days did not show a difference in the incidence of thrombotic events when compared to a control group of 56 individuals during the one-month follow-up period2. Furthermore, recently published extended observation safety data for baricitinib in the treatment of rheumatoid arthritis (RA) with follow-up of up to 8.4 years found incidence rates for venous thromboembolism events (VTE) events between baricitinib dose groups (2 mg and 4 mg) to be comparable to those reported in patients with RA9. It remains unclear why in pooled data from clinical trials of baricitinib in RA, 6 individuals in the treatment group developed VTE; however, the long-term observational data are reassuring that this potential risk may not persist overtime10. Baricitinib in combination with remdesivir is being evaluated in a randomized, placebo-controlled trial (ACTT2) of COVID-19 treatment (NCT04401579), which has completed recruitment of over 1,000 patients. VTE of any grade have been regularly monitored by the Data Safety and Monitoring Board (DSMB) for ACTT2. To date, the DSMB has not recommended unblinding or halting the trial, which is reassuring. This does not, however, preclude the possibility of an imbalance between arms that could emerge during the final trial analysis. Baricitinib through its immunomodulatory effects as highlighted by Jorgensen et al. may in fact be beneficial in terms of reducing coagulopathy in patients with COVID-19, which is thought to be primarily mediated by hyper-inflammation and endothelial damage. All of the cohort studies of baricitinib for COVID-19 treatment led to significant decline in inflammatory
markers for patients who received the drug\textsuperscript{2,3,8}. We agree that in the pursuit of effective therapeutics against COVID-19, there is a need to balance the potential adverse effects of any intervention with its hypothesized benefits and to perform randomized, controlled trials. Regarding baricitinib, ACTT2 should provide clarity on the VTE issue in the near future and its role in the treatment of COVID-19 in moderate to severe patients.
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Conflicts of Interest

Dr. Vincent C. Marconi has consulted or received research support from ViiV, Gilead, Lilly and Bayer. Dr. Raymond Schinazi served as an unpaid consultant for Eli Lilly whose drugs are being evaluated in the research described in this paper. In addition, Dr. Schinazi owns shares in Eli Lilly and Gilead, and is issued patents 20190134039, 10022378, and 9662332. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. All other authors do not have any conflicts to declare.
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