

Baricitinib as Treatment for Coronavirus Disease 2019 (COVID-19): Friend or Foe of the Pancreas?

TO THE EDITOR—We read with great interest the article published by Titanji et al regarding the use of baricitinib as a potential drug to mitigate inflammation and reduce mortality associated to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. Although this study provides useful information to support the development of randomized clinical trials, many of which have already begun recruiting, some researchers remain cautious about its use [2].

As part of a local clinical trial for coronavirus disease 2019 (COVID-19), we treated a 72-year-old woman whose prior medical history was relevant for obesity, diabetes, and hypertension. Due to severe hypoxia, she had to be intubated on the day of her arrival. She was admitted to the intensive care unit (ICU), and a positive reverse transcription polymerase chain reaction for SARS-COV-2 was reported. The patient started receiving dexamethasone and baricitinib as part of the study protocol in addition to atracurium, midazolam, propofol, and enoxaparin.

Despite significant ventilatory improvement the patient developed shock that required vasopressors to maintain adequate mean arterial pressure. As no apparent cause was found, additional paraclinics were obtained revealing an amylase level of 1789 U/L.

Following the suspicion of pancreatitis, further laboratories were ordered finding a lipase of 1247 U/L, a corrected calcium of 7.1 mg/dL, and triglycerides of 194 mg/dL. As she was sedated, we could not get information regarding abdominal pain, and thus an abdominal computed tomography (CT) was obtained. The study revealed pancreatic edema (Figure 1), which led to the decision of initiating bowel rest and aggressive fluid resuscitation. Forty-eight hours later the patient developed anuria, neutrophilic leukocytosis, and succumbed.

Elevation of both amylase and lipase has been described in COVID-19 patients without documented pancreatitis [3]. The latter has led to the theorization that damage to the pancreatic cells by the virus could cause leaking of enzymes and possibly, but not necessarily, to pancreatitis [4]. In vivo murine studies suggest that inhibition of Janus kinase/signal transducer and activator of transcription

(JAK/STAT) signaling reduces activation of pancreatic cells and may consequently limit pancreatitis [5]. As this is baricitinib's mechanism of action, one could assume that some degree of protection against pancreatitis could be achieved with the drug's administration. Ironically, 2 cases of acute pancreatitis were reported in the drug's safety analysis [6, 7].

Although we cannot assume causality between baricitinib administration and pancreatitis, we do forecast a landscape where this pathology could represent problems for clinicians. Caring for intubated patients that may not be able to communicate abdominal pain, with an infection that may cause pancreatic damage, in obese subjects receiving drugs that may increase lipids (ie., propofol) could all lead to unsuspected and difficult to diagnose pancreatitis.

Both interleukin (IL)-6 and the JAK/STAT signaling pathways play a crucial role in the progression of pancreatitis [8]. Despite this fact, the specific effect of their inhibition using drugs is a field yet to be explored. Until then, pilot studies as the one we read from Titanji et al should continue encouraging the production of clinical trials where security is a priority. The latter is especially true in the context of a relatively recent drug class that may still have unfamiliar effects.

Notes

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Figure 1. Abdominal computed tomography showing diffuse pancreatic enlargement with edema and surrounding fat stranding.

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Baricitinib: Impact on Coronavirus Disease 2019 (COVID-19) Coagulopathy?

TO THE EDITOR—We read the recent report by Titanji and colleagues describing the use of the Janus-associated kinase (JAK) inhibitor, baricitinib, in the treatment of 15 coronavirus disease 2019 (COVID-19) patients with great interest [1]. Baricitinib

interrupts the signaling of multiple cytokines implicated in COVID-19 immunopathology and may also exert antiviral effects by targeting host factors that viruses rely on for cell entry, making it a plausible candidate for further evaluation [2, 3]. As pointed out by the authors of this and other reports, the primary concern with the use of baricitinib in COVID-19 patients is the potential for it to delay viral clearance and increase vulnerability to secondary nosocomial infections through its immunosuppressive properties [1, 4].

An adverse effect (AE) that has received less attention but that could be problematic for COVID-19 patients is baricitinib's dose-dependent association with arterial and venous thromboembolic events (VTE) [5, 6]. In the present report, 2 patients, both of whom received baricitinib at a higher than US Food and Drug Administration (FDA) approved dose, experienced VTE. In pooled safety data from the baricitinib development program a total of 39 VTEs were reported among baricitinib-treated patients compared to zero with placebo (incidence rates 0.6/100 patient years [4 mg/day] vs 0.4/100 patient years [2 mg/day]) [5]. A safety signal for VTE was also identified in postmarketing surveillance data collected in the World Health Organization's (WHO's) global database of individual case safety reports [7]. Thromboembolic events, coupled with other dose-related AEs, were partly responsible for baricitinib's failure to be granted marketing approval by the FDA in 2017 [5]. The drug was approved in 2018 but only at 2 mg/day and with, as pointed out by Titanji and colleagues, FDA warnings for infections, malignancy, and thrombosis included in the prescribing information [1, 5]. Although the authors postulate that the short duration of baricitinib therapy may confer a lower risk of thromboembolic events, the relationship between duration of therapy and thromboembolism remains uncertain; it has been reported to occur within 6 weeks of therapy initiation in

rheumatoid arthritis patients and up to 1 week following drug discontinuation [5].

The mechanism responsible for thrombotic events is currently not known. Baricitinib has been associated with a rapid increase in platelet counts during the first 2 weeks of therapy [5]. This is believed to be related to reduced JAK2-mediated thrombopoietin clearance by megakaryocytes and mature platelets [5]. However, no clear temporal or quantitative association between increased platelet counts and thromboembolic events has been established [5]. An increased incidence of thromboembolic events was also reported with higher doses of tofacitinib, another JAK-inhibitor that does not increase platelets [7].

The immune, inflammatory, and coagulation pathways are intimately intertwined, and patients with COVID-19 appear to have an increased proclivity toward immunothrombosis [6]. Drugs like baricitinib, which target the hyperinflammatory immune response to infection that drives coagulopathy, could potentially decrease activation of the coagulation cascade and protect against thromboembolic events. However, it is also possible baricitinib's pro-thrombotic tendencies could exacerbate a hypercoagulable state.

Balancing the potential risks and benefits of immunomodulatory therapies for patients with COVID-19 is challenging, and the remaining uncertainties underscore the importance of restricting use to clinical trials.

Note

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