Baricitinib as treatment for COVID-19: friend or foe of the pancreas?

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Dear 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 SARS-CoV-2 infection.[1] While 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 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 ICU and a positive reverse transcriptase 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 CT was obtained. The study revealed pancreatic edema (Fig. 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 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, two cases of acute pancreatitis were reported in the drug's safety analysis.[6,7]

While 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 (i.e. propofol) could all lead to unsuspected and difficult to diagnose pancreatitis.

Both 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.

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Figure Legends:

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

Figure 1