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# JAK inhibitors in COVID-19: the need for vigilance regarding increased inherent thrombotic risk

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**JAK inhibitors have promising therapeutic potential in COVID-19 with dual anti-inflammatory and anti-viral effects. Vigilance to the potentially increased thrombotic risk associated with JAKi is recommended, given the hypercoagulability of COVID-19.** <https://bit.ly/2NQ15K5>

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## To the Editor:

There is accumulating evidence that coronavirus disease 2019 (COVID-19) is a hypercoagulable state. Reports of thrombotic events and autopsy findings of pulmonary thrombotic microangiopathy in patients with COVID-19 are rising [1]. BOMPARD *et al.* [2] recently reported a cohort study of 137 patients with COVID-19 pneumonia, in which retrospective review of computed tomography pulmonary angiography scans demonstrated a cumulative incidence of pulmonary emboli (PE) of 24% overall and 50% in intensive care. Although it was initially thought that insidious venous thromboembolic events (VTE) were mainly confined to ventilated patients [3], we now understand thrombotic risk to be a wider problem in COVID-19. An overexuberant host inflammatory response in selected patients with severe COVID-19 may contribute to the high mortality. We recently recommended screening for virally driven hyperinflammation in COVID-19 and proposed that immunomodulation in this subgroup of patients may improve outcomes [4]. There are several ongoing, randomised controlled trials evaluating the therapeutic potential of janus kinase inhibitors (JAKi) in severe COVID-19 (table 1). JAKi have a purported advantage over other immunomodulatory strategies in COVID-19, as they may exert dual anti-inflammatory (blockade of multiple, pro-inflammatory cytokines simultaneously) and anti-viral effects (impeding cellular viral endocytosis [5, 6]) and have convenient oral administration, with relatively short half-lives. JAKi may interrupt the signalling of several pro-inflammatory cytokines implicated in the pathogenesis of hyperinflammation, including interleukin-6, which has been the focus of several clinical trials in COVID-19. JAKi may also inhibit the entry of severe acute respiratory syndrome coronavirus 2 virus into the alveolar type 2 alveolar epithelial cells; baricitinib (a JAK1/2 inhibitor) is a numb-associated kinase inhibitor, with a particularly high affinity for alveolar type 2 cell-associated protein kinase 1, a pivotal regulator of clathrin-mediated viral endocytosis [5]. We recommend vigilance to the potentially

increased thrombotic risk associated with JAKi, given the hypercoagulability of COVID-19 and our recent thromboprophylaxis recommendations for all hospitalised patients with COVID-19 [7].