# Baricitinib for COVID-19: a suitable treatment?

## Authors' reply

We thank Ennio Favalli and colleagues for their Correspondence regarding our suggestion to use baricitinib for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.[1,2] We also appreciate their recognition that inhibition of numb-associated kinase enzymes could indeed be beneficial in preventing virus infectivity via inhibition of clathrin-mediated endocytosis.

We welcome the opportunity to more fully explain the possible use of baricitinib in the current pandemic. Indeed, we accept that using a JAK1 and JAK2 inhibitor to treat a viral disease might appear illogical given that the antiviral effects of interferons are largely mediated by the JAK–STAT signalling pathway. However, the administration of pegylated-interferon has not had the beneficial antiviral effects originally hoped for,[4] and clinical trials with interferons have yielded inconsistent results, with pathogenic effects of interferons being observed in some viral infections.

We speculate here that in early asymptomatic disease and stages of the disease not requiring admittance to hospital, approximately 80% of patients with coronavirus disease 2019 (COVID-19) are able to clear the virus, largely through endogenous antiviral mechanisms, almost certainly including the interferons. Therefore, we do not recommend that baricitinib or other JAK inhibitors be given to these individuals. However, in patients with moderate disease requiring hospital care, the peak SARS-CoV-2 load occurs within approximately 7 days of symptom onset, and later, as the viral titre decreases in some patients, hyper-inflammation causes the severe phase of the disease,[5] akin to a so-called cytokine storm. This clinically severe phase is accompanied by high levels of signalling, including increased levels of interferons α and β and IL-6, all of which signal through the JAK–STAT pathway. In a microarray study by Cameron and colleagues,[3] the authors intriguingly showed that patients with severe acute respiratory syndrome (SARS) who had been discharged from hospital had low interferon α and interferon γ signalling activity, whereas in those with hypoxaemia who had died, interferon α and interferon γ signalling was prominent. In animal models designed to understand the temporal profiles of the SARS and Middle East respiratory syndrome diseases, the authors showed that interferon α and interferon β action early in the disease was beneficial, but it was damaging in the later stages.[4]

This finding suggests that when hospital care is required for patients with a pathogenic SARS-CoV-2 infection, JAK–STAT pathway inhibition might be a potential strategy. In the current outbreak, we need to understand which patients might benefit from treatment with such cytokine inhibitors and whether more than one pattern of disease progression exists; stratification and prognostic models are required. Additionally, we need to identify the optimum time to administer cytokine inhibitors, which requires identification of appropriate biomarkers.[5] Anecdotal experience suggests that the short time baricitinib might be used (duration of doses is 7–14 days) will not cause reactivation of any latent infections, such as herpes viruses or tuberculosis.

We and others are awaiting the results of investigator-led and other prospective studies (eg, NCT04320277 and NCT04321993) with numerous treatments, including baricitinib, in individuals with COVID-19. Because of the single-arm nature of such studies, data might be difficult to interpret, and we caution against headlines of a so-called cure when most infected individuals will recover. We also suggest that the systemic administration of interferons α and β to patients being treated in hospital might be harmful and explains why previous studies with interferons have yielded inconsistent results. Although we have ongoing concerns regarding the design of, and the drugs used in, the multicountry WHO SOLIDARITY trial (NCT04321616), which includes use of interferon β, the reality is that all of these opinions, however valid, only lend credence to the evidence-based view that the optimal data are ultimately best obtained from randomised controlled trials.

PJR is an employee of Benevolent AI. JS is editor-in-chief of Oncogene. JS has sat on a number of scientific advisory boards, including Benevolent AI, and consults with Lansdowne partners and Vitruvian; he sits on the Board of Directors for BB Biotech Healthcare Trust and chairs Xerion Healthcare. MC declares no competing interests. Events in relation to the COVID-19 outbreak are evolving rapidly, and we make our initial thoughts available in this Correspondence in good faith and to assist in the global response. Our early investigations and suggestions require further detailed work and analysis and should not be relied on as constituting any kind of medical or other advice or recommendation.

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1 Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020; **395:** e30–31.
2 Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis* 2020; **20:** 400–02.
3 Cameron MJ, Ran L, Xu L, et al. Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome. *J Virol* 2007; **81:** 8692–706.
4 Channappanavar R, Fehr AR, Zheng J, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. *J Clin Invest* 2019; **130:** 3625–39.
5 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395:** 1033–34.

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