
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

by two members of the numb-associated kinase family is one of the many unfamiliar effects of a relatively recent drug class, the real safety profile of which still remains to be definitively clarified. Undoubtedly, the fact that baricitinib can provide this antiviral effect at the approved dose for rheumatoid arthritis therapy is an undeniable advantage over other potential inhibitors of the same pathway.

However, some concern could arise from the best-known aspects of the mechanism of action of the drug and its safety profile. Interferon is one of the most powerful innate immune responses to prevent viral replication during the early phases of infection. Transcription through the JAK–STAT signalling pathway (mainly mediated by JAK1 and JAK2), activated by interferons, leads to the upregulation of many interferon-controlled genes that quickly kill viruses in infected cells. The importance of this defense mechanism is confirmed by the fact that most viruses have developed strategies to counteract the effects of interferons by blocking their signalling pathway, and viral-encoded factors that antagonise the JAK–STAT pathway are crucial determinants of virulence.[2] As a consequence, JAK–STAT signal blocking by baricitinib (a selective JAK1 and JAK2 inhibitor) produces an impairment of interferon-mediated antiviral response, with a potential facilitating effect on the evolution of SARS-CoV-2 infection. This mechanism is thought to be involved in an increased risk of herpes zoster and simplex infection, which was reported in the development programme of baricitinib 4 mg compared with placebo (herpes zoster 4·2 per 100 person-years *vs* 1·0 per 100 person-years [p<0·05]; herpes simplex 5·4 per 100 person-years *vs* 2·2 per 100 person-years [p<0·05]).[3] Notably, this complication also seems to be shared by the new JAK1 selective inhibitors upadacitinib and filgotinib.[4] Viral infections (including herpes zoster and herpes simplex) in intensive care units can account for up to 10% of community-acquired and up to 5% of ventilator-associated pneumonia,[5] the incidence of which might be expected to be higher in immunocompromised patients given JAK inhibitors.

In conclusion, we believe that, beyond the intriguing opportunity to directly block the penetration of SARS-CoV-2 into the cell, the use of baricitinib in susceptible patients with ongoing pneumonia associated with COVID-19 should be considered with extreme caution.

We declare no competing interests.

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## 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

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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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## Utility of hyposmia and hypogeusia for the diagnosis of COVID-19

Early and accurate diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is key to the management of the coronavirus disease 2019 (COVID-19) pandemic. Following its emergence in China in December, 2019, SARS-CoV-2 has spread in the northern hemisphere during the winter season, when other respiratory viruses, including influenza, co-circulate. This epidemiological conjunction complicates clinical diagnosis of COVID-19 because patients often present with influenza-like illness (ILI). Consequently, the definite diagnosis of COVID-19 mostly relies on positive RT-PCR on respiratory samples, although discriminant features have been reported on thoracic CT scan.[1] However, access to these diagnostic tests is limited in the context of this large-scale pandemic. Distinctive clinical features would be welcome to better select patients who require investigations. During the early phase of the COVID-19 outbreak in France, we noticed that many patients reported loss of smell (hyposmia) and taste (hypogeusia). We aimed to investigate the diagnostic value of these symptoms.

Rennes, Angers, and Nantes are referral centres for emerging infectious diseases in western France (population catchment area includes 5 million inhabitants). The study was done from March 15–18, 2020, at which time there was no public awareness of the potential link between taste or smell disorders and COVID-19 (the first report[2] was on March 21). All patients who underwent tests for SARS-CoV-2 by RT-PCR on nasopharyngeal samples since Feb 16 were invited by e-mail or telephone to complete a web-based questionnaire comprised of four questions: Have you been diagnosed with COVID-19 following diagnostic screening? Did you notice a loss of smell during your disease? Did you notice a loss of taste? Do you regularly suffer from ear, nose, and throat (ENT) disorders? The study was approved by the Rennes University Hospital institutional review board. Informed consent was waiived.

Of the 452 patients contacted, 259 (57%) replied, of whom 68 (26%) reported a positive test for SARS-CoV-2.