Baricitinib for COVID-19: a suitable treatment?

As rheumatologists used to treating rheumatoid arthritis with Janus kinase (JAK) inhibitors and working in an area (Lombardy, Italy) with a high incidence of coronavirus disease 2019 (COVID-19), we read with great interest the Comment in *The Lancet Infectious Diseases* by Justin Stebbing and colleagues[1] about the potential use of baricitinib for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The described mechanism affecting viral endocytosis mediated 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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