

Should baricitinib be used for COVID-19?

This write-up summarises a rapid evidence review of baricitinib as a potential treatment for patients with COVID-19. The information may be revised as new evidence emerges.

Background

Baricitinib is a Janus-associated kinase inhibitor (JAK inhibitor) acting against JAK1 and JAK2. It is currently approved by regulatory agencies (including US FDA, EMA and HSA) to treat rheumatoid arthritis.

Artificial intelligence has identified a group of drugs (including baricitinib) that could inhibit receptor-mediated endocytosis, which is the mechanism that most viruses use to enter cells.^{1,2} A known regulator of endocytosis is the adaptor-associated protein kinase-1 (AAK1) and disruption of this regulator may interrupt the passage of the virus into cells and the intracellular assembly of virus particles. Baricitinib has shown particularly high affinity for AAK1 and also binds cyclin G-associated kinase (GAK) another regulator of endocytosis.^{1,2} Further, there is growing interest in using baricitinib in combination with direct-acting antivirals, including lopinavir, ritonavir and remdesivir, since it has minimal interaction with the relevant cytochrome P450 drug-metabolising enzyme.^{1,2} However, there are also concerns with its use as baricitinib can inhibit a variety of inflammatory cytokines including interferon- α , which plays an important role in curbing virus activity.^{3,4}

While other JAK inhibitors such as ruxolitinib and fedratinib may also have activity against COVID-19, the predicted unbound plasma exposure required to inhibit receptor mediated endocytosis with these treatments greatly exceeds their tolerated doses. Therefore, they are unlikely to be suitable for patients with COVID-19 to reduce viral infectivity.²

Recently, online news articles have listed JAK inhibitors, such as baricitinib, as potential COVID-19 treatment options.^{5,6}

Clinical evidence

No published clinical trial evidence for baricitinib as a treatment for COVID-19 is available. A non-peer-reviewed article on in vitro testing of anti-SARS-CoV-2 activities of several drugs reported that baricitinib showed no inhibitory activities against SARS-CoV-2 at the concentration of 3 μ M or 3.2 μ M.⁷

In clinical trials when used for the treatment of rheumatoid arthritis (with a median treatment duration of two years) the most significant side-effect report was a small increase in upper respiratory infection and severe infections such as herpes zoster. As the use of baricitinib for COVID-19 is expected to be short-term, and the risk of infection is low, baricitinib is considered to have a relatively acceptable side-effect profile.^{2,8}

Two trials of baricitinib in COVID-19 have been registered and are in planning or active recruitment stages with data anticipated to mature in the near future.

Table 1: Ongoing or planned studies for baricitinib in patients with COVID-19

Study identifier	Study Design	Intervention	Comparator(s)	Date of primary completion
NCT04320277 ⁹	SC*, OL, pHIII, cross-over	Baricitinib + ritonavir	Antiviral and/or hydroxychloroquine	April 2020
NCT04321993 ¹⁰	OL, pHII, non-randomised parallel assignment	Baricitinib Other arms: Lopinavir/ritonavir Hydroxychloroquine Sarilumab	Standard of care	February 2021

Abbreviations: OL, open label, pHII, phase II; pHIII, phase III; SC, single centre.

* Italy

Recommendations from professional bodies

The World Health Organization (WHO) has yet to recommend any specific medicine to prevent or treat COVID-19. This view is also shared locally by the Singapore National Centre for Infectious Disease (NCID).^{11,12}

Interim clinical guidance from the Centers for Disease Control and Prevention (CDC, USA) on the management of coronavirus and the seventh edition of the China National Health Commission (NHC) clinical guidance for COVID-19 diagnosis and treatment do not specifically refer to baricitinib.^{13,14}

Conclusion

Given the current lack of existing evidence, no firm scientific conclusion can be made on the efficacy and safety of baricitinib to treat COVID-19 infection although the drug appears to be relatively safe and well tolerated in its use for rheumatoid arthritis. Two ongoing studies of baricitinib for COVID-19 are likely to report results in the months ahead, and the findings of these will determine whether baricitinib should be used more widely in this setting.

References

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