Baricitinib as the treatment of choice for hospitalised individuals with COVID-19

Peter J. Richardson,[a] *and Justin Stebbing* [b]*

[a]Benevolent AI, Maple Street, London
[b]Department of Surgery and Cancer, Imperial College, London

eClinicalMedicine 2022;49: 101493
Published online xxx
https://doi.org/10.1016/j.eclinm.2022.101493

In this issue of *eClinicalMedicine*, Selvaraj et al[1] describe a meta-analysis of four randomised placebo controlled clinical trials comprising 10,815 patients, studying the efficacy of the JAK1/2 inhibitor baricitinib in hospitalised patients with COVID-19. The simple use of one tablet per day of baricitinib for different durations was consistently and reproducibly associated with a statistically significant reduction in mortality (OR 0.69, p=0.04), whilst also preventing progression to invasive mechanical ventilation or death (OR 0.89, p=0.03), alongside reduced time to recovery and discharge.

Despite widespread vaccination efforts against SARS-CoV-2, there remains a need for therapies capable of reducing mortality in hospitalised patients, especially with rapid evolution of new variants. In addition, the unwillingness of a significant proportion of the population to be vaccinated, the escape of variants from immune control (our own immune control following previous infection, from vaccination including waning efficacy over time and monoclonal antibodies as treatments), and the probability that other viruses with potentially similar pathogenic mechanisms may arise in the future means that there is a requirement for broadly effective anti-viral therapeutics in the acute phase.

Baricitinib was first recommended for use in the pandemic in early February 2020 after we used the artificial intelligence (AI) enabled drug discovery algorithms at London-based BenevolentAI.[2] Using AI and focusing on already approved drugs which could inhibit both the virus infection and the resultant hyperinflammation,[3] baricitinib was identified as an inhibitor of both Numb-associated and Janus-associated kinases (NAKs and JAKs). Since NAKs regulate clathrin-mediated endocytosis of many viruses (including the coronaviruses[4]) partly by phosphorylating the clathrin adapter protein AP2M1, and JAKs mediate actions of many pro-inflammatory cytokines, those algorithms predicted that baricitinib could be an effective treatment. It has also been suggested that baricitinib could block SARS-CoV-2 entry by inhibiting interferon (IFN)-stimulated expression of one of the virus receptor's ACE2. Some data suggest that the perceived IFN-induced increase in ACE2 is probably that of an inactive splice variant and interestingly the clinical trials suggest baricitinib's use is most transformative for those patients with an Ordinal Scale of 5 or 6, approaching intensive care admission, at which time the anti-viral IFN response is probably waning.

After a number of observational trials and translational laboratory-based experiments using organoids,[5] following the Adaptive Covid Treatment Trial (ACTT)-2 comparing remdesivir alone versus baricitinib with remdesivir in over 1000 patients,[6] the US Food and Drug Administration (FDA) granted an Emergency Use Authorisation (with remdesivir) in November 2020. Then, after the COV-BARRIER trial[7] (July 2021) comparing baricitinib with placebo, the use of baricitinib as a single agent in hospitalised patients was authorised. It is now strongly recommended by the World Health Organization, and has been fully approved by the FDA for the treatment of hospitalised patients with COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation. Surprisingly, there was a great difference in the speed with which the use of baricitinib for COVID-19 was authorised: the USA first authorised use of baricitinib in November 2020, Japan in April 2021, India in May 2021, the UK in May 2022 and the EMA is still reviewing the matter, to the best of our knowledge, though it is used off label regularly.

The anti-interleukin-6 receptor antibody tocilizumab is also in the highest evidence rank alongside baricitinib[8] but it appears that tocilizumab was more effective if co-dosed with corticosteroids,[9] an effect not seen with baricitinib, which was as effective in the presence or absence of steroids. This probably reflects the fact that tocilizumab only inhibits the action of one cytokine pathway (IL-6), whereas baricitinib inhibits many being a JAK inhibitor.[10] Its effects in particular appear different to steroids, use of which has typically confounded treatment and control arms in hospitalised patients. Baricitinib has a short half-life, however, compared to tocilizumab (12.5 hours vs 13 days), has few drug-drug

DOI of original article: http://dx.doi.org/10.1016/j.eclinm.2022.101489.

*Corresponding author. Honorary Professor of Cancer Medicine, Editor-in-Chief Oncogene, Imperial College, Hammersmith Hospital, London, W12 0NN.
E-mail address: j.stebbing@imperial.ac.uk (J. Stebbing).

interactions, variable dosing and unlike remdesivir can be given to patients with a glomerular filtration rate of <60 mls/minute. It is cheap when used for a short duration, and unlike tocilizumab or remdesivir, its oral administration as a 2mg or 4mg tablet (depending for example on frailty) lends itself for use in low-income or middle-income countries.

In summary, this is a timely report confirming the efficacy of baricitinib for the treatment of hospitalised patients with COVID-19, based exclusively on data from randomised studies. Thus far glucocorticoids have been standard of care but baricitinib appears to have greater mortality benefits, and a more favourable toxicity profile.

Contributors

Both authors wrote the manuscript, examined data and approved the final submitted version.

Declaration of interests

PJR is an employee of Benevolent AI, JS has conflicts as listed at: https://www.nature.com/onc/editors as follows:

From 2020 - present Professor Stebbing, the Editor-in-Chief of Oncogene has sat on SABs for Vaccitech, Heat Biologics, Eli Lilly, Alveo Technologies, Pear Bio, Agenus, Equilibre Biopharmaceuticals, Graviton Bioscience Corporation, Celltrion, Volvox, Certis, Greenmantle, vTv Therapeutics, APIM Therapeutics, Bryologyx and Benevolent AI. He has consulted with Lansdowne partners and Vitruvian. He chairs the Board of Directors for Xerion and previously BB Biotech Healthcare Trust PLC.

Funding

None.

References

1 Selvaraj V, Finn A, Lal A, et al. Baricitinib in hospitalised patients with COVID-19: a meta-analysis of randomised controlled trials. *eClinicalMedicine*. 2022.
2 Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020; 395:e30–e31. https://doi.org/10.1016/S0140-6736(20)30304-4.
3 Stebbing J, Phelan A, Griffin I, Tucker C. COVID-19: Combining antiviral and anti-inflammatory treatments. *Lancet Infect. Dis.* 2020; 20:400–402. https://doi.org/10.1016/S1473-3099(20)30132-8.
4 Bayati A, Kumar R, Francis V, McPherson PS. SARS-CoV-2 infects cells following viral entry via clathrin-mediated endocytosis. *J Biol Chem*. 2021;296:100306. https://doi.org/10.1016/j.jbc.2021.100306.
5 Stebbing J, Sanchez Nievas G, Falcone M, et al. JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality. *Sci Adv*. 2021;7: eabe4724. https://doi.org/10.1126/sciadv.abe4724.
6 Kalil AC, Patterson TF, Mehta AK, et al. ACTT-2 Study Group Members. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med*. 2021;384:795–807. https://doi.org/10.1056/nejmoa2031994.
7 Marconi VC, Ramanan AV, de Bono S, COV-BARRIER Study Group. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med*. 2021;9:1407–1418. https://doi.org/10.1016/S2213-2600(21)00331-3.
8 Agarwal A, Rochwerg B, Lamontagne F, et al. A living WHO guideline on drugs for covid-19. *BMJ*. 2020;370:m3379.
9 Shankar-Hari M, Vale CL, Godolphin PJ, et al. WHO rapid evidence appraisal for 770 COVID-19 therapies (REACT) working group association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a Meta-analysis. *JAMA*. 2021;326:499–518. https://doi.org/10.1001/jama.2021.11330.
10 Sims JT, Krishnan V, Chang C, et al. Characterization of the cytokine storm reflects hyperinflammatory endothelial dysfunction in COVID-19. *J Allergy Clin Immunol*. 2021;147:107–111. https://doi.org/10.1016/j.jaci.2020.08.031.