Clinical Infectious Diseases

EDITORIAL COMMENTARY

The Emergence of Baricitinib: A Story of Tortoises Versus Hares

Heinz-Josef Lenz,[1] Peter Richardson,[2] and Justin Stebbing[3]

[1]Division of Oncology, USC Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA, [2]BenevolentAI, London, United Kingdom, and [3]Department of Surgery and Cancer, Imperial College, London, United Kingdom

Keywords. COVID-19; SARS-CoV-2; baricitinib; anti-viral; cytokine storm; trial.

Baricitinib is a once daily orally administered JAK1/2 inhibitor, which inhibits the signaling of many cytokines and has been approved for the treatment of moderate to severe rheumatoid arthritis (RA) based on long-term randomized dosing against both placebo and standard of care [1], notably tumor necrosis factor (TNF)-alpha blockade. Its use for the treatment of coronavirus disease 2019 (COVID-19) was originally suggested after a search of the extensive BenevolentAI knowledge graph for approved drugs that could be used in this pandemic [2]. An advantage of approved drugs is that they have a known safety profile and can therefore be rapidly approved in fast moving pandemics. The artificial intelligence algorithms predicted that baricitinib would inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of cells [2], (an effect later confirmed in human liver spheroids) [3], combined with its better-known anti-inflammatory properties. The doses required were predicted to be the same as used for the treatment of RA. At these doses, interleukin 6 (IL-6) levels were reduced both in COVID19 patients as well as dose dependently in RA patients in a previous phase 2b randomized RA trial, the first time this was shown in humans [4]. What was more intriguing was its inhibition of members of the numb associated kinase family, thought in turn to translate to reduced AP-2 mediated viral propagation early in the infectious cycle, suggesting antiviral activity; this was shown in liver spheroid models, which express detectable albeit low levels of the ACE2 receptor.

In hospitalized patients it is anticipated that residual virus that propagates itself in airway epithelial tissues maintains and amplifies the exaggerated inflammatory response typical of COVID-19. Consequently, the combined potential antiviral and anti-inflammatory effects of this dually acting drug could be ideal for halting the progression of the disease in hospitalized patients, when taken for a limited duration. At the University of Southern California now, a randomized placebo-controlled phase 2 study with remdesivir with/without baricitinib is ongoing to test the efficacy to prevent mechanical ventilation including significant biomarker research.

In this issue of *Clinical Infectious Diseases*, Titanji et al describe the outcome of 15 moderate-to-critically ill patients with COVID-19 treated with baricitinib and hydroxychloroquine. This therapy was associated with a reduction in inflammatory markers including fever, C reactive protein (CRP), improvement of oxygen requirements, and recovery in 12 of the 15 (80%) patients studied. Although it is possible that the antiviral and anti-inflammatory effects of hydroxychloroquine contributed to this positive outcome, this would seem unlikely according to the recently reported National Institutes of Health (NIH) randomized trials) [5], among many other studies. This new paper in the journal extends the previous published reports of baricitinib treatment in mild-to-moderate COVID19 patients and provides further evidence that baricitinib could be a potential treatment for unwell hospitalized patients with this disease, independent of severity. Indeed, in mild-to-moderate patients, baricitinib therapy was also associated with a reduction in the requirement for intensive care unit (ICU) care when compared with matched case controls [6, 7]. In each series baricitinib treatment has been associated with a reduction in inflammation and recovery from the disease in the vast majority of patients, consistent with the present report, but we do not know if this is simply an association or represents a causative effect of the drug. In this new paper, 3 patients died, 2 of which had very high plasma IL-6 levels prior to starting baricitinib therapy consistent with previous data that high IL-6 is a predictor of mortality in COVD19 infections [8, 9]. These useful results retrospectively justified the testing of the anti-IL6/

Received 25 June 2020; editorial decision 30 June 2020; accepted 2 July 2020; published online July 6, 2020.

Correspondence: Justin Stebbing, Imperial College, ICTEM building, Hammersmith Hospital, Du Cane Road, London, W12 0NN, UK (j.stebbing@imperial.ac.uk).

Clinical Infectious Diseases® 2020;XX(XX):0–0

DOI: 10.1093/cid/ciaa940

IL6R antibodies Kevzara (sarilumab) and Actemra (tocilizumab) in severely unwell patients, although randomized studies are yet to show benefits.

Baricitinib treatment over prolonged periods in RA patients has been associated with increased infections and thromboembolism, but the short duration of treatment in COVID-19 patients may mitigate against such side effects. In this report it is difficult to say whether one incident of pulmonary embolism and methicillin-resistant *Staphylococcus aureus* (MRSA) infection were due to the complications of COVID-19 or baricitinib, but the much larger numbers of patients in the yet to report randomized studies should clarify this. One would be advised to remain vigilant of such signals reflecting thromboembolic or infection risk in randomized controlled trials testing a variety of immunomodulatory therapies in COVID-19 patients, either alone or in combination, especially in view of associations between clots and SARS-CoV-2 infection [10]. Specifically, severe endothelial injury associated with intracellular SARS-CoV-2 virus and disrupted endothelial cell membranes, widespread vascular thrombosis with microangiopathy, and occlusion of alveolar capillaries including significant new vessel growth through a mechanism of intussusceptive angiogenesis has been described [11].

The first report of a significant reduction in COVID-19 mortality in any randomized study recently came from the RECOVERY trial in the United Kingdom showing that low dose dexamethasone had a significant effect in reducing mortality when given with standard of care (21.6% vs 24.6% of the patients dying within 28 days) [12]; this effect was greatest in ventilated patients (a 30% reduction in mortality) and slightly less in those provided with noninvasive supplemental oxygen (a 20% reduction) [12]. It is tempting to speculate that a similar or greater reduction in mortality could be expected with baricitinib in randomized trials, especially because baricitinib is now reported to be associated with recovery from COVID-19 in different series of patients. It may even be possible to combine the baricitinib with dexamethasone, at least in critically ill patients, although once again it would of course be important to assess the risk of infection when administering these 2 potent anti-inflammatory agents together.

As acknowledged by Titanji et al, and reiterated by us, randomized trials are required for us to be certain if baricitinib is an effective and safe therapy for COVID-19 patients [3]. This report, and others like it, have supported the selection of baricitinib in a number of studies including the ACTT2 randomized trial, where it is being tested in combination with remdesivir, and a further placebo-controlled phase 3 trial recently commenced. It is anticipated that these trials should provide a robust estimate of the efficacy of baricitinib in COVID-19 and would be complementary to each other. These initial case series warrant further confirmation from the ongoing larger, randomized and controlled trials. Thus far, these data sets also validate use of artificial intelligence at a time of a biomedical crisis, to help speed drug development. The use of an oral medicine taken once daily for a short duration should also lend itself to low- and middle-income countries.

Note

Potential conflicts of interest. P. J. R. is an employee of BenevolentAI and has received honoraria for giving a lecture to Lilly with J. S. And J. S. has sat on SABs for Vaccitech, Heat Biologics, Eli Lilly, Replete, Alveo, Certis Oncology Solutions, Greenmantle and BenevolentAI, has consulted with Lansdowne partners and Vitruvian. He sits on the Board of Directors for BB Biotech Healthcare Trust. H.-J. L. has no reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Taylor PC, Keystone EC, Van Der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med **2017**. doi:10.1056/NEJMoa1608345.
2. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet **2020**; 395:e30–1.
3. Stebbing J, Krishnan V, de Bono S, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. EMBO Mol Med **2020**. doi:10.15252/emmm.202012697.
4. Tanaka Y, Emoto K, Cai Z, et al. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis receiving background methotrexate therapy: a 12-week, double-blind, randomized placebo-controlled study. J Rheumatol **2016**. doi:10.3899/jrheum.150613.
5. Wang Y, Liang S, Qiu T, et al. Rapid systematic review on clinical evidence of chloroquine and hydroxychloroquine in COVID-19 critical assessment and recommendation for future clinical trials. medRxiv **2020**. doi:10.1101/2020.06.01.20118901.
6. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. J Infect **2020**. doi:10.1016/j.jinf.2020.04.017.
7. Matarrese D, Edoardo M, Natale D, et al. Retrospective, multicenter study on the impact of baricitinib in COVID-19 moderate pneumonia. J Infect **2020**. doi:10.1016/j.jinf.2020.06.052.
8. Liu T, Zhang J, Yang Y, et al. The potential role of IL-6 in monitoring coronavirus disease 2019. SSRN Electron J **2020**. doi:10.2139/ssrn.3548761.
9. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med **2020**. doi:10.1007/s00134-020-05991-x.
10. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol **2020**. doi:10.1016/S2665-9913(20)30121-1.
11. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med **2020**. doi:10.1056/nejmoa2015432.
12. Horby P, Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. medRxiv **2020.** doi:10.1101/2020.06.22.20137273.