~~The Evolution of Baricitinib in treatment of COVID-19~~
Baricitinib in COVID-19: from bytes to bedside

Or
Baricitinib in COVID-19: from artificial intelligence predictions to patients

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Immunomodulatory therapies targeting excessive host immune responses[1], vaccination and immunity from natural infection have changed the course of the COVID-19 pandemic. However, the rapid emergence of SARS-CoV-2 variants has stymied progress towards ending the pandemic. An unmet need remains for accessible therapies which reduce mortality. In this issue of the Lancet, the RECOVERY Collaborative Group assessed the use of baricitinib, a Janus Kinase inhibitor (JAKi) for the treatment of hospitalized patients with COVID-19, in the randomised, controlled, open-label platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]).[2] These results mark a coming-of-age for baricitinib, whose potential use in COVID-19 was first identified from an artificial intelligence (AI) enabled drug discovery algorithm,[3] . Baricitinib can suppress

multiple cytokine-signaling pathways simultaneously and impede viral propagation through inhibition of numb-associated kinases (NAKs) important for clarthrin-mediated endocytosis.[4]

RECOVERY was conducted in the UK and 8156 patients (mean age 58.1 years, 66% male, 34% female, 80% white) were randomly allocated to receive usual care plus baricitinib or usual care alone (which included corticosteroids). Patients receiving baricitinib plus usual care, had a significant reduction in the primary outcome of 28-day mortality. Of the patients randomized, 514 (12%) of 4148 patients in the baricitinib group died compared to 546 (14%) of 4008 patients in the usual care group (age-adjusted rate ratio 0·87; 95% CI 0·77–0·99; p=0·028) with a number-needed-to-treat (NNT) to prevent one additional death of 50. The authors conducted a meta-analysis of all randomized trials of JAKi for COVID-19 including the results of this study (n=9) and found a proportional 20% reduction in mortality associated with JAKi. RECOVERY is the largest trial of baricitinib for COVID-19 and confirms the findings of previous studies thus unequivocally validating the addition of this drug to the arsenal of COVID-19 therapies.

The RECOVERY trial is an international trial but the evaluation baricitinib was conducted only in the UK and these findings may be less generalizable to populations with different demographics and higher prevalence of HIV and latent TB (<1% enrolled). Baricitinib is an oral agent and of lower cost in many countries compared with intravenous tocilizumab, which also confers a mortality benefit. Baricitinib could be more accessible in lower-resourced settings, although its effects on non-COVID infections in these countries needs better characterisation. The open-label design of RECOVERY is often criticized for risk of bias, however unlikely to influence an unambiguous primary outcome of mortality. The adaptive design has yielded timely and invaluable results amidst the challenges of conducting practice changing research in pandemic.

Meta-analyses of previous JAKi trials in COVID-19, as well as analyses restricted to baricitinib-only trials (n=4, including RECOVERY), strongly supports targeting the JAK-STAT axis in COVID-19, although mechanistically the influence of JAK isoform selectivity is unclear. The mortality risk reduction with baricitinib in RECOVERY was smaller than anticipated, probably explained by a broader eligibility in RECOVERY compared with other baricitinib studies (appendix), which all mandated hypoxaemia. COV-BARRIER demonstrated a 5% absolute

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reduction in mortality at both day 28 and 60, NNT 20,[5] and included an entry requirement of evidence of inflammation; although lower thresholds than the tocilizumab arm of RECOVERY (hypoxaemia and CRP≥ 75mg/L).[6] Subgroup analyses in ACTT-2[7] and COV-BARRIER,[5] both suggested greater benefit in more severe disease.

WHO's living guidance recommends baricitinib for patients with severe/critical COVID-19 in combination with corticosteroids.[8] The precise positioning of baricitinib is unclear, but expanding choice stimulates questions regarding personalized immunomodulation regimens, incorporating side-effect profiles, routes of administration, cost and patient co-morbidities. The ACTT-4 trial did not show a difference in outcomes for baricitinib and dexamethasone arms, although dexamethasone was associated with significantly more adverse events.[9] Available evidence is insufficient to suggest that baricitinib would routinely replace dexamethasone, however it could be a viable steroid-sparing option in patients at high-risk of glucocorticoid side-effects. In RECOVERY, 23% patients in both groups received tocilizumab, yet the benefits of baricitinib were consistent irrespective of co-administration. Data are insufficient for further interpretation, but notably both agents may increase the risk of gastrointestinal perforation (also applicable to concomitant corticosteroids), and cause pharmacodynamic CRP suppression. JAKi have a broader, but shorter immunosuppressive effect than selective cytokine blockade i.e., in adults 12-hour half-life (baricitinib) compared with 11-13 days (tocilizumab). Where there is a higher risk of secondary infections, baricitinib's broader immunosuppressive effect, may be considered an advantage given the faster-onset of action or a disadvantage with greater dampening of host defenses. However, faster wash-out when discontinued is of undoubted value. Baricitinib can be dose-adjusted in renal impairment and delivered by nasogastric tube in ventilated patients. It may also have a role in other hyperinflammatory disorders of immune dysregulation, including sepsis and other viral epidemics e.g., dengue syndrome.[10]

Safety data for baricitinib is reassuring, especially related to thrombotic events, probably due to the limited treatment duration in anti-coagulated patients in COVID-19; different to chronic dosing in in rheumatoid arthritis studies, where safety signals were detected.[11]. Guidelines do not recommend JAKi in pregancy[12] and pharmacokinetic studies suggest that the half-life of baricitinib children is substantially shorter than adults, requiring dosing up to four-times-per-day.[13].

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Commented [PH6]: ACCT-4 was designed as a superiority trial (powered to detect if baricitinib was superior to dexamethasone) and was terminated early for futility because there was very low probability of demonstrating superiority. The trial did not therefore demonstrate non-inferiority (which this sentence implies), rather it failed to show a difference. A subtle but important point.

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Bari: https://www.medicines.org.uk/emc/product/2434/smpc

TOC: https://www.medicines.org.uk/emc/product/6673/smpc

Tocilizumab may be preferred in pregnant and paediatric patients, given greater clinical experience and convenient dosing respectively.

From early days in AI algorithms to pharmacogenomic predictions we now have compelling efficacy and safety data for baricitinib in COVID-19. Baricitinib's evolution is an exemplar of modern-day candidate selection, proof-of-concept testing and drug repurposing, serving as a template for drug discovery - a powerful tool in future pandemic preparedness.

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