Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Baricitinib in COVID-19: a coming-of-age from artificial intelligence to reducing mortality

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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 that reduce mortality. In *The Lancet*, the RECOVERY Collaborative Group assessed the use of baricitinib, a Janus kinase (JAK) inhibitor, for the treatment of patients hospitalised with COVID-19, in the randomised, controlled, open-label platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]).[2] The potential use of baricitinib in COVID-19 was first identified from an artificial-intelligence-enabled drug discovery algorithm.[3] Baricitinib can suppress multiple cytokine-signalling pathways simultaneously and impede viral propagation through inhibition of numb-associated kinases important for clarthrin-mediated endocytosis.[4]

See **Online** for appendix

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 randomly assigned, 514 (12%) of 4148 patients in the baricitinib group died compared with 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 did a meta-analysis of all nine completed randomised trials of JAK inhibitors for COVID-19 including the results of this study and found a proportional 20% reduction in mortality associated with JAK inhibitors. RECOVERY is the largest trial of baricitinib for COVID-19 and confirms the findings of previous studies thus validating the addition of this drug to the arsenal of COVID-19 therapies.

The RECOVERY trial is an international trial but baricitinib was only evaluated in the UK and these findings might be less generalisable to populations with different demographics and higher prevalence of HIV and latent tuberculosis (<1% enrolled). Baricitinib is an oral agent and of lower cost in many countries compared with intravenous tocilizumab, which also confers a mortality benefit.[5] Baricitinib could be more accessible in lower-resourced settings, although its effects on non-COVID-19 infections in these countries needs better characterisation. The open-label design of RECOVERY has been criticised for risk of bias;[6] it is, however, unlikely to influence an unambiguous primary outcome of mortality. The adaptive design has yielded timely and invaluable results amid the challenges of doing practice-changing research during a pandemic.

Meta-analyses of previous JAK inhibition trials in patients with COVID-19, as well as analyses restricted to baricitinib-only trials (n=4, including RECOVERY), strongly support targeting the JAK-STAT (signal transducer and activator of transcription) 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, which is probably explained by a broader eligibility in RECOVERY compared with other studies of baricitinib for hospitalised patients with COVID-19 (appendix), which all mandated hypoxaemia. COV-BARRIER showed a 5% absolute reduction in mortality at both day 28 and 60, NNT 20,[7] and included an entry requirement of evidence of inflammation, although had lower thresholds than the tocilizumab group of RECOVERY (hypoxaemia and C-reactive protein ≥75 mg/L).[5] Subgroup analyses in both ACTT-2[8] and COV-BARRIER,[7] suggested greater benefit of baricitinib in more severe disease.

WHO's living guidance recommends baricitinib for patients with severe or critical COVID-19 in combination with corticosteroids.[9] The precise positioning of baricitinib is unclear, but expanding choice stimulates questions regarding personalised immunomodulation regimens, incorporating side-effect profiles, routes of administration, cost, and patient comorbidities. The ACTT-4 trial did not show a difference in outcomes between the baricitinib and dexamethasone groups, although dexamethasone was associated with significantly more adverse events.[10] 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% of 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 might increase the risk of gastrointestinal perforation (also applicable to concomitant corticosteroids), and cause pharmacodynamic C-reactive protein suppression. JAK inhibitors have a broader but shorter immunosuppressive effect than selective cytokine blockade (ie, in adults, 12-h half-life for baricitinib compared with 11–13 days for tocilizumab). Where there is a higher risk of secondary infections, baricitinib's broader immunosuppressive effect might be considered an advantage given the faster onset of action or a disadvantage with greater dampening of host defences. However, faster wash-out when discontinued is of undoubted value. Baricitinib can be dose-adjusted in renal impairment and delivered by nasogastric tube in patients who are ventilated. Further research is awaited to establish whether baricitinib might also have a role in other hyperinflammatory disorders of immune dysregulation, including sepsis and other viral epidemics (eg, dengue syndrome).[11]

Safety data for baricitinib is reassuring, especially related to thrombotic events, probably owing to the limited treatment duration in patients with COVID-19 who are anticoagulated. This finding differs from chronic JAK inhibitor dosing in rheumatoid arthritis studies, where safety signals were detected.[12] Guidelines do not recommend JAK inhibitors in pregancy[13] and pharmacokinetic studies suggest that the half-life of baricitinib in children is substantially shorter than in adults, requiring dosing up to four times per day.[14] Tocilizumab might be preferred in patients who are pregnant or paediatric, given greater clinical experience and convenient dosing respectively.

From early days in artificial intelligence algorithms to pharmacogenomic predictions[15] we now have compelling efficacy and safety data for baricitinib in patients with 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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For **barcitinib details** see https://www.medicines.org.uk/emc/product/2434/smpc

For **tocilizumab details** see https://www.medicines.org.uk/emc/product/6673/smpc

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