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

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Summary

Background **Baricitinib is an oral selective Janus kinase 1/2 inhibitor with known anti-inflammatory properties. This study evaluates the efficacy and safety of baricitinib in combination with standard of care for the treatment of hospitalised adults with COVID-19.**

Methods **In this phase 3, double-blind, randomised, placebo-controlled trial, participants were enrolled from 101 centres across 12 countries in Asia, Europe, North America, and South America. Hospitalised adults with COVID-19 receiving standard of care were randomly assigned (1:1) to receive once-daily baricitinib (4 mg) or matched placebo for up to 14 days. Standard of care included systemic corticosteroids, such as dexamethasone, and antivirals, including remdesivir. The composite primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28, assessed in the intention-to-treat population. All-cause mortality by day 28 was a key secondary endpoint, and all-cause mortality by day 60 was an exploratory endpoint; both were assessed in the intention-to-treat population. Safety analyses were done in the safety population defined as all randomly allocated participants who received at least one dose of study drug and who were not lost to follow-up before the first post-baseline visit. This study is registered with ClinicalTrials.gov, NCT04421027.**

Findings **Between June 11, 2020, and Jan 15, 2021, 1525 participants were randomly assigned to the baricitinib group (n=764) or the placebo group (n=761). 1204 (79·3%) of 1518 participants with available data were receiving systemic corticosteroids at baseline, of whom 1099 (91·3%) were on dexamethasone; 287 (18·9%) participants were receiving remdesivir. Overall, 27·8% of participants receiving baricitinib and 30·5% receiving placebo progressed to meet the primary endpoint (odds ratio 0·85 [95% CI 0·67 to 1·08], p=0·18), with an absolute risk difference of –2·7 percentage points (95% CI –7·3 to 1·9). The 28-day all-cause mortality was 8% (n=62) for baricitinib and 13% (n=100) for placebo (hazard ratio [HR] 0·57 [95% CI 0·41–0·78]; nominal p=0·0018), a 38·2% relative reduction in mortality; one additional death was prevented per 20 baricitinib-treated participants. The 60-day all-cause mortality was 10% (n=79) for baricitinib and 15% (n=116) for placebo (HR 0·62 [95% CI 0·47–0·83]; p=0·0050). The frequencies of serious adverse events (110 [15%] of 750 in the baricitinib group *vs* 135 [18%] of 752 in the placebo group), serious infections (64 [9%] *vs* 74 [10%]), and venous thromboembolic events (20 [3%] *vs* 19 [3%]) were similar between the two groups.**

Interpretation **Although there was no significant reduction in the frequency of disease progression overall, treatment with baricitinib in addition to standard of care (including dexamethasone) had a similar safety profile to that of standard of care alone, and was associated with reduced mortality in hospitalised adults with COVID-19.**

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Introduction

Hospitalised patients with SARS-CoV-2 infection often develop an intense hyperinflammatory state that can lead to multiple organ dysfunction, including acute respiratory distress syndrome, septic shock, and death.[1–4] Despite treatment advances with remdesivir, dexamethasone, and tocilizumab, reducing mortality among hospitalised patients remains a crucial unmet need.[5–8]

Baricitinib is a selective Janus kinase (JAK)1/JAK2 inhibitor[9–11] with a known anti-inflammatory profile in patients with autoimmune diseases.[12–14] In February, 2020, baricitinib was identified by an artificial intelligence platform as a potential intervention for the treatment of

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Research in context

Evidence before this study

We searched PubMed using the terms "COVID-19", "SARS-CoV-2", "treatment", "baricitinib", and "JAK inhibitor" for articles in English, published until April 31, 2020, regardless of article type. We considered previous and current clinical trials of investigational medications in COVID-19, as well as previous clinical trials of the Janus kinase (JAK)1 and JAK2 inhibitor baricitinib conducted before this study. At the time the COV-BARRIER study was designed, there were no approved therapies for the treatment of COVID-19. Management of COVID-19 was supportive, and few phase 3 randomised placebo-controlled studies had been completed. Some phase 2 and 3 data on the antimalarial hydroxychloroquine and protease inhibitor lopinavir–ritonavir were available, and trials investigating the use of the antiviral remdesivir were ongoing. Baricitinib was identified as a potential intervention for COVID-19 due to its mechanism of action as a JAK1 and JAK2 inhibitor, its known anticytokine properties, and a potential antiviral mechanism via targeting host proteins. Additionally, early case series evaluating the efficacy and safety of baricitinib in populations of hospitalised patients supported further evaluation of baricitinib as a potential treatment option for hospitalised patients with COVID-19. While the COV-BARRIER study was enrolling, ACTT-2, a phase 3 study evaluating baricitinib plus remdesivir, was completed and showed that baricitinib in combination with remdesivir improved time to recovery and other outcomes.

Added value of this study

This was the first phase 3 study to evaluate baricitinib in addition to the current standard of care, and included patients receiving antivirals, anticoagulants, and corticosteroids. After the earliest publication of the RECOVERY study in June, 2020, the treatment of hospitalised patients with COVID-19 changed with the adoption of dexamethasone as the standard of care. As a result of its design, COV-BARRIER became the first trial to evaluate the benefit and risk of baricitinib when added to the most current standard of care (dexamethasone) in these patients. This was a randomised, double-blind, placebo-controlled trial conducted globally in regions with high COVID-19 hospitalisation rates. The reduction in the composite primary endpoint of progression to non-invasive ventilation, high-flow oxygen, invasive mechanical ventilation, or death for baricitinib plus standard of care (including dexamethasone) compared with placebo plus standard of care was not statistically significant. However, analysis of a prespecified key secondary endpoint showed that treatment with baricitinib reduced 28-day all-cause mortality by 38·2% compared with placebo (HR 0·57 [95% CI 0·41–0·78], nominal p=0·0018), with one additional death prevented per 20 baricitinib-treated participants. The reduction of all-cause mortality with baricitinib was maintained up to day 60 in an exploratory analysis. The frequency of serious adverse events, serious infections, and venous thromboembolic events was similar between the baricitinib and placebo groups.

Implications of all the available evidence

In this phase 3 trial, baricitinib administered in addition to standard of care (which predominantly included dexamethasone) did not reduce the incidence of a composite endpoint of disease progression, but showed a strong effect on reduction of mortality by 28 days, an effect which was maintained up to 60 days. In the ACTT-2 study, baricitinib further reduced time to recovery above the background use of remdesivir. Taken together, these findings suggest that baricitinib has synergistic effects with other standard-of-care treatment modalities, including remdesivir and dexamethasone. Based on all available evidence, baricitinib is a potentially effective oral treatment option to decrease mortality in hospitalised patients with COVID-19.

COVID-19 because of its known anticytokine properties and potential for targeting host proteins for its antiviral mechanism.[15,16] The biochemical inhibitory effects of baricitinib on human Numb-associated kinases (AAK1, BIKE, and GAK) responsible for SARS-CoV-2 viral propagation were subsequently confirmed.[17] Baricitinib was also shown to reduce multiple cytokines and biomarkers implicated in COVID-19 pathophysiology.[18–20] Following the publication of these findings, several observational studies including small cohorts of hospitalised patients with COVID-19 (including older adults) were done and provided the first evidence of clinical improvement associated with baricitinib treatment.[21–24]

The Adaptive COVID-19 Treatment Trial 2 (ACTT-2)—a US National Institutes of Health-sponsored, double-blind, randomised, placebo-controlled, phase 3 trial in hospitalised adults with COVID-19—found that treatment with baricitinib plus remdesivir was superior to treatment with remdesivir alone in reducing time to recovery (rate ratio 1·16 [95% CI 1·01–1·32], p=0·03) and was associated with fewer serious adverse events, although 28-day mortality did not differ significantly between groups (5·1% with baricitinib and remdesivir *vs* 7·8% with remdesivir).[6] The US Food and Drug Administration issued an emergency use authorisation for baricitinib in hospitalised patients with COVID-19 who required oxygen supplementation,[25] addressing an unmet need in the treatment of COVID-19.[26] Globally, however, evaluations of new treatment options to reduce mortality in hospitalised patients with COVID-19 are still urgently needed to reduce the high frequency of deaths that persists despite improvements in standards of care.

The COV-BARRIER study was designed to evaluate the efficacy and safety of baricitinib in combination with standard of care, including dexamethasone, for the treatment of hospitalised adults with COVID-19. To the