

# The COVID-19 Treatment Guidelines Panel’s Statement on Baricitinib for the Treatment of Adults with COVID-19

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Baricitinib is an oral Janus kinase (JAK) inhibitor that is selective for JAK1 and JAK2. It is being evaluated for the treatment of COVID-19 because it may prevent cellular immune activation and inflammation. Baricitinib is approved by the Food and Drug Administration (FDA) to treat moderate to severe rheumatoid arthritis. On November 19, 2020, the FDA issued an Emergency Use Authorization (EUA) for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged  $\geq 2$  years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.<sup>1</sup>

On December 14, 2020, the COVID-19 Treatment Guidelines Panel (the Panel) issued a statement regarding the baricitinib EUA that included recommendations based on findings from ACTT-2.<sup>2</sup> This trial demonstrated that baricitinib improved time to recovery when given in combination with remdesivir to patients who require supplemental oxygen but not invasive mechanical ventilation. However, a key limitation of ACTT-2 was the inability to evaluate the effect of baricitinib in addition to corticosteroids.

Since the statement was issued, the Panel has reviewed the recent findings from COV-BARRIER, a trial of baricitinib in hospitalized adults.<sup>3</sup> COV-BARRIER included patients with COVID-19 who required supplemental oxygen at enrollment but not invasive mechanical ventilation. The trial reported an additional survival benefit of baricitinib when added to the standard of care of corticosteroids (with or without remdesivir).

Based on the preliminary results (not yet peer reviewed) from COV-BARRIER, the Panel has updated its recommendations on the use of baricitinib for the treatment of adults with COVID-19.

## Summary Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using either **baricitinib<sup>a</sup> (BIIa)** or **tocilizumab (BIIa)** (listed alphabetically) in combination with **dexamethasone** alone or **dexamethasone plus remdesivir** for the treatment of COVID-19 in hospitalized patients on high-flow oxygen or noninvasive ventilation who have evidence of clinical progression or increased markers of inflammation.
- Among hospitalized patients with hypoxemia who require supplemental oxygen therapy, there is insufficient evidence to identify which patients would benefit from the addition of baricitinib or tocilizumab to dexamethasone (with or without remdesivir). Some Panel members would add either baricitinib<sup>a</sup> or tocilizumab to patients who are exhibiting signs of systemic inflammation and rapidly increasing oxygen needs while on dexamethasone, but who do not yet require noninvasive ventilation or high-flow oxygen.
- In the rare circumstance when corticosteroids cannot be used, the Panel recommends using **baricitinib<sup>a</sup>** in combination with **remdesivir** for the treatment of COVID-19 in hospitalized, nonintubated patients who require oxygen supplementation (**BIIa**).
- There is insufficient evidence for the Panel to recommend either for or against the use of baricitinib in combination with dexamethasone for the treatment of COVID-19 in hospitalized patients who require invasive mechanical ventilation.
- The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19, except in a clinical trial (**AIII**). Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.
- There is insufficient evidence for the Panel to recommend either for or against the use of baricitinib for the treatment of COVID-19 in children.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

<sup>a</sup> Baricitinib dose is 4 mg orally (PO) daily for 14 days or until hospital discharge. Baricitinib has not been evaluated in clinical studies in patients with estimated glomerular filtration rate (eGFR)  $\leq 30$  mL/min. Dose reduction from baricitinib 4 mg to 2 mg PO daily is recommended for eGFR  $\geq 30$  mL/min to  $< 60$  mL/min and to 1 mg PO daily for eGFR of 15 mL/min to  $< 30$  mL/min. Baricitinib **is not recommended** for patients with eGFR  $< 15$  mL/min.

## Clinical Trial Data

The Panel's updated recommendations for the use of baricitinib are largely based on data from COV-BARRIER, a multinational, randomized, placebo-controlled trial.<sup>3</sup> This trial included 1,525 hospitalized patients with COVID-19 who had evidence of pneumonia and an elevation in  $\geq 1$  inflammatory markers. Patients requiring invasive mechanical ventilation and patients with estimated glomerular filtration rate (eGFR)  $< 30$  mL/min/1.73m<sup>2</sup> were excluded from the trial. Participants were randomized 1:1 to receive baricitinib 4 mg orally or placebo in addition to the local standard of care for up to 14 days (or until hospital discharge). The baricitinib dose was reduced to 2 mg daily for participants with eGFR  $\geq 30$  mL/min/1.73m<sup>2</sup> to  $< 60$  mL/min/1.73m<sup>2</sup>. The standard of care included corticosteroids for 79% of the participants (91% of these participants received dexamethasone) and remdesivir for 19% of the participants.

The primary endpoint in COV-BARRIER was the proportion of patients who progressed to high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or death by Day 28. All-cause mortality within 28 days was a key secondary endpoint. All participants received prophylaxis for venous thromboembolism unless contraindicated.

Among the participants, 27.8% in the baricitinib arm versus 30.5% in the placebo arm progressed to the primary endpoint (OR 0.85; 95% CI, 0.67–1.08;  $P = 0.18$ ). All-cause mortality by Day 28 was 8.1% in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality (HR 0.57; 95% CI, 0.41–0.78; nominal  $P = 0.002$ ). Across all the prespecified baseline disease severity subgroups, mortality estimates were numerically lower among those who received baricitinib than among those who received placebo. The difference in mortality was most pronounced in the subgroup of participants who were receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% for the baricitinib recipients vs. 29.4% for the placebo recipients; HR 0.52; 95% CI, 0.33–0.80; nominal  $P = 0.007$ ). In the subgroup of participants receiving remdesivir as part of standard care at baseline (91.6% of these participants also received corticosteroids), a numerical reduction in mortality with baricitinib use was observed but did not reach statistical significance. The occurrence of adverse events, serious adverse events, serious infections, and venous thromboembolic events was comparable in the baricitinib and placebo arms.

## References

1. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization (EUA) of baricitinib. 2020. Available at: <https://www.fda.gov/media/143823/download>.
2. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2021;384(9):795-807. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33306283>.
3. Marconi VC, Ramanan AV, de Bono S, et al. Baricitinib plus standard of care for hospitalized adults with COVID-19. *medRxiv*. 2021;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2021.04.30.21255934v1>.