



Janus Kinase Inhibitors

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The primary mechanism of Janus kinase (JAK) inhibitors is interference with phosphorylation of the signal transducer and activator of transcription (STAT) proteins^{1,2} involved in vital cellular functions, including signaling, growth, and survival. JAK inhibitors are used as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).³ Multiple JAK inhibitors are available, but only baricitinib and tofacitinib have been studied for the treatment of COVID-19.

In May 2022, the Food and Drug Administration (FDA) approved the use of baricitinib for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, noninvasive ventilation (NIV), mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).⁴

Recommendation

- See [Therapeutic Management of Hospitalized Adults With COVID-19](#) for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of baricitinib in hospitalized patients who require conventional oxygen, high-flow nasal cannula oxygen, NIV, or mechanical ventilation.

Additional Consideration

- If none of the recommended immunomodulatory therapies discussed in [Therapeutic Management of Hospitalized Adults With COVID-19](#) are available or feasible to use, **oral tofacitinib** can be used in combination with dexamethasone (**CHa**).

Rationale

Several large randomized controlled trials have demonstrated that some patients who require supplemental oxygen and most patients who require oxygen through a high-flow device, NIV, or mechanical ventilation benefit from the use of dexamethasone in combination with a JAK inhibitor.

In the RECOVERY trial, baricitinib was associated with a survival benefit among hospitalized patients, with a treatment effect that was most pronounced among patients receiving NIV or oxygen supplementation through a high-flow device.⁵ The COV-BARRIER trial also demonstrated a survival benefit from baricitinib that was most pronounced among patients receiving high-flow oxygen or NIV.⁶ In the addendum to the COV-BARRIER trial, the benefit extended to patients receiving mechanical ventilation.⁷ Data from the ACTT-2⁸ and ACCT-4⁹ trials support the overall safety of baricitinib and the potential for benefit, but neither trial studied the drug in combination with dexamethasone as standard care.

The STOP-COVID study examined the use of tofacitinib in people with COVID-19 pneumonia who were not receiving NIV, mechanical ventilation, or ECMO at the time of enrollment.¹⁰ The study demonstrated a survival benefit in patients who received tofacitinib, nearly all of whom also received corticosteroids. If none of the other recommended immunomodulatory therapies are available or feasible to use, tofacitinib may be used as a substitute based on the findings from the STOP-COVID study.

Clinical trial data on the use of baricitinib and tofacitinib in patients with COVID-19 are summarized

below and in [Table 5d](#).

Baricitinib

In May 2022, the FDA approved the use of baricitinib for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, NIV, mechanical ventilation, or ECMO.⁴

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2. It can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6–induced STAT3 phosphorylation.¹¹ Baricitinib has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.¹² See [Table 5d](#) for details on clinical trial data for baricitinib.

Tofacitinib

Tofacitinib is the prototypical JAK inhibitor, predominantly selective for JAK1 and JAK3, with modest activity against JAK2, and, as such, can block signaling from gamma-chain cytokines (e.g., IL-2, IL-4) and glycoprotein 130 proteins (e.g., IL-6, IL-11, interferons). It is an oral agent first approved by the FDA for the treatment of rheumatoid arthritis and has been shown to decrease levels of IL-6 in patients with this disease.¹³ Tofacitinib is also approved by the FDA for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.¹⁴ See [Table 5d](#) for additional details on clinical trial data for tofacitinib.

Monitoring, Adverse Effects, and Drug-Drug Interactions

An FDA review of a large, randomized, safety clinical trial in people with rheumatoid arthritis compared tofacitinib to tumor necrosis factor inhibitors over 4 years and found that tofacitinib was associated with additional serious adverse events, including heart attack or stroke, cancer, blood clots, and death.¹⁵ Therefore, the FDA now requires new and updated warnings for drugs in the JAK inhibitor class, including baricitinib and tofacitinib. Data from randomized trials evaluating the safety of short-term use of JAK inhibitors in patients with COVID-19 have not revealed significant safety signals, including thrombosis.^{5,6,8-10} Because of the immunosuppressive effects of JAK inhibitors, all patients receiving either baricitinib or tofacitinib should be monitored for new infections.

Tofacitinib is a cytochrome P450 (CYP) 3A4 substrate. Dose modifications are required when the drug is administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor. Coadministration with a strong CYP3A4 inducer is not recommended. See [Table 5e](#) for kinase inhibitor drug characteristics and dosing information.

Considerations in Pregnant and Lactating People

See [Pregnancy, Lactation, and COVID-19 Therapeutics](#) for the Panel’s guidance regarding the use of baricitinib during pregnancy and lactation. Pregnancy registries provide some outcome data on tofacitinib use during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the cases reported, pregnancy outcomes were similar to those among the general population.¹⁶⁻¹⁸

Considerations in Children

See [Therapeutic Management of Hospitalized Children With COVID-19](#) for the Panel’s recommendations regarding the use of baricitinib or tofacitinib in children with COVID-19.

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