Janus Kinase Inhibitors

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Janus kinase (JAK) inhibitors interfere with phosphorylation of the signal transducer and activator of transcription (STAT) proteins[1,2] that are involved in vital cellular functions, including signaling, growth, and survival. JAK inhibitors are used to treat 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] Several JAK inhibitors are available for clinical use, 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 who require supplemental oxygen, noninvasive ventilation (NIV), mechanical ventilation, or extracorporeal membrane oxygenation.[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.[5]

Tofacitinib is a JAK inhibitor that is predominantly selective for JAK1 and JAK3. However, it also has modest activity against JAK2; thus, it 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 that was 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.[6] Tofacitinib is also approved by the FDA for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.[7]

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 combination with dexamethasone 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 **(CIIa)**.

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 who were receiving NIV or oxygen supplementation through a high-flow device.[8] The COV-BARRIER trial also demonstrated a survival benefit for baricitinib that was most pronounced among patients who were receiving high-flow oxygen or NIV.[9] In the addendum to the COV-BARRIER trial, the benefit extended to patients who were receiving mechanical ventilation.[10] Data from the ACTT-2[11] and ACTT-4[12] trials support the overall

safety of baricitinib and the potential for benefit, but neither trial studied baricitinib use 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 extracorporeal membrane oxygenation at the time of enrollment.[13] The study demonstrated a survival benefit in patients who received tofacitinib; nearly all of these patients also received corticosteroids. If none of the other recommended immunomodulatory therapies for the treatment of COVID-19 are available or feasible to use, tofacitinib may be used as a substitute based on the findings from the STOP-COVID study.

The clinical trial data on the use of baricitinib and tofacitinib in patients with COVID-19 are summarized in Table 5d.

Monitoring, Adverse Effects, and Drug-Drug Interactions

The FDA reviewed the data from a large, randomized, safety clinical trial that compared the use of tofacitinib to tumor necrosis factor inhibitors in people with rheumatoid arthritis over 4 years.[14] The FDA review reported that the use of tofacitinib was associated with a higher incidence of serious adverse events, including heart attack, stroke, cancer, blood clots, and death. Therefore, the FDA now requires new and updated warnings for drugs in the JAK inhibitor class, including baricitinib and tofacitinib. The data from randomized trials that have evaluated the safety of short-term use of JAK inhibitors in patients with COVID-19 have not revealed significant safety signals, such as thrombosis.[8,9,11-13] Because JAK inhibitors have immunosuppressive effects, all patients who are receiving either baricitinib or tofacitinib should be monitored for new infections.

No clinically significant drug-drug interactions are expected between baricitinib and concomitant drugs. Tofacitinib is a cytochrome P450 (CYP) 3A4 substrate. Dose modifications are required when the drug is coadministered with strong CYP3A4 inhibitors, or when it is used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor. Coadministering tofacitinib with a strong CYP3A4 inducer is not recommended. See Table 5e for JAK 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.[15-17]

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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