Kinase Inhibitors: Janus Kinase Inhibitors and Bruton’s Tyrosine Kinase Inhibitors

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Janus Kinase Inhibitors

Janus kinase (JAK) inhibitors such as baricitinib and tofacitinib have been shown to improve clinical outcomes among hospitalized patients with COVID-19. The primary mechanism of JAK inhibitors is interference with phosphorylation of the signal transducer and activator of transcription (STAT) proteins involved in vital cellular functions, including signaling, growth, and survival. These kinase 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). Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing SARS-CoV-2 from entering and infecting susceptible cells.

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).

Recommendations

- Baricitinib or tofacitinib is recommended in combination with dexamethasone in hospitalized patients with evidence of inflammation and increasing oxygen needs. See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel’s (the Panel) detailed recommendations and ratings on the use of baricitinib and tofacitinib.
- The Panel recommends against the use of JAK inhibitors other than baricitinib or tofacitinib for the treatment of COVID-19, except in a clinical trial (AIII).

Rationale

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

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. The COV-BARRIER trial also demonstrated a survival benefit from baricitinib that was most pronounced among patients receiving high-flow oxygen or NIV. In the addendum to the COV-BARRIER trial, the benefit extended to patients receiving mechanical ventilation. Data from the ACTT-2 and ACCT-4 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 mechanical ventilation at the time of enrollment. The study demonstrated a survival benefit in patients who received tofacitinib, nearly all of whom also received corticosteroids. Tofacitinib has less clinical data support than baricitinib, but tofacitinib can be used as an alternative if baricitinib is not available.
Clinical trial data on the use of JAK inhibitors, including baricitinib and tofacitinib, in patients with COVID-19 are summarized below and in Table 5d. All related treatment recommendations are reviewed in Therapeutic Management of Hospitalized Adults With COVID-19.

**Monitoring, Adverse Effects, and Drug-Drug Interactions**

Adverse effects of JAK inhibitors include infections (typically respiratory and urinary tract infections), reactivation of herpes virus infections, myelosuppression, transaminase elevations, and, rarely, gastrointestinal perforation. 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. Therefore, the FDA now requires new and updated warnings for drugs in the JAK inhibitor class, including tofacitinib and baricitinib. 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.

A complete blood count with differential, liver enzyme, and kidney function tests should be obtained from all patients before administering baricitinib or tofacitinib and during treatment as clinically indicated. Because of the immunosuppressive effects of baricitinib, all patients receiving the drug should also 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 5f for kinase inhibitor drug characteristics and dosing information.

**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. It is also FDA approved for the treatment of rheumatoid arthritis.

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. Baricitinib has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells. In macaques infected with SARS-CoV-2, baricitinib reduced inflammation and lung pathology, but an antiviral effect was not confirmed.

**Clinical Data for COVID-19**

For additional details on clinical trial data for baricitinib, see Table 5d. For information on the Panel’s recommendations for the use of baricitinib in hospitalized patients with COVID-19, see Therapeutic Management of Hospitalized Adults With COVID-19.

**Clinical Trials**

Please see ClinicalTrials.gov for the latest information on studies of baricitinib for the treatment of COVID-19.

**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. Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.

**Clinical Data for COVID-19**

For additional details on clinical trial data for tofacitinib, see Table 5d.

**Clinical Trials**

Please see ClinicalTrials.gov for the latest information on studies of tofacitinib for the treatment of COVID-19.

**Ruxolitinib**

Ruxolitinib is an oral JAK inhibitor selective for JAK1 and JAK2 that is currently approved for myelofibrosis, polycythemia vera, and acute graft-versus-host disease. Like baricitinib, it can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation. Ruxolitinib also has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.

**Clinical Data for COVID-19**

A small, single-blind, Phase 2 randomized controlled trial in patients with COVID-19 in China compared ruxolitinib 5 mg orally twice daily (n = 20) with placebo (administered as vitamin C 100 mg; n = 21), both given in combination with standard of care. Treatment with ruxolitinib was associated with a nonsignificant reduction in the median time to clinical improvement (12 days for ruxolitinib recipients vs. 15 days for placebo recipients; \( P = 0.15 \)), defined as a 2-point improvement on a 7-category ordinal scale or hospital discharge. There was no difference between the arms in the median time to discharge (17 days for ruxolitinib arm vs. 16 days for placebo arm; \( P = 0.94 \)). Limitations of this study include the small sample size.

A Phase 3 trial of ruxolitinib in patients with COVID-19-associated acute respiratory distress syndrome is currently in progress (ClinicalTrials.gov Identifier NCT04377620).

**Clinical Trials**

Please see ClinicalTrials.gov for the latest information on studies of ruxolitinib for the treatment of COVID-19.

**Considerations in Pregnancy**

There is a paucity of data on the use of JAK inhibitors in pregnancy. As small-molecule drugs, JAK inhibitors are likely to pass through the placenta; therefore, fetal risk cannot be ruled out. Decisions regarding the administration of JAK inhibitors must include shared decision-making between pregnant individuals and their health care providers, and potential maternal benefit and fetal risks should be considered. In the decision-making process, factors to be considered include maternal COVID-19 severity, comorbidities, and gestational age. Pregnancy registries provide some outcome data on tofacitinib use during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general population.

**Considerations in Children**

Please see Therapeutic Management of Hospitalized Children With COVID-19 for the Panel’s recommendations regarding the use of baricitinib or tofacitinib in children.
Bruton’s Tyrosine Kinase Inhibitors

Bruton’s tyrosine kinase (BTK) is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. The potential benefit of BTK inhibition as a treatment for COVID-19 would be a reduction in the immunopathology associated with severe disease.

Recommendation

- The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII).

Acalabrutinib

Acalabrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat B-cell malignancies (i.e., chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma). It has a better toxicity profile than first-generation BTK inhibitors (e.g., ibrutinib) because it has less off-target activity for other kinases. Acalabrutinib is proposed for use in patients with COVID-19 because it can modulate signaling that promotes inflammation.

Clinical Data for COVID-19

Data regarding acalabrutinib are limited to the results from a prospective case series of 19 patients with severe COVID-19. The small sample size and lack of a control group limit evaluation of the data to discern any clinical benefit.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of acalabrutinib for the treatment of COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies and to prevent chronic graft-versus-host disease in stem cell transplant recipients. Based on results from a small case series, ibrutinib has been theorized to reduce inflammation and protect against ensuing lung injury in patients with COVID-19.

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of 6 patients with COVID-19 who received the drug for a condition other than COVID-19. The small sample size and lack of a control group limit evaluation of the data to discern any clinical benefit.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of ibrutinib for the treatment of COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma. It has been shown to have fewer toxicities than first-generation BTK inhibitors (e.g., ibrutinib) because it has less off-target activity for other kinases. Zanubrutinib is proposed to benefit patients with COVID-19 by modulating signaling that promotes inflammation.

Clinical Data for COVID-19

There are no clinical data on the use of zanubrutinib to treat COVID-19.
Clinical Trials
Please see ClinicalTrials.gov for the latest information on studies of zanubrutinib for the treatment of COVID-19.

Adverse Effects and Monitoring
Hemorrhage and cardiac arrhythmia have occurred in patients who received BTK inhibitors.

Considerations in Pregnancy
There is a paucity of data on human pregnancy and BTK inhibitor use. In animal studies, acalabrutinib and ibrutinib in doses exceeding the therapeutic human dose were associated with interference with embryofetal development.\textsuperscript{26,31} Based on these data, use of BTK inhibitors that occurs during organogenesis may be associated with fetal malformations. The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.

Considerations in Children
The safety and efficacy of BTK inhibitors have not been evaluated in pediatric patients with COVID-19, and data on the use of the drugs in children with other conditions are extremely limited. The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19 in pediatric patients, except in a clinical trial (AIII).

References


27. Food and Drug Administration. FDA expands ibrutinib indications to chronic GVHD. 2017. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-ibrutinib-indications-chronic-

