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

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Janus Kinase Inhibitors

Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins\(^1,2\) that are involved in vital cellular functions, including signaling, growth, and survival. These kinase inhibitors are proposed 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).\(^3\)

Immunosuppression induced by JAK inhibitors could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. 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.\(^4\)

Recommendations

- 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 and tofacitinib for certain hospitalized patients who require oxygen supplementation.
- 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

The Panel’s recommendations are based on data from the ACTT-2,\(^5\) COV-BARRIER,\(^6\) and STOP-COVID\(^7\) clinical trials. The ACTT-2 trial demonstrated that baricitinib improved time to recovery when given in combination with remdesivir to hospitalized patients with COVID-19 who require supplemental oxygen but not mechanical ventilation. However, a key limitation of the ACTT-2 trial is that corticosteroids were not used as the standard of care; thus, it was not possible to evaluate the effect of baricitinib when given in addition to corticosteroids.

The COV-BARRIER trial enrolled patients with COVID-19 pneumonia and at least 1 elevated inflammatory marker at enrollment who were not on mechanical ventilation. This trial reported an additional survival benefit of baricitinib when added to the standard of care of corticosteroids (with or without remdesivir). If baricitinib is not available, tofacitinib may be an alternative because it has demonstrated clinical benefit in the STOP-COVID trial.

The clinical trial data on the use of baricitinib and tofacitinib in patients with COVID-19 is summarized below, and all related treatment recommendations are reviewed in Therapeutic Management of Hospitalized Adults With COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Most of the data on adverse effects of JAK inhibitors were reported based on chronic use of the agents for the treatment of autoimmune diseases. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses; myelosuppression; transaminase elevations; and, rarely, gastrointestinal perforation. The Food and Drug Administration (FDA) review of a large, randomized, safety clinical trial comparing tofacitinib to antitumor necrosis factor inhibitors in people with rheumatoid arthritis found that tofacitinib was associated with additional serious adverse
events, including heart attack or stroke, cancer, blood clots, and death. The FDA is therefore requiring 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 are limited. The data to date have not revealed significant safety signals, including thrombosis; however, these trials may be underpowered for detecting rare adverse events.

A complete blood count with differential, liver function tests, and kidney function tests should be obtained in all patients before baricitinib is administered and during treatment as clinically indicated. Screening for viral hepatitis and tuberculosis should be considered. Considering its immunosuppressive effects, all patients receiving baricitinib should also be monitored for new infections.

Tofacitinib is a cytochrome P 450 (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.

The ACTT-2 and COV-BARRIER trials evaluated oral baricitinib 4 mg once daily, which is twice the standard baricitinib dose (2 mg once daily) for FDA-approved indications. In patients with severe hepatic impairment, baricitinib should only be used if the potential benefit outweighs the potential risk.

Baricitinib has not been evaluated in clinical studies for FDA-approved indications in patients with an estimated glomerular filtration rate (eGFR) ≤30 mL/min. When baricitinib is used for the treatment of COVID-19 in adults with renal insufficiency, the Panel recommends reducing the dose of baricitinib from 4 mg to 2 mg daily for adults with an eGFR ≥30 to <60 mL/min and to 1 mg daily for those with an eGFR of 15 to <30 mL/min. Baricitinib is not recommended for patients with an eGFR <15 mL/min. There are limited clinical data on the use of baricitinib in combination with strong organic anion transporter 3 inhibitors, and, in general, coadministration is not advised.

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, and therefore fetal risk cannot be ruled out. Decisions regarding the administration of JAK inhibitors must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks. Factors that may weigh into the decision-making process 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

An FDA Emergency Use Authorization (EUA) has been issued for the use of baricitinib in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The safety and efficacy of baricitinib have not been evaluated in pediatric patients with COVID-19. As noted above, tofacitinib was shown to decrease the risk of respiratory failure and death in adults with COVID-19 in the STOP-COVID trial. Tofacitinib is FDA approved for a pediatric indication; however, the safety and efficacy of tofacitinib have not been evaluated in pediatric patients with COVID-19. Thus, there is insufficient evidence to recommend either for or against the use of baricitinib in combination with corticosteroids and/or remdesivir for the treatment of COVID-19 in hospitalized children.

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and is FDA approved for the
treatment of rheumatoid arthritis. Baricitinib 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. Baricitinib reduced inflammation and lung pathology in macaques infected with SARS-CoV-2, but an antiviral effect was not confirmed.

Clinical Data for COVID-19

In the ACTT-2 trial, 1,033 patients hospitalized with COVID-19 were randomized 1:1 to receive baricitinib 4 mg daily for 14 days (or until hospital discharge) or placebo, both given in combination with remdesivir. The primary endpoint was time to recovery as measured on an 8-category ordinal scale. Recovery time was shorter in the baricitinib arm (7 days) than in the placebo arm (8 days) (rate ratio for recovery 1.16; 95% CI, 1.01–1.32; \( P = 0.03 \)). Mortality by 28 days was lower in the baricitinib arm than in the placebo arm, but the difference was not statistically significant. A key limitation of the study is that corticosteroids were not used as background standard care for patients with severe or critical COVID-19 pneumonia.

In the COV-BARRIER trial, 1,525 hospitalized patients with COVID-19 pneumonia and an elevation in 1 or more inflammatory markers were randomized 1:1 to receive baricitinib 4 mg orally or placebo for up to 14 days (or until hospital discharge). Patients on mechanical ventilation were excluded from study enrollment. Overall, 79% of patients received corticosteroids and 19% received remdesivir. The primary endpoint was the proportion of patients who progressed to high-flow oxygen, noninvasive ventilation, mechanical ventilation, or death by Day 28. Progression to the primary endpoint occurred among 27.8% of patients in the baricitinib arm versus 30.5% in the placebo arm (OR 0.85; 95% CI, 0.67–1.08; \( P = 0.18 \)). All-cause mortality within 28 days, which was a key secondary endpoint, was 8.1% in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality associated with baricitinib (HR 0.57; 95% CI, 0.41–0.78). The mortality difference was most pronounced in the subgroup of patients receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% for baricitinib recipients vs. 29.4% for placebo recipients; HR 0.52; 95% CI, 0.33–0.80). However, subgroup analyses did not identify a statistically significant benefit of baricitinib versus placebo among patients receiving low-flow oxygen at baseline. The occurrence of adverse events, serious adverse events, serious infections, and venous thromboembolic events was comparable in the baricitinib and placebo arms.

The COV-BARRIER trial added a critically ill cohort to the original study. In this cohort, participants on mechanical ventilation or ECMO at baseline (n = 101) were randomly assigned to baricitinib 4 mg (n = 51) or placebo (n = 50) for up to 14 days in combination with the standard of care. At baseline, 86% of participants were receiving corticosteroids and 2% were receiving remdesivir. Baricitinib significantly reduced the prespecified endpoint of 28-day all-cause mortality when compared with placebo (39.2% vs. 58.0%; HR 0.54; 95% CI, 0.31–0.96; \( P = 0.03 \)). Significant reductions were also reported with baricitinib versus placebo in 60-day mortality (45% vs. 62%; \( P = 0.027 \)) and hospital days (23.7 vs. 26.1 days; \( P = 0.05 \)). The implications of these findings are limited due to the very small sample size of this addendum trial population.

The collective data from these studies have informed the Panel’s recommendations on the use of baricitinib in hospitalized patients with COVID-19. The specific recommendations and additional information on the rationale can be found in 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.
Drug Availability
Baricitinib is approved by the FDA for the treatment of rheumatoid arthritis. On November 19, 2020, the FDA issued an initial EUA for the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in certain hospitalized children and adults who require supplemental oxygen, mechanical ventilation, or ECMO. The EUA was revised on July 28, 2021, to remove the requirement that baricitinib be used only in combination with remdesivir for the treatment of COVID-19.9

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.20 Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.21

Clinical Data for COVID-19
The double-blind STOP-COVID trial randomized 289 hospitalized patients with COVID-19 in Brazil to receive tofacitinib 10 mg or placebo orally twice daily for up to 14 days (or until hospital discharge). Patients who were on mechanical ventilation or who had an immunocompromising condition were excluded from the trial. The background standard of care included corticosteroids (79.2% of patients were receiving corticosteroids at randomization and overall, 89.3% received corticosteroids during the study) but not remdesivir. The primary outcome of death or respiratory failure through Day 28 occurred in 18.1% of patients in the tofacitinib arm and 29.0% in the placebo arm (risk ratio 0.63; 95% CI, 0.41–0.97). All-cause mortality within 28 days was 2.8% in the tofacitinib arm and 5.5% in the placebo arm (risk ratio 0.49; 95% CI, 0.15–1.63). Serious adverse events occurred in 14.2% of the patients in the tofacitinib arm and 12.0% in the placebo arm. Limitations of the trial include the small sample size.7

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.22 Like baricitinib, it can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.16 Ruxolitinib also has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.17

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 as 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.23 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.

Bruton’s Tyrosine Kinase Inhibitors
Bruton’s tyrosine kinase (BTK) is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways.

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. Evaluation of the data to discern any clinical benefit is limited by the study’s small sample size and lack of a control group.

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 were receiving the drug for a condition other than COVID-19. Evaluation of the data for any clinical benefit is limited by the series’ small sample size and lack of a control group.

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 of 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.\(^{26,31}\) 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. Use of BTK inhibitors for the treatment of COVID-19 in pediatric patients is not recommended, except in a clinical trial.

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.

