REVIEW

Janus Kinase inhibitors for the treatment of hospitalized patients with COVID-19

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Purpose of review
Janus Kinase (JAK) inhibitors have been successfully utilized in the clinical treatment of several rheumatologic (e.g. rheumatoid arthritis) and inflammatory diseases (e.g. hemophagocytic lymphohistiocytosis). Based on the growing evidence that moderate and severe COVID-19 infections are associated with a dysregulated inflammatory state, this class of medications has been repurposed as a potential therapy for COVID-19, an infection caused by Severe Acute Respiratory Syndrome Coronavirus 2.

Recent findings
Three JAK inhibitors have been evaluated in human studies of COVID-19: Baricitinib, Tofacitinib, and Ruxolitinib. Most published studies are observational, but three randomized placebo-controlled double-blind trials have been completed: two large trials ($N = 2,558$ patients) with baricitinb demonstrated significant faster improvement in clinical status and reduction in the recovery time, as well as, significant reduction in the progression to invasive mechanical ventilation and mortality. One smaller randomized trial ($N = 289$) involving tofacitinib showed significant reduction in the progression to invasive ventilation or death. Notably, these three randomized placebo-controlled trials with close to 3,000 patients did not reveal any safety concerns associated with JAK inhibitors in terms of secondary infections or venous thromboembolism. Based on this high-quality evidence, both the Infectious Diseases Society of America and the National Institutes of Health guidelines recommend using baricitinib as part of the treatment approach for hospitalized patients with COVID-19.

Summary
JAK inhibitors are novel treatment agents in the field of infectious diseases. One JAK inhibitor, baricitinib has demonstrated significant clinical and survival benefits in hospitalized patients with COVID-19 in phase III randomized placebo-controlled trials. Baricitinib is already recommended for clinical practice by multiple guidelines.

Keywords
baricitinib, COVID-19, Janus Kinases inhibitors, ruxolitinib, tofacitinib

INTRODUCTION

Janus Kinases (JAK) are cytoplasmatic kinases and transmembrane proteins normally expressed in most cells that participate in the signaling of a broad range of cell surface receptors and play a role in the mediation and amplification of extracellular signals from cytokines and growth factors [1]. A large number of cytokines are dependent on JAK1, including IL-2, IL-4, IL-7, IL-9, IL-15, IL-21, and JAK 1 is also relevant for the family that uses the shared receptor gp130, including IL-6, IL-11, oncostatin M, leukemia inhibitory factor, ciliary neutrophilic factor, and granulocyte colony-stimulating factor [2].

Patients who progress to a moderate to severe form of COVID-19 and require hospitalization are more likely to develop a dysregulated immunological response that is associated with abnormal inflammatory and coagulation responses, resembling a cytokine release syndrome [3–7].

JAK inhibitors are targeted synthetic drugs that inhibiting primarily JAK1 and/or JAK2 receptors. These drugs can modulate the immunological and inflammatory abnormal responses associated with COVID-19 [8]. Among the seven JAK inhibitors that have been developed (baricitinib, tofacitinib, ruxolitinib, peficitinib, decernotinib, upadacitinib, and

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KEY POINTS

- Immunomodulation treatment with several JAK inhibitors has been evaluated in observational and randomized studies in patients with COVID-19.
- One JAK inhibitor, baricitinib has already demonstrated significant clinical and survival benefits in hospitalized patients with COVID-19.
- JAK inhibitors are novel therapeutic agents in the field of infectious diseases.

filgotinib), there are three inhibitors that have already been approved for clinical use in the treatment of rheumatologic and inflammatory diseases and have been tested in COVID-19 clinical trials – baricitinib, tofacitinib, and ruxolitinib.

BARICITINIB

Baricitinib inhibits the signaling of multiple cytokines related to JAK-1 and 2 receptors, and has been approved for the treatment of moderate to severe rheumatoid arthritis and psoriatic arthritis based on a large randomized controlled trial [9]. In the search for known and approved drugs as potential therapies against COVID-19, artificial intelligence studies suggested that baricitinib could be potentially beneficial [10▪,11]. In addition to its inflammation-modulating properties, artificial intelligence algorithms predicted that baricitinib could inhibit Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection by reducing the AP-2 mediated viral propagation, which would suggest a direct antiviral activity.

Both published observational and clinical trial data suggest a benefit of baricitinib for the treatment of COVID-19. Five observational studies showed that baricitinib was associated with a more rapid decrease of inflammatory markers, faster clinical improvement, better respiratory status, less need of intensive care, and lower mortality [12▪,13–16]. Two randomized, placebo-controlled, double-blind trials evaluating the effect of baricitinib therapy in hospitalized patients with COVID-19 have also been performed [17▪▪,18▪▪]. The first trial by Kalil *et al.* [17▪▪], enrolled 1033 patients and compared baricitinib plus remdesivir versus baricitinib plus placebo; this trial demonstrated that baricitinib plus remdesivir was superior in reducing recovery time (RR = 1.16, 95% CI 1.01–1.32), particularly in patients receiving high-flow or noninvasive ventilation (1.51 95% CI 1.10–2.08), and accelerating improvement in clinical status (OR = 1.3, 95% CI 1.0–1.6) in hospitalized patients with COVID-19; additionally, the combination was associated with a significant reduction in the new use of oxygen from 40% to 23%, significant reduction of new use of mechanical ventilation from 15% to 10%, a significant 31% reduction in the progression to invasive ventilation or death (0.69 95% CI 0.50–0.95), and 11 days less on mechanical ventilation compared to placebo (see Table 1). Notably, the baricitinib/remdesivir combination was associated with significantly less serious adverse events (16% versus 21%; $P = 0.03$), and lower rate of new infections (5.9% versus 11.2%; $P = 0.003$) compared to placebo. The second trial by Marconi *et al.* [18▪▪], enrolled 1525 patients, and compared baricitinib plus standard of care versus standard of care. Although the primary endpoint – a reduction of disease progression – was not achieved, a significant relative mortality reduction was demonstrated with baricitinib compared to placebo (HR = 0.57, 95% CI 0.41–0.78, $P = 0.0018$). This survival benefit with baricitinib was independent of the use of steroids or remdesivir. Baricitinib has not been evaluated in combination with other immunomodulators such as IL-6 antagonists, but

Table 1. Published studies: mortality and invasive mechanical ventilation outcomes

JAK inhibitor	Number of observational studies	Number of randomized trials	Number of randomized and placebo controlled trials	28-day mortality hazard ratio	28-day progression to invasive ventilation or Death Hazard ratio
BARICITINIB	5	2	2	[1]Overall: 0.65 (95% CI 0.39–1.09) [1]Low/High-flow: 0.47 (95%CI 0.24–0.93) [2]Overall: 0.57 (95% CI 0.41–0.78)	[1]0.69 (95% CI 0.50–0.95) [2]Not Available
TOFACITINIB	2	1	1	[3]0.49 (95% CI 0.15–1.63)	[3]0.63 (95% CI 0.41–0.97)
RUXOLITINIB	8	1	0	Not Available	Not Available

Kalil *et al.* (1); Marconi *et al.* (2); Guimaraes *et al.* (3).

1. 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.
2. Marconi VC, Ramanan AV, deBono S., *et al.* Baricitinib plus standard of care for hospitalized adults with COVID-19. medRxiv preprint doi: https://doiorg/101101/2021043021255934. 2021.
3. Guimaraes PO, Quirk D, Furtado RH, *et al.* Tofacitinib in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021.

considering the potential additional immunosuppression, these combinations will need to be evaluated in randomized controlled trials to determine safety and efficacy. The safety profile was similar between baricitinib and placebo despite the fact that most patients also received steroids. Importantly, both randomized trials above did not show differences in venous thromboembolic events between the treatment and control arms, assuaging concerns that baricitinib treatment could be thrombogenic.

TOFACITINIB

Two observational studies [19,20], and one randomized placebo-controlled double-blind trial [21▪▪] have evaluated the use of tofacitinib in hospitalized patients with COVID-19. Both observational trials suggested a better clinical response with tofacitinib. The randomized trial enrolled 289 patients, and showed that tofacitinib was associated with a significant lower risk of death or respiratory failure at day 28 (RR = 0.63, 95% CI 0.41–0.97) compared to placebo. Also, no safety differences, including rates of secondary infections and thromboembolic events, were noted between treatment and control arm. Several ongoing trials are evaluating tofacitinib and expected to be completed soon.

RUXOLITINIB

There are several observational studies already published regarding the use of ruxolitinib in patients with COVID-19 [22–29], and these case reports and case series suggest improvement of pulmonary function and hospital discharge with ruxolitinib. One small randomized single-blind controlled trial which enrolled 43 patients was performed by Cao *et al.* [30]; this study suggested a faster clinical and tomographic improvement, and a numerically lower mortality with ruxolitinib, and differences were not significant. Trials on ruxolitinib are ongoing, thus more information will further clarify the potential role of this drug in patients with COVID-19.

CONCLUSION

JAK inhibitors have been successfully utilized in the clinical treatment of several rheumatologic (e.g. rheumatoid arthritis) and inflammatory diseases (e.g. hemophagocytic lymphohistiocytosis). Based on the growing evidence that moderate and severe COVID-19 infections are associated with a dysregulated inflammatory state, this class of medications has been repurposed as a potential therapy for COVID-19, an infection caused by SARS-CoV-2.

Three JAK inhibitors have been evaluated in human studies of COVID-19: Baricitinib, Tofacitinib, and Ruxolitinib. Most published studies are observational, but three randomized placebo-controlled double-blind trials have been completed: two large trials ($N = 2{,}558$ patients) with baricitinb demonstrated significant faster improvement in clinical status and reduction in the recovery time, as well as, significant reduction in the progression to invasive mechanical ventilation and mortality. One smaller randomized trial ($N = 289$) involving tofacitinib showed significant reduction in the progression to invasive ventilation or death. Notably, these three randomized placebo-controlled trials with close to 3,000 patients did not reveal any safety concerns associated with JAK inhibitors in terms of secondary infections or venous thromboembolism. Based on this high-quality evidence, both the Infectious Diseases Society of America [31] and the National Institutes of Health [32] guidelines recommend using baricitinib as part of the treatment approach for hospitalized patients with COVID-19.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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