Janus Kinase Inhibitors: Baricitinib

Section last reviewed and updated 4/29/2022

Last literature search conducted 3/31/2022

Recommendation 1 (UPDATED 4/29/2022): Among hospitalized adults with severe* COVID-19, the IDSA panel suggests baricitinib with corticosteroids rather than no baricitinib. (Conditional recommendation, Moderate certainty of evidence)

Remarks:
- Baricitinib 4 mg per day (or appropriate renal dosing) up to 14 days or until discharge from hospital.
- Baricitinib appears to demonstrate the most benefit in those with severe COVID-19 on high-flow oxygen/non-invasive ventilation at baseline.
- Limited additional data suggest a mortality reduction even among patients requiring mechanical ventilation.

Recommendation 2: Among hospitalized patients with severe* COVID-19 who cannot receive a corticosteroid (which is standard of care) because of a contraindication, the IDSA guideline panel suggests use of baricitinib with remdesivir rather than remdesivir alone. (Conditional recommendation, Low certainty of evidence)

- Remark: Baricitinib 4 mg daily dose for 14 days or until hospital discharge. The benefits of baricitinib plus remdesivir for persons on mechanical ventilation are uncertain.

*Severe illness is defined as patients with SpO₂ ≤94% on room air, including patients on supplemental oxygen, oxygen through a high-flow device, or non-invasive ventilation.

Why is baricitinib considered for treatment?

Baricitinib, a selective Janus kinase 1 and 2 (JAK1 and JAK2, respectively) inhibitor currently U.S. Food and Drug Administration (FDA)-approved for the treatment of rheumatoid arthritis (RA), is being investigated in multiple studies for treatment of COVID-19. The proposed benefits of baricitinib in the management of COVID-19 may be two-fold as it has both anti-inflammatory and potential antiviral activity [1]. Janus kinase (JAK) mediates cytokine signaling, which contributes to inflammation; JAK inhibitors, therefore, may decrease cytokine-mediated inflammation. Baricitinib inhibits host intracellular membrane proteins AP2-associated protein
kinase 1 (AAK1) and also binds cyclin G-associated kinase (GAK), both thought to play a role in receptor mediated endocytosis of many viruses including Ebola, dengue, hepatitis C, and SARS-CoV-2 [2-4]. Baricitinib has been evaluated in people with COVID-19 in both randomized and non-randomized studies [5-9].

Based on experience in clinical trials for RA, baricitinib has been associated with an increased risk of adverse effects including infections (especially upper respiratory tract infections), thrombosis, lymphopenia, anemia, increases in lipids, elevations in liver enzymes, and elevations in creatinine phosphokinase [1]. In clinical trials for RA, baricitinib was associated with a numerically higher risk of upper respiratory tract infections and herpes simplex and herpes zoster infections compared with placebo [10]. Opportunistic infections such as herpes simplex, herpes zoster, and tuberculosis [11, 12] have been reported in patients taking baricitinib. Many of these side effects appear to be dose related, with increased incidence in patients taking baricitinib 4 mg compared with 2 mg. Patients enrolled in Adaptive COVID-19 Treatment Trial (ACTT-2), COV-BARRIER and RECOVERY (Randomized evaluation of COVID-19 Therapy) received baricitinib 4 mg daily for 2-14 days or until discharge, a shorter duration than those taking the drug for RA.

Patients with COVID-19 have been found to have abnormalities in coagulation parameters and might have an elevated risk of thrombosis [13]. Baricitinib receipt was associated with an increased incidence of thrombosis when compared with placebo receipt in clinical trials for its FDA approval for RA, especially at a higher dose of 4 mg daily [1]. During the 16-week treatment period in RA trials, venous thromboembolism (VTE) occurred in five patients treated with baricitinib 4 mg daily, compared with zero in the 2 mg daily and placebo groups. Arterial thrombosis occurred in two patients treated with baricitinib 4 mg, two patients treated with baricitinib 2 mg, and one patient on placebo. In ACTT-2, the percentage of patients reported to have VTE was numerically higher in the combination group (21 patients [4.1%] vs. 16 patients [3.1%]) although it was similar overall (absolute difference 1%, 95% CI -1.3 to 3.3) [14]. Of note, all patients in ACTT-2 were recommended to receive VTE prophylaxis if they had no contraindication. We do not have long-term data, especially on safety, development of the aforementioned adverse effects, and opportunistic infections from these two trials.

Summary of the evidence

Baricitinib

Our literature search identified two randomized controlled trials (RCTs) that compared the use of baricitinib (4 mg daily dose up to 14 days) to placebo in hospitalized adults. One trial, COV-BARRIER, included patients with severe COVID (NIAID OS: 4 – hospitalized, not requiring supplemental oxygen; 5 – hospitalized, requiring supplemental oxygen; or 6 – hospitalized, receiving non-invasive ventilation or high-flow oxygen devices) [9, 15, 16]. Critically ill and
mechanically ventilated patients (OS7) were excluded from COV-BARRIER study. In the COV-BARRIER trial, randomization was stratified by disease severity, age, region, and use of corticosteroids. Participants in both arms had ≥1 elevated inflammatory marker (CRP, d-dimer, LDH [lactate dehydrogenase], ferritin) and also received standard of care, which included corticosteroids in 79% and/or antivirals (e.g., remdesivir in 18.9%). The RECOVERY, trial included patients hospitalized for COVID-19. Approximately, 70% of patients received supplemental oxygen, 25% received non-invasive ventilation, and 3% received invasive ventilation. Participants in both arms received standard of care, which included corticosteroids in approximately 95% and/or antivirals (e.g., remdesivir in 20%).

An additional exploratory trial subsequent to the COV-BARRIER primary trial of baricitinib treatment for critically ill (OS-7) patients with COVID-19 pneumonia requiring invasive mechanical ventilation was identified that reported on the outcomes of mortality, need for invasive mechanical ventilation, days of hospitalization, and serious adverse events [17].

**Baricitinib without corticosteroids, with remdesivir**

Our literature search identified one RCT that reported on the use of baricitinib (4 mg daily dose) plus remdesivir in hospitalized patients with moderate and severe COVID-19 ([14]. This trial was conducted as the second stage of the ACTT-2, where subjects were randomized to receive combination therapy with baricitinib and remdesivir or remdesivir alone [14] (Table 3). Randomization was stratified by disease severity classified by an OS of clinical status (4+5 vs 6+7 [7 –patients with an ordinal scale of 6 (high-flow oxygen and non-invasive ventilation) or 7 (mechanical ventilation or ECMO). Mild to moderate disease was defined as patients with an ordinal scale of 4 (hospitalized, but not requiring supplemental oxygen) or 5 (requiring supplemental oxygen). The trial was initiated before corticosteroids were commonly used for severe COVID-19.

**Benefits**

**Baricitinib**

Treatment of hospitalized patients with severe COVID-19 with baricitinib rather than no baricitinib reduced 60-day mortality (RR 0.87; 95% CI: 0.78 to 0.96; moderate CoE). The odds of COVID-19 disease progression trends toward a reduction in persons receiving treatment with baricitinib (OR: 0.85; 95% CI: 0.67, 1.08; moderate CoE), as well as the risk of needing mechanical ventilation (RR: 0.85; 95% CI: 0.73, 0.99; moderate CoE).

Treatment of critically ill hospitalized patients with baricitinib rather than no baricitinib reduced the risk of 60-day mortality (RR 0.74; 95% CI: 0.57 to 0.97; moderate CoE).
Baricitinib without corticosteroids, with remdesivir

In ACTT-2, the combination of baricitinib and remdesivir showed a trend towards lower mortality (4.7% vs. 7.1%; rate ratio: 0.65; 95% CI 0.39, 1.09; moderate CoE). In patients stratified within the severe COVID-19 pneumonia group, defined as 6 or 7 on the ordinal scale, subjects who received baricitinib and remdesivir were more likely to experience clinical recovery (defined as a value of <4 on the ordinal scale) at day 28 (69.3% vs. 59.7%; rate ratio 1.29; 95% CI 1.00, 1.66; moderate CoE). The original stratification was altered as 40 subjects were misclassified at baseline; however, re-analysis of the original stratified data produced a similar result. Patients in the baricitinib arm were less likely to require initiation of mechanical ventilation or ECMO through day 29 (10% vs. 15.2%; RR: 0.66; 95% CI 0.46, 0.93; low CoE). In summary, it appeared that patients requiring supplemental oxygen or non-invasive ventilation at baseline benefitted most from baricitinib; the benefit was less clear in patients already on mechanical ventilation.

Harms

The risk of serious adverse events in hospitalized patients with severe or critical COVID-19 receiving baricitinib was not greater than those not receiving baricitinib (RR: 0.82; 95% CI: 0.65, 1.03; moderate CoE and RR 0.70; 95% CI: 0.50 to 0.97, moderate CoE, respectively). Patients who were immunocompromised (i.e., received immunosuppressant drugs or were neutropenic) and had a history of recent of thromboembolism were not excluded from the RECOVERY trial, unlike BARRIER-COV trial. Non-comparative SAEs were reported in the RECOVERY 2022 trial (baricitinib N=4,148): 13 total (5 serious infections, 3 bowel perforations, 2 pulmonary embolisms, 1 each of ischemic colitis, elevated transaminases and seizure).

In ACTT-2, patients receiving baricitinib and remdesivir had a lower risk of developing any serious adverse events through day 28 (16% vs. 21%; RR 0.76; 95% CI 0.59, 0.99; moderate CoE) whether or not thought to be related to the study drug. In this trial, the overall rate of new infections was lower in the baricitinib plus remdesivir group compared with remdesivir alone (30 patients [5.9%] versus 57 patients [11.2%]) [14]. However, patients who received concomitant glucocorticoids had a higher incidence of serious or non-serious infections as compared with those who did not: 25.1% and 5.5%, respectively. It was not specified what proportion of these patients in the study were in the baricitinib combination group versus the control group.

Other considerations

Baricitinib
The panel agreed on the overall certainty of evidence as moderate due to concerns with imprecision, as some outcomes have concerns with fragility. The guideline panel recognized the resource implications based on the dose and duration reported in the trial (4 mg daily up to 14 days). Additional data from hospitalized patients with critical COVID-19 suggest consistent benefits; however, there are concerns with imprecision based on a small sample in this group.

**Baricitinib without corticosteroids**

The panel agreed that the overall certainty of evidence was low due to concerns with risk of bias, driven by the use of data from post hoc analyses and imprecision, which recognized the limited events and concerns with fragility in the group who likely benefited most (those requiring supplemental oxygen or non-invasive ventilation). The guideline panel noted the importance of suggesting baricitinib plus remdesivir as an option for persons unable to receive corticosteroids.

**Conclusions and research needs for this recommendation**

The guideline panel suggests baricitinib in addition to standard of care for patients hospitalized with severe COVID-19. The guideline panel suggests baricitinib with remdesivir for persons for whom corticosteroids are indicated but who cannot receive them due to a contraindication. Baricitinib plus remdesivir should be reserved for patients who cannot take corticosteroids because dexamethasone has been proven to reduce mortality in patients hospitalized with COVID-19 who require supplemental oxygen or mechanical ventilation and, for this reason, dexamethasone is recommended by the panel for this group. It is uncertain whether baricitinib plus remdesivir will have the same benefit as dexamethasone. As of the time of this narrative, there are no head-to-head trials evaluating either the combination of baricitinib plus tocilizumab or evaluating baricitinib compared to tocilizumab. A post hoc subgroup analysis in the RECOVERY trial showed no difference in measured outcomes with concomitant baricitinib and tocilizumab, but further well-done studies are needed [16].
Table 1. GRADE evidence profile, Recommendation 1

**Question:** Baricitinib compared to no baricitinib for hospitalized patients receiving standard of care for severe COVID-19

**Last reviewed and updated 4/29/2022**

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<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
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<td>not serious</td>
<td>serious (^c)(^d)</td>
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**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Risk of bias:** Study limitations
- **Inconsistency:** Unexplained heterogeneity across study findings
- **Indirectness:** Applicability or generalizability to the research question
- **Imprecision:** The confidence in the estimate of an effect to support a particular decision
- **Publication bias:** Selective publication of studies

**NB:** Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.
CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio; RR: Risk ratio

Explanations

a. 95% CI cannot exclude no benefit.
b. Multiple imputation includes N=756 for placebo and N=762 for baricitinib
c. Number of events does not meet optimal information size
d. 95% CI cannot exclude no harm.
e. Non-comparative SAEs were reported in the RECOVERY 2022 trial (baricitinib N=4,148): 13 total (5 serious infections, 3 bowel perforations, 2 pulmonary embolisms, 1 each of ischemic colitis, elevated transaminases and seizure)

References

### Table 2. GRADE evidence profile, Recommendation 1

**Question:** Baricitinib compared to no baricitinib for critically ill (OS-7) patients with COVID-19 pneumonia requiring invasive mechanical ventilation

**Last reviewed and updated 4/29/2022**

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<th>Certainty</th>
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<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
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<td><strong>Invasive mechanical ventilation free days (follow-up: 60 days)</strong></td>
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<tr>
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<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

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IDSA Guideline on the Treatment and Management of COVID-19

JAK Inhibitors – **UPDATE ALERT (5/10/2022)**

CI: Confidence interval; HR: Hazard Ratio; MD: Mean difference; RR: Risk ratio

Explanations

- Few number of events, does not meet optimal information size
- 95% CI includes both the possibility of benefit and risk of harm
- Adjusted for age (<65, ≥65) and region (U.S., rest of the world)
- 95% CI cannot exclude no benefit.

Reference

### Table 3. GRADE evidence profile, Recommendation 2

**Question:** Baricitinib with remdesivir compared to remdesivir for hospitalized patients with COVID-19  
*Last updated 5/16/2021; last reviewed 10/11/2021*

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<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
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<td>Clinical recovery - hospitalized requiring supplemental (O_2)/receiving noninvasive ventilation or high-flow (O_2) (ordinal 5+6) (assessed with: Ordinal scale &lt;4)</td>
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<tr>
<td>Clinical recovery - receiving noninvasive ventilation or high-flow (O_2), invasive mechanical ventilation or ECMO (ordinal 6+7; stratified) (assessed with: Ordinal scale &lt;4)</td>
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<td>New use of mechanical ventilation or ECMO (follow up: 29 days)</td>
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<td>1</td>
<td>randomized trials</td>
<td>not serious</td>
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<td>serious</td>
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</table>
GRADE Working Group grades of evidence

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Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; ECMO: Extracorporeal mechanical oxygenation; HR: Hazard Ratio; OR: Odds ratio; RR: Risk ratio

Explanations

a. 95% CI includes substantial benefits as well as substantial harms
b. Non-stratified subgroup post hoc analysis.
c. Lower boundary of the 95% CI crosses our threshold for a meaningful difference.
d. Data from table S6. Although described as "analysis as randomized" in this stratum of severe COVID-19 patients, the analysis included moving patient from a baseline of "moderate" to "severe" post hoc (19 in the baricitinib group vs 21 in the placebo group), thus altering the original stratification. However, re-analysis using to original strata data (ordinal scale 6 and 7 from table 2) and 28-day cutoff (as a binary, non-time to event analysis) produce a similar result (RR 1.2, 95% CI 1.005 to 1.43). Not rated down for post hoc analysis concerns.
e. 95% CI includes substantial benefits as well as no effect
f. Not a predefined stratum. Secondary analysis.
g. Less than 300 events; concern for fragility
h. SAEs in 5 or more participants in any preferred term by treatment group. 6/507 were thought related to study drug in the baricitinib group; 5/509 were thought to be related to the study drug in the placebo group.

Reference

Janus Kinase Inhibitors: Tofacitinib

Section last reviewed and updated 8/21/2021

Last literature search conducted 7/31/2021

Recommendation 3: Among hospitalized adults with severe* COVID-19, but not on non-invasive or invasive mechanical ventilation, the IDSA panel suggests tofacitinib rather than no tofacitinib. (Conditional recommendation, Low certainty of evidence)

Remarks:

- Tofacitinib appears to demonstrate the most benefit in those with severe COVID-19 on supplemental or high-flow oxygen.
- Patients treated with tofacitinib should be on at least prophylactic dose anticoagulant.
- Patients who receive tofacitinib should not receive tocilizumab or other IL-6 inhibitor for treatment of COVID-19.
- The STOP-COVID Trial did not include immunocompromised patients.

*Severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen or oxygen through a high-flow device.

Why is tofacitinib considered for treatment?

Tofacitinib is a JAK inhibitor that preferentially inhibits JAK-1 and JAK-3 though it is active on all other JAK isoforms. It is FDA-approved for moderate to severe RA, active psoriatic arthritis, and moderate to severe ulcerative colitis. Like baricitinib, it is expected that JAK inhibition leads to downstream suppression of cytokine production, thereby modulating the inflammatory cascade that results in systemic inflammation in patients with severe COVID-19. See baricitinib section (above) for additional rationale on considerations for treatment.

Summary of the evidence

Our literature search identified one RCT that compared the use of tofacitinib 10 mg every 12 hours for up to 14 days or placebo [18]. Patients included were those who had laboratory-confirmed SARS-CoV-2 infection and evidence of COVID-19 pneumonia on imaging and who were hospitalized for less than 72 hours. Patients in this study could not be receiving non-invasive ventilation, mechanical ventilation, or ECMO at baseline. Additionally, patients with a history of or current thrombosis, personal or first-degree family history of blood clotting...
disorders, immunosuppression, any active cancer, or those with certain cytopenias were excluded from this trial. Patients who received other potent immunosuppressants, or other biologic agents were excluded, while the use of glucocorticoids for the management of COVID-19 was permitted. A composite outcome of death at day 28 or respiratory failure (defined as progression to NIAID ordinal scale 6, 7, or 8) was the primary outcome.

**Benefits**

Treatment of hospitalized patients with COVID-19 pneumonia with tofacitinib resulted in a lower risk of the composite outcome of death or respiratory failure compared to no tofacitinib (RR: 0.63; 95% CI: 0.41, 0.97; low CoE). However, results failed to show or to exclude a beneficial or detrimental effect on mortality alone (RR: 0.49; 95% CI: 0.15, 1.63; low CoE) or progression to mechanical ventilation or ECMO by day 28 (RR: 0.25; 95% CI: 0.03, 2.20; low CoE).

**Harms**

Patients who received tofacitinib experienced more serious adverse events; however, this may not be meaningfully different from those that received placebo (RR: 1.18; 95%CI: 0.64, 2.15; low CoE). Use of tofacitinib for other indications has shown an increase in thrombotic events which prompted a black box warning by the FDA [19, 20]. As COVID-19 infection itself increases the risk for VTE events; it is important to note that the patients studied were either on prophylactic or full dose anticoagulation during treatment with tofacitinib.

Tofacitinib carries four black boxed warnings for its labeled indications including a warning for 1) serious infections including tuberculosis, invasive fungal infections, bacterial, viral and other opportunistic pathogens; 2) mortality; 3) thrombosis; and 4) lymphoma and other malignancies, including an increased rate of EBV-mediated post-transplant lymphoproliferative disorder [19-22].

**Other considerations**

The panel agreed that the overall certainty of evidence was low due to concerns of imprecision, which recognized the limited number of events and concerns about fragility of the results in the group who likely would benefit the most (those requiring supplemental oxygen or oxygen through a high-flow device).

**Conclusions and research needs for this recommendation**

The guideline panel suggests tofacitinib in addition to standard of care for patient hospitalized for severe COVID-19. Due to the increased risk of VTE with treatment with tofacitinib, patients should receive at least prophylactic doses of anticoagulants during their
hospital stay. Patients who received JAK inhibitors should not receive tocilizumab or other immunomodulators as no adequate evidence is available for its combined use.
| Table 4. GRADE evidence profile, Recommendation 3 |
| Question: Tofacitinib compared to no tofacitinib for hospitalized patients with COVID-19 |

**New evidence profile developed 8/21/2021**

### GRADE Working Group grades of evidence

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
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<th>Certainty assessment</th>
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</table>

**Risk of bias: Study limitations**
- **Inconsistency:** Unexplained heterogeneity across study findings
- **Indirectness:** Applicability or generalizability to the research question
- **Imprecision:** The confidence in the estimate of an effect to support a particular decision

**Publication bias:** Selective publication of studies

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<sup>a</sup> Includes 2 studies with high risk of bias.
<sup>b</sup> Includes 2 studies with high risk of bias.
<sup>c</sup> Includes 2 studies with high risk of bias.
<sup>d</sup> Includes 2 studies with high risk of bias.
NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; ECMO: Extracorporeal mechanical oxygenation; RR: Risk ratio

Explanations
a. Small number of events; fragility present.
b. Upper boundary of the 95% CI crosses a threshold of meaningful effect.
c. 95% CI cannot exclude no harm.
d. One DVT was observed in the tofacitinib group vs zero in the placebo group.

Reference
References (Baricitinib and Tofacitinib)


Supplementary Materials

Study characteristics

- **Table s1.** Should hospitalized patients with severe COVID-19 receive treatment with remdesivir plus baricitinib vs. remdesivir alone?

- **Table s3.** Should hospitalized patients with COVID-19 receive tofacitinib vs. no tofacitinib?

Risk of bias

- **Table s2.** Randomized controlled studies (baricitinib plus remdesivir vs. remdesivir alone)

- **Table s4.** Non-randomized studies (tofacitinib vs. no tofacitinib)
Table s1. Should hospitalized patients with severe COVID-19 receive treatment with remdesivir plus baricitinib vs. remdesivir alone?

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Country/hospital</th>
<th>Study design</th>
<th>N subjects (intervention/comparator)</th>
<th>% female</th>
<th>Age mean (SD)/median (IQR)</th>
<th>Severity of disease</th>
<th>Intervention (study arms)</th>
<th>Comparator</th>
<th>Co-interventions</th>
<th>Outcomes reported</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ely/2021¹</td>
<td>18 institution s in 4 countries (Argentina, Brazil, Mexico, United States)</td>
<td>RCT</td>
<td>101 (51/50)</td>
<td>45.5</td>
<td>Mean: 58.6 (13.8)</td>
<td>Invasive mechanical ventilation or extracorporeal membrane oxygenation at randomization with at least one elevated marker of inflammation</td>
<td>Baricitinib 4mg daily (or 2mg daily if eGFR ≥ 30 to &lt; 60 mL/min/1.73 m2) crushed and given via nasogastric tube (or by mouth when feasible) for 14 days or until discharge plus SoC</td>
<td>SoC</td>
<td>SoC based on clinical practice at trial hospital, including use of corticosteroids, antivirals, VTE prophylaxis, or other treatments</td>
<td>Mortality at day 28 and day 60</td>
<td>Ely/2021</td>
</tr>
<tr>
<td>Kalil/2021²</td>
<td>United States (55 sites), Singapore (4), South Korea (2), Mexico (2), Japan (1), Spain (1), United Kingdom (1), Denmark (1)</td>
<td>RCT</td>
<td>1033 (515/518)</td>
<td>36.9</td>
<td>Mean: 55.4 (15.7)</td>
<td>Met at least one of the following criteria suggestive of lower respiratory tract infection at enrollment: radiographic infiltrates by imaging study, SpO₂ ≤ 94% on room air, requiring supplemental oxygen, mechanical</td>
<td>Baricitinib 4mg daily (or 2mg daily if eGFR &lt; 60 mL/min) for 14 days or until discharge plus remdesivir 200mg loading dose once day 1, 100mg maintenance dose once daily days 2-10 or until discharge</td>
<td>Remdesivir 200mg loading dose once day 1, 100mg maintenance dose once daily days 2-10 or until discharge and matching placebo tablets</td>
<td>Supportive care according to the standard of care for the trial site hospital; if a hospital had a written policy or guideline for use of other treatments for COVID-19, patients could receive those treatments. All patients without contraindications received</td>
<td>Mortality at day 14 and day 28</td>
<td>Time to recovery (days)</td>
</tr>
<tr>
<td>Study/ year</td>
<td>Country/ hospital</td>
<td>Study design</td>
<td>N subjects (intervention/ comparator)</td>
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<tr>
<td>Marconi 2021</td>
<td>101 centers from 12 countries (Argentina, Brazil, Germany, India, Italy, Japan, South Korea, Mexico, Russia, Spain, United Kingdom, United States)</td>
<td>RCT</td>
<td>1525 (764/761)</td>
<td>36.9</td>
<td>Mean: 57.6 (14.1)</td>
<td>Hospitalized with evidence of pneumonia or active, symptomatic COVID-19, and had ≥ 1 elevated inflammatory marker (C reactive protein, D-dimer, lactate dehydrogenase, ferritin)</td>
<td>Baricitinib 4mg by mouth daily (or 2mg daily for eGFR &lt; 60 mL/min/1.73m²) for up to 14 days or until hospital discharge plus standard of care</td>
<td>Standard of care plus matching placebo tablets</td>
<td>Standard of care according to local clinical practice, and could include: corticosteroids (including dexamethasone), antibiotics, antivirals (including remdesivir), antifungals, and antimalarials. VTE prophylaxis required unless</td>
<td>Mortality at day 28, Disease progression by day 28, Time to recovery (days), Clinical improvement on disease severity scale, Length of hospitalization, Ventilator-free days</td>
<td>Eli Lilly and Company</td>
</tr>
</tbody>
</table>
**Study/ year** | **Country/ hospital** | **Study design** | **N subjects (intervention/ comparator)** | **% female** | **Age mean (SD) / median (IQR)** | **Severity of disease** | **Intervention (study arms)** | **Comparator** | **Co-interventions** | **Outcomes reported** | **Funding source**  
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | ---  
RECOVERY Collaborative Group (Horby) / 2022 | United Kingdom (156 hospitals) | RCT | 8156 (4148/4008) | 34.1 | Mean: 58.1 (15.5) | Patients at least 2 years old admitted to the hospital with clinically suspected or laboratory confirmed SARS-CoV-2 | Baricitinib 4mg daily for 10 days or until discharge plus standard of care (or 2mg daily if eGFR ≥ 30 to < 60 mL/min/1.73 m², 2mg every other day if eGFR ≥ 15 to < 30 mL/min/1.73 m², or 2mg every other day for pediatric patients if eGFR ≥ 30 to < 60 mL/min/1.73 m²) | SoC | Tocilizumab in 23% patients at randomization Also eligible for other platform trial treatments - colchicine, aspirin, dimethyl fumarate, casirivimab/ imdevimab, empagliflozin | Mortality at day 28 Time to hospital discharge Composite of mechanical ventilation or death Adverse events | UK Research and Innovation National Institute of Health Research
Table s2. Risk of bias for randomized control studies (baricitinib plus remdesivir vs. remdesivir alone)

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ely 2021¹</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalil 2020²</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
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<tr>
<td>Marconi 2021³</td>
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<tr>
<td>Marconi 2021⁴</td>
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<td>High</td>
<td>Unclear</td>
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<td></td>
</tr>
<tr>
<td>RECOVERY Collaborative Group (Horby) 2022⁵</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Low, High, Unclear
Table s3. Should hospitalized patients with COVID-19 receive tofacitinib vs. no tofacitinib?

<table>
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<th>Country/hospital</th>
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<th>N subjects (intervention/comparator)</th>
<th>% female</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Guimaraes/2021</td>
<td>15 study sites in Brazil</td>
<td>RCT</td>
<td>289 (144/145)</td>
<td>34.9%</td>
<td>Mean: 56 (14)</td>
<td>Patients ≥ 18 with RT-PCR positive for SARS-CoV-2 with evidence of COVID-19 pneumonia on radiographic imaging and who had been hospitalized for &lt; 72 hours.</td>
<td>Tofacitinib 10 mg twice daily for up to 14 days or until hospital discharge</td>
<td>Placebo</td>
<td>Patients treated according to local standards which included glucocorticoids, antibiotic agents, anticoagulants, and antiviral agents</td>
<td>Death or respiratory failure through day 28 Clinical deterioration Avoidance of mechanical ventilation or ECMO at day 14 and day 28 Scores on the NIAID ordinal scale of disease severity at day 14 and day 28 Adverse events</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
Table s4. Risk of bias for randomized control studies (tofacitinib vs. no tofacitinib)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Guimaraes 2021⁶</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Legend: Low, High, Unclear
References for Supplementary Materials

**Baricitinib**


**Tofacitinib**