

Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

Summary Recommendations
<p>See Therapeutic Management of Patients with COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations on the use of the following:</p> <ul style="list-style-type: none">• Dexamethasone (or other corticosteroids) with or without remdesivir• Baricitinib with remdesivir. <p>See additional recommendations on the use of baricitinib below.</p> <p>See Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the Panel's recommendations on the use of tocilizumab and sarilumab.</p> <p>Other Immunomodulators</p> <p>There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19:</p> <ul style="list-style-type: none">• Baricitinib in combination with corticosteroids. Because both agents are potent immunosuppressants, there is potential for an additive risk of infection.• Baricitinib in combination with remdesivir for hospitalized COVID-19 patients when corticosteroids can be used• Interleukin (IL)-1 inhibitors (e.g., anakinra)• Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild to moderate COVID-19 <p>The Panel recommends against the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial:</p> <ul style="list-style-type: none">• Siltuximab, an anti-IL-6 monoclonal antibody (AIII)• Baricitinib without remdesivir (AIII)• Interferons (alfa or beta) for the treatment of severely or critically ill patients with COVID-19 (AIII)• Kinase inhibitors:<ul style="list-style-type: none">• Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib) (AIII)• Janus kinase inhibitors other than baricitinib (e.g., ruxolitinib, tofacitinib) (AIII)• Non-SARS-CoV-2-specific intravenous immune globulin (IVIG) (AIII). This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>

Corticosteroids

Last Updated: November 3, 2020

Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, randomized, open-label trial in hospitalized patients with COVID-19, showed that the mortality from COVID-19 was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care.¹ Details of the RECOVERY trial are discussed in [Table 4a](#).¹

The safety and efficacy of combination therapy of corticosteroids and an antiviral agent targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the treatment of COVID-19 have not been rigorously studied in clinical trials. However, there are theoretical reasons that such combination therapy may be beneficial in patients with severe disease. See [Therapeutic Management of Patients with COVID-19](#) for the Panel's recommendations on use of dexamethasone with or without remdesivir in certain hospitalized patients.

Rationale for Use of Corticosteroids in Patients With COVID-19

Both beneficial and deleterious clinical outcomes have been reported with use of corticosteroids (mostly prednisone or methylprednisolone) in patients with other pulmonary infections. In patients with *Pneumocystis jirovecii* pneumonia and hypoxia, prednisone therapy reduced the risk of death;² however, in outbreaks of other novel coronavirus infections (i.e., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid therapy was associated with delayed virus clearance.^{3,4} In severe pneumonia caused by influenza viruses, corticosteroid therapy appears to result in worse clinical outcomes, including secondary bacterial infection and death.⁵

Corticosteroids have been studied in critically ill patients with acute respiratory distress syndrome (ARDS) with conflicting results.⁶⁻⁸ Seven randomized controlled trials that included a total of 851 patients evaluated use of corticosteroids in patients with ARDS.⁷⁻¹³ A meta-analysis of these trial results demonstrated that, compared with placebo, corticosteroid therapy reduced the risk of all-cause mortality (risk ratio 0.75; 95% CI, 0.59–0.95) and duration of mechanical ventilation (mean difference, -4.93 days; 95% CI, -7.81 to -2.06 days).^{14,15}

Recommendations on the use of corticosteroids for COVID-19 are largely based on data from the RECOVERY trial, a large, multicenter, randomized, open-label trial performed in the United Kingdom. This trial compared hospitalized patients who received up to 10 days of dexamethasone to those who received the standard of care. Mortality at 28 days was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care.¹ This benefit was observed in patients who were mechanically ventilated or required supplemental oxygen at enrollment. No benefit of dexamethasone was seen in patients who did not require supplemental oxygen at enrollment. Details of the RECOVERY trial are discussed in [Table 4a](#).¹

Corticosteroids used in various formulations and doses and for varying durations in patients with COVID-19 were also studied in several smaller randomized controlled trials.¹⁶⁻²⁰ Some of these trials were stopped early due to under enrollment following the release of the results from the RECOVERY trial. Given that the sample size of many these trials was insufficient to assess efficacy, evidence to support the use of methylprednisolone and hydrocortisone for the treatment of COVID-19 is not as robust as that demonstrated for dexamethasone in the RECOVERY trial. Data from some of these

studies can be found in [Table 4a](#).

Corticosteroids Other Than Dexamethasone

- If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be used.
- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (oral or intravenous [IV])²¹ are:
 - Prednisone 40 mg
 - Methylprednisolone 32 mg
 - Hydrocortisone 160 mg
- Half-life, duration of action, and frequency of administration vary among corticosteroids.
 - *Long-acting corticosteroid*: dexamethasone; half-life: 36 to 72 hours, administer once daily.
 - *Intermediate-acting corticosteroids*: prednisone and methylprednisolone; half-life: 12 to 36 hours, administer once daily or in two divided doses daily.
 - *Short-acting corticosteroid*: hydrocortisone; half-life: 8 to 12 hours, administer in two to four divided doses daily.
- Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; see [Care of Critically Ill Patients With COVID-19](#) for more information. Unlike other corticosteroids previously studied in patients with ARDS, dexamethasone lacks mineralocorticoid activity and thus has minimal effect on sodium balance and fluid volume.¹⁰

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus infections, strongyloidiasis, tuberculosis).
- The risk of reactivation of latent infections for a 10-day course of dexamethasone (6 mg once daily) is not well-defined. When initiating dexamethasone, appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in patients at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities)²²⁻²⁴ or fulminant reactivations of HBV²⁵ should be considered.
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. As such, it may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should review a patient's medication regimen to assess potential interactions.
- Coadministration of remdesivir and dexamethasone has not been formally studied, but a clinically significant pharmacokinetic interaction is not predicted.
- Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first.

Considerations in Pregnancy

A short course of betamethasone and dexamethasone, which are known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.^{26,27}

Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for a short course of dexamethasone therapy, the Panel recommends using **dexamethasone** in hospitalized pregnant women with COVID-19 who are mechanically ventilated (**AIII**) or who require supplemental oxygen but who are not mechanically ventilated (**BIII**).

Considerations in Children

The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Importantly, the RECOVERY trial did not include a significant number of pediatric patients, and mortality from COVID-19 is significantly lower among pediatric patients than among adult patients. Thus, caution is warranted when extrapolating the results of the RECOVERY trial to patients aged <18 years. Dexamethasone may be beneficial in pediatric patients with COVID-19 respiratory disease who require mechanical ventilation. Use of dexamethasone in patients who require other forms of supplemental oxygen support should be considered on a case-by-case basis and is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only). Additional studies are needed to evaluate the use of steroids for the treatment of COVID-19 in pediatric patients, including for multisystem inflammatory syndrome in children (MIS-C).

Clinical Trials

Several clinical trials to evaluate corticosteroids for the treatment of COVID-19 are currently underway or in development. Please see [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information.

References

1. Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19 - preliminary report. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
2. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990;323(21):1451-1457. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2233917>.
3. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29161116>.
4. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16968120>.
5. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26950335>.
6. Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med*. 2016;42(5):829-840. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26508525>.
7. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest*. 2007;131(4):954-963. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17426195>.
8. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354(16):1671-1684. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16625008>.

9. Liu L, Li J, Huang YZ, et al. [The effect of stress dose glucocorticoid on patients with acute respiratory distress syndrome combined with critical illness-related corticosteroid insufficiency]. *Zhonghua Nei Ke Za Zhi*. 2012;51(8):599-603. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23158856>.
10. Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32043986>.
11. Rezk NA, Ibrahim AM. Effects of methyl prednisolone in early ARDS. *Egypt J Chest Dis Tuberc*. 2013;62(1):167-172. Available at: <https://www.sciencedirect.com/science/article/pii/S0422763813000265>.
12. Tongyoo S, Permpikul C, Mongkolpun W, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care*. 2016;20(1):329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27741949>.
13. Zhao WB, Wan SX, Gu DF, Shi B. Therapeutic effect of glucocorticoid inhalation for pulmonary fibrosis in ARDS patients. *Med J Chinese PLA*. 2014;39(9):741-745. Available at: <http://www.plamj.org/index.php/plamj/article/view/1009>.
14. Mammen MJ, Aryal K, Alhazzani W, Alexander PE. Corticosteroids for patients with acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials. *Pol Arch Intern Med*. 2020;130(4):276-286. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32186831>.
15. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32224769>.
16. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32785710>.
17. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876695>.
18. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876689>.
19. Writing Committee for the R-CAPI, Angus DC, Derde L, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876697>.
20. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876694>.
21. Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet*. 2005;44(1):61-98. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15634032>.
22. Centers for Disease Control and Prevention. Parasites - strongyloides: resources for health professionals. 2020; https://www.cdc.gov/parasites/strongyloides/health_professionals/index.html. Accessed October 30, 2020.
23. Lier AJ, Tuan JL, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020. Available at: <http://www.ajtmh.org/docserver/fulltext/14761645/103/4/tpmd200699.pdf?expires=1606941469&id=id&accname=guest&checksum=9728AC8BEDF3E8369A7D3E6C2AFEB27E>.

24. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761166>.
25. Liu J, Wang T, Cai Q, et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic HBV infection. *Hepatol Res*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761993>.
26. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics*. 1972;50(4):515-525. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/4561295>.
27. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*. 2016;374(14):1311-1320. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26842679>.

Table 4a. Corticosteroids: Selected Clinical Data

Last Updated: February 11, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for corticosteroids. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report (RECOVERY Trial)¹			
<p>Multi-center, randomized open-label adaptive trial in hospitalized patients with suspected or confirmed COVID-19 (n = 6,425)</p> <p>Country: United Kingdom</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Hospitalization with clinically suspected or laboratory-confirmed SARS-CoV-2 infection <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Physician determination that risks of participation too great based on patient's medical history or an indication for corticosteroid therapy outside of the study <p>Interventions:</p> <ul style="list-style-type: none"> Patients randomized 2:1 to receive: <ul style="list-style-type: none"> Dexamethasone 6 mg PO or IV once daily plus SOC for up to 10 days or until hospital discharge, whichever came first, <i>or</i> SOC alone <p>Primary Endpoint:</p> <ul style="list-style-type: none"> All-cause mortality at 28 days after randomization 	<p>Number of Participants:</p> <ul style="list-style-type: none"> Dexamethasone plus SOC (n = 4,321) and SOC (n = 2,104) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 66 years. 64% of participants were men. 56% of participants had ≥1 comorbidity; 24% had diabetes. 89% of participants had laboratory-confirmed SARS-CoV-2 infection. At randomization, 16% of participants received invasive mechanical ventilation or ECMO, 60% required supplemental oxygen but not invasive ventilation, and 24% required no oxygen supplementation. 0% to 3% of the participants in both arms received RDV, HCQ, LPV/RTV, or tocilizumab; approximately 8% of participants in SOC alone arm received dexamethasone after randomization. <p>Outcomes:</p> <ul style="list-style-type: none"> 28-day mortality was 22.9% in dexamethasone arm and 25.7% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; <i>P</i> < 0.001). 	<p>Limitations:</p> <ul style="list-style-type: none"> Open label study This preliminary study analysis did not include the results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), AEs, and the efficacy of dexamethasone in key subgroups (e.g., patients with comorbidities). Study participants with COVID-19 who required oxygen (but not mechanical ventilation) had variable disease severity; it is unclear whether all patients in this heterogeneous group derived benefit from dexamethasone, or whether benefit is restricted to those requiring higher levels of supplemental oxygen or oxygen delivered through a high-flow device. The age distribution of participants differed by respiratory status at randomization. The survival benefit of dexamethasone for mechanically ventilated patients aged >80 years is unknown because only 1% of the participants in this group were ventilated.

Study Design	Methods	Results	Limitations and Interpretation
Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report (RECOVERY Trial)¹, continued			
		<ul style="list-style-type: none"> • The treatment effect of dexamethasone varied by baseline severity of COVID-19. Survival benefit appeared greatest among participants who required invasive mechanical ventilation at randomization. Among these participants, 28-day mortality was 29.3% in dexamethasone arm vs. 41.4% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81). • Among patients who required supplemental oxygen but not mechanical ventilation at randomization, 28-day mortality was 23.3% in dexamethasone arm vs. 26.2% in SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94). • No survival benefit in participants who did not require oxygen therapy at enrollment. Among these participants, 28-day mortality was 17.8% in dexamethasone arm vs. 14.0% in SOC arm (rate ratio 1.19; 95% CI, 0.91–1.55). 	<ul style="list-style-type: none"> • It is unclear whether younger patients were more likely to receive mechanical ventilation than patients aged >80 years, given similar disease severity at baseline, with older patients preferentially assigned to oxygen therapy. • The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> • In hospitalized patients with severe COVID-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days, with the greatest benefit seen in those who were mechanically ventilated at baseline. • There was no observed survival benefit of dexamethasone in patients who did not require oxygen support at baseline.
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-Analysis (REACT Working Group)²			
<p>Meta-analysis of 7 RCTs of corticosteroids in critically ill patients with COVID-19 (n = 1,703)</p> <p>Countries: Multinational</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • RCTs evaluating corticosteroids in critically ill patients with COVID-19 (identified via comprehensive search of ClinicalTrials.gov, Chinese Clinical Trial Registry, and EU Clinical Trials Register) 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Corticosteroids (n = 678) and usual care or placebo (n = 1,025) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 60 years. • 29% of patients were women. • 1,559 patients (91.5%) were on mechanical ventilation. 	<p>Limitations:</p> <ul style="list-style-type: none"> • The design of the trials included in the meta-analysis differed in several ways, including the following: <ul style="list-style-type: none"> • Definition of critical illness • Specific corticosteroid used • Dose of corticosteroid • Duration of corticosteroid treatment

Study Design	Methods	Results	Limitations and Interpretation
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-Analysis (REACT Working Group)², continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • Corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone) • Usual care or placebo <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • All-cause mortality up to 30 days after randomization 	<ul style="list-style-type: none"> • 47% of patients were on vasoactive agents at randomization across the 6 trials that reported this information. <p>Outcomes:</p> <ul style="list-style-type: none"> • Mortality was assessed at 28 days in 5 trials, 21 days in 1 trial, and 30 days in 1 trial. • Reported all-cause mortality at 28 days: Death occurred in 222 of 678 patients (32.7%) in corticosteroids group vs. 425 of 1,025 patients (41.5%) in usual care or placebo group; summary OR 0.66 (95% CI, 0.53–0.82; $P < 0.001$). • The fixed-effect summary ORs for the association with all-cause mortality were: <ul style="list-style-type: none"> • Dexamethasone: OR 0.64 (95% CI, 0.50–0.82; $P < 0.001$) in 3 trials with 1,282 patients • Hydrocortisone: OR 0.69 (95% CI, 0.43–1.12; $P = 0.13$) in 3 trials with 374 patients. • Methylprednisolone: OR 0.91 (95% CI, 0.29–2.87; $P = 0.87$) in 1 trial with 47 patients • For patients on mechanical ventilation ($n = 1,559$): OR 0.69 (95% CI, 0.55–0.86), with mortality of 30% for corticosteroids vs. 38% for usual care or placebo • For patients not on mechanical ventilation ($n = 144$): OR 0.41 (95% CI, 0.19–0.88) with mortality of 23% for corticosteroids vs. 42% for usual care or placebo • Across the 6 trials that reported SAEs, 18.1% of patients randomized to corticosteroids and 23.4% randomized to usual care or placebo experienced SAEs. 	<ul style="list-style-type: none"> • Type of control group (i.e., usual care or placebo) • Reporting of SAEs • The RECOVERY trial accounted for 59% of the participants, and 3 trials enrolled <50 patients each. • Some studies confirmed SARS-CoV-2 infection for participant inclusion while others enrolled participants with either probable or confirmed infection. • Although the risk of bias was low in 6 of the 7 trials, it was assessed as “some concerns” for 1 trial (which contributed only 47 patients). <p>Interpretation:</p> <ul style="list-style-type: none"> • Systemic corticosteroids decrease 28-day mortality in critically ill patients with COVID-19 without safety concerns. • Most of the participants were from the RECOVERY trial, thus the evidence of benefit in the meta-analysis is strongest for dexamethasone, the corticosteroid used in the RECOVERY trial.

Study Design	Methods	Results	Limitations and Interpretation
Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial³			
<p>Randomized, double-blind, placebo-controlled, single-center study of short-course methylprednisolone in hospitalized patients with confirmed or suspected COVID-19 pneumonia (n = 416)</p> <p>Country: Brazil</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Suspected or confirmed COVID-19 • SpO₂ ≤94% on room air <i>or</i> while using supplementary oxygen <i>or</i> under invasive mechanical ventilation <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Hypersensitivity to methylprednisolone • Chronic use of corticosteroids or immunosuppressive agents • HIV, decompensated cirrhosis, chronic renal failure <p>Interventions:</p> <ul style="list-style-type: none"> • Methylprednisolone IV 0.5 mg/kg twice daily for 5 days • Placebo (saline) IV <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mortality by Day 28 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Early mortality at Days 7 and 14 • Need for mechanical ventilation by Day 7 • Need for insulin by Day 28 • Positive blood culture at Day 7, sepsis by Day 28 • Mortality by Day 28 in specified subgroups 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • mITT analysis (n = 393): Methylprednisolone (n = 194) and placebo (n = 199) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 55 years. • 65% of patients were men. • 29% of patients had diabetes. • At enrollment, 34% of participants in each group required invasive mechanical ventilation; 51% in methylprednisolone group and 45% in placebo group required supplemental oxygen. • Median time from illness onset to randomization was 13 days (IQR 9–16). • None of the participants received anti-IL-6, anti-IL-1, RDV, or convalescent plasma. • Hydrocortisone use for shock among patients was 8.7% in methylprednisolone group and 7.0% in placebo group. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • No difference in 28-day mortality: 37.1% in methylprednisolone arm vs. 38.2% in placebo arm (HR 0.92; 95% CI, 0.67–1.28; <i>P</i> = 0.63). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • No difference between groups in early mortality at Day 7 (HR 0.68; 95% CI, 0.43–1.06) or Day 14 (HR 0.82; 95% CI, 0.57–1.18) • No difference in need for mechanical ventilation by Day 7: 19.4% of methylprednisolone recipients vs. 16.8% of placebo recipients (<i>P</i> = 0.65) 	<p>Limitations:</p> <ul style="list-style-type: none"> • The median days from illness onset to randomization was longer than in other corticosteroid studies. • The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> • Use of weight-based methylprednisolone for 5 days did not reduce overall 28-day mortality. • In a post hoc subgroup analysis, mortality among those aged >60 years was lower in the methylprednisolone group than in the placebo group.

Study Design	Methods	Results	Limitations and Interpretation
Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial³, continued			
		<ul style="list-style-type: none"> • No significant difference between the methylprednisolone and placebo groups in need for insulin (59.5% vs. 49.4% of patients), positive blood cultures at Day 7 (8.3% vs. 8.0% of patients), or sepsis by Day 28 (38.1% vs. 38.7% of patients) • In post hoc analysis, 28-day mortality in participants aged >60 years was lower in methylprednisolone group than in placebo group (46.6% vs. 61.9%; HR 0.63; 95% CI, 0.41–0.98). 	
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial⁴			
<p>Multicenter, randomized, clinical trial in patients with COVID-19 and moderate to severe ARDS (n = 299)</p> <p>Country: Brazil</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Confirmed or suspected COVID-19 • On mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with PaO₂/FiO₂ ≤200 mm Hg <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Recent corticosteroid use • Use of immunosuppressive drugs in the past 21 days • Expected death in next 24 hours <p>Interventions:</p> <ul style="list-style-type: none"> • Dexamethasone 20 mg IV daily for 5 days, then 10 mg IV daily for 5 days or until ICU discharge plus SOC • SOC alone 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis (n = 299): Dexamethasone plus SOC (n = 151) and SOC alone (n = 148) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Dexamethasone group included more women than the SOC group (40% vs. 35%), more patients with obesity (31% vs. 24%), and fewer patients with diabetes (38% vs. 47%). • Other baseline characteristics were similar for the dexamethasone and SOC groups: <ul style="list-style-type: none"> • Mean age was 60 vs. 63 years; vasopressor use by 66% vs. 68% of patients; mean PaO₂/FiO₂ of 131 mm Hg vs. 133 mm Hg. • Median time from symptom onset to randomization was 9–10 days. • Median time from mechanical ventilation to randomization was 1 day. • No patients received RDV; anti-IL-6 and convalescent plasma were not widely available. • Median duration of dexamethasone therapy was 10 days (IQR 6–10 days). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Open-label study • The study was underpowered to assess some outcomes because it stopped enrollment after data from the RECOVERY trial were released. • During the study, 35% of the patients in the SOC group received corticosteroids for shock, bronchospasm, or other reasons. • Patients who were discharged from the hospital before 28 days were not followed for rehospitalization or mortality. • The high baseline mortality of the patient population may limit generalizability of the study results to populations with a lower baseline mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared with SOC alone, dexamethasone at a higher dose than used in the RECOVERY trial plus SOC

Study Design	Methods	Results	Limitations and Interpretation
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial⁴, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mean number of days alive and free from mechanical ventilation by Day 28 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • All-cause mortality at Day 28 • ICU-free days by Day 28 • Duration of mechanical ventilation by Day 28 • Score on 6-point WHO ordinal scale at Day 15 • SOFA score at 7 days • Components of the primary outcome or in the outcome of discharged alive within 28 days 	<ul style="list-style-type: none"> • 35% of patients in SOC alone group also received corticosteroids. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • The mean number of days alive and free from mechanical ventilation by Day 28 was higher in the dexamethasone group than in the SOC group (6.6 vs. 4.0 days, estimated difference of 2.3 days; 95% CI, 0.2–4.4; <i>P</i> = 0.04). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • There were no differences between the dexamethasone and SOC groups for the following outcomes: <ul style="list-style-type: none"> • All-cause mortality at Day 28 (56.3% vs. 61.5%; HR 0.97; 95% CI, 0.72–1.31; <i>P</i> = 0.85) • ICU-free days by Day 28 (mean of 2.1 vs. 2.0 days; <i>P</i> = 0.50) • Duration of mechanical ventilation by Day 28 (mean of 12.5 vs. 13.9 days; <i>P</i> = 0.11) • Score on 6-point WHO ordinal scale at Day 15 (median score of 5 for both groups) • The mean SOFA score at 7 days was lower in the dexamethasone group than in the SOC group (6.1 vs. 7.5, difference -1.16; 95% CI, -1.94 to -0.38; <i>P</i> = 0.004). • The following safety outcomes were comparable for dexamethasone and SOC groups: need for insulin (31.1% vs. 28.4%), new infections (21.9% vs. 29.1%), bacteremia (7.9% vs. 9.5%), and other SAEs (3.3% vs. 6.1%). • In post hoc analysis, the dexamethasone group had a lower cumulative probability of death or mechanical ventilation at Day 15 than the SOC group (67.5% vs. 80.4%; OR 0.46; 95% CI, 0.26–0.81; <i>P</i> = 0.01). 	<p>increased the number of days alive and free of mechanical ventilation over 28 days of follow-up in patients with COVID-19 and moderate to severe ARDS.</p> <ul style="list-style-type: none"> • Dexamethasone was not associated with an increased risk of AEs in this population. • More than one-third of those randomized to the standard care alone group also received corticosteroids; it is impossible to determine the effect of corticosteroid use in these patients on the overall study outcomes.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial⁵			
<p>Multicenter, randomized, double-blind, sequential trial in patients with confirmed or suspected COVID-19 and acute respiratory failure (n = 149)</p> <p>Country: France</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Confirmed SARS-CoV-2 infection or radiographically suspected COVID-19, with at least 1 of 4 severity criteria: <ul style="list-style-type: none"> • Need for mechanical ventilation with PEEP ≥5 cm H₂O • High-flow oxygen with PaO₂/FiO₂ <300 mm Hg and FiO₂ ≥50% • Reservoir mask oxygen with PaO₂/FiO₂ <300 mm Hg (estimated) • Pneumonia severity index >130 (scoring table) <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Septic shock • Do-not-intubate orders <p>Interventions:</p> <ul style="list-style-type: none"> • Continuous infusion hydrocortisone 200 mg/day until Day 7, then hydrocortisone 100 mg/day for 4 days, and then hydrocortisone 50 mg/day for 3 days, for a total treatment duration of 14 days • Patients who showed clinical improvement by Day 4 were switched to a shorter 8-day regimen. 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis (n = 149 participants): Hydrocortisone (n = 76) and placebo (n = 73) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age of participants was 62 years; 70% were men; median BMI was 28. • 96% of participants had confirmed SARS-CoV-2 infection. • Median symptom duration before randomization was 9 days in hydrocortisone group vs. 10 days in placebo group. • 81% of the patients overall were mechanically ventilated, and 24% in hydrocortisone group and 18% in placebo group were receiving vasopressors. • Among the patients receiving concomitant COVID-19 treatment, 3% received RDV, 14% LPV/RTV, 13% HCQ, and 34% HCQ plus AZM. • Median treatment duration was 10.5 days in hydrocortisone group vs. 12.8 days in placebo group (P = 0.25). <p>Primary Outcome:</p> <ul style="list-style-type: none"> • There was no difference in the proportion of patients with treatment failure by Day 21, which occurred in 32 of 76 patients (42.1%) in hydrocortisone group and 37 of 73 patients (50.7%) in placebo group (difference -8.6%; 95% CI, -24.9% to 7.7%; P = 0.29). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • There was no difference between the groups in the need for intubation, rescue strategies, or oxygenation (i.e., change in PaO₂/FiO₂). • Among the patients who did not require mechanical ventilation at baseline, 8 of 16 patients (50%) in hydrocortisone group required subsequent 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size. Planned sample size of 290, but 149 enrolled because study was terminated early after the release of results from the RECOVERY trial. • Limited information about comorbidities (e.g., hypertension) • Participants' race and/or ethnicity were not reported. • Nosocomial infections were recorded but not adjudicated. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to placebo, hydrocortisone did not reduce treatment failure (defined as death or persistent respiratory support) at Day 21 in ICU patients with COVID-19 and acute respiratory failure. • Because this study was terminated early, it is difficult to make conclusions about the efficacy and safety of hydrocortisone therapy. • The starting dose of hydrocortisone used in this study were slightly higher than the 6 mg dose of dexamethasone used in the RECOVERY study. The hydrocortisone dose was adjusted according to clinical response.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial⁵, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> Treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen) by Day 21 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Need for intubation, rescue strategies, or oxygenation (i.e., change in PaO₂/FiO₂) Nosocomial infections on Day 28 Clinical status on Day 21 	<p>intubation vs. 12 of 16 (75%) in placebo group.</p> <ul style="list-style-type: none"> 3 SAEs were reported (cerebral vasculitis, cardiac arrest due to PE, and intra-abdominal hemorrhage from anticoagulation for PE); all occurred in the hydrocortisone group, but none were attributed to the intervention. There was no difference between the groups in proportion of patients with nosocomial infections on Day 28. In post hoc analysis, clinical status on Day 21 did not significantly differ between the groups except for fewer deaths in the hydrocortisone group (14.7% of patients died vs. 27.4% in placebo group; <i>P</i> = 0.06): By Day 21, 57.3% of patients in hydrocortisone group vs. 43.8% in placebo group were discharged from the ICU and 22.7% in hydrocortisone group vs. 23.3% in placebo group were still mechanically ventilated. 	
Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial (CAPE COD)⁶			
<p>Randomized, embedded, multifactorial, adaptive platform trial of patients with severe COVID-19 (n = 403)</p> <p>Countries: Multinational</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Aged ≥18 years Presumed or confirmed SARS-CoV-2 infection ICU admission for respiratory or cardiovascular organ support <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Presumed imminent death Systemic corticosteroid use >36 hours since ICU admission 	<p>Number of Participants:</p> <ul style="list-style-type: none"> mITT analysis (n = 384): Fixed-dose hydrocortisone (n=137), shock-based hydrocortisone (n = 146), and no hydrocortisone (n = 101) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 60 years. 71% of patients were men. Mean BMI was 29.7–30.9. 50% to 64% of patients received mechanical ventilation. 	<p>Limitations:</p> <ul style="list-style-type: none"> Early termination following release of RECOVERY study results Randomized study, but open label <p>Interpretation:</p> <ul style="list-style-type: none"> Corticosteroids did not significantly increase support-free days in either the fixed-dose hydrocortisone or the shock-dependent hydrocortisone group, although the early termination of the trial led to limited power to detect difference between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial (CAPE COD)⁶, continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> Hydrocortisone 50 mg 4 times daily for 7 days Septic shock-based hydrocortisone 50 mg 4 times daily for the duration of shock No hydrocortisone <p>Primary Endpoint:</p> <ul style="list-style-type: none"> Days free of respiratory and cardiovascular organ support up to Day 21. (For this ordinal outcome, patients who died were assigned -1 day.) <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> In-hospital mortality SAEs 	<p>Primary Outcome:</p> <ul style="list-style-type: none"> No difference between the groups in organ-support free-days at Day 21 (median of 0 days in each group). Compared to the no hydrocortisone group, median adjusted OR for the primary outcome: <ul style="list-style-type: none"> OR 1.43 (95% credible interval, 0.91–2.27) with 93% Bayesian probability of superiority for the fixed-dose hydrocortisone group OR 1.22 (95% credible interval, 0.76–1.94) with 80% Bayesian probability of superiority for the shock-based hydrocortisone group <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> No difference between the groups in mortality; 30%, 26%, and 33% of patients died in the fixed-dose, shock-based, and no hydrocortisone groups, respectively. SAEs reported in 3%, 3%, and 1% of patients in the fixed-dose, shock-based, and no hydrocortisone groups, respectively. 	
Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study⁷			
<p>Retrospective cohort study in patients with nonsevere COVID-19 pneumonia and propensity score-matched controls (n = 55 matched case-control pairs)</p> <p>Country: China</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Confirmed COVID-19 Pneumonia on chest CT scan Aged ≥16 years <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Severe pneumonia defined as having any of the following: respiratory distress, respiratory rates >30 breaths/min, SpO₂ <93%, oxygenation index <300 mm Hg, mechanical ventilation, or shock 	<p>Number of Participants:</p> <ul style="list-style-type: none"> Corticosteroids (n = 55): IV methylprednisolone (n=50) and prednisone (n = 5) No corticosteroids (n = 55 matched controls chosen from 420 patients who did not receive corticosteroids) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 58–59 years. Median oxygen saturation was 95%. 42% of patients in corticosteroids group and 46% in no corticosteroids group had comorbidities, including 35% to 36% with hypertension and 11% to 13% with diabetes. 	<p>Limitations:</p> <ul style="list-style-type: none"> Retrospective, case-control study Small sample size (55 case-control pairs) Corticosteroid therapy was selected preferentially for patients who had more risk factors for severe progression of COVID-19; the propensity score matching may not have adjusted for some of the unmeasured confounders.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study⁷, continued			
	<ul style="list-style-type: none"> • Immediate ICU admission upon hospitalization • Use of corticosteroids after progression to severe disease <p>Interventions:</p> <ul style="list-style-type: none"> • Early, low-dose corticosteroids: <ul style="list-style-type: none"> • IV methylprednisolone 20 mg/day or 40 mg/day for 3–5 days • PO prednisone 20 mg/day for 3 days • No corticosteroids <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Rates of severe disease and death <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Duration of fever • Virus clearance time • Length of hospital stay • Use of antibiotics 	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> • 7 patients (12.7%) in the corticosteroids group developed severe disease vs. 1 (1.8%) in the no corticosteroids group ($P = 0.03$); time to severe disease: HR 2.2 (95% CI, 2.0–2.3; $P < 0.001$). • There was 1 death in the methylprednisolone group vs. none in the no corticosteroids group. <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • Each of the following outcomes was longer in the corticosteroids group than in the no corticosteroids group ($P < 0.001$ for each outcome): duration of fever (5 vs. 3 days), virus clearance time (18 vs. 11 days), and length of hospital stay (23 vs. 15 days). • More patients in the corticosteroids group than in the no corticosteroids group were prescribed antibiotics (89% vs. 24%) and antifungal therapy (7% vs. 0%). 	<ul style="list-style-type: none"> • Selection bias in favor of the no corticosteroids group may have been introduced by excluding patients who used corticosteroids after progression to severe disease from the study. <p>Interpretation:</p> <ul style="list-style-type: none"> • In this nonrandomized, case-control study, methylprednisolone therapy in patients with nonsevere COVID-19 pneumonia was associated with worse outcomes, but this finding is difficult to interpret because of potential confounding factors. • It is unclear whether the results for methylprednisolone therapy can be generalized to therapy with other corticosteroids.

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; AZM = azithromycin; BMI = body mass index; CT = computerized tomography; ECMO = extracorporeal membrane oxygenation; EU = European Union; HCQ = hydroxychloroquine; ICU = intensive care unit; IL = interleukin; ITT = intention-to-treat; IV = intravenous; LPV/RTV = lopinavir/ritonavir; mITT = modified intention-to-treat; the Panel = the COVID-19 Treatment Guidelines Panel; PaO₂/FiO₂ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PE = pulmonary embolism; PEEP = positive end-expiratory pressure; PO = oral; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SOFA = sequential organ failure assessment; SpO₂ = saturation of oxygen; WHO = World Health Organization

References

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med*. 2020;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
2. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330-1341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876694>.
3. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, Phase IIb, placebo-controlled trial. *Clin Infect Dis*. 2020;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32785710>.
4. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307-1316.. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876695>.
5. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298-1306. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876689>.
6. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324(13):1317-1329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876697>.
7. Li Q, Li W, Jin Y, et al. Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a retrospective cohort study. *Infect Dis Ther*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32880102>.

Interferons (Alfa, Beta)

Last Updated: August 27, 2020

Interferons are a family of cytokines with antiviral properties. They have been suggested as a potential treatment for COVID-19 because of their *in vitro* and *in vivo* antiviral properties.

Recommendation

The COVID-19 Treatment Guidelines Panel **recommends against** the use of interferons for the treatment of patients with severe or critical COVID-19, except in a clinical trial (**AIII**). There are insufficient data to recommend either for or against the use of **interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

Rationale

Studies have shown no benefit of interferons in patients with other coronavirus infections (i.e., Middle East respiratory syndrome [MERS], severe acute respiratory syndrome [SARS]) who have severe or critical disease. In addition, interferons have significant toxicities that outweigh the potential for benefit. Interferons may have antiviral activity early in the course of infection. However, there is insufficient data to assess the potential benefit of interferon use during early disease versus the toxicity risks.

Clinical Data for COVID-19

Interferon Beta-1a

Press release, July 20, 2020: A double-blind, placebo-controlled trial conducted in the United Kingdom evaluated inhaled interferon beta-1a (once daily for up to 14 days) in nonventilated patients hospitalized with COVID-19. Compared to the patients receiving placebo (n = 50), the patients receiving inhaled interferon beta-1a (n = 48) were more likely to recover to ambulation without restrictions (HR 2.19; 95% CI, 1.03–4.69; P = 0.04), had decreased odds of developing severe disease (OR 0.21; 95% CI, 0.04–0.97; P = 0.046), and had less breathlessness. Additional detail is required to fully evaluate these findings and their implications. Of note, inhaled interferon beta-1a as used in this study is not commercially available in the United States.¹

Preprint manuscript posted online, July 13, 2020: An open-label, randomized trial at a single center in Iran evaluated subcutaneous interferon beta-1a (three times weekly for 2 weeks) in patients with severe COVID-19. There was no difference in the primary outcome of time to clinical response between the interferon beta-1a group (n = 42) and the control group (n = 39), and there was no difference between the groups in overall length of hospital stay, length of intensive care unit stay, or duration of mechanical ventilation. The reported 28-day overall mortality was lower in the interferon beta-1a group; however, four patients in the interferon beta-1a group who died before receiving the fourth dose of interferon beta-1a were excluded from the analysis, which makes it difficult to interpret these results.²

Combination of Interferon Beta-1b, Lopinavir/Ritonavir, and Ribavirin in the Treatment of Hospitalized Patients With COVID-19

An open-label, Phase 2 clinical trial randomized 127 participants (median age of 52 years) 2:1 to combination antiviral therapy or lopinavir/ritonavir. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants hospitalized within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (interferon beta-1b 8 million units administered subcutaneously every other day for up to 7 days total, lopinavir/ritonavir,

and ribavirin); those hospitalized ≥ 7 days after symptom onset ($n = 51$) were randomized to double therapy (lopinavir/ritonavir and ribavirin) because of concerns regarding potential inflammatory effects of interferon. Patients in the control group received lopinavir/ritonavir alone regardless of the time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were hospitalized, regardless of disease severity, until they had two negative nasopharyngeal (NP) swab tests.

The time to a negative result on a polymerase chain reaction SARS-CoV-2 test on an NP swab (the primary endpoint) was shorter in the combination therapy group than in the control group (median of 7 days vs. 12 days; $P = 0.001$). The combination group had more rapid clinical improvement as assessed by the National Early Warning Score (NEWS) 2 and Sequential Organ Failure Assessment (SOFA) score and a shorter hospital stay (median of 9 days for the combination group vs. 14.5 days for the control group; $P = 0.016$). There was no difference in oxygen use between the groups. The antiviral and clinical effect was more pronounced in the patients hospitalized within 7 days of symptom onset, suggesting that interferon beta-1b with or without ribavirin was the critical component of the combination antiviral therapy. The study provides no information about the effect of interferon beta-1b when administered ≥ 7 days after symptom onset.³

Interferon Alfa-2b

In a retrospective cohort study of 77 adults with moderate COVID-19 in China, participants were treated with nebulized interferon alfa-2b, nebulized interferon alfa-2b with umifenovir, or umifenovir only. The time to viral clearance in the upper respiratory tract and reduction in systemic inflammation was faster in the interferon alfa-2b groups than in the umifenovir only group. However, the results of this study are difficult to interpret because participants in the interferon alfa-2b with umifenovir group were substantially younger than those in the umifenovir only group (mean age of 40 years in the interferon alfa-2b with umifenovir group vs. 65 years in the umifenovir only group) and had fewer comorbidities (15% in the interferon alfa-2b with umifenovir group vs. 54% in the umifenovir only group) at study entry. The nebulized interferon alfa-2b formulation is not approved by the Food and Drug Administration for use in the United States.⁴

Clinical Data for SARS and MERS

Interferon beta used alone and in combination with ribavirin in patients with SARS and MERS has failed to show a significant positive effect on clinical outcomes.⁵⁻⁹

In a retrospective observational analysis of 350 critically ill patients with MERS⁶ from 14 hospitals in Saudi Arabia, the mortality rate was higher among patients who received ribavirin and interferon (beta-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug.

A randomized clinical trial that included 301 patients with acute respiratory distress syndrome¹⁰ found that intravenous interferon beta-1a had no benefit over placebo as measured by ventilator-free days over a 28-day period (median of 10.0 days in the interferon beta-1a group vs. 8.5 days in the placebo group) or mortality (26.4% in the interferon beta-1a group vs. 23.0% in the placebo group).

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) for a list of [ongoing clinical trials for interferon and COVID-19](#).

Adverse Effects

The most frequent adverse effects of interferon alfa include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (e.g., depression and

suicidal ideation). Interferon beta is better tolerated than interferon alfa.^{11,12}

Drug-Drug Interactions

The most serious drug-drug interactions with interferons are the potential for added toxicity with concomitant use of other immunomodulators and chemotherapeutic agents.^{11,12}

Considerations in Pregnancy

Analysis of data from several large pregnancy registries did not demonstrate an association between exposure to interferon beta-1b preconception or during pregnancy and an increased risk of adverse birth outcomes (e.g., spontaneous abortion, congenital anomaly),^{13,14} and exposure did not influence birth weight, height, or head circumference.¹⁵

Considerations in Children

There are limited data on the use of interferons for the treatment of respiratory viral infections in children.

References

1. Synairgen announces positive results from trial of SNG001 in hospitalised COVID-19 patients [press release]. July 20, 2020. Available at: <https://www.synairgen.com/wp-content/uploads/2020/07/200720-Synairgen-announces-positive-results-from-trial-of-SNG001-in-hospitalised-COVID-19-patients.pdf>. Accessed August 24, 2020.
2. Davoudi-Monfared E, Rahmani H, Khalili H, et al. A randomized clinical trial of the efficacy and safety of interferon beta-1a in treatment of severe COVID-19. *Antimicrob Agents Chemother*. 2020;64(9):e01061-20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32661006>.
3. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, Phase 2 trial. *Lancet*. 2020;395(10238):1695-1704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32401715>.
4. Zhou Q, Chen V, Shannon CP, et al. Interferon-alpha2b treatment for COVID-19. *Front Immunol*. 2020;11:1061. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32574262>.
5. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. *Int J Infect Dis*. 2014;20:42-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24406736>.
6. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clin Infect Dis*. 2020;70(9):1837-1844. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31925415>.
7. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14985565>.
8. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090-1095. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25278221>.
9. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alpha2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129-2132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25900158>.
10. Ranieri VM, Pettila V, Karvonen MK, et al. Effect of intravenous interferon beta-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32065831>.

11. Interferon alpha-2b (Intron A) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103132Orig1s5199lbl.pdf.
12. Interferon beta-1a (Rebif) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103780s5204lbl.pdf.
13. Sandberg-Wollheim M, Alteri E, Moraga MS, Kornmann G. Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy. *Mult Scler*. 2011;17(4):423-430. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21220368>.
14. Hellwig K, Duarte Caron F, Wicklein EM, Bhatti A, Adamo A. Pregnancy outcomes from the global pharmacovigilance database on interferon beta-1b exposure. *Ther Adv Neurol Disord*. 2020;13:1756286420910310. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32201504>.
15. Burkill S, Vattulainen P, Geissbuehler Y, et al. The association between exposure to interferon-beta during pregnancy and birth measurements in offspring of women with multiple sclerosis. *PLoS One*. 2019;14(12):e0227120. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31887199>.

Interleukin-1 Inhibitors

Last Updated: July 17, 2020

Recommendation

- There are insufficient data to recommend for or against the use of interleukin (IL)-1 inhibitors, such as **anakinra**, for the treatment of COVID-19.

Rationale

There are case series data but no clinical trial data on the use of IL-1 inhibitors in patients with COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved by the Food and Drug Administration (FDA) to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease.¹ It is also used off-label for severe chimeric antigen receptor T cell (CAR T-cell)-mediated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis.

Rationale for Use in Patients with COVID-19

Endogenous IL-1 is elevated in patients with COVID-19 and other conditions, such as severe CAR T-cell-mediated CRS. Case reports and case series have described favorable responses to anakinra in patients with these syndromes, including a survival benefit in patients with sepsis and reversal of cytokine storm after tocilizumab failure in adults with MAS.^{2,3}

Clinical Data for COVID-19

- A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra and 44 historical controls. The patients in both groups were all admitted to the same hospital in Paris, France. Case patients were consecutive admissions from March 24 to April 6, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia ($\text{SpO}_2 \leq 93\%$ with $\geq 6\text{L}/\text{min O}_2$) or worsening hypoxia ($\text{SpO}_2 \leq 93\%$ with $>3\text{L}/\text{min O}_2$ and a loss of $\geq 3\%$ of O_2 saturation on room air in the previous 24 hours). The historic controls were patients who fulfilled the same eligibility criteria and admitted to the hospital during the same period. As standard of care for both groups, some patients received hydroxychloroquine, azithromycin, or parenteral beta-lactam antibiotics. Anakinra was dosed as 100 mg subcutaneous (SQ) twice daily for 72 hours, followed by anakinra 100 mg SQ daily for 7 days. Clinical characteristics were similar between the groups, except that the cases had a lower mean body mass index than the controls ($25.5 \text{ kg}/\text{m}^2$ vs. $29.0 \text{ kg}/\text{m}^2$, respectively), longer duration of symptoms (mean of 8.4 days for cases vs. 6.2 days for controls), and a higher frequency of hydroxychloroquine use (90% for cases vs. 61% for controls) and azithromycin use (49% for cases vs. 34% for controls). The primary outcome of admission to the intensive care unit for mechanical ventilation or death occurred among 13 case patients (25%) and 32 control patients (73%) (hazard ratio 0.22; 95% confidence interval, 0.11 to 0.41). However, within the first 2 days of follow up, in the control group, six patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. C-reactive protein (CRP) levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) who received anakinra and in five control patients (11%). The clinical implications of these findings are uncertain due to limitations in the

study design related to unmeasured confounding combined with the very high early event rate among the retrospective controls.⁴

- A single-center, retrospective cohort study compared outcomes in 29 patients following open-label use of anakinra to outcomes in 16 historical controls enrolled at the same medical center in Italy. All patients had COVID-19 with moderate to severe acute respiratory distress syndrome (ARDS) that required non-invasive ventilation and evidence of hyperinflammation (CRP \geq 100 mg/L and/or ferritin \geq 900 ng/mL). High-dose intravenous anakinra 5 mg/kg twice daily was administered for a median of 9 days, followed by SQ administration of anakinra 100 mg twice daily for 3 days to avoid inflammatory relapses. Patients in both the anakinra and control groups received hydroxychloroquine and lopinavir/ritonavir. In the anakinra group, reductions in CRP levels were noted over several days following anakinra initiation, and the 21-day survival rate was higher than in the control group (90% vs. 56%, respectively; $P = 0.009$). However, the patients in the anakinra group were younger than those in the control group (median age 62 years vs. 70 years, respectively), and fewer patients in the anakinra group had chronic kidney disease. High-dose anakinra was discontinued in seven patients (24%) because of adverse events (four patients developed bacteremia and three patients had elevated liver enzymes); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of seven patients received low-dose SQ anakinra 100 mg twice daily; however, treatment in this group was stopped after 7 days because of lack of clinical or anti-inflammatory effects.⁵
- Other small case series have reported anakinra use for the treatment of COVID-19 and anecdotal evidence of improvement in outcomes.⁶

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) for a list of clinical trials evaluating anakinra for the treatment of COVID-19.

Adverse Effects

Anakinra was not associated with any significant safety concerns when used in clinical trials for the treatment of sepsis.⁷⁻⁹ Increased rates of infection were reported with prolonged anakinra use in combination with tumor necrosis factor-alpha blockade, but not with short-term use.¹⁰

Considerations in Pregnancy

There is limited evidence on which to base a recommendation in pregnancy, but unintentional first trimester exposure is unlikely to be harmful.¹¹

Considerations in Children

Anakinra has been used extensively in the treatment of severely ill children with complications of rheumatologic conditions, including MAS. Pediatric data on the use of anakinra in ARDS/sepsis are limited.

Drug Availability

Procuring anakinra may be a challenge at some hospitals in the United States. Anakinra is FDA-approved only for SQ injection.

References

1. Anakinra (kineret) [package insert]. Food and Drug Administration. 2012. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf. Accessed April 8, 2020.

2. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior Phase III trial. *Crit Care Med*. 2016;44(2):275-281. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26584195>.
3. Monteagudo LA, Boothby A, Gertner E. Continuous intravenous anakinra infusion to calm the cytokine storm in macrophage activation syndrome. *ACR Open Rheumatol*. 2020;2(5):276-282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32267081>.
4. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatology*. 2020;2(7):e393-e400. Available at: [https://www.theLancet.com/pdfs/journals/lanrhe/PIIS2665-9913\(20\)30164-8.pdf](https://www.theLancet.com/pdfs/journals/lanrhe/PIIS2665-9913(20)30164-8.pdf).
5. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatology*. 2020;2(6): e325-e331. Available at: [https://www.theLancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30127-2/fulltext](https://www.theLancet.com/journals/lanrhe/article/PIIS2665-9913(20)30127-2/fulltext).
6. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32376597>.
7. Fisher CJ, Jr., Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA*. 1994;271(23):1836-1843. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8196140>.
8. Fisher CJ, Jr., Slotman GJ, Opal SM, et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med*. 1994;22(1):12-21. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8124953>.
9. Opal SM, Fisher CJ, Jr., Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a Phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med*. 1997;25(7):1115-1124. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9233735>.
10. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbiol Infect*. 2018;24 Suppl 2:S21-S40. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29447987>.
11. Flint J, Panchal S, Hurrell A, et al. BSR and BHRP guideline on prescribing drugs in pregnancy and breastfeeding-Part II: analgesics and other drugs used in rheumatology practice. *Rheumatology (Oxford)*. 2016;55(9):1698-1702. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26750125>.

Interleukin-6 Inhibitors

Last Updated: August 27, 2020

Interleukin (IL)-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the severe acute respiratory syndrome-associated coronavirus (SARS-CoV) induces a dose-dependent production of IL-6 from bronchial epithelial cells.¹ COVID-19-associated systemic inflammation and hypoxic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.²⁻⁴ It is hypothesized that modulating the levels of IL-6 or its effects may alter the course of disease.

There are two classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) and anti-IL-6 monoclonal antibodies (siltuximab). These classes of drugs have been evaluated for the management of patients with COVID-19 who have systemic inflammation. The COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations and clinical data to date are described below.

Recommendation

- The Panel **recommends against** the use of anti-IL-6 receptor monoclonal antibodies (e.g., **sarilumab, tocilizumab**) or anti-IL-6 monoclonal antibody (**siltuximab**) for the treatment of COVID-19, except in a clinical trial (**BI**).

Rationale

Preliminary, unpublished data from randomized, controlled trials failed to demonstrate efficacy of sarilumab or tocilizumab in patients with COVID-19. There are only limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19.¹¹

Anti-Interleukin-6 Receptor Monoclonal Antibodies

Sarilumab

Sarilumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that is approved by the FDA for use in patients with rheumatoid arthritis. It is available as a subcutaneous (SQ) formulation and is not approved for the treatment of cytokine release syndrome (CRS). A placebo-controlled clinical trial is evaluating the use of an intravenous (IV) formulation of sarilumab administered as a single dose for COVID-19.

Clinical Data for COVID-19

Press Release: July 2, 2020: The efficacy and safety of sarilumab 400 mg IV and sarilumab 200 mg IV versus placebo was evaluated in patients hospitalized with COVID-19 in an adaptive Phase 2 and 3, randomized (2:2:1), double-blind, placebo-controlled trial (*ClinicalTrials.gov* Identifier [NCT04315298](https://clinicaltrials.gov/ct2/show/study/NCT04315298)). Randomization was stratified by severity of illness (i.e., severe, critical, multisystem organ dysfunction) and use of systemic corticosteroids for COVID-19. The Phase 2 component of the trial verified that sarilumab (at either dose) reduced CRP levels. The primary outcome for Phase 3 of the trial was change on a seven-point ordinal scale, and this phase was modified to focus on the dose of sarilumab 400 mg among the patients in the critically ill group. During the conduct of the trial, there were numerous amendments that increased the sample size and modified the dosing strategies being studied, and multiple interim analyses were performed. Ultimately, the trial findings to date do not support a clinical benefit of sarilumab for any of the disease severity subgroups or dosing strategies studied. Additional

detail (as would be included in a published manuscript) is required to fully evaluate the implications of these study findings.⁵

Adverse Effects

The primary lab abnormalities that have been reported with sarilumab treatment are transient and/or reversible elevations in liver enzymes that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia. Risk for serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation have been reported only with long-term use of sarilumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Drug Availability

The SQ formulation of sarilumab is not approved for the treatment of CRS. The IV formulation is not approved by the FDA, but it is being studied in a clinical trial of hospitalized patients with COVID-19. A list of current clinical trials is available at [ClinicalTrials.gov](https://clinicaltrials.gov).

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that is approved by the FDA for use in patients with rheumatologic disorders and CRS induced by chimeric antigen receptor T cell (CAR-T) therapy. Tocilizumab can be dosed for IV or SQ injection. For CRS, the IV formulation should be used.⁶

Clinical Data for COVID-19

Press Release: July 29, 2020: In the industry-sponsored Phase 3 COVACTA trial ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier [NCT04320615](https://clinicaltrials.gov/ct2/show/study/NCT04320615)), 450 adults hospitalized with severe COVID-19-related pneumonia were randomized to receive tocilizumab or placebo. The trial failed to meet its primary endpoint or several key secondary endpoints. The primary outcome was improved clinical status, which was measured using a seven-point ordinal scale to assess clinical status based on the need for intensive care and/or ventilator use and the requirement for supplemental oxygen over a 4-week period. Key secondary outcomes included 4-week mortality. Differences in the primary outcome between the tocilizumab and placebo groups were not statistically significant (OR 1.19; 95% CI, 0.81–1.76; $P = 0.36$). At Week 4, mortality rates did not differ between the tocilizumab and placebo groups (19.7% vs. 19.4%; difference of 0.3%; 95% CI, -7.6% to 8.2%; $P = 0.94$). The difference in median number of ventilator-free days between the tocilizumab and placebo groups did not reach statistical significance (22 days for tocilizumab group vs. 16.5 days for placebo group; difference of 5.5 days; 95% CI, -2.8 to 13.0 days; $P = 0.32$). Infection rates at Week 4 were 38.3% in the tocilizumab group and 40.6% in the placebo group; serious infection rates were 21.0% and 25.9% in the tocilizumab and placebo groups, respectively.⁷

Published Study

Sixty-three adult patients hospitalized with COVID-19 were enrolled in a prospective, open-label study of tocilizumab for severe COVID-19. Criteria for inclusion in the study were polymerase chain reaction-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; pulmonary involvement, assessed either by oxygen saturation (SaO_2) <93% on room air or $\text{PaO}_2/\text{FiO}_2$ ratio <300 mm Hg; and at least three of the following:

- CRP >10 times normal values,
- Ferritin >1,000 ng/mL,
- D-dimer >10 times normal values, *or*
- Lactate dehydrogenase >2 times the upper limit of normal.

The patients' mean age was 62.6 years and most of the patients (88%) were male; 39.7% of the patients were febrile, and 95.7% had bilateral pulmonary infiltrates. Five patients were on mechanical ventilation at baseline. All patients received off-label antiretroviral protease inhibitors. Patients received either tocilizumab (8 mg/kg) IV or tocilizumab (324 mg) SQ; within 24 hours after this initial dose of tocilizumab, a second dose was administered to 52 of the 63 patients. Following administration of tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO₂/FiO₂ ratio of the patients increased between admission (152 +/- 53 mm Hg) and Day 7 of hospitalization (284 +/- 116 mm Hg). No moderate or severe adverse events attributable to tocilizumab were reported. The overall mortality rate was 11% (7 of 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association between earlier use of tocilizumab and reduced mortality; however, interpretation of this result is limited because the study results did not describe a comparison group or specify an a priori comparison.⁸

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) for ongoing trials that are evaluating the use of tocilizumab for the treatment of COVID-19.

Adverse Effects

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional adverse effects, such as risk for serious infections (e.g., TB, bacterial or fungal infections) and bowel perforation, have been reported only in the context of continuous dosing of tocilizumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Considerations in Children

In children, tocilizumab is frequently used for CRS following CAR-T therapy⁹ and it is occasionally used for macrophage activation syndrome.¹⁰ Pediatric data for its use in acute respiratory distress syndrome/sepsis are limited.

Drug Availability

Procuring IV tocilizumab may be a challenge at some hospitals in the United States.

Anti-Interleukin-6 Monoclonal Antibody

Siltuximab

Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 and is approved by the FDA for use in patients with Castleman's disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors, inhibiting IL-6 signaling. Siltuximab is dosed as an IV infusion.

Clinical Data in COVID-19

There are limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19.¹¹ There are no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]).

Clinical Trials

See [ClinicalTrials.gov](https://www.clinicaltrials.gov) for a list of current clinical trials for siltuximab and COVID-19.

Adverse Effects

The primary adverse effects reported for siltuximab have been related to rash. Additional adverse effects (e.g., serious bacterial infections) have been reported only with long-term dosing of siltuximab once every 3 weeks.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses in utero in the exposed fetus.

Drug Availability

Procuring siltuximab may be a challenge at some hospitals in the United States.

References

1. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2009;83(7):3039-3048. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19004938>.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32171076>.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31986264>.
4. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32176772>.
5. Sanofi. Sanofi and Regeneron provide update on Kevzara® (sarilumab) Phase 3 U.S. trial in COVID-19 patients. 2020. Available at: <https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00>. Accessed August 10, 2020.
6. Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist*. 2018;23(8):943-947. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29622697>.
7. Roche. Roche provides an update on the Phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. 2020. Available at: <https://www.roche.com/investors/updates/inv-update-2020-07-29.htm>. Accessed August 10, 2020.
8. Sciascia S, Apra F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol*. 2020;38(3):529-532. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32359035>.
9. Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome

without attenuation of antileukemic efficacy. *Blood*. 2019;134(24):2149-2158. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31697826>.

10. Yokota S, Itoh Y, Morio T, Sumitomo N, Daimaru K, Minota S. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis under treatment with tocilizumab. *J Rheumatol*. 2015;42(4):712-722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25684767>.
11. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. *medRxiv*. 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1>.

Kinase Inhibitors: Baricitinib and Other Janus Kinase Inhibitors, and Bruton's Tyrosine Kinase Inhibitors

Last Updated: February 11, 2021

Janus Kinase Inhibitors

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

Immunosuppression induced by this class of drugs 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 entry into and infection of susceptible cells.⁴

Recommendations

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients, when corticosteroids can be used.
- In the rare circumstance when corticosteroids cannot be used, the Panel recommends **baricitinib** in combination with **remdesivir** for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation (**BIIa**).
- The Panel **recommends against** the use of **baricitinib without remdesivir**, except in a clinical trial (**AIII**).
- There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with corticosteroids for the treatment of COVID-19. Because both baricitinib and corticosteroids are potent immunosuppressants, there is potential for an additive risk of infection.
- The Panel **recommends against** the use of **JAK inhibitors other than baricitinib** for the treatment of COVID-19, except in a clinical trial (**AIII**).

Rationale

The Panel's recommendations for the use of baricitinib are based on data from the Adaptive COVID-19 Treatment Trial 2 (ACTT-2), a multinational, randomized, placebo-controlled trial of baricitinib use in hospitalized patients with COVID-19 pneumonia (see below for a full description of the ACTT-2 data for baricitinib). Participants (n = 1,033) were randomized 1:1 to oral baricitinib 4 mg or placebo, for up to 14 days, in combination with intravenous (IV) remdesivir, for up to 10 days. Participants who received baricitinib had a shorter time to clinical recovery than those who received placebo (median recovery time of 7 vs. 8 days, respectively). This treatment effect was most pronounced among those who required high-flow oxygen or non-invasive ventilation but were not on invasive mechanical ventilation. The difference in mortality between the treatment groups was not statistically significant.⁵

Corticosteroids have established efficacy in the treatment of severe and critical COVID-19 pneumonia (see the [Therapeutic Management](#) and [Corticosteroids](#) sections). The Panel's recommendations for the use of baricitinib are based on data for the benefit of corticosteroids and the uncertain clinical impact of

the modest difference in time to recovery between the placebo-treated and baricitinib-treated patients in the ACTT-2 trial. The Panel also considered the infrequent use of corticosteroids in the ACTT-2 trial, given that patients receiving corticosteroids for the treatment of COVID-19 at study entry were excluded.

On November 19, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥ 2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).⁶

The issuance of an EUA does not constitute FDA approval. An EUA indicates that a product may be effective in treating a serious or life-threatening disease or condition. FDA approval occurs when a product has been determined to provide benefits that outweigh its known and potential risks for the intended population.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Most of the data on adverse effects of JAK inhibitors refer to chronic use of the agents. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses. Additional toxicities include myelosuppression and transaminase elevations. In addition, there may be a slightly higher risk of thrombotic events and gastrointestinal perforation in patients who receive JAK inhibitors.

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.

The ACTT-2 study evaluated oral baricitinib 4 mg once daily;⁵ however, the standard dosage of baricitinib for FDA-approved indications is 2 mg once daily. Baricitinib use is not recommended in patients with impaired hepatic or renal function (estimated GFR < 60 mL/min/1.73 m²).⁷ 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.^{7,8}

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.⁹ Decisions about the administration of JAK inhibitors must include shared decision-making with the pregnant individual, 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. When the benefits outweigh the risks, use of JAK inhibitors may be considered.

Considerations in Children

An EUA has been issued for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥ 2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or ECMO. The safety and efficacy of baricitinib or other JAK inhibitors has 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. Thus, there are insufficient data to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children when corticosteroids cannot be used. Use of JAK inhibitors other than baricitinib for the treatment of COVID-19 in pediatric patients is not recommended, except in a clinical trial.

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and FDA approved for the treatment of rheumatoid arthritis.⁷ Baricitinib can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.¹⁰ Baricitinib has postulated antiviral effects by blocking severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from entering and infecting lung cells.¹¹ Baricitinib reduced inflammation and lung pathology in macaques infected with SARS-CoV-2 but an antiviral effect was not confirmed.¹²

Clinical Data for COVID-19

The multicenter, randomized, double-blind ACTT-2 trial compared (1:1 allocation) oral baricitinib 4 mg daily (for up to 14 days or until hospital discharge) versus placebo, both given in combination with IV remdesivir (for 10 days or until hospital discharge). The trial included 1,033 patients hospitalized with moderate to severe COVID-19. The primary endpoint was time to recovery, which was defined as reaching Category 1 (not hospitalized, no limitations), Category 2 (not hospitalized, with limitations), or Category 3 (hospitalized, no active medical problems) on an eight-category ordinal scale within 28 days of treatment initiation. Patients who were using a medication off-label as a specific treatment for COVID-19, including corticosteroids, at study entry were excluded from the trial. In the overall cohort, the median time to recovery was shorter in the baricitinib plus remdesivir arm (7 days) than in the placebo plus remdesivir arm (8 days) (rate ratio for recovery 1.16; 95% CI, 1.01–1.32; $P = 0.03$). In subgroup analyses according to disease severity, the difference in time to recovery was greatest among the participants who required high-flow oxygen or non-invasive ventilation (10 vs. 18 days for the baricitinib and placebo recipients, respectively; rate ratio for recovery 1.51; 95% CI, 1.10–2.08). However, the treatment effect within this subgroup should be interpreted with caution given the relatively small sample size. Within the subgroup of patients on invasive mechanical ventilation or ECMO at study entry, it was not possible to estimate the median time to recovery within the first 28 days following treatment initiation, and there was no evidence of benefit with baricitinib use (rate ratio for recovery 1.08; 95% CI, 0.59–1.97). Improvement across ordinal categories at Day 15 was a key secondary endpoint, and again baricitinib demonstrated a significant benefit only in the subgroup of patients requiring high-flow oxygen or non-invasive ventilation (OR 2.3; 95% CI, 1.4–3.7). Mortality by 28 days was lower in the baricitinib arm than in the placebo arm, but the difference was not statistically significant (OR 0.65; 95% CI, 0.39–1.09). There was no evidence that the risk of serious adverse events or new infections was higher in the baricitinib arm than in the placebo arm (16% vs. 20% for adverse events and 6% vs. 11% for new infections in the baricitinib and placebo arms, respectively).⁵

Even though the use of corticosteroids for the treatment of COVID-19 was prohibited at study entry, the protocol allowed for the adjunctive use of corticosteroids at the discretion of the treating provider for the treatment of standard medical indications (e.g., asthma exacerbation, acute respiratory distress syndrome, chronic obstructive pulmonary disease). During the study, 10.9% of the patients in the baricitinib group and 12.9% in the placebo group were prescribed corticosteroids. Overall, the incidence of serious or non-serious infections was lower in the baricitinib group (30 patients [6%]) than in the placebo group (57 patients [11%]) (RD -5; 95% CI, -9 to -2). There were no statistically significant differences between the baricitinib and placebo arms in the frequency of pulmonary embolism (5 vs. 2 patients, respectively) or deep vein thrombosis (11 vs. 9 patients, respectively).

Preliminary results of this study suggest that baricitinib improves time to recovery in patients who require supplemental oxygen but not invasive mechanical ventilation. However, a key limitation of the study is the inability to evaluate the treatment effect of baricitinib in addition to, or in comparison to, corticosteroids used as standard treatment for severe or critical COVID-19 pneumonia.

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of baricitinib and 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.¹³ Like baricitinib, it can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.¹⁰ Ruxolitinib also has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.¹¹

Clinical Data for COVID-19

A small, single-blind, randomized, controlled Phase 2 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 SOC therapy. The median age of the patients was 63 years. There were no significant demographic differences between the two arms. Treatment with ruxolitinib was associated with a nonsignificant reduction in the median time to clinical improvement (12 days for ruxolitinib vs. 15 days for placebo; $P = 0.15$), defined as a two-point improvement on a seven-category ordinal scale or as hospital discharge. There was no difference between the groups in the median time to discharge (17 days for ruxolitinib vs. 16 days for placebo; $P = 0.94$). More patients in the ruxolitinib group than in the placebo group had radiographic improvement on computed tomography scans of the chest at Day 14 (90% for ruxolitinib vs. 61.9% for placebo; $P = 0.05$) and a shorter time to recovery from initial lymphopenia (5 days for ruxolitinib vs. 8 days for placebo; $P = 0.03$), when it was present. The use of ruxolitinib was not associated with an increased risk of adverse events or mortality (no deaths in the ruxolitinib arm vs. three deaths [14% of patients] in the control arm). Despite the theoretical antiviral properties of JAK inhibitors, there was no significant difference in the time to viral clearance among the patients who had detectable viral loads at the time of randomization to ruxolitinib treatment (n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of ventilated patients at study entry, and the concomitant use of antivirals and steroids by 70% of the patients.¹⁴

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of ruxolitinib and 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 gp 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.¹⁵ Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.¹⁶

Clinical Data for COVID-19

There are no clinical data on the use of tofacitinib to treat COVID-19.

Considerations in Pregnancy

Pregnancy registries provide some outcome data on tofacitinib used 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 pregnant population.¹⁷⁻¹⁹

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of tofacitinib and 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 of less off-target activity for other kinases.²⁰ 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 retrospective case series of 19 patients with severe COVID-19.²¹ 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 check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of acalabrutinib and COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies²² and to prevent chronic graft-versus-host disease in stem cell transplant recipients.²³ 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-19.²⁴

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of six patients with COVID-19 who were receiving the drug for a condition other than COVID-19.²⁴ 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 check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of ibrutinib and COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.²⁵ 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.²⁶ 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 check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information on studies of zanubrutinib and 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.^{22,27} 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

1. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clin Immunol*. 2020;214:108393. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32222466>.
2. Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN. The molecular regulation of Janus kinase (JAK) activation. *Biochem J*. 2014;462(1):1-13. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25057888>.
3. Bousoik E, Montazeri Aliabadi H. “Do we know jack” about JAK? A closer look at JAK/STAT signaling pathway. *Front Oncol*. 2018;8:287. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30109213>.
4. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20(4):400-402. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32113509>.
5. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2020;Published online ahead of print. Available at: <https://pubmed.ncbi.nlm.nih.gov/33306283/>.
6. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of baricitinib. 2020. Available at: <https://www.fda.gov/media/143823/download>. Accessed December 11, 2020.
7. Baricitinib (Olumiant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.
8. Posada MM, Cannady EA, Payne CD, et al. Prediction of transporter-mediated drug-drug interactions for baricitinib. *Clin Transl Sci*. 2017;10(6):509-519. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28749581>.
9. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol*. 2020;72(4):529-556. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32090480>.
10. McInnes IB, Byers NL, Higgs RE, et al. Comparison of baricitinib, upadacitinib, and tofacitinib mediated regulation of cytokine signaling in human leukocyte subpopulations. *Arthritis Res Ther*. 2019;21(1):183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31375130>.

11. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30-e31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32032529>.
12. Hoang TN, Pino M, Boddapati AK, et al. Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. *Cell*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33278358>.
13. Ruxolitinib (JAKAFI) [package insert]. 2020. Available at: <https://www.jakafi.com/pdf/prescribing-information.pdf>. Accessed: May 28, 2020.
14. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32470486>.
15. Migita K, Izumi Y, Jiuchi Y, et al. Effects of Janus kinase inhibitor tofacitinib on circulating serum amyloid A and interleukin-6 during treatment for rheumatoid arthritis. *Clin Exp Immunol*. 2014;175(2):208-214. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24665995>.
16. Tofacitinib (Xeljanz) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s024_208246s010lbl.pdf.
17. Clowse ME, Feldman SR, Isaacs JD, et al. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf*. 2016;39(8):755-762. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27282428>.
18. Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis*. 2018;24(12):2494-2500. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29982686>.
19. Wieringa JW, van der Woude CJ. Effect of biologicals and JAK inhibitors during pregnancy on health-related outcomes in children of women with inflammatory bowel disease. *Best Pract Res Clin Gastroenterol*. 2020;44-45:101665. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32359679>.
20. Owen C, Berinstein NL, Christofides A, Sehn LH. Review of Bruton tyrosine kinase inhibitors for the treatment of relapsed or refractory mantle cell lymphoma. *Curr Oncol*. 2019;26(2):e233-e240. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31043832>.
21. Roschewski M, Lionakis MS, Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol*. 2020;5(48). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32503877>.
22. Ibrutinib (Imbruvica) [package insert]. Food and Drug Administration. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf.
23. 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-gvhd>. Accessed February 1, 2021.
24. Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. *Blood*. 2020;135(21):1912-1915. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32302379>.
25. Zanubrutinib (Brukinsa) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf.
26. Tam C, Grigg AP, Opat S, et al. The BTK inhibitor, Bgb-3111, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: initial report of a Phase 1 first-in-human trial. *Blood*. 2015;126(23):832. Available at: <https://ashpublications.org/blood/article/126/23/832/136525/The-BTK-Inhibitor-Bgb-3111-Is-Safe-Tolerable-and>.
27. Acalabrutinib (Calquence) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf.

Immunoglobulins: Non-SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of non-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific **intravenous immunoglobulin (IVIG)** for the treatment of COVID-19, except in a clinical trial (**AIII**). This recommendation **should not preclude** the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rationale for Recommendation

It is unknown whether products derived from the plasma of donors without confirmed SARS-CoV-2 infection contain high titer of SARS-CoV-2 neutralizing antibodies. Furthermore, although other blood components in IVIG may have general immunomodulatory effects, it is unclear whether these theoretical effects will benefit patients with COVID-19.

Clinical Data for COVID-19

This study has not been peer reviewed.

A retrospective, non-randomized cohort study of IVIG for the treatment of COVID-19 was conducted across eight treatment centers in China between December 2019 and March 2020. The study showed no difference in 28-day or 60-day mortality between 174 patients who received IVIG and 151 patients who did not receive IVIG.¹ More patients in the IVIG group had severe disease at study entry (71 patients [41%] with critical status in the IVIG group vs. 32 patients [21%] in the non-IVIG group). The median hospital stay was longer in the IVIG group (24 days) than in the non-IVIG group (16 days), and the median duration of disease was also longer (31 days in the IVIG group vs. 23 days in the non-IVIG group). A subgroup analysis that was limited to the critically ill patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days.

The results of this study are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive either IVIG or no IVIG, and the patients in the IVIG group were older and more likely to have coronary heart disease than those in the non-IVIG group. In addition, the IVIG group had a higher proportion of patients with severe COVID-19 disease at study entry. Patients in both groups also received many concomitant therapies for COVID-19.

Considerations in Pregnancy

IVIG is commonly used in pregnancy for other indications such as immune thrombocytopenia with an acceptable safety profile.^{2,3}

Considerations in Children

IVIG has been widely used in children for the treatment of a number of conditions, including Kawasaki disease, and is generally safe.⁴ IVIG has been used in pediatric patients with COVID-19 and multiorgan inflammatory syndrome in children (MIS-C), especially those with a Kawasaki disease-like presentation, but the efficacy of IVIG in the management of MIS-C is still under investigation.

References

1. Shao Z, Feng Y, Zhong L, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: A multicenter retrospective cohort study. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.11.20061739v2>.
2. Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin No. 207: thrombocytopenia in pregnancy. *Obstet Gynecol*. 2019;133(3):e181-e193. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30801473>.
3. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21325604>.
4. Agarwal S, Agrawal DK. Kawasaki disease: etiopathogenesis and novel treatment strategies. *Expert Rev Clin Immunol*. 2017;13(3):247-258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27590181>.

Table 4b. Characteristics of Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

- The information in this table is derived from data on the use of these drugs for FDA-approved indications or in investigational trials, and it is supplemented with data on their use in patients with COVID-19, when available.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the [FDA Medwatch program](#).

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Corticosteroids					
Dexamethasone	Dose for COVID-19: <ul style="list-style-type: none"> • Dexamethasone 6 mg IV or PO once daily, for up to 10 days or until hospital discharge, whichever comes first¹ 	<ul style="list-style-type: none"> • Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Avascular necrosis • Adrenal insufficiency • Increased blood pressure 	<ul style="list-style-type: none"> • Blood glucose • Blood pressure • Signs and symptoms of new infection • When initiating dexamethasone, consider appropriate screening and treatment to reduce the risk of <i>Strongyloides</i> hyperinfection in patients at high-risk of strongyloidiasis 	<ul style="list-style-type: none"> • Moderate CYP3A4 inducer • CYP3A4 substrate • Although coadministration of RDV and dexamethasone has not been formally studied, a clinically significant PK interaction is not predicted (Gilead, written communication, August 2020). 	<p>For the Panel's recommendations on the use of corticosteroids, please see Therapeutic Management of Patients With COVID-19.</p> <ul style="list-style-type: none"> • If dexamethasone is not available, an alternative corticosteroid such as prednisone, methylprednisolone, or hydrocortisone can be used. • The approximate total daily dose equivalencies for these glucocorticoids to

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Corticosteroids , continued					
Dexamethasone, continued		<ul style="list-style-type: none"> Peripheral edema Myopathy (particularly if used with neuromuscular blocking agents) When used during outbreaks of other novel coronavirus infections (i.e., MERS and SARS), corticosteroid therapy was associated with delayed virus clearance.^{2,3} 	(e.g., patients from tropical, subtropical, or warm temperate regions or who engage in agricultural activities) or fulminant reactivations of HBV. ⁴⁻⁶		<p>dexamethasone 6 mg (PO or IV) are: prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg.</p> <ul style="list-style-type: none"> A list of clinical trials is available: Dexamethasone
Interferons					
Interferon Alfa	<p>PegIFN Alfa-2a Dose for MERS:</p> <ul style="list-style-type: none"> PegIFN alfa-2a 180 mcg SQ once weekly for 2 weeks^{7,8} <p>IFN Alfa-2b Dose for COVID-19 in Clinical Trials:</p> <ul style="list-style-type: none"> Nebulized IFN alfa-2b 5 million international units twice daily (no duration listed in the study methods)⁹ 	<ul style="list-style-type: none"> Flu-like symptoms (e.g., fever, fatigue, myalgia)¹⁰ Injection site reactions Liver function abnormalities Decreased blood counts Worsening depression Insomnia Irritability Nausea Vomiting Hypertension Induction of autoimmunity 	<ul style="list-style-type: none"> CBC with differential Liver enzymes; avoid if Child-Pugh Score >6 Depression, psychiatric symptoms Reduce dose in patients with CrCl <30 mL/min. 	<ul style="list-style-type: none"> Low potential for drug interactions Inhibition of CYP1A2 	<ul style="list-style-type: none"> The Panel recommends against the use of IFNs for the treatment of patients with severe and critical COVID-19, except in a clinical trial (AIII). For COVID-19, IFN alfa has primarily been used as nebulization and usually as part of a combination regimen. Neither nebulized IFN alfa-2b nor IFN alfa-1b are FDA-approved for use in the United States. Use with caution with other hepatotoxic agents.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons , continued					
Interferon Alfa , continued					<ul style="list-style-type: none"> • Reduce dose if ALT >5 times ULN; discontin-ue if bilirubin level also increases. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon
Interferon Beta	<p>IFN Beta-1a Dose for MERS:</p> <ul style="list-style-type: none"> • IFN beta-1a 44 mcg SQ 3 times weekly⁸ <p>Dose for COVID-19:</p> <ul style="list-style-type: none"> • Dose and duration unknown <p>IFN Beta-1b Dose for COVID-19:</p> <ul style="list-style-type: none"> • IFN beta-1b 8 million international units SQ every other day, up to 7 days total¹¹ 	<ul style="list-style-type: none"> • Flu-like symptoms (e.g., fever, fatigue, myalgia)¹² • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity 	<ul style="list-style-type: none"> • Liver enzymes • CBC with differential • Worsening CHF • Depression, suicidal ideation 	<ul style="list-style-type: none"> • Low potential for drug interactions 	<ul style="list-style-type: none"> • The Panel recommends against the use of IFNs for the treatment of patients with severe or critical COVID-19, except in a clinical trial (AllI). • There are insufficient data to recommend either for or against the use of IFN beta for the treatment of early (i.e., <7 days from symptom onset) mild to moderate COVID-19. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • A list of clinical trials is available: Interferon <p>Availability:</p> <ul style="list-style-type: none"> • Several products are available in the United States; product doses differ.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons, continued					
Interferon Beta, continued					<i>IFN Beta-1a Products:</i> <ul style="list-style-type: none"> • Avonex, Rebif <i>IFN Beta-1b Products:</i> <ul style="list-style-type: none"> • Betaseron, Extavia
Interleukin-1 Inhibitor					
Anakinra	Dose for Rheumatoid Arthritis: <ul style="list-style-type: none"> • Anakinra 100 mg SQ once daily Dose for COVID-19: <ul style="list-style-type: none"> • Dose and duration vary by study • Has also been used as IV infusion 	<ul style="list-style-type: none"> • Neutropenia (particularly with concomitant use of other agents that can cause neutropenia) • Anaphylaxis • Headache • Nausea • Diarrhea • Sinusitis • Arthralgia • Flu-like symptoms • Abdominal pain • Injection site reactions • Liver enzyme elevations 	<ul style="list-style-type: none"> • CBC with differential • Renal function (reduce dose in patients with CrCl <30 mL/min) • Liver enzymes 	<ul style="list-style-type: none"> • Use with TNF-blocking agents is not recommended due to increased risk of infection 	<ul style="list-style-type: none"> • There are insufficient data for the Panel to recommend either for or against the use of IL-1 inhibitors (e.g., anakinra) for the treatment of COVID-19. • A list of clinical trials is available: Anakinra
Interleukin-6 Inhibitors					
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies</i>					
Sarilumab ¹³	Dose for COVID-19 in Clinical Trial (See ClinicalTrials.gov Identifier NCT04315298): <ul style="list-style-type: none"> • Sarilumab 400 mg IV (single dose)¹⁴ 	<ul style="list-style-type: none"> • Neutropenia, thrombocytopenia • Gastrointestinal perforation • HSR 	<ul style="list-style-type: none"> • Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets 	<ul style="list-style-type: none"> • Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are 	<ul style="list-style-type: none"> • For patients who are within 24 hours of admission to the ICU and who require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO₂/30 L/min of oxygen

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors , continued					
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies</i> , continued					
Sarilumab ¹³	<ul style="list-style-type: none"> • REMAP-CAP evaluated sarilumab for IV administration, which is not the approved formulation in the United States. 	<ul style="list-style-type: none"> • Increased liver enzymes • HBV reactivation • Infusion reaction possible 	<ul style="list-style-type: none"> • Liver enzymes 	CYP450 substrates. <ul style="list-style-type: none"> • Effects on CYP450 may persist for weeks after therapy. 	flow), there are insufficient data to recommend either for or against the use of sarilumab for the treatment of COVID-19. <ul style="list-style-type: none"> • For patients who do not require ICU-level care or who are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of sarilumab for the treatment of COVID-19, except in a clinical trial (BIIa). • Treatment with sarilumab may mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). • A list of clinical trials is available: Sarilumab
Tocilizumab ¹⁵	Dose for COVID-19 in Clinical Trial: <ul style="list-style-type: none"> • Tocilizumab 8 mg/kg IV once • Dose should not exceed tocilizumab 800 mg. • If tocilizumab is used, administer with a course of dexamethasone therapy. 	<ul style="list-style-type: none"> • Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and liver enzymes 	<ul style="list-style-type: none"> • Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets • Liver enzymes 	<ul style="list-style-type: none"> • Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> • For patients who are within 24 hours of admission to the ICU and who require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO₂/30 L/min of oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab for the treatment of COVID-19.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors , continued					
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies</i> , continued					
Tocilizumab ¹⁵ , continued		<ul style="list-style-type: none"> • HBV reactivation 			<ul style="list-style-type: none"> • Some Panel members would administer a single dose of tocilizumab (8 mg/kg actual body weight up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure. • For patients who do not require ICU-level care or who are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of tocilizumab for the treatment of COVID-19, except in a clinical trial (BIIa). • May mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). • The SQ formulation of tocilizumab is not intended for IV administration. • A list of clinical trials is available: Tocilizumab

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors , continued					
<i>Anti-Interleukin-6 Monoclonal Antibody</i>					
Siltuximab	<p>Dose for Multicentric Castleman Disease:</p> <ul style="list-style-type: none"> Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks¹⁶ <p>Dose for COVID-19:</p> <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Infusion-related reaction HSR Gastrointestinal perforation Neutropenia Hypertension Dizziness Rash Pruritus Hyperuricemia 	<ul style="list-style-type: none"> Monitor for HSR Monitor for infusion reactions Neutrophils 	<ul style="list-style-type: none"> Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP450 substrates. Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> The Panel recommends against the use of siltuximab for the treatment of COVID-19, except in a clinical trial (Alla). May mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). A list of clinical trials is available: Siltuximab
Kinase Inhibitors					
<i>Bruton's Tyrosine Kinase Inhibitors</i>					
Acalabrutinib	<p>Dose for FDA-Approved Indications:</p> <ul style="list-style-type: none"> Acalabrutinib 100 mg PO every 12 hours <p>Dose for COVID-19:</p> <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Hemorrhage Cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia) Atrial fibrillation and flutter Infection Headache Diarrhea Fatigue Myalgia 	<ul style="list-style-type: none"> CBC with differential Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) Monitor for cardiac arrhythmias Monitor for new infections 	<ul style="list-style-type: none"> Avoid concomitant use with strong CYP3A inhibitors or inducers. Dose reduction may be necessary with moderate CYP3A4 inhibitors. Avoid concomitant PPI use. H2-receptor antagonist should be administered 2 hours after acalabrutinib. 	<ul style="list-style-type: none"> The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (Alli). Avoid use in patients with severe hepatic impairment. Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to atrial fibrillation. A list of clinical trials is available: Acalabrutinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors , continued					
<i>Bruton's Tyrosine Kinase Inhibitors</i> , continued					
Ibrutinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> Ibrutinib 420 mg or 560 mg PO once daily Dose for COVID-19: <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Hemorrhage Cardiac arrhythmias Serious infections Cytopenias (thrombocytopenia, neutropenia, anemia) Hypertension Diarrhea Musculoskeletal pain Rash 	<ul style="list-style-type: none"> CBC with differential Blood pressure Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) Monitor for cardiac arrhythmias Monitor for new infections 	<ul style="list-style-type: none"> Avoid concomitant use with strong CYP3A inhibitors or inducers. Dose reduction may be necessary with moderate CYP3A4 inhibitors. 	<ul style="list-style-type: none"> The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). Avoid use in patients with severe baseline hepatic impairment. Dose modifications required in patients with mild or moderate hepatic impairment. Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to cardiac arrhythmias. A list of clinical trials is available: Ibrutinib
Zanubrutinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily Dose for COVID-19: <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Hemorrhage Cytopenias (neutropenia, thrombocytopenia, anemia, leukopenia) Atrial fibrillation and flutter Infection Rash Bruising Diarrhea Cough Musculoskeletal pain 	<ul style="list-style-type: none"> CBC with differential Signs and symptoms of bleeding Monitor for cardiac arrhythmias Monitor for new infections 	<ul style="list-style-type: none"> Avoid concomitant use with moderate or strong CYP3A inducers. Dose reduction required with moderate and strong CYP3A4 inhibitors. 	<ul style="list-style-type: none"> The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). Dose reduction required in patients with severe hepatic impairment. A list of clinical trials is available: Zanubrutinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors , continued					
<i>Janus Kinase Inhibitors</i>					
Baricitinib ¹⁷	Dose for Rheumatoid Arthritis: <ul style="list-style-type: none"> • <i>Adults:</i> Baricitinib 2 mg PO once daily Dose for COVID-19: ¹⁸ <ul style="list-style-type: none"> • <i>Adults:</i> Baricitinib 4 mg PO once daily for 14 days or until hospital discharge • <i>Children:</i> Limited data are available. Dose per the FDA EUA: <ul style="list-style-type: none"> • Aged ≥9 years: Baricitinib 4 mg PO once daily for 14 days or until hospital discharge • Aged ≥2 years to <9 years: Baricitinib 2 mg PO once daily for 14 days or until hospital discharge • See full prescribing information for dosage recommendations in patients with renal impairment or hepatic impairment.¹⁷ 	<ul style="list-style-type: none"> • Lymphoma and other malignancies • Thrombosis • Gastrointestinal perforation • Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes • HSV • Herpes zoster 	<ul style="list-style-type: none"> • CBC with differential • Renal function • Liver enzymes • Monitor for new infections 	<ul style="list-style-type: none"> • Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor. • Avoid administration of live vaccines. 	<ul style="list-style-type: none"> • There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with RDV for the treatment of COVID-19 in hospitalized patients, when corticosteroids can be used. • In the rare circumstance when corticosteroids cannot be used, the Panel recommends baricitinib in combination with RDV for the treatment of COVID-19 in hospitalized nonintubated patients who require oxygen supplementation (BIIa). • The Panel recommends against the use of baricitinib without RDV, except in a clinical trial (AIII). • There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with corticosteroids for the treatment of COVID-19. Because both agents are potent immunosuppressants, there is a potential for an additive risk of infection. • Baricitinib is not recommended for patients with severe hepatic or renal impairment.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors , continued					
<i>Janus Kinase Inhibitors</i> , continued					
Baricitinib ¹⁷ , continued					<ul style="list-style-type: none"> • Baricitinib is available through the FDA EUA for the treatment of COVID-19 in combination with RDV for hospitalized adults and pediatric patients aged ≥ 2 years who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.¹⁸ • A list of clinical trials is available: Baricitinib
Ruxolitinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> • Ruxolitinib 5 mg– 20 mg PO twice daily Dose for COVID-19 in Clinical Trials: <ul style="list-style-type: none"> • Ruxolitinib 5 mg– 20 mg PO twice daily, for 14 days 	<ul style="list-style-type: none"> • Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster 	<ul style="list-style-type: none"> • CBC with differential • Liver enzymes • Monitor for new infections 	<ul style="list-style-type: none"> • Dose modifications required when administered with strong CYP3A4 inhibitors. • Avoid use with doses of fluconazole >200 mg. 	<ul style="list-style-type: none"> • The Panel recommends against the use of JAK inhibitors (other than baricitinib) for the treatment of COVID-19, except in a clinical trial (AIII). • Dose modification may be required in patients with moderate or severe renal impairment, hepatic impairment, or thrombocytopenia. • A list of clinical trials is available: Ruxolitinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors , continued					
<i>Janus Kinase Inhibitors</i> , continued					
Tofacitinib	<p>Dose for FDA-Approved Indications:</p> <ul style="list-style-type: none"> Tofacitinib 5 mg PO twice daily for rheumatoid and psoriatic arthritis Tofacitinib 10 mg PO twice daily for ulcerative colitis <p>Dose for COVID-19:</p> <ul style="list-style-type: none"> Dose and duration unknown; a planned COVID-19 clinical trial will evaluate tofacitinib 10 mg twice daily for 14 days. 	<ul style="list-style-type: none"> Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) Anemia Risk of infection Gastrointestinal perforation Diarrhea Headache Herpes zoster Lipid elevations Liver enzyme elevations Lymphoma and other malignancies 	<ul style="list-style-type: none"> CBC with differential Liver enzymes Monitor for new infections 	<ul style="list-style-type: none"> Dose modifications required when administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor coadministered with a strong CYP2C19 inhibitor. Avoid administration of live vaccines. 	<ul style="list-style-type: none"> The Panel recommends against the use of JAK inhibitors (other than baricitinib) for the treatment of COVID-19, except in a clinical trial (AIII). Avoid use in patients with ALC <500 cells/mm³, ANC <1,000 cells/mm³, or Hgb <9 grams/dL. Dose modification may be required in patients with moderate or severe renal impairment or moderate hepatic impairment. A list of clinical trials is available: Tofacitinib
Non-SARS-CoV-2 Specific Immunoglobulin					
Non-SARS-CoV-2 Specific Immunoglobulin	<ul style="list-style-type: none"> Dose varies based on indication and formulation. 	<ul style="list-style-type: none"> Allergic reactions including anaphylaxis Renal failure Thrombotic events Aseptic meningitis syndrome Hemolysis TRALI Transmission of infectious pathogens 	<ul style="list-style-type: none"> Monitor for transfusion-related reactions Monitor vital signs at baseline and during and after infusion Discontinue if renal function deteriorates during treatment. 	<ul style="list-style-type: none"> IVIG may interfere with immune response to certain vaccines. 	<ul style="list-style-type: none"> The Panel recommends against the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in a clinical trial (AIII). This recommendation should not preclude the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19. A list of clinical trials is available: Intravenous Immunoglobulin

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Non-SARS-CoV-2 Specific Immunoglobulin , continued					
Non-SARS-CoV-2 Specific Immunoglobulin , continued		<ul style="list-style-type: none"> • AEs may vary by formulation. • AEs may be increased with high-dose, rapid infusion, or in patients with underlying conditions. 			

Key: AE = adverse effect or adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BTK = Bruton's tyrosine kinase; CBC = complete blood count; CHF = congestive heart failure; CrCl = creatinine clearance; CPK = creatine phosphokinase; CRP = C-reactive protein; CYP = cytochrome P; DVT = deep vein thrombosis; EIND = Emergency Investigational New Drug; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; FiO₂ = fraction of inspired oxygen; HBV = hepatitis B; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; IFN = interferon; IL-1 = interleukin-1; IL-6 = interleukin-6; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; PEG-IFN = pegylated interferon; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; REMAP-CAP = A Randomised, Embedded, Multi-Factorial, Adaptive Platform Trial for Community-Acquired Pneumonia; RDV = remdesivir; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous; TACO = transfusion-associated circulatory overload; TB = tuberculosis; the Panel = the COVID-19 Treatment Guidelines Panel; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

References

1. Randomised Evaluation of COVID-19 Therapy (RECOVERY). Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. 2020; <https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19>. Accessed February 9, 2021.
2. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29161116>.
3. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16968120>.
4. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761166>.

5. Liu J, Wang T, Cai Q, et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic hepatitis B virus infection. *Hepatol Res*. 2020;50(11):1211-1221. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761993>.
6. Centers for Disease Control and Prevention. Parasites—strongyloides: resources for health professionals. 2020; https://www.cdc.gov/parasites/strongyloides/health_professionals/index.html. Accessed February 9, 2021.
7. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090-1095. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25278221>.
8. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alpha2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129-2132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25900158>.
9. Zhou Q, Chen V, Shannon CP, et al. Interferon-alpha2b treatment for COVID-19. *Front Immunol*. 2020;11:1061. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32574262>.
10. Peginterferon alpha-2a (Pegasys) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103964s5270lbl.pdf.
11. Hung IFN, Lung KC, Tso EYK, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, Phase 2 trial. *Lancet*. 2020;395(10238):1695-1704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32401715>.
12. Interferon beta-1a (Rebif) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103780s5204lbl.pdf.
13. Sarilumab (Kevzara) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf.
14. Regeneron and Sanofi provide update on U.S. Phase 2/3 adaptive-designed trial of KEVZARA® (sarilumab) in hospitalized COVID-19 patients [press release]. 2020.
15. Tocilizumab (Actemra) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125276s127,125472s040lbl.pdf.
16. Siltuximab (Sylvant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125496s018lbl.pdf.
17. Baricitinib (Olumiant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.
18. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization (EUA) of baricitinib. 2020; <https://www.fda.gov/media/143823/download>. Accessed February 9, 2021.