Immunomodulators Under Evaluation for the Treatment of COVID-19

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Summary Recommendations

See Therapeutic Management of Adults with COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations on the use of the following:
• Baricitinib in combination with remdesivir when corticosteroids cannot be used,
• Dexamethasone (or other corticosteroids) with or without remdesivir, *and*
• Tocilizumab with dexamethasone (with or without remdesivir).
See additional recommendations on the use of baricitinib and tocilizumab below.
Other Immunomodulators
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:
• Baricitinib in combination with a corticosteroid; because both agents are potent immunosuppressants, there is a potential additive risk of infection.
• Baricitinib in combination with remdesivir for hospitalized patients with COVID-19 when corticosteroids can be used
• Colchicine for nonhospitalized patients with COVID-19
• Fluvoxamine
• 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
• Sarilumab for patients who are within 24 hours of admission to the intensive care unit (ICU) and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen (>0.4 FiO_2/30 L/min of oxygen flow)
• Tocilizumab for most hospitalized patients with hypoxemia who require conventional oxygen therapy (see Therapeutic Management of Adults With COVID-19 for more detailed information)
The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial:
• **Baricitinib** without **remdesivir (AIII)**
• **Colchicine** for hospitalized patients with COVID-19 **(AIII)**
• **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)**
• Kinase inhibitors:
  • 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 immunoglobulin (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.
• **Sarilumab** for patients who do not require ICU-level care or who are admitted to the ICU for >24 hours but do not require invasive mechanical ventilation, noninvasive ventilation, or supplemental oxygen administered through a high-flow device **(BIIa)**
• The anti-IL-6 monoclonal antibody **siltuximab (AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional **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

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Colchicine

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Colchicine is an anti-inflammatory drug that is used to treat a variety of conditions, including gout, recurrent pericarditis, and familial Mediterranean fever.[1] Recently, the drug has been studied for the prevention of major cardiovascular events in those with coronary artery disease.[2] Colchicine has several potential mechanisms of action, including mechanisms that reduce the chemotaxis of neutrophils, inhibit inflammasome signaling, and decrease the production of cytokines such as interleukin-1 beta.[3] When colchicine is administered early in the course of COVID-19, these mechanisms may potentially mitigate or prevent inflammation-associated manifestations of the disease. These anti-inflammatory properties (as well as the drug's limited immunosuppressive potential, widespread availability, and favorable safety profile) have prompted investigation of colchicine for the treatment of COVID-19.

Recommendations

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of colchicine for the treatment of nonhospitalized patients with COVID-19.
  - A large, randomized trial in outpatients, the Colchicine Coronavirus SARS-CoV-2 Trial (COLCORONA), did not reach its primary efficacy endpoint of reducing hospitalizations and death. However, a slight reduction in hospitalizations was observed in the subset of patients whose diagnosis was confirmed by a positive nasopharyngeal swab on a SARS-CoV-2 polymerase chain reaction (PCR) test.
- The Panel **recommends against** the use of colchicine in hospitalized patients for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Clinical Data for COVID-19

Colchicine in Nonhospitalized Patients With COVID-19: The COLCORONA Trial

COLCORONA was a contactless, double-blind, placebo-controlled randomized trial in outpatients who were diagnosed with COVID-19 within 24 hours of enrollment.[4] Participants had to have at least one risk factor for COVID-19 complications, including age ≥70 years, body mass index ≥30, diabetes mellitus, uncontrolled hypertension, known respiratory disease, heart failure or coronary disease, fever ≥38.4°C within the last 48 hours, dyspnea at presentation, bicytopenia, pancytopenia, or the combination of high neutrophil count and low lymphocyte count. Participants were randomized 1:1 to receive colchicine 0.5 mg twice daily for 3 days and then once daily for 27 days or placebo. The primary endpoint was a composite of death or hospitalization by Day 30; secondary endpoints included components of the primary endpoint, as well as the need for mechanical ventilation by Day 30. Given the contactless design of the study, outcomes were ascertained by patient self-report via telephone at 15 and 30 days after randomization; in some cases, clinical data was confirmed by medical chart review.

Results

- The study enrolled a total of 4,488 participants.
- The primary endpoint was reached in 104 of 2,235 participants (4.7%) in the colchicine arm versus in 131 of 2,253 participants (5.8%) in the placebo arm (OR 0.79; 95% CI, 0.61–1.03; P = 0.08).
- There were no statistically significant differences in the secondary outcomes between the arms.

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- In a prespecified analysis of 4,159 participants who had a SARS-CoV-2 diagnosis confirmed by a nasopharyngeal PCR test (93% of those enrolled), those in the colchicine arm were significantly less likely to reach the primary endpoint (96 of 2,075 participants [4.6%]) than those in the placebo arm (126 of 2,084 participants [6.0%]; OR 0.75; 95% CI, 0.57–0.99; *P* = 0.04). In this subgroup of patients who were SARS-CoV-2 positive, there were fewer hospitalizations (a secondary outcome) in the colchicine arm (4.5% of patients) than in the placebo arm (5.9% of patients; OR 0.75; 95% CI, 0.57–0.99).
- More gastrointestinal adverse events occurred in the colchicine arm, including diarrhea (occurred in 13.7% of patients vs. in 7.3% of patients in the placebo arm; *P* <0.001). Unexpectedly, more pulmonary emboli were reported among patients in the colchicine arm (11 events [0.5% of patients] vs. 2 [0.1% of patients] in the placebo arm; *P* = 0.01).

Limitations

- Due to logistical difficulties with staffing, the trial was stopped at approximately 75% of the target enrollment, which may have limited the study's power to detect differences for the primary outcome.
- There was uncertainty as to the accuracy of COVID-19 diagnoses in presumptive cases.
- Patient-reported clinical outcomes were potentially misclassified.

Colchicine in Hospitalized Patients With COVID-19: The RECOVERY Trial

This study has not been published.

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial randomized hospitalized patients with COVID-19 to receive colchicine (1 mg loading dose, followed by 0.5 mg 12 hours later, and then 0.5 mg twice daily for 9 days or until discharge) or usual care.[5]

Results

- In a preliminary, unpublished report of results for 11,162 patients randomized to colchicine or usual care, there was no significant difference in the primary endpoint of 28-day mortality between the arms.
- Of the 2,178 patients who died, 20% were in the colchicine arm versus 19% in the usual care arm (risk ratio 1.02; 95% CI, 0.94–1.11; *P* = 0.63).
- Among the patients who died, 94% had received concomitant corticosteroids.

Study of the Effects of Colchicine in Hospitalized Patients With COVID-19: The GRECCO-19 Trial

The GReek Study in the Effects of Colchicine in Covid-19 cOmplications Prevention (GRECCO-19) was a small, prospective, open-label randomized clinical trial in 105 patients hospitalized with COVID-19 across 16 hospitals in Greece. Patients were assigned 1:1 to receive standard of care with colchicine (1.5 mg loading dose, followed by 0.5 mg after 60 minutes and then 0.5 mg twice daily until hospital discharge or up to 3 weeks) or standard of care alone.[6]

Results

- Fewer patients in the colchicine arm (1 of 55 patients) than in the standard of care arm (7 of 50 patients) reached the primary clinical endpoint of deterioration in clinical status from baseline by two points on a seven-point clinical status scale (OR 0.11; 95% CI, 0.01–0.96).
- Participants in the colchicine group were significantly more likely to experience diarrhea

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(occurred in 45.5% vs. 18.0% of participants in the colchicine and standard of care arms, respectively; $P = 0.003$).

Limitations

- The number of clinical events reported for the trial was small.
- The study design was open-label treatment assignment.

The results of several small randomized trials and retrospective cohort studies that have evaluated various doses and durations of colchicine in hospitalized patients with COVID-19 have been published in peer-reviewed journals or made available as preliminary, non-peer-reviewed reports.[7-10] Some have shown benefits of colchicine use, including less need for supplemental oxygen, improvements in clinical status on an ordinal clinical scale, and reductions in certain inflammatory markers. In addition, some studies have reported higher discharge rates or fewer deaths among patients who received colchicine than among those who received comparator drugs or placebo. However, these studies also had significant design or methodological limitations, including small sample sizes, open-label designs, and differences between the treatment arms in participants' clinical and demographic characteristics and the permitted use of various cotreatments (e.g., remdesivir, corticosteroids), that limit interpretability of the studies.

Adverse Effects, Monitoring, and Drug-Drug Interactions

Common side effects of colchicine include diarrhea, nausea, vomiting, cramping, abdominal pain, bloating, and loss of appetite. In rare cases, colchicine is associated with serious adverse events, such as neuromyotoxicity and blood dyscrasias. Use of colchicine should be avoided in patients with severe renal insufficiency, and patients with moderate renal insufficiency who receive the drug should be monitored for adverse effects. Caution should be used when colchicine is coadministered with drugs that inhibit cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp) because such use may increase the risk of colchicine-induced adverse effects due to significant increases in colchicine plasma levels. The risk of myopathy may be increased with the concomitant use of certain HMG-CoA reductase inhibitors, such as atorvastatin, lovastatin, and simvastatin, due to potential competitive interactions mediated by CYP3A4 and P-gp pathways.[11,12] Fatal colchicine toxicity has been reported in individuals with renal or hepatic impairment who received colchicine in conjunction with P-gp inhibitors or strong CYP3A4 inhibitors.

Considerations in Pregnancy

There are limited data on the use of colchicine in pregnancy. Fetal risk cannot be ruled out based on data from animal studies and the drug's mechanism of action. Colchicine crosses the placenta and has antimitotic properties, which raises a theoretical concern for teratogenicity. However, a recent systematic review of the literature did not find higher rates of miscarriage or major fetal malformations in pregnant women who were exposed to colchicine than in pregnant women who were not exposed to the drug. There are no data for colchicine use in pregnant women with acute COVID-19. Risks of use should be balanced against potential benefits.[11,13]

Considerations in Children

Colchicine use in children is limited to the treatment of periodic fever syndromes, primarily familial Mediterranean fever. There are no data on the use of colchicine to treat pediatric acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C).

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Corticosteroids

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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.

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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 HBV[25] 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

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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* for the latest information.

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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]			

Multi-center, randomized open-label adaptive trial in hospitalized patients with suspected or confirmed COVID-19 (n = 6,425)
 	
Country: United Kingdom
	Key Inclusion Criteria:
	• Hospitalization with clinically suspected or laboratory-confirmed SARS-CoV-2 infection
	
	Key Exclusion Criteria:
	• Physician determination that risks of participation too great based on patient's medical history or an indication for corticosteroid therapy outside of the study
	
	Interventions:
	• Patients randomized 2:1 to receive:
	  • Dexamethasone 6 mg PO or IV once daily plus SOC for up to 10 days or until hospital discharge, whichever came first, *or*
	  • SOC alone
	
	Primary Endpoint:
	• All-cause mortality at 28 days after randomization
		Number of Participants:
		• Dexamethasone plus SOC (n = 4,321) and SOC (n = 2,104)
		
		Participant Characteristics:
		• 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.
		
		Outcomes:
		• 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; $P < 0.001$).
			Limitations:
			• 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.

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Study Design	Methods	Results	Limitations and Interpretation
Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report (RECOVERY Trial)[1], continued			
		• 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).	• 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. **Interpretation:** • 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]			

Meta-analysis of 7 RCTs of corticosteroids in critically ill patients with COVID-19 (n = 1,703)
Countries: Multinational
	Key Inclusion Criteria:
	• 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)
		Number of Participants:
		• Corticosteroids (n = 678) and usual care or placebo (n = 1,025)
		Participant Characteristics:
		• Median age was 60 years.
		• 29% of patients were women.
		• 1,559 patients (91.5%) were on mechanical ventilation.
			Limitations:
			• The design of the trials included in the meta-analysis differed in several ways, including the following:
			  • Definition of critical illness
			  • Specific corticosteroid used
			  • Dose of corticosteroid
			  • Duration of corticosteroid treatment

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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			

	Interventions:
	• Corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone)
	• Usual care or placebo
	Primary Endpoint:
	• All-cause mortality up to 30 days after randomization
		• 47% of patients were on vasoactive agents at randomization across the 6 trials that reported this information.
		Outcomes:
		• 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:
		  • 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.
			• 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).
			Interpretation:
			• 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.

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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 Trial[3]			
Randomized, double-blind, placebo-controlled, single-center study of short-course methylprednisolone in hospitalized patients with confirmed or suspected COVID-19 pneumonia (n = 416) Country: Brazil	**Key Inclusion Criteria:** • Aged ≥18 years • Suspected or confirmed COVID-19 • SpO_2 ≤94% on room air *or* while using supplementary oxygen *or* under invasive mechanical ventilation **Key Exclusion Criteria:** • Hypersensitivity to methylprednisolone • Chronic use of corticosteroids or immunosuppressive agents • HIV, decompensated cirrhosis, chronic renal failure **Interventions:** • Methylprednisolone IV 0.5 mg/kg twice daily for 5 days • Placebo (saline) IV **Primary Endpoint:** • Mortality by Day 28 **Secondary Endpoints:** • 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	**Number of Participants:** • mITT analysis (n = 393): Methylprednisolone (n = 194) and placebo (n = 199) **Participant Characteristics:** • 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. **Primary Outcomes:** • 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; $P = 0.63$). **Secondary Outcomes:** • 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 ($P = 0.65$)	**Limitations:** • 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. **Interpretation:** • 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.

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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 Trial[3], continued			
		• 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 Trial[4]			

Multicenter, randomized, clinical trial in patients with COVID-19 and moderate to severe ARDS (n = 299)
Country: Brazil
	Key Inclusion Criteria:
	• Aged ≥18 years
	• Confirmed or suspected COVID-19
	• On mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with PaO_2/FiO_2 ≤200 mm Hg
	Key Exclusion Criteria:
	• Recent corticosteroid use
	• Use of immunosuppressive drugs in the past 21 days
	• Expected death in next 24 hours
	Interventions:
	• Dexamethasone 20 mg IV daily for 5 days, then 10 mg IV daily for 5 days or until ICU discharge plus SOC
	• SOC alone
		Number of Participants:
		• ITT analysis (n = 299): Dexamethasone plus SOC (n = 151) and SOC alone (n = 148)
		Participant Characteristics:
		• 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:
		  • Mean age was 60 vs. 63 years; vasopressor use by 66% vs. 68% of patients; mean PaO_2/FiO_2 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).
			Limitations:
			• 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.
			Interpretation:
			• Compared with SOC alone, dexamethasone at a higher dose than used in the RECOVERY trial plus SOC

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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 Trial[4], continued			
	Primary Endpoint: • Mean number of days alive and free from mechanical ventilation by Day 28 **Secondary Endpoints:** • 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	• 35% of patients in SOC alone group also received corticosteroids. **Primary Outcomes:** • 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; *P* = 0.04). **Secondary Outcomes:** • There were no differences between the dexamethasone and SOC groups for the following outcomes: • All-cause mortality at Day 28 (56.3% vs. 61.5%: HR 0.97; 95% CI, 0.72–1.31; *P* = 0.85) • ICU-free days by Day 28 (mean of 2.1 vs. 2.0 days; *P* = 0.50) • Duration of mechanical ventilation by Day 28 (mean of 12.5 vs.13.9 days; *P* = 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; *P* = 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; *P* = 0.01).	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. • 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.

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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 Trial[5]			

Multicenter, randomized, double-blind, sequential trial in patients with confirmed or suspected COVID-19 and acute respiratory failure (n = 149)
 	
Country: France
	Key Inclusion Criteria:
	• Aged ≥18 years
	• Confirmed SARS-CoV-2 infection or radiographically suspected COVID-19, with at least 1 of 4 severity criteria:
	  • Need for mechanical ventilation with PEEP ≥5 cm H_2O
	  • High-flow oxygen with PaO_2/FiO_2 <300 mm Hg and FiO_2 ≥50%
	  • Reservoir mask oxygen with PaO_2/FiO_2 <300 mm Hg (estimated)
	  • Pneumonia severity index >130 (scoring table)
	
	Key Exclusion Criteria:
	• Septic shock
	• Do-not-intubate orders
	
	Interventions:
	• 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.
		Number of Participants:
		• ITT analysis (n = 149 participants): Hydrocortisone (n = 76) and placebo (n = 73)
		
		Participant Characteristics:
		• 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).
		
		Primary Outcome:
		• 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).
		
		Secondary Outcomes:
		• There was no difference between the groups in the need for intubation, rescue strategies, or oxygenation (i.e., change in PaO_2/FiO_2).
		  • Among the patients who did not require mechanical ventilation at baseline, 8 of 16 patients (50%) in hydrocortisone group required subsequent
			Limitations:
			• 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.
			
			Interpretation:
			• 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.

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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 Trial[5], continued			
	Primary Endpoint: • Treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen) by Day 21 **Secondary Endpoints:** • Need for intubation, rescue strategies, or oxygenation (i.e., change in PaO_2/FiO_2) • Nosocomial infections on Day 28 • Clinical status on Day 21	intubation vs. 12 of 16 (75%) in placebo group. • 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; *P* = 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]			
Randomized, embedded, multifactorial, adaptive platform trial of patients with severe COVID-19 (n = 403) Countries: Multinational	**Key Inclusion Criteria:** • Aged ≥18 years • Presumed or confirmed SARS-CoV-2 infection • ICU admission for respiratory or cardiovascular organ support **Key Exclusion Criteria:** • Presumed imminent death • Systemic corticosteroid use • >36 hours since ICU admission	**Number of Participants:** • mITT analysis (n = 384): Fixed-dose hydrocortisone (n=137), shock-based hydrocortisone (n = 146), and no hydrocortisone (n = 101) **Participant Characteristics:** • 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.	**Limitations:** • Early termination following release of RECOVERY study results • Randomized study, but open label **Interpretation:** • 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.

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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			

	Interventions:
	• 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
	Primary Endpoint:
	• Days free of respiratory and cardiovascular organ support up to Day 21. (For this ordinal outcome, patients who died were assigned -1 day.)
	Secondary Endpoints:
	• In-hospital mortality
	• SAEs
		Primary Outcome:
		• 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:
		  • 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
		Secondary Outcomes:
		• 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 Study[7]			
Retrospective cohort study in patients with nonsevere COVID-19 pneumonia and propensity score-matched controls (n = 55 matched case-control pairs) Country: China	**Key Inclusion Criteria:** • Confirmed COVID-19 • Pneumonia on chest CT scan • Aged ≥16 years **Key Exclusion Criteria:** • Severe pneumonia defined as having any of the following: respiratory distress, respiratory rates >30 breaths/min, SpO_2 <93%, oxygenation index <300 mm Hg, mechanical ventilation, or shock	**Number of Participants:** • 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) **Participant Characteristics:** • 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.	**Limitations:** • 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.

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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 Study[7], continued			

	• Immediate ICU admission upon hospitalization
	• Use of corticosteroids after progression to severe disease
	Interventions:
	• Early, low-dose corticosteroids:
	  • IV methylprednisolone 20 mg/day or 40 mg/day for 3–5 days
	  • PO prednisone 20 mg/day for 3 days
	• No corticosteroids
	Primary Endpoint:
	• Rates of severe disease and death
	Secondary Endpoints:
	• Duration of fever
	• Virus clearance time
	• Length of hospital stay
	• Use of antibiotics
		Primary Outcomes:
		• 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.
		Secondary Outcomes:
		• 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%).
			• 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.
			Interpretation:
			• 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; PaO_2/FiO_2 = 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; SpO_2 = saturation of oxygen; WHO = World Health Organization

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Fluvoxamine

Last Updated: April 23, 2021

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is approved by the Food and Drug Administration (FDA) for the treatment of obsessive-compulsive disorder and is used for other conditions, including depression. Fluvoxamine is not FDA-approved for the treatment of any infection.

Anti-Inflammatory Effect of Fluvoxamine and Rationale for Use in COVID-19

In a murine sepsis model, fluvoxamine was found to bind to the sigma-1 receptor in immune cells, resulting in reduced production of inflammatory cytokines.[1] In an in vitro study of human endothelial cells and macrophages, fluvoxamine reduced the expression of inflammatory genes.[2] Further studies are needed to establish whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans beings and are clinically relevant in the setting of COVID-19.

Recommendation

There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of fluvoxamine for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19.

Clinical Trial Data

Placebo-Controlled Randomized Trial in Nonhospitalized Adults With Mild COVID-19

In this contactless, double-blind, placebo-controlled randomized trial, nonhospitalized adults with mild COVID-19 confirmed by SARS-CoV-2 polymerase chain reaction (PCR) assay within 7 days of symptom onset were randomized to receive fluvoxamine up to 100 mg three times daily or matching placebo for 15 days. The primary endpoint was clinical deterioration (defined as having dyspnea or hospitalization for dyspnea or pneumonia and oxygen saturation [SpO_2] <92% on room air or requiring supplemental oxygen to attain SpO_2 ≥92%) within 15 days of randomization. Participants self-assessed their blood pressure, temperature, oxygen saturation, and COVID-19 symptoms and reported the information by email twice daily.[3]

Participant Characteristics

- A total of 152 participants were randomized to receive fluvoxamine (n = 80) or placebo (n = 72).
- The mean age of the participants was 46 years; 72% were women, 25% were Black, and 56% had obesity.

Results

- None of 80 participants (0%) who received fluvoxamine and six of 72 participants (8.3%) who received placebo reached the primary endpoint (absolute difference 8.7%; 95% CI, 1.8% to 16.5%; $P = 0.009$).
- Five participants in the placebo arm and one in the fluvoxamine arm required hospitalization.
- Only 76% of the participants completed the study, and 20% of the participants stopped responding to the electronic survey during the study period but were included in the final analysis.

Limitations

- The study had a small sample size.

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- A limited number of events occurred.
- Ascertaining clinical deterioration was challenging because all assessments were done remotely.

Interpretation

In this small placebo-controlled trial, none of the participants who received fluvoxamine and six (8.3%) of those who received placebo reached the primary endpoint. However, due to the study's reliance on participant self-reports and missing data, it is difficult to draw definitive conclusions about the efficacy of fluvoxamine for the treatment of COVID-19.[3]

Prospective Observational Study During an Outbreak of SARS-CoV-2 Infections

A prospective, nonrandomized observational cohort study evaluated fluvoxamine for the treatment of COVID-19 in 113 outpatients who tested positive for SARS-CoV-2 antigen with the result confirmed by a PCR test. The trial was conducted in an occupational setting during an outbreak of COVID-19. Patients were offered the option of receiving fluvoxamine 50 mg twice daily for 14 days or no therapy.[4]

Patient Characteristics

- Of the 113 participants with positive SARS-CoV-2 antigen, 65 opted to take fluvoxamine and 48 did not.
- More of the patients who did not take fluvoxamine had hypertension. In addition, more of those who were Latinx and more of those who were initially symptomatic opted to take fluvoxamine.

Results

- At Day 14, none of the patients who received fluvoxamine versus 60% of those who did not had persistent symptoms (e.g., anxiety, difficulty concentrating, fatigue) ($P < 0.001$).
- By Day 14, none of the fluvoxamine-treated patients were hospitalized; six patients who did not receive fluvoxamine were hospitalized, including two patients who required care in the intensive care unit.
- No serious adverse events were reported following receipt of fluvoxamine.

Limitations

- The study was a nonrandomized trial.
- The study had a small sample size.
- Limited data were collected during the study.

Limitations (e.g., small sample size) and differences in study populations and fluvoxamine doses make it difficult to interpret and generalize the findings of these trials.

Additional studies, including a Phase 3 randomized controlled trial (*ClinicalTrials.gov* Identifier: NCT04668950), are ongoing to provide more specific evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19.

Adverse Effects, Monitoring, and Drug-Drug Interactions

When fluvoxamine is used to treat psychiatric conditions, the most common adverse effect is nausea, but adverse effects can include other gastrointestinal effects (e.g., diarrhea, indigestion), neurologic effects (e.g., asthenia, insomnia, somnolence), dermatologic reactions (sweating), and rarely suicidal ideation.

Fluvoxamine is a cytochrome P450 (CYP) D6 substrate and a potent inhibitor of CYP1A2 and 2C19 and a moderate inhibitor of CYP2C9, 2D6, and 3A4.[5] Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants. In addition, it can enhance the serotonergic effects of other SSRIs

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or monoamine oxidase inhibitors (MAOIs) resulting in serotonin syndrome. Fluvoxamine should not be used within 2 weeks of receipt of other SSRIs or MAOIs and should be used with caution with other QT-interval prolonging medications.

Considerations in Pregnancy

Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnancy are limited.[6,7] A small, increased risk of primary persistent pulmonary hypertension in the newborn associated with SSRI use in the late third trimester has not been excluded, although the absolute risk is likely low.[8] The risk of fluvoxamine use in pregnancy for the treatment of COVID-19 should be balanced with the potential benefit.

Considerations in Children

Fluvoxamine is approved by the FDA for the treatment of obsessive compulsive disorder in children aged ≥8 years.[9] Adverse effects due to SSRI use seen in children are similar to those seen in adults, although children and adolescents appear to have higher rates of behavioral activation and vomiting than adults.[10] There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in children.

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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-IVG 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.

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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,

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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 MERS[6] 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 syndrome[10] 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* 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

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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.

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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 (SpO_2 ≤93% with ≥6L/min O_2) or worsening hypoxia (SpO_2 ≤93% with >3L/min O_2 and a loss of ≥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 kg/m^2 vs. 29.0 kg/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

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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 ≥100 mg/L and/or ferritin ≥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* 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.

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Interleukin-6 Inhibitors

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Interleukin (IL)-6 is a pleiotropic, proinflammatory 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 reduce the duration and/or severity of COVID-19 illness.

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 (i.e., siltuximab). These 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 on the use IL-6 inhibitors in patients with COVID-19 and related clinical data to date are described below.

Recommendations

- The Panel recommends using **tocilizumab** (single intravenous [IV] dose of tocilizumab 8 mg/kg actual body weight up to 800 mg) **in combination with dexamethasone** (6 mg daily for up to 10 days) in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. These patients are:
  - Recently hospitalized patients (i.e., within first 3 days of admission) who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow nasal canula (HFNC) oxygen (>0.4 FiO_2/30 L/min of oxygen flow) **(BIIa)**; *or*
  - Recently hospitalized patients (i.e., within first 3 days of admission) not admitted to the ICU who have rapidly increasing oxygen needs and require noninvasive ventilation or HFNC oxygen and who have significantly increased markers of inflammation (CRP ≥75 mg/L) **(BIIa)**.
- For hospitalized patients with hypoxemia who require conventional oxygen therapy, there is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also give tocilizumab to patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥75 mg/L, but who do not yet require noninvasive ventilation or HFNC oxygen as described above.
- There are insufficient data for the Panel to recommend either for or against the use of sarilumab for hospitalized patients with COVID-19 who are within 24 hours of admission to the ICU and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen (>0.4 FiO_2/30 L/min of oxygen flow).
- The Panel **recommends against** the use of anti-IL-6 monoclonal antibody therapy (i.e., **siltuximab**) for the treatment of COVID-19, except in a clinical trial **(BI)**.

Additional Considerations

- Tocilizumab **should be avoided** in patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs, and in patients who have alanine aminotransferase >5 times the upper limit of normal; high risk for gastrointestinal perforation; an uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral

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infection; absolute neutrophil count <500 cells/µL; platelet count <50,000 cells/µL; or known hypersensitivity to tocilizumab.

- Tocilizumab should only be given in combination with a course of dexamethasone (or an alternative corticosteroid at a dose equivalency to dexamethasone 6 mg) therapy.
- Some clinicians may assess the patient's clinical response to dexamethasone before deciding whether tocilizumab is needed.
- Although some patients in the Randomised, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial received a second dose of tocilizumab at the discretion of treating physicians, there are insufficient data to indicate which patients, if any, would benefit from an additional dose of tocilizumab.
- Cases of severe and disseminated strongyloidiasis have been reported with use of tocilizumab and corticosteroids in patients with COVID-19.[5,6] Prophylactic treatment with ivermectin should be considered for patients who are from strongyloidiasis endemic areas.[7]

Rationale

The results of the RECOVERY trial and REMAP-CAP provide consistent evidence that tocilizumab, when administered with corticosteroids, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill, rapidly deteriorating with increasing oxygen needs, and have a significant inflammatory response. However, the Panel found it challenging to define the specific patient population(s) that would benefit from this intervention. See an overview of the clinical trial data on the use of tocilizumab in patients with COVID-19 below.

Sarilumab and tocilizumab have a similar mechanism of action. However, in REMAP-CAP, the number of participants who received sarilumab was relatively small. Moreover, the trial evaluated sarilumab for IV administration, which is not the approved formulation in the United States. The results of randomized controlled trials of sarilumab that are underway will further define the role sarilumab plays in the treatment of COVID-19.

There are only limited data describing the potential for efficacy of siltuximab in patients with COVID-19.[11]

Anti-Interleukin-6 Receptor Monoclonal Antibodies

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 cytokine release syndrome (CRS) induced by chimeric antigen receptor T cell (CAR T-cell) therapy. Tocilizumab can be dosed for IV or subcutaneous (SQ) injection. The IV formulation should be used to treat CRS.[8]

Clinical Data for COVID-19

Clinical data on the use of tocilizumab (and other IL-6 inhibitors) for the treatment of COVID-19, including data from several randomized trials and large observational studies, are summarized in Table 4b.

Initial studies that evaluated the use of tocilizumab for the treatment of COVID-19 produced conflicting results. Many of these trials were limited by low power, heterogenous populations, and/or a low frequency of concomitant use of corticosteroids (now the standard of care for patients with severe COVID-19).[9-11] For example, trials that reported a treatment benefit of tocilizumab enrolled patients who

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were receiving higher levels of oxygen support (e.g., HFNC oxygen, noninvasive ventilation, invasive mechanical ventilation) and/or included more patients who used corticosteroids.[12,13] Subsequently, REMAP-CAP and the RECOVERY trial—the two largest randomized controlled tocilizumab trials—reported a mortality benefit of tocilizumab in certain patients, including patients exhibiting rapid respiratory decompensation associated with an inflammatory response. REMAP-CAP enrolled a narrowly defined population of critically ill patients who were enrolled within 24 hours of starting respiratory support in an ICU and randomized to receive open-label tocilizumab or usual care.[14] The RECOVERY trial enrolled hospitalized patients with COVID-19 into an open label, platform trial of several treatment options;[15] a subset of participants with hypoxemia and CRP ≥75 mg/L were offered enrollment into a second randomization to tocilizumab versus usual care. Additional findings from REMAP-CAP and the RECOVERY trial and the rationale for using tocilizumab in certain hospitalized patients who are exhibiting rapid respiratory decompensations due to COVID-19 can be found in Therapeutic Management of Adults With COVID-19.

The Panel's recommendations for using tocilizumab are based on the collective evidence from clinical trials reported to date (see Table 4b).

Clinical Trials

Ongoing trials are evaluating the use of tocilizumab for the treatment of COVID-19. See *ClinicalTrials.gov* for the latest information.

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., tuberculosis [TB], bacterial or fungal infections) and bowel perforation, have been reported only in the context of tocilizumab use for the treatment of chronic disease.

Considerations in Pregnancy

There are insufficient data to determine whether there is a tocilizumab-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. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy.[16] Decisions about tocilizumab administration during pregnancy must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks.

Considerations in Children

There are no systematic observational or randomized controlled trial data available on the effectiveness of tocilizumab for the treatment of COVID-19 or multisystem inflammatory syndrome in children (MIS-C) in children. Tocilizumab has been used for children with CRS associated with CAR T-cell therapy and systemic and polyarticular juvenile idiopathic arthritis.[17] There are insufficient data for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or MIS-C.

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 an SQ formulation and is not approved for the treatment of CRS.

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Clinical Data for COVID-19

Clinical data for sarilumab (and other IL-6 inhibitors) as treatment for COVID-19, including data from several randomized trials and large observational studies, are summarized in Table 4b.

An adaptive Phase 2 and 3 double-blind, placebo-controlled randomized (2:2:1) trial compared the efficacy and safety of sarilumab 400 mg IV and sarilumab 200 mg IV versus placebo in patients hospitalized with COVID-19 (*ClinicalTrials.gov* Identifier NCT04315298). Results from this trial did not support a clinical benefit of sarilumab in hospitalized patients receiving supplemental oxygen.[18] Preliminary efficacy results from REMAP-CAP for sarilumab were similar to those for tocilizumab. Compared to placebo, sarilumab reduced both mortality and time to ICU discharge, and increased the number of organ support-free days; however, the number of participants who received sarilumab in this trial was relatively small, limiting the conclusions and implications of these findings.[19]

Clinical Trials

Ongoing trials are evaluating the use of sarilumab for the treatment of COVID-19. See *ClinicalTrials.gov* for the latest information.

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., 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 sarilumab-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

There are no data on the use of sarilumab in children other than data from ongoing trials assessing the drug's safety in children with juvenile idiopathic arthritis. There are no systematic observational or randomized controlled trial data available on the efficacy of sarilumab for the treatment of COVID-19 or MIS-C in children.

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.

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 multicentric Castleman 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 for COVID-19

There are limited data describing the efficacy of siltuximab in patients with COVID-19.[20] There are no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections

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(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 siltuximab-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 the exposed fetus.

Considerations in Children

The safety and efficacy of siltuximab have not been established in pediatric patients.

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Table 4b. Interleukin-6 Inhibitors: Selected Clinical Data

Last Updated April 21, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for IL-6 inhibitors. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab in Hospitalized Patients With COVID-19 (RECOVERY Trial)[1]			
Second randomization of the RECOVERY trial, an open-label, randomized controlled-platform trial assessing several treatments in hospitalized patients with COVID-19 in the United Kingdom (n = 4,116; 19% of all RECOVERY trial participants [n = 21,550])	**Key Inclusion Criteria:** • Suspected or laboratory-confirmed COVID-19 • Participant within 21 days of enrollment into the initial randomization of the RECOVERY trial • Hypoxia evidenced by SpO_2 <92% on room air or receipt of supplemental oxygen • CRP ≥75 mg/L **Key Exclusion Criteria:** • Tocilizumab unavailable at participating hospital • Evidence of active non-SARS-CoV-2 infection, including TB or other bacterial, fungal, or viral infection **Interventions** *1: 1 Randomization:* • Single dose of tocilizumab 8 mg/kg, and possible second dose, *or* • Usual care **Primary Endpoint:** • All-cause mortality through 28 days **Secondary Endpoints:** • Time to discharge alive • Among those not on mechanical ventilation at enrollment, receipt of mechanical ventilation or death	**Number of Participants:** • Tocilizumab (n = 2,022) and usual care (n = 2,094) • Recruitment period: April 14, 2020, through January 24, 2021 Participant Characteristics: • Mean age was 63.6 years. • 67% of participants were men. • 68% of participants were white. • 94% of participants had PCR-confirmed SARS-CoV-2 infection. • Median time from hospitalization until enrollment was 2 days (IQR 1–5 days). • Median CRP 143 mg/L (IQR 107–204 mg/L). • At baseline, 45% of participants were on conventional oxygen, 41% on HFNC/noninvasive ventilation, and 14% on mechanical ventilation. • At enrollment, 82% of participants were taking corticosteroids. **Primary Outcomes:** • Mortality by Day 28 was lower in the tocilizumab arm than in the usual care arm (29% vs. 33%; rate ratio 0.86; 95% CI, 0.77–0.96). • Subgroup analysis: Among those who required mechanical ventilation at baseline, mortality by Day 28 was similar in the tocilizumab and usual care arms (47% vs. 48%).	**Limitations:** • Open-label study • Limited collection of AEs • Only a small proportion of the participants were from ethnic or racial minority groups. • Difficult to define exact subset of hospitalized patients in full RECOVERY cohort who were subsequently selected for secondary randomization/ tocilizumab trial. • Arbitrary cut off of CRP ≥75 mg/L **Interpretation:** • Among hospitalized patients with severe or critical COVID-19 with hypoxia and elevated CRP levels (≥75 mg/L), tocilizumab was associated with reduced all-cause mortality and shorter time to discharge.

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Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab in Hospitalized Patients With COVID-19 (RECOVERY Trial)[1], continued			
		Secondary Outcomes: • The proportion of patients who were discharged alive within 28 days was greater in tocilizumab arm than usual care arm (54% vs. 47%; rate ratio 1.22; 95% CI, 1.12–1.34). • Among those not on mechanical ventilation at baseline, the percentage of participants who met the secondary outcome of mechanical ventilation or death was lower in the tocilizumab arm than in the usual care arm (33% vs. 38%; risk ratio 0.85; 95% CI, 0.78–0.93).	
Interleukin-6 Receptor Antagonists in Critically Ill Patients With COVID-19–Preliminary Report (REMAP-CAP)[2]			
Multinational RCT in critically ill, hospitalized patients with COVID-19 (n = 865)	**Key Inclusion Criteria:** • Suspected or laboratory-confirmed COVID-19 • Admitted to ICU and receiving respiratory or cardiovascular organ support **Key Exclusion Criteria:** • >24 hours since admission to ICU • Presumption of imminent death with lack of commitment to full support • Immunosuppression • ALT >5 times ULN **Interventions** *1:1 Randomization:* • Single dose of tocilizumab 8 mg/kg, and possible second dose, plus SOC, *or* • SOC	**Number of Participants:** • Tocilizumab plus SOC (n = 353), sarilumab plus SOC (n = 48), and SOC (n = 402) • Recruitment period: April 19 through October 28, 2020 **Participant Characteristics:** • Mean age was 61.4 years. • 73% of participants were men. • 72% of participants were White. • 84.4% of participants had a positive SARS-CoV-2 PCR test. • Median time from hospitalization until enrollment: 1.2 days (IQR 0.8–2.8 days). • Median time from ICU admission until enrollment: 13.6 hours (IQR 6.6–19.4 hours). • Baseline level of oxygen support: 28.8% of participants on HFNC, 41.5% on noninvasive ventilation, 29.4% on mechanical ventilation. • In mITT analysis, majority of patients (719 of 792 [90%]) received corticosteroids.	**Limitations:** • Open-label study • Very few patients randomized to receive sarilumab. • Limited collection of AEs • Low proportion of participants from ethnic/racial minority populations **Interpretation:** • Among the patients with severe/critical COVID-19 who were on high-flow oxygen or noninvasive ventilation or who were mechanically ventilated and within 24 hours of ICU admission, the tocilizumab arm had lower mortality and shorter duration of organ support. This benefit of tocilizumab may be in conjunction with concomitant corticosteroids given the high rate of corticosteroid use among trial participants.

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Study Design	Methods	Results	Limitations and Interpretation
Interleukin-6 Receptor Antagonists in Critically Ill Patients With Covid-19–Preliminary Report (REMAP-CAP)[2], continued			
	Alternative 1:1:1 Randomization: • Single dose of tocilizumab 8 mg/kg, and possible second dose, plus SOC, *or* • Single dose of sarilumab 400 mg IV plus SOC, *or* • SOC **Primary Endpoint:** • Composite endpoint measured on an ordinal scale combining in-hospital mortality (assigned value: -1) and days free of respiratory or cardiovascular organ support up to Day 21	**Primary Outcomes:** • Median number of organ support-free days was 10 (IQR -1 to 16 days), 11 (IQR 0–16 days), and 0 (IQR -1 to 15 days) for the tocilizumab, sarilumab, and SOC arms, respectively. • Adjusted OR 1.64 (95% CrI, 1.25–2.14) for tocilizumab arm vs. SOC arm • In-hospital mortality: 28.0% for patients receiving tocilizumab and 35.8% for patients receiving SOC (aOR 1.64; 95% CrI, 1.14–2.35). • Percentage of patients who were not mechanically ventilated who progressed to intubation or death: 41.3% in tocilizumab arm vs. 52.7% in SOC arm.	• REMAP-CAP enrolled patients within 24 hours of ICU level care who were undergoing rapid progression of respiratory dysfunction, a key difference to other tocilizumab trials.
Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia (COVACTA)[3]			
Multinational, double-blind, placebo-controlled randomized trial in hospitalized patients with COVID-19 (n = 452)	**Key Inclusion Criteria:** • COVID-19 confirmed by positive PCR test • Severe COVID-19 pneumonia evidenced by hypoxemia and bilateral chest infiltrates **Key Exclusion Criteria:** • Death imminent within 24 hours • Active TB or bacterial, fungal, or viral infection (other than SARS-CoV-2) **Interventions** *2:1 Randomization:* • Single dose of tocilizumab 8 mg/kg, and possible second dose, plus SOC • Placebo plus SOC	**Number of Participants:** • mITT analysis: tocilizumab (n = 294) and placebo (n = 144) **Participant Characteristics:** • Mean age was 61 years. • 70% of participants were men. • 58% of participants were White. • Median time from symptom onset to randomization: 11 days • Clinical status at baseline by ordinal scale category: 28% of participants on supplemental oxygen (category 3); 30% on HFNC/noninvasive ventilation (category 4); 14% on mechanical ventilation (category 5); and 25% with multiorgan failure (category 6). • Percentage of participants who received corticosteroids at entry or during follow-up: 36% in tocilizumab arm vs. 55% in placebo arm.	**Limitations:** • Modest power to detect differences in clinical status on Day 28 (the primary outcome) between the study arms • Corticosteroids only used by a subset of patients, which included more patients from the placebo arm; RDV use was rare. • Results mostly generalizable to the sickest patients with COVID-19. **Interpretation:** • There was no difference between tocilizumab and placebo for clinical status (including death) at Day 28 (the primary outcome), but tocilizumab did demonstrate a shorter time to recovery and shorter length of ICU stay (secondary outcomes).

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Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia (COVACTA)[3], continued			
	Primary Endpoint: • Clinical status at Day 28 (as measured on a 7-category ordinal scale) **Secondary Endpoints:** • Time to discharge • Length of ICU stay • Mortality at Day 28 **Ordinal Scale Categories:** 1. Discharged or ready for discharge 2. Hospitalized on medical ward, not on supplemental oxygen 3. Hospitalized on medical ward, on supplemental oxygen 4. On oxygen by HFNC or noninvasive ventilation 5. On mechanical ventilation 6. Multiorgan failure (with ECMO or mechanical ventilation plus other support) 7. Death	**Primary Outcome:** • There was no significant difference in clinical status on 7-category ordinal scale on Day 28 between the arms: median of category 1 for the tocilizumab arm vs. category 2 for the placebo arm (difference -1.0; 95% CI, -2.5 to 0.0; $P = 0.31$). **Secondary Outcomes:** • The time to discharge was shorter in the tocilizumab arm than in the placebo arm (median of 20 days vs. 28 days; HR 1.35; 95% CI, 1.02–1.79). • ICU stays were shorter in the tocilizumab arm than in the placebo arm (median of 9.8 days vs. 15.5 days; difference of 5.8 days; 95% CI, -15.0 to -2.9). • There was no difference in mortality by Day 28 between the arms (19.7% in tocilizumab arm vs. 19.4% in placebo arm; 95% CI, -7.6 to 8.2; $P = 0.94$). • SAEs occurred in 34.9% of patients in the tocilizumab arm vs. 38.5% in the placebo arm.	
Effect of Tocilizumab on Clinical Outcomes at 15 Days in Patients With Severe or Critical COVID-2019 (TOCIBRAS)[4]			
RCT in severe or critically ill hospitalized patients with COVID-19 in Brazil (n = 129)	**Key Inclusion Criteria:** • COVID-19 confirmed by PCR test and radiographic imaging • Receiving oxygen to maintain SpO_2 >93% or mechanical ventilation for <24 hours **Key Exclusion Criteria:** • Active, uncontrolled infection • Elevated AST or ALT >5 times ULN • Reduced renal function with eGFR <30 mL/min/1.72 m^2	**Number of Participants:** • Tocilizumab (n = 65) and SOC (n = 64) **Participant Characteristics:** • Mean age was 57 years. • 68% of participants were men. • Mean time from symptom onset to randomization: 10 days • Baseline level of oxygen support: 52% of participants on conventional oxygen, 32% on HFNC or noninvasive ventilation, and 16% on mechanical ventilation.	**Limitations:** • Open-label study • Relatively small sample size • Study was stopped early during the first interim review because of increased risk of death at Day 15. **Interpretation:** • In this study population, tocilizumab demonstrated no benefit with respect to mechanical ventilation or death at Day 15 or key secondary outcomes.

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Study Design	Methods	Results	Limitations and Interpretation
Effect of Tocilizumab on Clinical Outcomes at 15 Days in Patients With Severe or Critical COVID-2019 (TOCIBRAS)[4], continued			
	Interventions: • Single dose of tocilizumab 8 mg/kg plus SOC • SOC **Primary Endpoints:** • Clinical status at 15 days by ordinal scale category. • Following the statistical analysis plan, the primary outcome for the final analysis was changed to mechanical ventilation or death at Day 15 (categories 6 and 7), because the assumption of proportional odds was not met for the original 7-category ordinal outcome. **Key Secondary Endpoint:** • All-cause mortality to Day 28 **Ordinal Scale:** 1. Not hospitalized, no limitation in activities 2. Not hospitalized, limitation in activities 3. Hospitalized, not receiving supplemental oxygen 4. Hospitalized, receiving supplemental oxygen 5. Hospitalized, receiving NIPPV or high-flow oxygen through a nasal cannula 6. Hospitalized, receiving mechanical ventilation 7. Death	• 86% of participants received corticosteroids. • No patient received RDV, which was unavailable in Brazil during the study period. **Primary Outcomes:** • There was no evidence for a treatment difference in the primary outcome: 28% of participants in the tocilizumab arm vs. 20% in the SOC arm had died or received mechanical ventilation at Day 15 (OR 1.54; 95% CI, 0.66–3.66; $P = 0.32$). • The study was stopped early by recommendation of the Data Monitoring Committee because of increased risk of death in the tocilizumab group: by Day 15, 16.9% of participants in the tocilizumab arm vs. 3.1% in SOC arm had died (OR 6.42; 95% CI, 1.59–43.2). **Key Secondary Outcomes:** • Tocilizumab was associated with a trend towards increased mortality at Day 28 (21% in tocilizumab arm vs. 9% in SOC arm; OR 2.70; 95% CI, 0.97–8.35). • AEs were reported in 43% of patients in the tocilizumab arm and 34% in the SOC arm.	• There were more deaths at Day 15 in the tocilizumab arm than in the SOC arm.

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Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab in Nonventilated Patients Hospitalized With COVID-19 Pneumonia (EMPACTA)[5]			

Multinational, double-blind, placebo-controlled, Phase 3 randomized trial in hospitalized patients with COVID-19 (n = 389)	**Key Inclusion Criteria:**
	• COVID-19 confirmed by PCR test and radiographic imaging
	• Severe COVID-19 pneumonia
	Key Exclusion Criteria:
	• Receipt of noninvasive ventilation or mechanical ventilation
	Interventions
	2:1 Randomization:
	• Single dose of tocilizumab 8 mg/kg plus SOC, possible second dose if not improving, *or*
	• Placebo plus SOC
	Primary Endpoint:
	• Mechanical ventilation or death by Day 28
	Key Secondary Endpoints:
	• Time to hospital discharge or readiness for discharge
	• All-cause mortality by Day 28
		Number of Participants:
		• mITT analysis: Tocilizumab (n = 249) and placebo (n = 128)
		Participant Characteristics:
		• Mean age was 55.9 years.
		• 59.2% of participants were men.
		• 56.0% of participants were Hispanic/Latinx, 14.9% were Black/African American, and 12.7% were American Indian/ Alaska Native.
		• 81% of participants were enrolled at sites in the United States.
		• Median time from symptom onset to randomization was 8 days.
		• Percentage of participants who received concomitant medications:
		  • Tocilizumab arm: 80.3% received corticosteroids (55.4% received dexamethasone) and 52.6% received RDV
		  • Placebo arm: 87.5% received corticosteroids (67.2% received dexamethasone) and 58.6% received RDV
		Primary Outcome:
		• By mITT analysis, the cumulative proportion of patients who required mechanical ventilation or who had died by Day 28 was 12.0% in the tocilizumab arm and 19.3% in the placebo arm (HR 0.56; 95% CI, 0.33–0.97; *P* = 0.04)
		Key Secondary Outcomes:
		• The median time to hospital discharge or readiness for discharge was 6.0 days in the tocilizumab arm and 7.5 days in placebo arm (HR 1.16; 95% CI, 0.91–1.48).
		• All-cause mortality by Day 28 was 10.4% (95% CI, 7.2% to 14.9%) in the tocilizumab arm and 8.6% (95% CI, 4.9% to 14.7%) in the placebo arm.
		• SAEs were reported in 15.2% of patients in the tocilizumab arm and 19.7% in the placebo arm.
			Limitation:
			• Interaction with steroids not explored
			Interpretation:
			• Among patients with severe COVID-19, tocilizumab lowered rates of mechanical ventilation or death by Day 28 but provided no benefit in 28-day mortality.

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Study Design	Methods	Results	Limitations and Interpretation
Efficacy of Tocilizumab in Patients Hospitalized With COVID-19 (BACC Bay Tocilizumab Trial)[6]			

Double-blind, placebo-controlled randomized trial in hospitalized patients with COVID-19 in the United States (n = 243)	**Key Inclusion Criteria:**
	• Hospitalized with COVID-19 confirmed by a positive PCR or serum IgM test
	• Moderate and severe COVID-19 with >2 of the following symptoms: fever >38°C, pulmonary infiltrates, need for oxygen to maintain saturation >92% *and* also 1 of the following: CRP ≥50 mg/L, D-dimer >1,000 ng/mL, LDH ≥250 U/L, ferritin >500 ng/mL
	Interventions
	2:1 Randomization:
	• Tocilizumab 8 mg/kg once plus usual care; or
	• Placebo plus usual care
	Primary Endpoint:
	• Time to intubation or death (if the patient died without intubation)
	Key Secondary Endpoints:
	• Clinical worsening
	• Discontinuation of supplemental oxygen among patients receiving it at baseline
		Number of Participants:
		• mITT analysis: Tocilizumab (n = 161) and placebo (n = 81)
		Participant Characteristics:
		• Median age was 59.8 years (range 21.7–85.4 years).
		• 58% of participants were men.
		• 45% of participants were Hispanic or Latinx.
		• 50% of participants had BMI ≥30; 49% had HTN, and 31% had diabetes.
		• 80% of participants were hospitalized in non-ICU wards and receiving supplemental oxygen ≤6 L/min; 4% received high-flow oxygen; 16% required no supplemental oxygen.
		• Median time from symptom onset to randomization was 9 days.
		• Percentage of participants receiving concomitant medications:
		  • Glucocorticoids: 11% in tocilizumab arm vs. 6% in placebo arm
		  • RDV: 33% in tocilizumab arm vs. 29% in placebo arm.
		Primary Outcomes:
		• There was no evidence of a treatment difference (i.e., time to intubation or death) between tocilizumab and placebo (HR 0.83; 95% CI, 0.38–1.81; $P = 0.64$).
		• By Day 28, 11% of the patients in the tocilizumab arm vs. 13% in the placebo arm had been intubated or had died.
		Key Secondary Outcomes:
		• By Day 28, 19% of patients in the tocilizumab arm vs. 17% in the placebo arm had experienced worsening of disease (HR 1.11; 95% CI, 0.59–2.10).
		• The median time to discontinuation of oxygen was 5.0 days in the tocilizumab arm vs. 4.9 days in placebo arm ($P = 0.69$).
		• Fewer serious infections occurred among participants in the tocilizumab arm than in the placebo arm (8.1% vs. 17.3%; $P = 0.03$).
			Limitations:
			• The relatively small sample size and low event rates resulted in wide confidence intervals for primary and secondary outcomes.
			• Some patients received RDV, and a few patients received steroids.
			Interpretation:
			• In this study population, tocilizumab provided no benefit in preventing intubation or death (the primary outcome) or reducing the risk of clinical worsening or time to discontinuation of supplemental oxygen (secondary outcomes).

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Study Design	Methods	Results	Limitations and Interpretation
Effect of Tocilizumab Versus Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia (CORIMUNO-TOCI-1)[7]			
Open-label, randomized clinical trial in hospitalized patients with COVID-19 in France (n = 131)	**Key Inclusion Criteria:** • COVID-19 confirmed by positive PCR test and/or findings/ abnormalities typical of COVID-19 on chest CT • Severe disease/pneumonia, requiring ≥3 L oxygen **Key Exclusion Criteria:** • Receipt of high-flow oxygen or mechanical ventilation **Interventions** *1:1 Randomization:* • Single dose of tocilizumab 8 mg/ kg on Day 1, possible second, fixed dose of tocilizumab 400 mg on Day 3 per provider if oxygen requirement not decreased by >50%, plus usual care, *or* • Usual care **Primary Endpoint:** • Scores >5 on the 10-point WHO Clinical Progression Scale on Day 4 • Survival without need of ventilation (including noninvasive ventilation) at Day 14 **Key Secondary Endpoint:** • Overall survival by Day 28	**Number of Participants:** • ITT analysis (n = 130): Tocilizumab (n = 63) and placebo (n = 67) **Participant Characteristics:** • Median age was 64 years. • 68% of the participants were men. • Diagnosis of COVID-19 was confirmed by PCR test in 90% of participants. • Median time from symptom onset to randomization: 10 days • Baseline corticosteroids use was balanced (received by approximately 17% of participants in each arm) at randomization, but post randomization, more participants received corticosteroids in the control group (55%) than in the tocilizumab group (30%). **Primary Outcome:** • In the Bayesian analyses, evidence for the superiority of tocilizumab vs. usual care did not reach the prespecified threshold for the proportion of patients who died or needed high-flow oxygen, noninvasive ventilation, or IMV by Day 4 (19% of patients in tocilizumab arm vs. 28% in usual care arm), but did reach the threshold by Day 14 (24% of patients in tocilizumab arm vs. 36% in usual care arm (HR 0.58; 90% CrI, 0.33–1.00). **Secondary Outcomes:** • There was no difference in overall survival by Day 28 between tocilizumab arm and usual care arm (89% vs. 88%; adjusted HR 0.92; 95% CI, 0.33–2.53). • SAEs occurred in 20 patients (32%) in the tocilizumab arm and 29 patients (43%) in the usual care arm (P = 0.21). • There were fewer serious bacterial infections in the tocilizumab arm (2) than in the usual care arm (11).	**Limitations:** • Not blinded • Underpowered • More patients received dexamethasone/corticosteroids in the usual care arm. **Interpretation:** • Among patients with severe COVID-19, tocilizumab led to improved ventilator-free survival at Day 14 suggesting possible benefit, but the clinical implications are unclear as there was no difference in survival for tocilizumab vs. usual care through Day 28.

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Study Design	Methods	Results	Limitations and Interpretation
Effect of Tocilizumab Versus Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia (RCT-TCZ-C19)[8]			

Open-label RCT in hospitalized patients with COVID-19 in Italy (n = 126)	**Key Inclusion Criteria:**
	• COVID-19 pneumonia confirmed by positive PCR test
	• Acute respiratory failure (i.e., PaO_2/FiO_2 200–300 mm Hg), fever, *and/or* a CRP ≥10 mg/dL *and/or* CRP level increased to at least twice admission value
	Key Exclusion Criteria:
	• Advanced age, multiple comorbidities, or any other condition precluding ICU-level care
	Interventions
	1:1 Randomization:
	• 2 doses of tocilizumab 8 mg/kg (maximum of 800 mg, second dose after 12 hours), *or*
	• Usual care
	Primary Endpoint:
	• Composite outcome defined as entry into ICU with IMV, death from all-causes, or clinical aggravation (PaO_2/FiO_2 <150 mm Hg) within 14 days
	Key Secondary Endpoint:
	• Mortality at 30 days
		Number of Participants:
		• ITT analysis (n = 123): Tocilizumab (n = 60) and usual care (n = 63)
		Participant Characteristics:
		• Median age was 60 years.
		• 61% of participants were men.
		• Participants in usual care arm had lower CRP, IL-6, ferritin, and D-dimer levels and received more antivirals than participants in tocilizumab arm.
		Primary Outcome:
		• No difference in the composite primary outcome of entry into ICU with mechanical ventilation, all-cause death, or clinical deterioration (PaO_2/FiO_2 <150 mm Hg) within 14 days: Met by 17 participants (28.3%) in tocilizumab arm vs. 17 (27.0%) in usual care arm (rate ratio 1.05; 95% CI, 0.59–1.86; P = 0.87)
		  • ICU admissions: 10.0% of participants in tocilizumab arm vs. 7.9% in usual care arm (rate ratio 1.26; 95% CI, 0.41–3.91)
		  • Mortality at 14 days: 1.7% in tocilizumab arm vs. 1.6% in usual care arm (rate ratio 1.05; 95% CI, 0.07–16.4)
		Key Secondary Outcomes:
		• There was no difference in mortality at 30 days between tocilizumab arm (3.3%) and usual care arm (1.6%; rate ratio 2.10; 95% CI, 0.20–22.6).
		• There were more AEs among the participants in tocilizumab arm (23.3%) than among those in usual care arm (11.1%). The reported AEs were mostly elevated ALT levels and reduced neutrophil counts.
			Limitations:
			• Not blinded
			• Small sample size
			• Mortality rate in the study population was significantly lower (2.4%) than in the general population in Italy (13.2%).[9]
			• Because 14 patients in the control group (22%) received tocilizumab after they reached the primary endpoint, mortality outcomes are difficult to interpret.
			• There were some differences between the arms in baseline participant characteristics, including higher inflammatory markers in the tocilizumab arm.
			Interpretation:
			• This study demonstrated no evidence for a benefit of tocilizumab in patients hospitalized with COVID-19 pneumonia.

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Study Design	Methods	Results	Limitations and Interpretation
Sarilumab in Hospitalized Patients With Severe or Critical COVID-19[10]			
Multinational, double-blind, placebo-controlled, Phase 3 randomized trial in patients hospitalized with COVID-19 (n = 420)	**Key Inclusion Criteria:** • Aged ≥18 years • Laboratory-confirmed COVID-19 and clinical or radiographic evidence of pneumonia • Severe or critical disease (i.e., receiving supplemental oxygen, including delivery by nasal cannula or high-flow device, noninvasive ventilation or invasive ventilation, or treatment in ICU) **Key Exclusion Criteria:** • Low probability of surviving or remaining at investigational site beyond 48 hours • Dysfunction of ≥2 organ systems, or need for ECMO or renal replacement therapy at screening **Interventions** *2:2:1 Randomization:* • Sarilumab IV 400 mg, *or* • Sarilumab IV 200 mg, *or* • Placebo **Primary Endpoint:** • Time from baseline to ≥2-point improvement in clinical status on a 7-point ordinal scale **Key Secondary Endpoint:** • Proportion of patients alive at Day 29	**Number of Participants:** • mITT analysis (n = 416): Sarilumab 400 mg (n = 173), sarilumab 200 mg (n = 159), and placebo (n = 84) **Participant Characteristics:** • Median age was 59 years. • 63% of participants were men. • 77% of participants were White and 36% were Hispanic or Latino. • 42% of participants had BMI ≥30. • 43% of participants had HTN and 26% had type 2 diabetes. • 61% of participants had severe disease and 39% had critical disease. • 20% of participants received systemic corticosteroids before receiving their assigned intervention. **Primary Outcome:** • There was no difference in the median time to ≥2-point improvement in clinical status from baseline on the 7-point ordinal scale for either dose of sarilumab compared to placebo: • 12 days for placebo vs. 10 days for sarilumab 200 mg (HR 1.03; 95% CI, 0.75–1.40) and 10 days for sarilumab 400 mg (HR 1.14; 95% CI, 0.84–1.54). **Key Secondary Outcome:** • There was no difference among the arms in proportion of patients who were alive at Day 29 (92% in placebo arm, 90% in sarilumab 200 mg arm, 92% in sarilumab 400 mg arm).	**Limitations:** • Low rate of baseline corticosteroid use and varying rate of overall corticosteroid use during the study • Moderate sample size with few participants in placebo arm **Interpretation:** • In hospitalized adults with severe or critical COVID-19, there was no benefit of sarilumab with respect to time to clinical improvement or mortality.

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Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab Plus Standard Care Versus Standard Care in Patients With Moderate to Severe COVID-19-Associated Cytokine Release Syndrome (COVINTOC)[11]			
Open-label, Phase 3 RCT in patients hospitalized with moderate to severe COVID-19 cytokine release syndrome in India	**Key Inclusion Criteria:** • Aged ≥18 years • SARS-CoV-2 infection confirmed by PCR test • Moderate disease (defined by respiratory rate 15–30 breaths/min, SpO_2 90% to 94%) to severe disease (defined by respiratory rate ≥30 breaths/min, SpO_2 <90% on ambient air, ARDS, or septic shock) **Key Exclusion Criteria:** • Low probability of surviving beyond 24 hours • Receipt of immunomodulatory drugs within previous 6 months • Serious medical conditions per judgment of investigators **Interventions** *1:1 Randomization:* • Tocilizumab 6 mg/kg (maximum dose 480 mg), second dose allowable if no improvement or worsening of clinical symptoms in next 7 days, *or* • Usual care **Primary Endpoint:** • Proportion of patients with progression from moderate to severe disease or from severe disease to death by Day 14 **Key Secondary Endpoints:** • Incidence of mechanical ventilation • Ventilator-free days	**Number of Participants:** • mITT analysis (n = 179): Tocilizumab (n = 91) and usual care (n = 88) **Participant Characteristics:** • Median age was 55 years. • 85% of participants were men. • The mean BMI was 27. • Approximately 40% of participants had HTN and 41% had type 2 diabetes. • In the tocilizumab arm, 45% of participants had moderate disease and 55% had severe disease. In the usual care arm, 53% of participants had moderate disease and 47% had severe disease. • 91% of participants received systemic corticosteroids during the study. **Primary Outcome:** • Overall, the percentage of patients with disease progression was 12.1% in tocilizumab arm and 18.2% in usual care arm. **Key Secondary Outcomes:** • There was no observed difference between the arms in incidence of mechanical ventilation or number of ventilator-free days. • In post hoc analysis, the percentage of patients who had progressed from severe COVID-19 to death was 16% in tocilizumab arm and 34% in usual care arm ($P = 0.04$).	**Limitations:** • Open-label study • Underpowered • Lower dose of tocilizumab than in other trials **Interpretation:** • There was no demonstrated benefit of tocilizumab in hospitalized adults with moderate to severe COVID-19.

Key: AE = adverse event; ALT = alanine transaminase; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; BMI = body mass index; BACC = Boston Area COVID-19 Consortium; CRP = C-reactive protein; CT = computed tomography; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EMPACTA = Evaluating Minority Patients With Actemra; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IgM = immunoglobulin M; IL-6 = interleukin 6; IMV = invasive mechanical ventilation; ITT = intention to treat; IV = intravenous; LDH = lactate dehydrogenase; mITT = modified intention to treat; NIPPV = noninvasive positive-pressure ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; RECOVERY = Randomized Evaluation of COVID-19 Therapy; REMAP-CAP = Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; SAE = serious adverse event; SOC = standard of care; SpO_2 = saturation of oxygen; TB = tuberculosis; ULN = upper limit of normal; WHO = World Health Organization

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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

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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 m^2).[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.

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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.

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Clinical Trials

Please check [ClinicalTrials.gov](https://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://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]

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Clinical Trials

Please check [ClinicalTrials.gov](https://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://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 malignancies[22] 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://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.

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Clinical Trials

Please check [ClinicalTrials.gov](https://www.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.

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

Last Updated: April 21, 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.
- For 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 certain combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *Medwatch* program.
- For the Panel's recommendations for the drugs listed in this table, please refer to the drug-specific sections of the Guidelines and to Therapeutic Management of Adults With COVID-19.

Drug Name	Dosing Regimen *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Colchicine					
Colchicine	**Dose for COVID-19 in Clinical Trial** *COLCORONA:* • Colchicine 0.5 mg twice daily for 3 days then once daily for 27 days	• Diarrhea • Nausea • Vomiting • Cramping • Abdominal pain • Bloating • Loss of appetite • Neuromyotoxicity (rare)[1] • Blood dyscrasias (rare)	• CBC • Renal function • Hepatic function	• P-gp and CYP3A4 substrate • The risk of myopathy may be increased with the concomitant use of certain HMG-CoA reductase inhibitors (e.g., atorvastatin, lovastatin, simvastatin) due to potential competitive interactions mediated by P-gp and CYP3A4 pathways. • Fatal colchicine toxicity has been reported in individuals with renal or hepatic impairment who used colchicine in conjunction with P-gp inhibitors or strong CYP3A4 inhibitors.	• Colchicine **should be avoided** in patients with severe renal insufficiency, and those with moderate renal insufficiency should be monitored for AEs. • A list of clinical trials is available: Colchicine **Availability:** • COLCORONA used 0.5 mg tablets for dosing; in the United States, colchicine is available as 0.6 mg tablets.

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Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Corticosteroids					
Dexamethasone	**Dose for COVID-19:** • Dexamethasone 6 mg IV or PO once daily, for up to 10 days or until hospital discharge, whichever comes first[2]	• Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Avascular necrosis • Adrenal insufficiency • Increased blood pressure • Peripheral edema • Myopathy (particularly if used with neuromuscular blocking agents)	• Blood glucose • Blood pressure • Signs and symptoms of new infection • When initiating dexamethasone, consider appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in patients at high risk of strongyloidiasis or fulminant reactivations of HBV.[3-5]	• 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).	• If dexamethasone is not available, an alternative corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) can be used. • The approximate total daily dose equivalencies for these glucocorticoids to dexamethasone 6 mg (PO or IV) are: prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. • A list of clinical trials is available: Dexamethasone
Fluvoxamine					
Fluvoxamine	**Dose for COVID-19 in Clinical Trials:** • Various dosing regimens used	• Nausea • Diarrhea • Dyspepsia • Asthenia • Insomnia • Somnolence • Sweating • Suicidal ideation (rare)	• Assess for drug interactions. • Hepatic function • Monitor for withdrawal symptoms when tapering dose.	• Fluvoxamine is a CYP2D6 substrate. • Fluvoxamine inhibits several CYP450 isoenzymes (CYP1A2, CYP2C9, CYP3A4, CYP2C19, CYP2D6). • Coadministration of tizanidine, thioridazine, alosetron, or pimozide with fluvoxamine is **contraindicated**.	• Fluvoxamine may enhance anticoagulant effects of antiplatelets and anticoagulants; consider additional monitoring when these drugs are used concomitantly with fluvoxamine. • The use of MAOIs concomitantly with fluvoxamine or within 14 days of treatment with fluvoxamine is **contraindicated**.

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Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Fluvoxamine, continued					
					• A list of clinical trials is available: Fluvoxamine
Interferons					
Interferon Alfa	**Peg-IFN Alfa-2a** *Dose for MERS:* • Peg-IFN alfa-2a 180 µg SQ once weekly for 2 weeks[6,7] **IFN Alfa-2b** *Dose for COVID-19 in Clinical Trials:* • Nebulized IFN alfa-2b 5 million international units twice daily (no duration listed in the study methods)[8]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[9] • Injection site reactions • Liver function abnormalities • Decreased blood counts • Worsening depression • Insomnia • Irritability • Nausea • Vomiting • HTN • Induction of autoimmunity	• CBC with differential • Liver enzymes; **avoid** if Child-Pugh Score >6 • Depression, psychiatric symptoms • Reduce dose in patients with CrCl <30 mL/min.	• Low potential for drug-drug interactions • Inhibition of CYP1A2	• For COVID-19, IFN alfa has primarily been used as nebulization and usually as part of a combination regimen. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN; discontinue if bilirubin level also increases. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon **Availability:** • Neither nebulized IFN alfa-2b nor IFN alfa-1b are FDA-approved for use in the United States.

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Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interferons, continued					
Interferon Beta	**IFN Beta-1a** *Dose for MERS:* • IFN beta-1a 44 mcg SQ 3 times weekly[7] *Dose for COVID-19:* • Dose and duration unknown **IFN Beta-1b** *Dose for COVID-19:* • IFN beta-1b 8 million international units SQ every other day, up to 7 days total[10]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[11] • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity	• Liver enzymes • CBC with differential • Worsening CHF • Depression, suicidal ideation	• Low potential for drug-drug interactions	• **Use with caution** with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • A list of clinical trials is available: Interferon **Availability:** • Several products are available in the United States; product doses differ. *IFN Beta-1a Products:* • Avonex, Rebif *IFN Beta-1b Products:* • Betaseron, Extavia

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Drug Name	Dosing Regimen *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-1 Inhibitor					
Anakinra	**Dose for Rheumatoid Arthritis:** • Anakinra 100 mg SQ once daily **Dose for COVID-19:** • Dose and duration vary by study • Has also been used as IV infusion	• 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	• CBC with differential • Renal function (reduce dose in patients with CrCl <30 mL/min) • Liver enzymes	• Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	• A list of clinical trials is available: Anakinra
Interleukin-6 Inhibitors					
Anti-Interleukin-6 Receptor Monoclonal Antibodies					
Sarilumab[12]	**Dose for COVID-19 in Clinical Trial (See *ClinicalTrials.gov* Identifier NCT04315298):** • Sarilumab 400 mg IV (single dose)[13]	• Neutropenia, thrombocytopenia • GI perforation • HSR • Increased liver enzymes • HBV reactivation • Infusion-related reaction	• Monitor for HSR. • Monitor for infusion reactions. • Neutrophils • Platelets • Liver enzymes	• Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• 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 **Availability:** • Sarilumab for IV administration is not an approved formulation in the United States.

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Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors, continued					
Anti-Interleukin-6 Receptor Monoclonal Antibodies, continued					
Tocilizumab[14]	**Dose for COVID-19 in Clinical Trial:** • Single dose of tocilizumab 8 mg/kg actual body weight IV • Dose **should not exceed** tocilizumab 800 mg. • Administer in combination with dexamethasone. • In clinical trials, some patients received a second dose of tocilizumab at the discretion of treating physicians; however, there are insufficient data to determine which patients, if any, would benefit from an additional dose of the drug.	• Infusion-related reaction • HSR • GI perforation • Hepatotoxicity • Treatment-related changes on laboratory tests for neutrophils, platelets, lipids, and liver enzymes • HBV reactivation	• Monitor for HSR. • Monitor for infusion reactions. • Neutrophils • Platelets • Liver enzymes • Cases of severe and disseminated strongyloidiasis have been reported with the use of tocilizumab and corticosteroids in patients with COVID-19.[15,16] Prophylactic treatment with ivermectin should be considered for persons who are from areas where strongyloidiasis is endemic.[3]	• 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.	• Tocilizumab use **should be avoided** in patients who are significantly immunocompromised. The safety of using tocilizumab plus a corticosteroid in immunocompromised patients is unknown. • 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

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Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors, continued					
Anti-Interleukin-6 Monoclonal Antibody					
Siltuximab	**Dose for Multicentric Castleman Disease:** • Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks[17] **Dose for COVID-19:** • Dose and duration unknown	• Infusion-related reaction • HSR • GI perforation • Neutropenia • HTN • Dizziness • Rash • Pruritus • Hyperuricemia	• Monitor for HSR. • Monitor for infusion reactions. • Neutrophils	• 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.	• 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					
Bruton's Tyrosine Kinase Inhibitors					
Acalabrutinib	**Dose for FDA-Approved Indications:** • Acalabrutinib 100 mg PO every 12 hours **Dose for COVID-19:** • Dose and duration unknown	• Hemorrhage • Cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia) • Atrial fibrillation and flutter • Infection • Headache • Diarrhea • Fatigue • Myalgia	• CBC with differential • Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) • Monitor for cardiac arrhythmias. • Monitor for new infections.	• **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.	• **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

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Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors, contined					
Bruton's Tyrosine Kinase Inhibitors, continued					
Ibrutinib	**Dose for FDA-Approved Indications:** • Ibrutinib 420 mg or 560 mg PO once daily **Dose for COVID-19:** • Dose and duration unknown	• Hemorrhage • Cardiac arrhythmias • Serious infections • Cytopenias (thrombocytopenia, neutropenia, anemia) • HTN • Diarrhea • Musculoskeletal pain • Rash	• 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.	• **Avoid** concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors.	• **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, HTN, or acute infections may be predisposed to cardiac arrhythmias. • A list of clinical trials is available: Ibrutinib
Zanubrutinib	**Dose for FDA-Approved Indications:** • Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily **Dose for COVID-19:** • Dose and duration unknown	• Hemorrhage • Cytopenias (neutropenia, thrombocytopenia, anemia, leukopenia) • Atrial fibrillation and flutter • Infection • Rash • Bruising • Diarrhea • Cough • Musculoskeletal pain	• CBC with differential • Signs and symptoms of bleeding • Monitor for cardiac arrhythmias. • Monitor for new infections.	• **Avoid** concomitant use with moderate or strong CYP3A inducers. • Dose reduction required with moderate and strong CYP3A4 inhibitors.	• Dose reduction required in patients with severe hepatic impairment. • A list of clinical trials is available: Zanubrutinib

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Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Janus Kinase Inhibitors					
Baricitinib[18]	**Dose for Rheumatoid Arthritis:** *Adults:* • Baricitinib 2 mg PO once daily **Dose for COVID-19:**[19] *Adults:* • Baricitinib 4 mg PO once daily for 14 days or until hospital discharge *Children:* • Limited data are available. Dose per the FDA EUA: • 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 dosing recommendations in patients with renal or hepatic impairment.[18]	• Lymphoma and other malignancies • Thrombosis • GI perforation • Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes • HSV reactivation • Herpes zoster	• CBC with differential • Renal function • Liver enzymes • Monitor for new infections.	• Dose modification is recommended when concurrently administering a strong OAT3 inhibitor. • **Avoid** concomitant administration of live vaccines.	• Baricitinib **is not recommended** for patients with severe hepatic or renal impairment. • A list of clinical trials is available: Baricitinib **Availability:** • Baricitinib is available through an FDA EUA. The EUA allows for the use of baricitinib, in combination with RDV, for the treatment of COVID-19 for hospitalized adults and pediatric patients aged ≥2 years who require supplemental oxygen, IMV, or ECMO.[19]

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Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Janus Kinase Inhibitors, continued					
Ruxolitinib	**Dose for FDA-Approved Indications:** • Ruxolitinib 5 mg–20 mg PO twice daily **Dose for COVID-19 in Clinical Trials:** • Ruxolitinib 5 mg–20 mg PO twice daily, for 14 days	• Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster	• CBC with differential • Liver enzymes • Monitor for new infections.	• Dose modifications required when administered with strong CYP3A4 inhibitors. • **Avoid** use with doses of fluconazole >200 mg.	• Dose modification may be required in patients with hepatic impairment, moderate or severe renal impairment, or thrombocytopenia. • A list of clinical trials is available: Ruxolitinib
Tofacitinib	**Dose for FDA-Approved Indications:** • Tofacitinib 5 mg PO twice daily for rheumatoid and psoriatic arthritis • Tofacitinib 10 mg PO twice daily for ulcerative colitis **Dose for COVID-19:** • Dose and duration unknown; a planned COVID-19 clinical trial will evaluate tofacitinib 10 mg twice daily for 14 days.	• Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) • Anemia • Risk of infection • GI perforation • Diarrhea • Headache • Herpes zoster • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies	• CBC with differential • Liver enzymes • Monitor for new infections.	• Dose modifications required when administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor. • **Avoid** administration of live vaccines.	• **Avoid** use in patients with ALC <500 cells/mm^3, ANC <1,000 cells/mm^3, 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

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Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Non-SARS-CoV-2 Specific Immunoglobulin					
Non-SARS-CoV-2 Specific Immunoglobulin	• Dose varies based on indication and formulation.	• Allergic reactions, including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens • AEs may vary by formulation. • AEs may be increased with high-dose, rapid infusion, or in patients with underlying conditions.	• Monitor for transfusion-related reactions. • Monitor vital signs at baseline and during and after infusion. • Discontinue if renal function deteriorates during treatment.	• IVIG may interfere with immune response to certain vaccines.	• A list of clinical trials is available: Intravenous Immunoglobulin

Key: AE = adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CBC = complete blood count; CHF = congestive heart failure; COLCORONA = Colchicine Coronavirus SARS-CoV2 Trial; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HBV = hepatitis B; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; HTN = hypertension; IFN = interferon; IL = interleukin; IMV = invasive mechanical ventilation; IV = intravenous; IVIG = intravenous immunoglobulin; MAOI = monoamine oxidase inhibitor; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; the Panel = the COVID-19 Treatment Guidelines Panel; Peg-IFN = pegylated interferon; P-gp= P-glycoprotein; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; RDV = remdesivir; SQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

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