9: Immunomodulators Under Evaluation for the Treatment of COVID-19

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Summary Recommendations
The hyperactive inflammatory response to SARS-CoV-2 infection plays a central role in the pathogenesis of COVID-19. See Therapeutic Management of Hospitalized Adults with COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of the following immunomodulators for hospitalized patients according to their disease severity: • Corticosteroids: Dexamethasone • Interleukin (IL-6) inhibitors: Tocilizumab (or sarilumab) • Janus kinase (JAK) inhibitors: Baricitinib (or tofacitinib) There is insufficient evidence for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19: • Anakinra • Colchicine for nonhospitalized patients • Fluvoxamine • Granulocyte-macrophage colony-stimulating factor inhibitors for hospitalized patients • Inhaled budesonide • Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild to moderate COVID-19 The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial: • **Baricitinib** plus **tocilizumab (AIII)** • **Canakinumab (BIIa)** • **Colchicine** for hospitalized patients **(AI)** • **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)** • **Intravenous immunoglobulin (IVIG)** (non-SARS-CoV-2-specific) for the treatment of patients with acute COVID-19 **(AIII)**. This recommendation should not preclude the use of IVIG for multisystem inflammatory syndrome in children (MIS-C) or when it is otherwise indicated. • Bruton's tyrosine kinase inhibitors (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) **(AIII)** • JAK inhibitors other than baricitinib and tofacitinib (e.g., **ruxolitinib**) **(AIII)** • **Siltuximab (BIII)**
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

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 shown to potentially reduce the risk of 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 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 is insufficient evidence 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.
- The Panel **recommends against** the use of colchicine for the treatment of hospitalized patients with COVID-19 **(AI)**.

Rationale

For Nonhospitalized Patients With COVID-19

A large randomized trial evaluating colchicine in outpatients with COVID-19 (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 SARS-CoV-2 polymerase chain reaction (PCR) result from a nasopharyngeal (NP) swab. Given that the trial did not reach its primary endpoint, only a very modest effect size was demonstrated in the subgroup of PCR-positive patients, and more gastrointestinal adverse events occurred in the colchicine arm than in the usual care arm, the Panel felt that additional evidence is needed to develop recommendations on using colchicine for the treatment of nonhospitalized patients with COVID-19.[4]

For Hospitalized Patients With COVID-19

In a randomized trial in hospitalized patients with COVID-19 (RECOVERY), colchicine demonstrated no benefit with regards to 28-day mortality or any secondary outcomes.[5] COLCORONA and RECOVERY are described more fully below.

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. 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 participant self-report via telephone at 15 and 30 days after randomization; in some cases, clinical data were confirmed by medical chart reviews.[4]

Results

- The study enrolled 4,488 participants.
- The primary endpoint occurred in 104 of 2,235 participants (4.7%) in the colchicine arm and 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.
- In a prespecified analysis of 4,159 participants who had a SARS-CoV-2 diagnosis confirmed by PCR testing of an NP specimen (93% of those enrolled), those in the colchicine arm were 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 with PCR-confirmed SARS-CoV-2 infection, 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; $P < 0.0001$). Unexpectedly, more pulmonary emboli were reported in the colchicine arm than in the placebo arm (11 events [0.5% of patients] vs. 2 events [0.1% of patients]; $P = 0.01$).

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.
- Some patient-reported clinical outcomes were potentially misclassified.

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

This study has not been peer reviewed.

RECOVERY 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

- The study enrolled 11,340 participants.
- At randomization, 10,603 patients (94%) were receiving corticosteroids.
- The primary endpoint of all-cause mortality at Day 28 occurred in 1,173 of 5,610 participants (21%) in the colchicine arm and 1,190 of 5,730 participants (21%) in the placebo arm (rate ratio 1.01; 95% CI, 0.93–1.10; $P = 0.77$).
- There were no statistically significant differences between the arms for the secondary outcomes of median time to being discharged alive, discharge from the hospital within 28 days, and receipt of invasive mechanical ventilation or death.
- The incidence of new cardiac arrhythmias, bleeding events, and thrombotic events was similar in the two arms. Two serious adverse events were attributed to colchicine: one case of severe acute kidney injury and one case of rhabdomyolysis.

Limitations

- The trial's open-label design may have introduced bias for assessing some of the secondary endpoints.

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

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

Limitations

- The overall sample size and the number of clinical events reported were 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, the ability to interpret the findings of these studies is also constrained by significant design or methodological limitations, including small sample size, open-label designs, and differences in the clinical and demographic characteristics of participants and permitted use of various cotreatments (e.g., remdesivir, corticosteroids) in the treatment arms.

Adverse Effects, Monitoring, and Drug-Drug Interactions

Common adverse effects of colchicine include diarrhea, nausea, vomiting, abdominal cramping and 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 (e.g., atorvastatin, lovastatin, 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 meta-analysis did not find that colchicine exposure during pregnancy increased the rates of miscarriage or major fetal malformations. 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.

Both beneficial and deleterious clinical outcomes have been reported with use of corticosteroids (mostly prednisone or methylprednisolone) in patients with pulmonary infections. In patients with *Pneumocystis jirovecii* pneumonia and hypoxemia, prednisone therapy reduced the risk of death.[1] However, during outbreaks of previous novel coronavirus infections (i.e., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid therapy was associated with delayed virus clearance.[2,3] In patients with severe pneumonia caused by influenza viruses, corticosteroid therapy appears to result in worse clinical outcomes, including secondary bacterial infections and death.[4]

Corticosteroid therapy has also been studied in critically ill patients with acute respiratory distress syndrome (ARDS) with conflicting results.[5-7] Use of corticosteroids in patients with ARDS was evaluated in seven randomized controlled trials that included a total of 851 patients.[6-12] 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 the duration of mechanical ventilation (mean difference -4.93 days; 95% CI, -7.81 to -2.06 days).[13,14]

Corticosteroid use for the treatment of COVID-19 has been studied in clinical trials (see Tables 4a and 4b for more information). The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the use of corticosteroids in patients with COVID-19 are based on the results from these studies.

Recommendations

For nonhospitalized patients with COVID-19:

- See Therapeutic Management of Nonhospitalized Adults with COVID-19 for the Panel's recommendations on the use of dexamethasone or other systemic corticosteroids in certain nonhospitalized patients.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled budesonide for the treatment of COVID-19.

For hospitalized patients with COVID-19:

- See Therapeutic Management of Hospitalized Adults with COVID-19 for the Panel's recommendations on the use of dexamethasone or other systemic corticosteroids in certain hospitalized patients.

Rationale

The Panel's recommendations on the use of corticosteroids for COVID-19 in nonhospitalized patients reflect a lack of data regarding their use in this population. In the RECOVERY trial (described below), dexamethasone was shown to reduce mortality in hospitalized patients with COVID-19 who required supplemental oxygen; however, treatment with dexamethasone was stopped at the time of hospital discharge. Because nonhospitalized patients were not included in the RECOVERY trial, the safety and efficacy of corticosteroid use for COVID-19 in this population have not been established. Moreover, the use of corticosteroids can lead to adverse events (e.g., hyperglycemia, neuropsychiatric symptoms,

secondary infections), which may be difficult to detect and monitor in an outpatient setting (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

The Panel's recommendations on the use of corticosteroids for COVID-19 in hospitalized patients are largely based on data from the RECOVERY trial. This large, multicenter, open-label randomized controlled trial performed in the United Kingdom randomized 6,425 hospitalized patients to receive up to 10 days of dexamethasone plus the standard of care or the standard of care only. Mortality at Day 28 was lower among the patients who received dexamethasone than among those who received the standard of care alone.[15] This mortality 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 summarized in Table 4d.[15]

Systemic corticosteroids used in combination with other agents including antivirals and immunomodulators, such as tocilizumab (see Interleukin-6 Inhibitors)[16,17] or baricitinib (see Kinase Inhibitors),[18] have demonstrated clinical benefit in subsets of hospitalized patients with COVID-19.

Various formulations of systemic corticosteroids used in different doses for varying durations have been studied in patients with COVID-19 in several smaller randomized controlled trials.[19-23] Some of these trials were stopped early due to under-enrollment following the release of the results from the RECOVERY trial. Consequently, the sample size of many these trials was insufficient to assess efficacy, and therefore evidence to support the use of methylprednisolone and hydrocortisone for the treatment of COVID-19 is not as strong as that demonstrated for dexamethasone in the RECOVERY trial.

Please see Tables 4a and 4b for data from clinical trials that have evaluated corticosteroid use for the treatment of COVID-19.

Systemic Corticosteroids Other Than Dexamethasone

- If dexamethasone is not available, alternative glucocorticoids (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (oral or intravenous [IV])[24] 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 Hemodynamics 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.[9]

Inhaled Corticosteroids

Budesonide is a synthetic, inhaled corticosteroid with potent glucocorticoid activity and weak mineralocorticoid activity. It has broad anti-inflammatory properties and has Food and Drug Administration-labeled indications for the management of chronic respiratory diseases including asthma and chronic obstructive pulmonary disease. Certain inhaled corticosteroids have been shown to impair viral replication of SARS-CoV-2[25] and downregulate expression of the receptors used for cell entry.[26,27] These mechanisms support the potential of inhaled corticosteroids as therapeutic agents for COVID-19. However, observational studies have found that long-term use of inhaled corticosteroids prescribed for non-COVID-19 respiratory diseases either had no effect on COVID-19 outcomes or increased the risk of hospitalization.[28,29] More recently, two open-label randomized controlled trials provided additional insights regarding the role of inhaled budesonide in outpatients with COVID-19, as described below and in Table 4b.

Recommendation

There is insufficient evidence for the Panel to recommend either for or against the use of inhaled budesonide for the treatment of COVID-19.

Rationale

Inhaled budesonide was studied in two open-label randomized controlled trials in outpatients with mild symptoms of COVID-19.[30,31] The small STOIC trial suggested that in adult outpatients with mild COVID-19, initiation of inhaled budesonide may reduce the need for urgent care or emergency department assessment or hospitalization.[30] PRINCIPLE, a larger open-label trial in nonhospitalized patients with COVID-19 at high risk of disease progression, found that inhaled budesonide did not affect the rate of hospitalization or death but did reduce time to self-reported recovery.[31] The findings from these trials should be interpreted with caution given the open-label design of the studies and other limitations as outlined in the study description in Table 4b. Additional trials of inhaled corticosteroids are ongoing.

Most of the patients included in the PRINCIPLE trial would also have been candidates for anti-SARS-CoV-2 monoclonal antibody (mAb) therapy, which has been shown to reduce the risk of hospitalization and death in patients who have mild to moderate COVID-19 and certain risk factors for disease progression. Whether inhaled budesonide provides any additional benefit for patients who have received anti-SARS-CoV-2 mAb therapy is unknown.

Monitoring, Adverse Effects, and Drug-Drug Interactions for Systemic Corticosteroids

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- The use of systemic corticosteroids may increase the risk of opportunistic fungal infections (e.g., mucormycosis, aspergillosis) and reactivation of latent infections (e.g., hepatitis B virus, herpesvirus infections, strongyloidiasis, tuberculosis).[32-36]
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[37,38] Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with ivermectin) with or without serologic testing in patients from areas where *Stronglyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[39]
- Combining systemic corticosteroids with other immunosuppressants, such as tocilizumab or baricitinib, could theoretically increase the risk of secondary infections. However, this adverse

effect has not been reported in clinical trials to date.

- 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.
- Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first (see Therapeutic Management of Hospitalized Adults With COVID-19).

Considerations in Pregnancy

A short course of betamethasone or dexamethasone, which are known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.[40,41]

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** for hospitalized pregnant patients 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 and caution is warranted when extrapolating recommendations for adults to patients aged <18 years. The Panel recommends using **dexamethasone** for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation **(BIII)**. Corticosteroids are not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., administered via a nasal cannula only). Use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated and may be harmful; therefore, such use should be considered only on a case-by-case basis. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days. Corticosteroid use has been described in the treatment of multisystem inflammatory syndrome in children (MIS-C) in multiple case series. It is the second most used therapy after IV immunoglobulin for MIS-C.[42,43] Please refer to Special Considerations in Children for more information on the management of MIS-C.

Clinical Trials

Several clinical trials evaluating 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. Systemic Corticosteroids: Selected Clinical Data

Last Updated: August 4, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for systemic 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
RECOVERY Trial: Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report[1]			
Multicenter, randomized open-label adaptive trial in hospitalized patients with suspected or confirmed COVID-19 in the United Kingdom (n = 6,425)	**Key Inclusion Criteria:** • Hospitalization with clinically suspected or laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Physician determination that risks of participation were too great based on patient's medical history or an indication for corticosteroid therapy outside of the study **Interventions** *2:1 Randomization:* • Dexamethasone 6 mg PO or IV once daily plus SOC for up to 10 days or until hospital discharge, whichever came first • SOC alone **Primary Endpoint:** • All-cause mortality at 28 days after randomization	**Number of Participants:** • Dexamethasone plus SOC (n = 2,104) and SOC (n = 4,321) **Participant Characteristics:** • Mean age was 66 years. • 64% of patients were men. • 56% of patients had ≥1 comorbidity; 24% had diabetes. • 89% of participants had laboratory-confirmed SARS-CoV-2 infection. • At randomization, 16% of patients received IMV or ECMO, 60% required supplemental oxygen but not IMV, 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; $P < 0.001$).	**Key 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.

Study Design	Methods	Results	Limitations and Interpretation
RECOVERY Trial: Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report[1], continued			
		• The treatment effect of dexamethasone varied by baseline severity of COVID-19. Survival benefit appeared greatest among participants who required IMV 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[2]			
Meta-analysis of 7 RCTs of corticosteroids in critically ill patients with COVID-19 in multiple countries (n = 1,703)	**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) **Interventions:** • Corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone) • Usual care or placebo	**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. • 47% of patients were on vasoactive agents at randomization across the 6 trials that reported this information.	**Key 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 • Type of control group (i.e., usual care or placebo) • Reporting of SAEs

Study Design	Methods	Results	Limitations and Interpretation
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19[2], continued			
	Primary Endpoint: • All-cause mortality up to 30 days after randomization	**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.	• 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.

Study Design	Methods	Results	Limitations and Interpretation
Metcovid: Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19[3]			
Double-blind, Phase 2b, RCT of short-course methylprednisolone in hospitalized patients with confirmed or suspected COVID-19 pneumonia in a single center in Brazil (n = 416)	**Key Inclusion Criteria:** • Aged ≥18 years • Suspected or confirmed COVID-19 • SpO_2 ≤94% in room air *or* while using supplementary oxygen *or* under IMV **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 IMV; 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).	**Key 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.

Study Design	Methods	Results	Limitations and Interpretation
Metcovid: Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19[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).	
CoDEX: Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19[4]			
Multicenter RCT in patients with COVID-19 and moderate to severe ARDS in Brazil (n = 299)	**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 **Primary Endpoint:** • Mean number of days alive and free from mechanical ventilation by Day 28	**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 of 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). • 35% of patients in SOC alone group also received corticosteroids.	**Key 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.

Study Design	Methods	Results	Limitations and Interpretation
CoDEX: Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19[4], continued			
	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	**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; $P = 0.01$).	**Interpretation:** • Compared with SOC alone, dexamethasone at a higher dose than used in the RECOVERY trial plus SOC 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.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19[5]			
Multicenter, double-blind, sequential RCT in patients with confirmed or suspected COVID-19 and acute respiratory failure in France (n = 149)	**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 **Primary Endpoint:** • Treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen) by Day 21	**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:** • 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:** • No difference 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 intubation vs. 12 of 16 (75%) in placebo group.	**Key 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.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19[5], continued			
	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	• 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. • 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.	
REMAP-CAP COVID-19 Corticosteroid Domain (CAPE COD): Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19[6]			
Randomized, embedded, multifactorial, adaptive platform trial of patients with severe COVID-19 in multiple countries (n = 403)	**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 **Interventions:** • Hydrocortisone 50 mg 4 times daily for 7 days	**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. **Primary Outcome:** • No difference in organ-support free-days at Day 21 (median of 0 days in each group).	**Key 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.

Study Design	Methods	Results	Limitations and Interpretation
REMAP-CAP COVID-19 Corticosteroid Domain (CAPE COD): Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19[6], continued			
	• 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	• Compared to the no hydrocortisone group, median adjusted OR for the primary outcome: • OR 1.43 (95% CrI, 0.91–2.27) with 93% Bayesian probability of superiority for the fixed-dose hydrocortisone group. • OR 1.22 (95% CrI, 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 of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Nonsevere COVID-19 Pneumonia[7]			
Retrospective cohort study in patients with nonsevere COVID-19 pneumonia and propensity score-matched controls in China (n = 55 matched case-control pairs)	**Key Inclusion Criteria:** • Aged ≥16 years • Confirmed COVID-19 • Pneumonia on chest CT scan **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 SpO_2 was 95%. • 42% of patients in corticosteroids group and 46% in no corticosteroids group had comorbidities, 35% to 36% had HTN, and 11% to 13% had diabetes.	**Key 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. • 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.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Nonsevere COVID-19 Pneumonia[7], continued			
	• Immediate ICU admission upon hospitalization • Use of corticosteroids after progression to severe disease **Interventions:** • Early, low-dose corticosteroids: • Methylprednisolone 20 mg/day IV or 40 mg/day IV for 3–5 days • Prednisone 20 mg/day PO 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; $P < 0.001$). • 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%).	**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; HTN = hypertension; ICU = intensive care unit; IL = interleukin; ITT = intention-to-treat; IV = intravenous; IMV = invasive mechanical ventilation; 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; SOC = standard of care; SOFA = sequential organ failure assessment; SpO_2 = saturation of oxygen; WHO = World Health Organization

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Table 4b. Inhaled Corticosteroids: Selected Clinical Data

Last Updated: October 19, 2021

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

Methods	Results	Limitations and Interpretation
PRINCIPLE: Open-Label, RCT of Inhaled Budesonide in Nonhospitalized Patients With COVID-19[1]		
Key Inclusion Criteria: • Aged ≥65 years **or** aged ≥50 years with comorbidities • PCR-confirmed or suspected COVID-19 • ≤14 days of symptoms **Key Exclusion Criteria:** • Already taking inhaled or systemic corticosteroids • Unable to use an inhaler • Use of inhaled budesonide contraindicated **Interventions:** • Usual care plus budesonide 800 mcg inhaled twice daily for 14 days (n = 1,069) • Usual care (n = 787) **Primary Endpoints:** • COVID-19-related hospitalization or death up to 28 days from randomization • Time to reported recovery up to 28 days from randomization	**Participant Characteristics:** • Mean age 64.2 years; 52% women; 92% White • 81% with comorbidities • Median of 6 days from symptom onset to randomization **Primary Outcomes:** • COVID-19-related hospitalization or death within 28 days: 6.8% in budesonide arm vs. 8.8% in usual care arm (OR 0.75; 95% CrI, 0.55–1.03). • Median days to reported recovery: 11.8 in budesonide arm vs. 14.7 in usual care arm (HR 1.21; 95% CrI, 1.08–1.36).	**Key Limitations:** • Open-label trial • Primary endpoint of time to reported recovery based on self-report **Interpretation:** • Inhaled budesonide reduced time to reported recovery but not COVID-related hospitalization or death. • The clinical significance of self-reported time to recovery in an open-label study is unclear.

Methods	Results	Limitations and Interpretation
STOIC: Open-Label, Phase 2, RCT of Inhaled Budesonide in Nonhospitalized Adults with Early COVID-19[2]		
Key Inclusion Criteria: • Aged ≥18 years • ≤7 days of symptoms **Key Exclusion Criteria:** • Use of inhaled or systemic glucocorticoids in past 7 days • Known allergy or contraindication to budesonide **Interventions:** • Usual care plus budesonide 800 mcg inhaled twice daily until symptom resolution (n = 73) • Usual care (n = 73) **Primary Endpoint:** • COVID-19-related urgent care visit, including ED visit or hospitalization	**Participant Characteristics:** • Mean age 45 years; 58% women • 9% with CVD; 5% with diabetes • 95% with positive SARS-CoV-2 RT-PCR result • Median of 3 days from symptom onset to randomization **Primary Outcomes:** • Median days of budesonide use: 7. • COVID-19-related urgent care visits or hospitalizations: 1% in budesonide arm vs.14% in usual care arm (relative risk reduction 91%).	**Key Limitations:** • Small, open label trial • Early termination after statistical analysis determined that additional participants would not alter outcome **Interpretation:** • In adult outpatients with mild COVID-19, inhaled budesonide may reduce the need for urgent care or ED assessment and/or hospitalization.

Key: CVD = cardiovascular disease; ED = emergency department; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction

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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 is insufficient evidence 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.

- 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

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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Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors

Last Updated: July 8, 2021

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a myelopoietic growth factor and proinflammatory cytokine that plays a central role in a broad range of immune-mediated diseases. GM-CSF, secreted by macrophages, T-cells, mast cells, natural killer cells, endothelial cells, and fibroblasts, regulates macrophage number and function. It acts as a pro-inflammatory signal, prompting macrophages to launch an immune cascade that ultimately results in tissue damage.[1,2] GM-CSF is believed to be a key driver of lung inflammation in severe and critical COVID-19 pneumonia, operating upstream of other pro-inflammatory cytokines and chemokines.[1-6] Anti-GM-CSF monoclonal antibodies may mitigate inflammation by inhibiting this signaling axis upstream and thus minimizing downstream production of numerous pro-inflammatory mediators involved in the pathogenesis of COVID-19.[7] Gimsilumab, lenzilumab, namilumab, and otilimab target GM-CSF directly, neutralizing the biological function of GM-CSF by blocking the interaction of GM-CSF with its cell surface receptor.[1,8,9] Mavrilimumab targets the alpha subunit of the GM-CSF receptor, blocking intracellular signaling of GM-CSF.[8,10] None of these agents are currently FDA-approved for any indication.

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of GM-CSF inhibitors for the treatment of hospitalized patients with COVID-19.

Rationale

Clinical data are lacking to definitively establish the potential benefits and risks associated with the use of GM-CSF inhibitors in patients with COVID-19. Preliminary data from a double-blind, placebo-controlled randomized trial of lenzilumab did show a significant improvement in the primary endpoint of ventilator-free survival through Day 28 among those who received the GM-CSF inhibitor. However, preliminary data from a large, double-blind randomized trial of otilimab (primary endpoint: alive and free of respiratory failure at Day 28) and published results of a small, double-blind randomized trial of mavrilimumab (primary endpoint: proportion alive and off supplemental oxygen at Day 14) did not show a survival benefit for the GM-CSF inhibitors compared to placebo.[11-13] The study populations differed; the lenzilumab and mavrilimumab studies primarily included patients on room air or low-flow oxygen and excluded patients receiving mechanical ventilation, whereas the otilimab study included only patients receiving high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation. Each of these GM-CSF inhibitors remains under investigation.

Clinical Data for COVID-19

Lenzilumab, mavrilimumab, and otilimab have been evaluated in clinical trials in hospitalized adults with SARS-CoV-2 pneumonia.[11-13] Clinical data are not yet available for gimsilumab or namilumab. The Panel's recommendations are based on the results of the available clinical studies. Clinical data on the use of anti-GM-CSF monoclonal antibodies for the treatment of COVID-19 are summarized in Table 4c.

Clinical Trials

See ClinicalTrials.gov for a list of ongoing clinical trials that are evaluating the use of GM-CSF inhibitors for the treatment of COVID-19.

Adverse Effects

The primary risks associated with GM-CSF inhibitors being reported and evaluated are related to bacterial infection. Other adverse events that have been reported with these agents include acute kidney injury and elevated liver transaminases.[10] Autoimmune pulmonary alveolar proteinosis has been associated with a high-titer of anti-GM-CSF auto-antibodies.[14]

Considerations in Pregnancy

Pregnant patients have been excluded from clinical trials evaluating GM-CSF inhibitors for the treatment of COVID-19. There is insufficient evidence to recommend for or against their use in pregnant individuals with COVID-19.

Considerations in Children

There are no data on the use of GM-CSF inhibitors in children.

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Table 4c. Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors: Selected Clinical Data

Last Updated: July 8, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for GM-CSF 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
Otilimab in Severe COVID-19 Pneumonia (OSCAR Trial)[1]			
Phase 2, double-blind RCT in patients with severe COVID-19 pulmonary disease in 17 countries, including the United States (n = 806) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Hospitalized adults with confirmed SARS-CoV-2 pneumonia • New onset of oxygenation impairment requiring high-flow oxygen (≥15 L/min), noninvasive ventilation, or IMV ≤48 hours before dosing • CRP or ferritin >ULN **Key Exclusion Criteria:** • Death considered likely within 48 hours • Multiple organ failure • SOFA score >10 if in the ICU • ECMO • Dialysis • High-dose noradrenaline (>0.15 ug/kg/min) or equivalent • More than 1 vasopressor **Interventions** *1:1 Randomization:* • Otilimab 90 mg IV as a single infusion • Placebo	**Number of Participants:** • mITT analysis (n = 793): otilimab (n = 395) and placebo (n = 398) • Participants were enrolled from May 28–November 15, 2020, across 108 study sites. **Participant Characteristics:** • Mean age was 59 years. • 77% received high-flow oxygen or noninvasive ventilation. • 22% were on IMV. • 52% were in the ICU but not on IMV. • 83% received corticosteroids; 34% received RDV • Participants were stratified by clinical status (ordinal scale 5 or 6) and age (<60 years, 60–69 years, and ≥70 years). **Primary Outcome:** • 277 of 389 participants (71%) in the otilimab arm vs. 262 of 393 participants (67%) in the placebo arm were alive and free of respiratory failure at Day 28 (model-adjusted absolute difference of 5.3%; 95% CI, -0.8 to 11.4; *P* = 0.09) **Key Secondary Outcomes:** • No difference in all-cause mortality at Day 60 between the otilimab arm and the placebo arm (23% vs. 24%; model-adjusted difference -2.4%; 95% CI, -8.0 to 3.3; *P* = 0.41)	**Key Limitations:** • Changes in SOC occurred during the study period and may have affected outcomes. • A preplanned subgroup analysis suggested a benefit of otilimab in participants aged ≥70 years, but subgroup analyses were not adjusted for multiple comparisons. **Interpretation:** • In this large study, no differences in outcomes were observed between the otilimab or placebo recipients with severe COVID-19 pneumonia, except for those in a subgroup of participants aged ≥70 years.

Study Design	Methods	Results	Limitations and Interpretation
Otilimab in Severe COVID-19 Pneumonia (OSCAR Trial)[1], continued			
	Primary Endpoint: • Proportion of participants alive and free of respiratory failure at Day 28 **Key Secondary Endpoints:** • All-cause mortality at Day 60 and time to all-cause mortality • Time to recovery • Admission to ICU • Time to ICU discharge	• No difference between the arms for other secondary endpoints • In a preplanned analysis, a benefit of otilimab was observed among those aged ≥70 years (n = 180): • 65.1% of otilimab recipients vs. 45.9% of placebo recipients met the primary endpoint (model-adjusted difference 19.1%; 95% CI, 5.2–33.1; *P* = 0.009) • Mortality at Day 60 was lower in otilimab arm than in placebo arm (27% vs. 41%; model-adjusted difference of 14.4%; 95% CI, 0.9–27.9; *P* = 0.04).	
Lenzilumab in Hospitalized Patients With COVID-19 Pneumonia (LIVE-AIR Trial)[2]			
Phase 3, double-blind RCT in hospitalized patients with severe COVID-19 pneumonia in the United States and Brazil (n = 520 across 29 study sites) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Hospitalized adults with confirmed SARS-CoV-2 pneumonia • SpO_2 ≤94% on room air or requiring low-flow supplemental oxygen, high-flow oxygen support, or NIPPV **Key Exclusion Criteria:** • Requiring IMV • Pregnancy • Confirmed bacterial pneumonia or active/uncontrolled fungal or viral infection • Not expected to survive the 48 hours following randomization • Use of IL-1 inhibitors, IL-6 inhibitors, kinase inhibitors, or SARS-CoV-2 neutralizing monoclonal antibodies within prior 8 weeks	**Number of Participants:** • mITT (n = 479): lenzilumab (n = 236) and placebo (n = 243) **Participant Characteristics:** • Mean age was 60.5 years. • 64.7% were men. • 43.2% were White. • 55.1% had a BMI ≥30. • 40.5% received high-flow oxygen support or NIPPV at baseline. • 93.7% received corticosteroids; 72.4% received RDV; 69.1% received both corticosteroids and RDV. **Primary Outcome:** • Lenzilumab improved ventilator-free survival through Day 28: • mITT participants: HR 1.54; 95% CI, 1.02–2.31; *P* = 0.041 • ITT participants: HR 1.90; 95% CI, 1.02–3.52; *P* = 0.043	**Key Limitations:** • The study was not powered to detect a survival benefit. • There were differences in access to supportive care across the study sites. **Interpretation:** • In this large, unpublished, placebo-controlled study, lenzilumab improved ventilator-free survival in participants who were hypoxic but not mechanically ventilated.

Study Design	Methods	Results	Limitations and Interpretation
Lenzilumab in Hospitalized Patients With COVID-19 Pneumonia (LIVE-AIR Trial)[2], continued			
	Interventions *1:1 Randomization:* • Lenzilumab 600 mg IV every 8 hours for 3 doses • Placebo **Primary Endpoint:** • Ventilator-free survival through Day 28 (composite endpoint of time to death and time to IMV) **Key Secondary Endpoints:** • Survival • Proportion of IMV, ECMO, or death • Time to recovery	• Kaplan-Meier estimate for proportion of participants who had required IMV or died through Day 28: • mITT lenzilumab arm: 15.6% (95% CI, 11.5–21.0); placebo arm: 22.1% (95% CI, 17.4–27.9) • ITT lenzilumab arm: 18.9% (95% CI, 14.5–24.3); placebo arm: 23.6% (95% CI, 18.8–29.3) • Primary outcome sensitivity mITT analyses showed lenzilumab improved the likelihood of ventilator-free survival in participants: • Aged <85 years with CRP <150 mg/L (n = 336): HR 2.96; 95% CI, 1.63–5.37; *P* = 0.0003 • Receiving corticosteroids plus RDV (n = 331): HR 1.92; 95% CI, 1.20–3.07; *P* = 0.0067 • Hospitalized ≤2 days prior to randomization (n = 297): HR 1.88; 95% CI, 1.13–3.12; *P* = 0.015 **Key Secondary Outcomes:** • No difference in proportion of participants who died: 9.6% in lenzilumab arm vs. 13.9% in placebo arm (HR 1.38; 95% CI, 0.81–2.37; *P* = 0.239) • No difference between the arms in the incidence of IMV, ECMO, or death: HR 0.67; 95% CI, 0.41–1.10; *P* = 0.111 • No difference between the arms in time to recovery: HR 1.09; 95% CI, 0.88–1.35; *P* = 0.43)	
Mavrilimumab in Patients With Severe COVID-19 Pneumonia and Systemic Hyperinflammation (MASH-COVID Trial)[3]			
Multicenter, double-blind RCT in hospitalized patients with COVID-19 pneumonia in the United States (n = 40)	**Key Inclusion Criteria:** • Hospitalization with SARS-CoV-2 pneumonia • Hypoxemia (SpO_2 <92% or requirement for supplemental oxygen) • CRP >5 mg/dL	**Number of Participants:** • Mavrilimumab (n = 21) and placebo (n = 19) • Study enrollment was from May 28–September 15, 2020. **Participant Characteristics:** • 65% were men. • 40% were African American.	**Key Limitations:** • The small sample size resulted in low power to identify a clinically meaningful treatment effect. • The study was stopped early due to slow enrollment.

Study Design	Methods	Results	Limitations and Interpretation
Mavrilimumab in Patients With Severe COVID-19 Pneumonia and Systemic Hyperinflammation (MASH-COVID Trial)[3], continued			
Multicenter, double-blind RCT in hospitalized patients with COVID-19 pneumonia in the United States (n = 40)	**Key Exclusion Criteria:** • Mechanical ventilation • ANC <1,500/mm^3 • Uncontrolled bacterial infection **Interventions** *1:1 Randomization:* • Mavrilimumab 6 mg/kg as a single IV infusion • Placebo **Primary Endpoint:** • Proportion of participants alive and off supplemental oxygen at Day 14 **Key Secondary Endpoints:** • Survival at Day 28 • Respiratory failure-free survival at Day 28	• 50% required nasal high-flow oxygen or noninvasive ventilation. • Corticosteroids use: 67% in the mavrilimumab arm, 63% in the placebo arm • RDV use: 76% in the mavrilimumab arm, 74% in the placebo arm **Primary Outcome:** • No significant difference in primary outcome: 12 of 21 participants (57%) in the mavrilimumab arm vs. 9 of 19 participants (47%) in the placebo arm (OR 1.48; 95% CI, 0.43–5.16; *P* = 0.76) **Key Secondary Outcomes:** • No difference in survival: 1 participant in the mavrilimumab arm vs. 3 in the placebo arm had died by Day 28 (HR 3.72; 95% CI, 0.39–35.79; *P* = 0.22) • No difference in respiratory failure free survival at Day 28: 20 participants (95%) in the mavrilimumab arm vs. 15 (79%) in the placebo arm (OR 5.33; 95% CI, 0.54–52.7; *P* = 0.43)	**Interpretation:** • In this small study, no differences in outcomes were observed between the mavrilimumab and placebo arms among participants who were not mechanically ventilated.

Key: ANC = absolute neutrophil count; BMI = body mass index; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; GM-CSF = granulocyte macrophage-colony stimulating factor; ICU = intensive care unit; IL = interleukin; IMV = invasive mechanical ventilation; ITT = intention-to-treat; IV = intravenous; mITT = modified intention-to-treat; NIPPV = noninvasive positive pressure ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SOFA = sequential organ failure assessment; SpO_2 = oxygen saturation; ULN = upper limit of normal

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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 is insufficient evidence to recommend either for or against the use of **interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

Rationale

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

Clinical Data for COVID-19

Interferon Beta-1a

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

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

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

An open-label, Phase 2 clinical trial randomized 127 participants (median age of 52 years) 2:1 to combination antiviral therapy or lopinavir/ritonavir. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants hospitalized within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (interferon beta-1b 8 million units administered subcutaneously every other day for up to 7 days total, lopinavir/ritonavir, and ribavirin); those hospitalized ≥7 days after symptom onset (n = 51) were randomized to double

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

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

Interferon Alfa-2b

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

Clinical Data for SARS and MERS

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

In a retrospective observational analysis of 350 critically ill patients with 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 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: October 19, 2021

Endogenous interleukin (IL)-1 is elevated in patients with COVID-19.[1,2] In addition, SARS-CoV-2 infection causes epithelial damage that leads to the release of IL-1 beta, which recruits inflammatory cells and induces the release of IL-1 beta in monocytes. This in turn leads to the release of more IL-1 to recruit and activate additional innate immune cells. Drugs that block the IL-1 receptor (e.g., anakinra) or drugs that block IL-1 signaling (e.g., canakinumab) can potentially interrupt this autoinflammatory loop. These drugs are being investigated as potential treatments for 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.[3] It is used off-label to treat severe chimeric antigen receptor T cell-mediated cytokine release syndrome and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis.

Canakinumab is a human monoclonal antibody that targets the beta subunit of IL-1 and is approved by the FDA for the treatment of systemic juvenile idiopathic arthritis and Still's disease.

Recommendations

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of anakinra for the treatment of COVID-19.
- The Panel **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

Rationale

In the SAVE-MORE trial, 594 hospitalized patients who had moderate or severe COVID-19 pneumonia and plasma-soluble urokinase plasminogen activator receptor (suPAR) levels ≥6 ng/mL were randomized to receive either anakinra or placebo. The study found that patients who received anakinra had a lower risk of clinical progression of COVID-19 than those who received placebo.[4] CORIMUNO-ANA-1, a randomized controlled trial that compared the use of anakinra to usual care in 116 hospitalized patients who were hypoxemic but did not require high-flow oxygen or ventilation, was stopped early for futility.[5] REMAP-CAP, an open-label, adaptive platform, randomized controlled trial that evaluated several immunomodulators in patients with COVID-19 who required organ support, found that anakinra was not effective in reducing the combined endpoint of in-hospital mortality and days of organ support.[6] Although the SAVE-MORE study suggests that suPAR levels could be used in risk stratification to identify populations that could benefit from IL-1 inhibition, the laboratory assay that is used to assess suPAR levels is not currently available in many countries, including the United States. After reviewing the results of the studies discussed above and taking into consideration the fact that suPAR assays are not widely available to guide the use of anakinra, the Panel has concluded that there is insufficient evidence to recommend either for or against the use of anakinra for the treatment of COVID-19 in hospitalized patients.

Finally, CAN-COVID, a randomized controlled trial that evaluated canakinumab in hospitalized patients with COVID-19 who were hypoxemic but did not require ventilatory support, reported that the use of canakinumab did not improve the likelihood of survival without invasive mechanical ventilation.[7] Because of these results, the Panel **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

Clinical Data for COVID-19

SAVE-MORE

SAVE-MORE was a randomized controlled trial in 594 hospitalized patients with moderate or severe COVID-19 pneumonia and plasma suPAR levels ≥6 ng/mL. Patients who required noninvasive or invasive mechanical ventilation were excluded from the study. Patients were randomized 2:1 to receive anakinra 100 mg subcutaneously once daily for 10 days or placebo. The primary endpoint was clinical status at Day 28 on the 11-point World Health Organization Clinical Progression Scale (WHO-CPS).[4]

Results

- Patients who were randomized to receive anakinra had a lower odds of progression of COVID-19 on the WHO-CPS (OR 0.36; 95% CI, 0.26–0.50; $P < 0.0001$).
- The secondary endpoints also favored anakinra, including the absolute decrease in WHO-CPS scores from baseline at Days 14 and 28, the absolute decrease in Sequential Organ Failure Assessment scores from baseline at Day 7, the median time to hospital discharge, and the median duration of intensive care unit (ICU) stays.
- A smaller proportion of patients in the anakinra arm experienced secondary infections, including ventilator-associated pneumonias, than in the placebo arm (8.4% vs. 15.9%; $P = 0.01$)
- Twenty-eight-day mortality was lower among patients who received anakinra than those who received placebo (3.2% vs. 6.9%; HR 0.45; 95% CI, 0.21–0.98; $P = 0.045$).

Limitations

- The laboratory assay that is used to assess suPAR levels is not currently available in many countries, including the United States.

REMAP-CAP

The REMAP-CAP trial is an open-label, adaptive platform trial in which eligible participants are randomized to several domains, including the Immune Modulation Therapy domain, which consists of two IL-6 inhibitors, anakinra, interferon beta-1a, and a control group. Participants are eligible for enrollment if they are within 24 hours of receiving respiratory or cardiovascular organ support in the ICU and they have suspected or microbiologically confirmed COVID-19.

Anakinra 300 mg was given intravenously (IV) as a loading dose, followed by anakinra 100 mg IV every 6 hours for 14 days until patients were either free from invasive mechanical ventilation for >24 hours or discharged from the ICU. The primary outcome was measured using an ordinal scale that included a composite of in-hospital mortality and duration of respiratory and cardiovascular organ support at 21 days; all deaths up to 90 days were assigned the worst outcome. The trial used a Bayesian design that allowed the authors to compare nonconcurrently randomized interventions across time periods.[6]

Results

- Of the 2,274 participants who were randomized to one of the arms in the Immune Modulation Therapy domain, 365 individuals were assigned to receive anakinra and included in the analysis, 406 were assigned to the usual care (control) arm, 943 were assigned to receive tocilizumab, and 483 were assigned to receive sarilumab.
- Of those assigned to receive anakinra, 37% were receiving invasive mechanical ventilation at study entry compared with 32% of patients in the other arms. The other patients received oxygen through a high-flow nasal cannula or noninvasive ventilation, with a few exceptions.
- The median number of organ support-free days was similar for patients who received anakinra and

those who received usual care (0 days [IQR 1–15 days] vs. 0 days [IQR -1 to 15 days]). The aOR for organ support-free days was 0.99 for anakinra (95% CrI, 0.74–1.35), with a 46.6% posterior probability of superiority to control. Sixty percent of those who were assigned to receive anakinra survived compared to 63% of those who were assigned to the control arm, with a 43.6% posterior probability that anakinra was superior to usual care.

- The risk of experiencing serious adverse events was similar between the arms.

Limitations

- Patients were not randomized contemporaneously to receive anakinra or usual care; the treatment effect was estimated from an overarching model that mostly included patients who were randomized to receive an IL-6 inhibitor (tocilizumab or sarilumab) or usual care, and patients who were randomized to receive an IL-6 inhibitor or anakinra. Thus, the estimate of the treatment effect is not fully protected by randomization.
- This study had an open-label design.

CORIMUNO-ANA-1

The CORIMUNO-ANA-1 trial randomized 116 hospitalized patients with COVID-19 pneumonia 1:1 to receive either usual care plus anakinra (200 mg IV twice a day on Days 1–3, 100 mg IV twice on Day 4, and 100 mg IV once on Day 5) or usual care alone. Patients were eligible for enrollment if they had laboratory-confirmed SARS-CoV-2 infection with COVID-19 pneumonia and they required >3 L/min of supplemental oxygen. Patients who required high-flow oxygen, ventilation, or ICU admission were excluded. The two coprimary outcomes were the proportion of patients who had died or who needed noninvasive or invasive mechanical ventilation by Day 4 (score of >5 on the WHO-CPS) and the proportion who survived without the need for noninvasive or invasive mechanical ventilation (including high-flow oxygen) by Day 14.[5]

Results

- There was no difference between the anakinra plus usual care arm and the usual care alone arm in the two coprimary outcomes: by Day 4, 36% of patients in the anakinra arm had died or required high-flow oxygen or ventilation compared with 38% in the usual care arm (90% CrI, -17.1 to 12.0, posterior probability of benefit 61%). By Day 14, 47% of patients in the anakinra arm had died or required noninvasive or invasive mechanical ventilation compared to 51% in the usual care arm (median HR 0.97; 90% CrI, 0.62–1.52; posterior probability of benefit 55%).
- Fifty-two percent of patients received corticosteroids at study entry.
- Serious adverse events occurred in 46% of patients in the anakinra arm compared to 38% in the usual care arm; 11 of 59 patients (18.6%) in the anakinra arm experienced bacterial or fungal infections compared to 4 of 55 patients (7.3%) who received usual care.

Limitations

- The limitations of this study include the small sample size, narrow eligibility criteria, and the fact that many patients did not receive current standard-of-care therapy (e.g., corticosteroids, remdesivir).

CAN-COVID

CAN-COVID was a double-blind, placebo-controlled randomized trial of 454 hospitalized patients with COVID-19 who were hypoxemic but not mechanically ventilated and had elevated C-reactive protein (≥ 20 mg/L) or ferritin (≥600 micrograms/L) levels. Patients were randomized 1:1 to receive a single dose of IV canakinumab (450 mg for a body weight of 40 kg to <60 kg, 600 mg for 60–80 kg, and 750

mg for >80 kg) or placebo. The primary outcome was survival without the need for invasive mechanical ventilation from Days 3 through 29.[7]

Results

- There was no statistical difference between the canakinumab arm and placebo arm in the proportion of patients who survived without invasive mechanical ventilation (88.8% vs. 85.7%; *P* = 0.29).
- The number of COVID-19-related deaths at 4 weeks was similar for the two arms (11 of 223 patients [4.9%] in the canakinumab arm vs. 16 of 222 patients [7.2%] in the placebo arm; OR 0.67; 95% CI, 0.30–1.50).
- Forty-one percent of patients in the canakinumab arm and 32% in the placebo arm received dexamethasone.
- Serious adverse events occurred in 16% of patients who received canakinumab and in 20.6% of patients who received placebo.

Limitations

- The use of corticosteroids was unbalanced in this study, with more patients receiving dexamethasone at baseline in the canakinumab arm than in the placebo arm.
- More patients received dexamethasone after the trial was underway in the placebo arm than in the canakinumab arm (22.5% vs. 14.5%), and more patients received tocilizumab in the placebo arm than in the canakinumab arm (8.8% vs. 2.2%).

Other small cohort studies, case-control studies, and case series have reported mixed findings with regard to improvement in outcomes among patients who received anakinra for the treatment of COVID-19.[8-11] The clinical implication of these findings is uncertain due to small sample sizes and unmeasured confounding factors. Therefore, these studies did not substantially influence the Panel's current recommendations for using IL-1 inhibitors.

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials that are evaluating anakinra and canakinumab for the treatment of COVID-19.

Adverse Effects

Headache, nausea, vomiting, and liver enzyme elevations can occur with both anakinra and canakinumab.

Anakinra was not associated with any significant safety concerns when used in clinical trials for the treatment of sepsis.[12-14] Increased rates of infection were reported with prolonged anakinra use in combination with tumor necrosis factor-alpha blockade, but not with short-term use.[15]

Considerations in Pregnancy

The data on using IL-1 inhibitors to treat COVID-19 in pregnant patients are currently limited. The American College of Rheumatology recommends against the use of anakinra during pregnancy.[16] Unintentional first-trimester exposure to anakinra is unlikely to be harmful, given the minimal transfer of monoclonal antibodies across the placenta early in pregnancy.[17]

Considerations in Children

Anakinra has been used in the treatment of severely ill children with rheumatologic conditions, including MAS. The data on the use of anakinra in pediatric patients with acute respiratory distress syndrome or sepsis are limited. Anakinra is rarely used to treat pediatric patients with acute COVID-19, and it has been used in approximately 10% of cases of multisystem inflammatory syndrome in children (MIS-C).[18,19] Anakinra is often included in institutional protocols for the treatment of MIS-C in the United States, and it is mentioned as an option for second-line therapy for refractory MIS-C in national consensus guidelines.[20-22] However, robust data on the effectiveness of anakinra for the treatment of MIS-C are not currently available. Data on using canakinumab in pediatric patients are limited to use in patients with periodic fever syndromes and systemic juvenile idiopathic arthritis. There are no data on its use in pediatric patients with acute COVID-19 or MIS-C. The Panel recommends consulting with a multidisciplinary team when using immunomodulating therapy (which may include anakinra) in children with MIS-C **(AIII)**.

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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 SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells.[1] COVID-19-associated systemic inflammation and hypoxemic 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 IL-6 levels or the effects of IL-6 may reduce the duration and/or severity of COVID-19.

There are two classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (mAbs) (e.g., sarilumab, tocilizumab) and anti-IL-6 mAbs (i.e., siltuximab). These drugs have been evaluated in patients with COVID-19 who have systemic inflammation.

Recommendations

- See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of IL-6 inhibitors (e.g., sarilumab, tocilizumab) in hospitalized patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation.
- The Panel **recommends against** the use of anti-IL-6 mAb therapy (i.e., **siltuximab**) for the treatment of COVID-19, except in a clinical trial **(BI)**.

Additional Considerations

- Tocilizumab and sarilumab **should be used with caution** in groups of patients with COVID-19 that have not been adequately studied in clinical trials. This includes patients who are significantly immunosuppressed, particularly those who have recently received other biologic immunomodulating drugs, and those with:
  - Alanine transaminase levels >5 times the upper limit of normal
  - A high risk for gastrointestinal perforation
  - An uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infection
  - Absolute neutrophil counts <500 cells/µL
  - Platelet counts <50,000 cells/µL
  - Known hypersensitivity to the drug
- Tocilizumab and sarilumab should only be given in combination with a course of dexamethasone (or an alternative corticosteroid at a dose that is equivalent to dexamethasone 6 mg). See the Corticosteroids section for more information.
- Some clinicians may decide to assess the patient's clinical response to dexamethasone before deciding whether tocilizumab or sarilumab is needed.
- In both the REMAP-CAP trial and the RECOVERY trial, 29% of patients received a second dose of tocilizumab at the discretion of the treating physicians. However, the available data are currently insufficient to recommend either for or against a second dose.[5,6]
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[7,8] Many clinicians would initiate empiric treatment (e.g., with ivermectin) with or without serologic testing in patients who are from areas

where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[9]

Rationale

The results of the RECOVERY and REMAP-CAP trials provide consistent evidence that tocilizumab, when administered with corticosteroids, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill, who are rapidly deteriorating and have increasing oxygen needs, and who have a significant inflammatory response.[5,6] However, the Panel found it challenging to define the specific patient populations that would benefit from this intervention. If tocilizumab is not available, sarilumab may be used as an alternative because it has demonstrated a similar clinical benefit in improving survival and reducing the duration of organ support in the REMAP-CAP trial.[10] However, the Panel recommends **sarilumab** only when tocilizumab is not available or is not feasible to use **(BIIa)** because the evidence for the efficacy of tocilizumab is more extensive than that for sarilumab; in addition, sarilumab is currently only approved for use as a subcutaneous (SQ) injection in the United States.

The data on the efficacy of siltuximab in patients with COVID-19 are currently limited.[11]

Anti-Interleukin-6 Receptor Monoclonal Antibodies

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6 receptor mAb that is approved by the FDA for use in patients with rheumatologic disorders and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR T-cell) therapy. Tocilizumab can be dosed as an intravenous (IV) infusion or a SQ injection. The IV formulation should be used to treat cytokine release syndrome.[11]

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 4d.

The 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).[12-14] For example, trials that reported a treatment benefit of tocilizumab enrolled patients who were receiving higher levels of oxygen support (e.g., high-flow nasal cannula oxygen, noninvasive ventilation, invasive mechanical ventilation) and/or included more patients who used corticosteroids.[15,16] Subsequently, the REMAP-CAP and RECOVERY trials—the two largest randomized controlled tocilizumab trials—both 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 intensive care unit and who were randomized to receive open-label tocilizumab or usual care.[5] The RECOVERY trial enrolled hospitalized patients with COVID-19 into an open-label platform trial that included several treatment options;[6] a subset of all trial participants who also had hypoxemia and CRP levels ≥75 mg/L were offered enrollment into a second randomization that evaluated tocilizumab versus usual care. Additional findings from the REMAP-CAP and RECOVERY trials 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 Hospitalized Adults With COVID-19.

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

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials that are evaluating the use of tocilizumab for the treatment of COVID-19.

Adverse Effects

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. In randomized trials, no excess secondary infections were seen among patients who received combination therapy compared to study controls. Additional adverse effects, such as serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation, have been reported.[17]

Considerations in Pregnancy

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. mAbs are actively transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this 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.[18] The decision to use tocilizumab during pregnancy should be a collaborative effort between pregnant individuals and their health care providers, and the decision-making process should include a discussion of the potential risks and benefits.

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). Tocilizumab has been used for children with cytokine release syndrome associated with CAR T-cell therapy and systemic and polyarticular juvenile idiopathic arthritis.[19] There is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or MIS-C.

Drug Availability

On June 24, 2021, the FDA issued an Emergency Use Authorization (EUA) for the use of tocilizumab in combination with corticosteroids in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.[20] Per this EUA, if a patient's clinical signs or symptoms worsen or do not improve after the first dose of tocilizumab, one additional infusion of tocilizumab may be administered at least 8 hours after the initial IV infusion. If there is a local or regional shortage of tocilizumab, sarilumab can be used as an alternative (see Therapeutic Management of Hospitalized Adults With COVID-19).[10]

Sarilumab

Sarilumab is a recombinant humanized anti-IL-6 receptor mAb 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 cytokine release syndrome.

Clinical Data for COVID-19

The clinical data on the use of sarilumab as a treatment for COVID-19 are summarized in Table 4d.

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 to placebo in hospitalized patients 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.[21]

A similar adaptive design study that was conducted in the United States in patients with severe and critical COVID-19 also failed to show a benefit of sarilumab. In this trial, there was a numerical decrease in mortality among participants with critical COVID-19 pneumonia who required mechanical ventilation and who received corticosteroids; however, because of the small sample size in this study, the result was not statistically significant.[22] In the REMAP-CAP trial, the efficacy results for sarilumab were similar to those for tocilizumab. Compared to the patients in the standard of care arm (n = 418), those who were randomized to receive sarilumab (n = 485) had more organ support-free days (OR 1.50; 95% CrI, 1.13–2.00) and better survival rates while hospitalized (OR 1.51; 95% CrI, 1.06–2.20). A notable limitation to the sarilumab findings in the REMAP-CAP trial is that patients in the standard of care arm were enrolled earlier in the pandemic than patients who received sarilumab (i.e., randomization for the standard of care arm closed on November 19, 2020, and randomization for the sarilumab arm continued through April 10, 2021).[10]

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials that are evaluating the use of sarilumab for the treatment of COVID-19.

Adverse Effects

The primary laboratory abnormalities that have been reported with sarilumab treatment are transient and/or reversible elevations in liver enzyme levels that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia. Additional adverse effects, such as serious infections (e.g., TB, bacterial or fungal infections) and bowel perforation, have been reported, but 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. mAbs are actively transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this 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 that are 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 IV formulation of sarilumab is not approved by the FDA, but it is being studied in a clinical trial of hospitalized patients with COVID-19. In the REMAP-CAP trial, a single SQ dose of sarilumab 400 mg was reconstituted in 100 cc 0.9% NaCl and given as an IV infusion over a 1-hour period.[22]

Anti-Interleukin-6 Monoclonal Antibody

Siltuximab

Siltuximab is a recombinant human-mouse chimeric mAb 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 on the efficacy of siltuximab in patients with COVID-19.[23] There are no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]).

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials that are evaluating the use of siltuximab for the treatment of 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. mAbs are transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this may affect immune responses in utero 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 4d. Interleukin-6 Inhibitors: Selected Clinical Data

Last Updated October 19, 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.

Methods	Results	Limitations and Interpretation
RECOVERY Trial: Open-Label RCT of Tocilizumab and Usual Care in Hospitalized Patients With COVID-19[1]		
Key Inclusion Criteria: • SpO_2 <92% on room air or receipt of supplemental oxygen • CRP ≥75 mg/L **Key Exclusion Criteria:** • Non-SARS-CoV-2 infection **Interventions:** • Single weight-based dose of tocilizumab (maximum 800 mg) and possible second dose (n = 2,022) • Usual care (n = 2,094) **Primary Endpoint:** • 28-day all-cause mortality **Key Secondary Endpoints:** • Time to discharge alive • Among those not on IMV at enrollment, receipt of IMV or death	**Participant Characteristics:** • Mean age 63.6 years; 67% male; 76% White • 95% had PCR-confirmed SARS-CoV-2 infection • At baseline: • 45% on conventional oxygen • 41% on HFNC or noninvasive ventilation • 14% on IMV • 82% on corticosteroids **Primary Outcomes:** • Day 28 mortality was lower in tocilizumab arm than in usual care arm (31% vs. 35%; rate ratio 0.85; 95% CI, 0.76–0.94; *P* = 0.003). • Among those who required IMV at baseline, Day 28 mortality was similar between arms (49% in tocilizumab arm vs. 51% in usual care arm; risk ratio 0.93; 95% CI, 0.74–1.18). **Secondary Outcomes:** • Proportion of patients discharged alive within 28 days was greater in tocilizumab arm (57% vs. 50%; rate ratio 1.22; 95% CI, 1.12–1.33; *P* < 0.0001). • Among those not on IMV at baseline, the percentage of patients who died or required IMV was lower in tocilizumab arm than usual care arm (35% vs. 42%; rate ratio 0.84; 95% CI, 0.77–0.92; *P* < 0.0001).	**Key Limitations:** • Arbitrary enrollment cut off at CRP ≥75 mg/L • Difficult to define exact subset of patients in RECOVERY cohort who were subsequently selected for secondary randomization/tocilizumab trial **Interpretation:** • Among hospitalized patients with hypoxemia and elevated CRP, tocilizumab was associated with reduced all-cause mortality and shorter time to discharge.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive Platform RCT of Tocilizumab and Sarilumab in Patients With COVID-19[2,3]		
Key Inclusion Criteria: • ICU admission • Suspected or laboratory-confirmed COVID-19 • Receipt of IMV, noninvasive ventilation, or cardiovascular support **Key Exclusion Criteria:** • >24 hours since ICU admission • Presumption of imminent death • Immunosuppression • ALT >5 times ULN **Interventions:** • Single dose of tocilizumab 8 mg/kg and possible second dose, plus SOC (n = 952) • Single dose of sarilumab 400 mg IV plus SOC (n = 485) • SOC (n = 406) **Randomization:** • Adaptative randomization. Patients were randomized to receive SOC only, SOC plus tocilizumab, or SOC plus sarilumab based on provider preference, availability, or adaptive probability. SOC arm was closed in November 2020 (n = 366 for tocilizumab, n = 48 for sarilumab, n = 412 for SOC). • After November 2020, patients were randomized mostly to receive tocilizumab, sarilumab, or anakinra until April 10, 2021.	**Participant Characteristics:** • Mean age 60 years; 69% male; 75% White • 86% had PCR-confirmed SARS-CoV-2 infection • Median time from ICU admission until enrollment was 14 hours • At baseline: • 67% on HFNC or noninvasive ventilation • 33% on IMV • 67% on corticosteroids in control arm, 82% in tocilizumab arm, and 89% in sarilumab arm **Primary Outcomes** *Tocilizumab Versus SOC:* • Median number of organ support-free days was 7 in tocilizumab arm and 0 in SOC arm. • Median adjusted OR for ordinal scale was 1.46 (95% CrI, 1.13–1.87). • In highest CRP tercile, aOR was 1.87 (95% CrI, 1.35–2.59). • Outcomes were consistent across subgroups of oxygen requirements at study entry. *Sarilumab Versus SOC:* • Median number of organ support-free days was 9 in sarilumab arm and 0 in SOC arm. • Median adjusted OR for ordinal scale was 1.50 (95% CrI, 1.13–2.00). • In highest CRP tercile, aOR was 1.85 (95% CrI, 1.24–2.69). • Outcomes were consistent across subgroups of oxygen requirements at study entry.	**Key Limitation:** • Enrollment in tocilizumab and sarilumab arms was partially nonconcurrent with SOC arm; while the comparisons to SOC arm were adjusted for time period, there is a possibility of bias **Interpretation:** • Among patients with respiratory failure who were within 24 hours of ICU admission, the tocilizumab and sarilumab arms had higher rates of in-hospital survival and shorter durations of organ support than the SOC arm. • The treatment effect appeared to be strongest in the highest CRP tercile. • Tocilizumab and sarilumab were similarly effective, with a 99% probability of noninferiority of sarilumab.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive Platform RCT of Tocilizumab and Sarilumab in Patients With COVID-19[2,3], continued		
Primary Endpoint: • Composite endpoint measured using an ordinal scale that combined mortality and days free of respiratory or cardiovascular support to Day 21 **Key Secondary Endpoint:** • In-hospital survival	**Secondary Outcomes** *Tocilizumab Versus SOC:* • In-hospital survival was 66% in tocilizumab arm and 63% in SOC arm (aOR 1.42; 95% CrI, 1.05–1.93). *Sarilumab Versus SOC:* • In-hospital survival was 67% in sarilumab arm and 63% in SOC arm (aOR 1.51; 95% CrI, 1.06–2.20).	
COVACTA: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[4]		
Key Inclusion Criteria: • PCR-confirmed SARS-CoV-2 infection • Hypoxemia • Bilateral chest infiltrates **Key Exclusion Criteria:** • Death imminent • Active infection other than SARS-CoV-2 **Interventions:** • Single dose of tocilizumab 8 mg/kg and possible second dose, plus SOC (n = 294) • Placebo plus SOC (n = 144) **Primary Endpoint:** • Day 28 clinical status (measured using ordinal scale) **Key Secondary Endpoints:** • Time to discharge • Length of ICU stay • Day 28 mortality	**Participant Characteristics:** • Mean age 61 years; 70% male; 58% White • 30% on HFNC or noninvasive ventilation • 14% on IMV • 25% with multiorgan failure • 36% in tocilizumab arm and 55% in placebo arm received corticosteroids at entry or during follow-up **Primary Outcome:** • No significant difference between arms in clinical status at Day 28. **Secondary Outcomes:** • Shorter median time to discharge in tocilizumab arm than placebo arm (20 vs. 28 days; HR 1.35; 95% CI, 1.02–1.79). • Shorter median ICU stay in tocilizumab arm than placebo arm (9.8 vs. 15.5 days). • No difference in Day 28 mortality between arms (19.7% in tocilizumab arm vs. 19.4% placebo).	**Key Limitations:** • Modest power to detect differences in Day 28 clinical status • Corticosteroids used by more patients in placebo arm than tocilizumab arm • Few patients on IMV **Interpretation:** • There was no difference between arms at Day 28 clinical status or survival. • Patients in tocilizumab arm had shorter median times for recovery and ICU stay than those in placebo arm.

Methods	Results	Limitations and Interpretation
EMPACTA: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[5]		
Key Inclusion Criteria: • PCR-confirmed SARS-CoV-2 infection • COVID-19 pneumonia **Key Exclusion Criteria:** • Noninvasive ventilation or IMV **Interventions:** • Single dose of tocilizumab 8 mg/kg plus SOC, possible second dose (n = 249) • Placebo plus SOC (n = 128) **Primary Endpoint:** • IMV, ECMO, or death by Day 28 **Key Secondary Endpoints:** • Time to hospital discharge or readiness for discharge (measured using ordinal scale) • All-cause mortality by Day 28	**Participant Characteristics:** • Mean age 56 years; 59% male; 56% Hispanic/Latinx, 15% Black/African American, 13% American Indian/Alaska Native • 84% with elevated CRP • Concomitant medications: • 80% on corticosteroids and 53% on RDV in tocilizumab arm • 88% on corticosteroids and 59% on RDV in placebo arm **Primary Outcome:** • Proportion of patients who required IMV or ECMO or who died by Day 28 was 12% in tocilizumab arm and 19% in placebo arm (HR 0.56; 95% CI, 0.33–0.97; *P* = 0.04). **Key Secondary Outcomes:** • Median number of days to hospital discharge or readiness for discharge was 6.0 in tocilizumab arm and 7.5 in placebo arm (HR 1.16; 95% CI, 0.91–1.48). • All-cause mortality by Day 28 was not statistically different between arms (10.4% in tocilizumab arm vs. 8.6% in placebo arm).	**Key Limitation:** • Moderate sample size **Interpretation:** • Among patients with COVID-19 pneumonia, tocilizumab lowered rates of IMV, ECMO, or death by Day 28 but provided no benefit for 28-day mortality.
BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[6]		
Key Inclusion Criteria: • Laboratory-confirmed SARS-CoV-2 infection • ≥2 of the following conditions: • Fever >38°C • Pulmonary infiltrates • Need for oxygen • ≥1 of the following laboratory criteria: • CRP ≥50 mg/L • D-dimer >1,000 ng/mL • LDH ≥250 U/L • Ferritin >500 ng/mL	**Participant Characteristics:** • Median age 60 years; 58% male; 45% Hispanic/Latinx • 50% with BMI ≥30; 49% with HTN; 31% with diabetes • 80% receiving oxygen ≤6 L/min; 4% receiving high-flow oxygen; 16% receiving no supplemental oxygen • Concomitant medications: • 11% on corticosteroids and 33% on RDV in tocilizumab arm • 6% on glucocorticoids and 29% on RDV in placebo arm **Primary Outcome:** • No difference between arms in Day 28 intubation or death (10.6% in tocilizumab arm vs. 12.5% in placebo arm; HR 0.83; 95% CI, 0.38–1.81; *P* = 0.64).	**Key Limitations:** • Wide confidence intervals due to small sample size and low event rates • Few patients received RDV or corticosteroids **Interpretation:** • There was no benefit of tocilizumab in preventing intubation or death, reducing the risk of clinical worsening, or reducing the time to discontinuation of oxygen. This could be due to the low rate of concomitant corticosteroid use among the study participants.

Methods	Results	Limitations and Interpretation
BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[6], continued		
Interventions: • Tocilizumab 8 mg/kg plus usual care (n = 161) • Placebo plus usual care (n = 81) **Primary Endpoint:** • Intubation or death, according to a time to event analysis; data censored at Day 28 **Key Secondary Endpoints:** • Clinical worsening by Day 28, based on an ordinal scale • Discontinuation of supplemental oxygen among patients receiving it at baseline	**Key Secondary Outcomes:** • No difference between arms in proportion of patients who experienced worsening of disease by Day 28 (19% in tocilizumab arm vs. 17% in placebo arm; HR 1.11; 95% CI, 0.59–2.10). • Median number of days to discontinuation of oxygen was 5.0 in tocilizumab arm and 4.9 in placebo arm (*P* = 0.69).	
Double-Blind, RCT of Sarilumab in Hospitalized Patients With Severe or Critical COVID-19[7]		
Key Inclusion Criteria: • Aged ≥18 years • Severe or critical laboratory-confirmed COVID-19 • COVID-19 pneumonia **Key Exclusion Criteria:** • Low probability of surviving or remaining at study site • Dysfunction of ≥2 organ systems and need for ECMO or renal replacement therapy **Interventions:** • Sarilumab 400 mg IV (n = 173) • Sarilumab 200 mg IV (n = 159) • Placebo (n = 84) **Primary Endpoint:** • Time to clinical improvement of ≥2 points on a 7-point scale **Key Secondary Endpoint:** • Survival at Day 29	**Participant Characteristics:** • Median age 59 years; 63% male; 77% White; 36% Hispanic/Latinx • 39% on HFNC, IMV, or noninvasive mechanical ventilation • 42% with BMI ≥30; 43% with HTN; 26% with type 2 diabetes • 20% received systemic corticosteroids before receiving intervention **Primary Outcome:** • No difference in median time to clinical improvement among the sarilumab arms (10 days for each) and placebo arm (12 days). **Key Secondary Outcome:** • No difference among the arms in survival at Day 29 (92% in placebo arm vs. 90% in sarilumab 200 mg arm vs. 92% in sarilumab 400 mg arm).	**Key Limitations:** • Only 20% of patients received corticosteroids • Moderate sample size and a small placebo arm **Interpretation:** • There was no benefit of sarilumab in hospitalized adults with COVID-19 in time to clinical improvement or mortality. This could be due to the low rate of concomitant corticosteroid use among the study participants.

Key: ALT = alanine transaminase; BMI = body mass index; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IL = interleukin; IMV = invasive mechanical ventilation; IV = intravenous; LDH = lactate dehydrogenase; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SpO_2 = oxygen saturation; ULN = upper limit of normal

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

Last Updated: October 19, 2021

Janus Kinase Inhibitors

Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins[1,2] that are involved in vital cellular functions, including signaling, growth, and survival. These kinase inhibitors are proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).[3]

Immunosuppression induced by JAK inhibitors could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing SARS-CoV-2 from entering and infecting susceptible cells.[4]

Recommendations

- See Therapeutic Management of Hospitalized Adults with COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of baricitinib and tofacitinib for hospitalized patients who require high-flow oxygen or noninvasive ventilation.
- The Panel **recommends against** the use of **JAK inhibitors other than baricitinib or tofacitinib** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Rationale

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

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

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

Most of the data on adverse effects of JAK inhibitors were reported based on chronic use of the agents for the treatment of autoimmune diseases. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses, myelosuppression, transaminase elevations, and, rarely, gastrointestinal perforation. The Food and Drug Administration (FDA) review of a large, randomized safety clinical trial comparing tofacitinib to anti-tumor necrosis factor inhibitors in people with rheumatoid arthritis found that tofacitinib was associated with additional serious adverse

events, including heart attack or stroke, cancer, blood clots, and death.[8] The FDA is therefore requiring new and updated warnings for drugs in the JAK inhibitor class, including tofacitinib and baricitinib. Data from randomized trials evaluating the safety of short-term use of JAK inhibitors in patients with COVID-19 are limited. The data to date have not revealed significant safety signals, including thrombosis; however, these trials may be underpowered for detecting rare adverse events.[5-7]

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

Tofacitinib is a cytochrome P 450 (CYP) 3A4 substrate. Dose modifications are required when the drug is administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor. Coadministration with a strong CYP3A4 inducer **is not recommended**.

The ACTT-2 and COV-BARRIER trials evaluated oral baricitinib 4 mg once daily, which is twice the standard baricitinib 2 mg once daily dose for FDA-approved indications.[5,6] In patients with severe hepatic impairment, baricitinib should only be used if the potential benefit outweighs the potential risk.[9] Baricitinib has not been evaluated in clinical studies for FDA-approved indications in patients with an estimated glomerular filtration rate (eGFR) ≤30 mL/min. When baricitinib is used for the treatment of COVID-19 in adults with renal insufficiency, the Panel recommends reducing the dose of baricitinib from 4 mg to 2 mg daily for adults with an eGFR ≥30 to <60 mL/min and to 1 mg daily for those with an eGFR of 15 to <30 mL/min. Baricitinib **is not recommended** for patients with an eGFR <15 mL/min.[9] 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.[10,11]

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.[12] Decisions regarding the administration of JAK inhibitors must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks. Factors that may weigh into the decision-making process include maternal COVID-19 severity, comorbidities, and gestational age. Pregnancy registries provide some outcome data on tofacitinib use during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general population.[13-15]

Considerations in Children

An FDA Emergency Use Authorization (EUA) has been issued for the use of baricitinib in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[9] The safety and efficacy of baricitinib have not been evaluated in pediatric patients with COVID-19. As noted above, tofacitinib was shown to decrease the risk of respiratory failure and death in adults with COVID-19 in the STOP-COVID trial.[7] Tofacitinib is FDA approved for a pediatric indication; however, the safety and efficacy of tofacitinib have not been evaluated in pediatric patients with COVID-19. Thus, there is insufficient evidence to recommend either for or against the use of baricitinib in combination with corticosteroids and/or remdesivir for the treatment of COVID-19 in hospitalized children.

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and is FDA approved for the

treatment of rheumatoid arthritis.[10] Baricitinib can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[16] Baricitinib has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.[17] Baricitinib reduced inflammation and lung pathology in macaques infected with SARS-CoV-2, but an antiviral effect was not confirmed.[18]

Clinical Data for COVID-19

In the ACTT-2 trial, 1,033 patients hospitalized with COVID-19 were randomized 1:1 to receive baricitinib 4 mg daily for 14 days (or until hospital discharge) or placebo, both given in combination with remdesivir. The primary endpoint was time to recovery as measured on an eight-category ordinal scale. Recovery time was shorter in the baricitinib arm (7 days) than in the placebo arm (8 days) (rate ratio for recovery 1.16; 95% CI, 1.01–1.32; $P = 0.03$). Mortality by 28 days was lower in the baricitinib arm than in the placebo arm, but the difference was not statistically significant. A key limitation of the study is that corticosteroids were not used as background standard care for patients with severe or critical COVID-19 pneumonia.[5]

In the COV-BARRIER trial, 1,525 hospitalized patients with COVID-19 pneumonia and an elevation in one or more inflammatory markers were randomized 1:1 to receive baricitinib 4 mg orally or placebo for up to 14 days (or until hospital discharge). Patients on invasive mechanical ventilation were excluded from study enrollment. Overall, 79% of patients received corticosteroids and 19% received remdesivir. The primary endpoint was the proportion of patients who progressed to high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or death by Day 28. Progression to the primary endpoint occurred among 27.8% of patients in the baricitinib arm versus 30.5% in the placebo arm (OR 0.85; 95% CI, 0.67–1.08; $P = 0.18$). All-cause mortality within 28 days, which was a key secondary endpoint, was 8.1% in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality associated with baricitinib (HR 0.57; 95% CI, 0.41–0.78). The mortality difference was most pronounced in the subgroup of patients receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% for baricitinib recipients vs. 29.4% for placebo recipients; HR 0.52; 95% CI, 0.33–0.80). The occurrence of adverse events, serious adverse events, serious infections, and venous thromboembolic events was comparable in the baricitinib and placebo arms.[6]

Additional findings from the ACTT-2 and COV-BARRIER trials and the rationale for using baricitinib in certain hospitalized patients with COVID-19 can be found in Therapeutic Management of Hospitalized Adults With COVID-19.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of baricitinib for the treatment of COVID-19.

Drug Availability

Baricitinib is approved by the FDA for the treatment of rheumatoid arthritis. On November 19, 2020, the FDA issued an initial EUA for the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in certain hospitalized children and adults who require supplemental oxygen, invasive mechanical ventilation, or ECMO. The EUA was revised on July 28, 2021, to remove the requirement that baricitinib be used only in combination with remdesivir for the treatment of COVID-19.[9]

Tofacitinib

Tofacitinib is the prototypical JAK inhibitor, predominantly selective for JAK1 and JAK3, with modest activity against JAK2, and, as such, can block signaling from gamma-chain cytokines (e.g., IL-2, IL-4) and glycoprotein 130 proteins (e.g., IL-6, IL-11, interferons). It is an oral agent first approved by the

FDA for the treatment of rheumatoid arthritis and has been shown to decrease levels of IL-6 in patients with this disease.[19] Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.[20]

Clinical Data for COVID-19

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

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of tofacitinib for the treatment of COVID-19.

Ruxolitinib

Ruxolitinib is an oral JAK inhibitor selective for JAK1 and JAK2 that is currently approved for myelofibrosis, polycythemia vera, and acute graft-versus-host disease.[21] Like baricitinib, it can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[16] Ruxolitinib also has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.[17]

Clinical Data for COVID-19

A small, single-blind, 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 standard of care. Treatment with ruxolitinib was associated with a nonsignificant reduction in the median time to clinical improvement (12 days for ruxolitinib recipients vs. 15 days for placebo recipients; $P = 0.15$), defined as a two-point improvement on a seven-category ordinal scale or as hospital discharge. There was no difference between the arms in the median time to discharge (17 days for ruxolitinib arm vs. 16 days for placebo arm; $P = 0.94$). Limitations of this study include the small sample size.[22] A Phase 3 trial of ruxolitinib in patients with COVID-19-associated acute respiratory distress syndrome is currently in progress (ClinicalTrials.gov Identifier NCT04377620).

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of ruxolitinib for the treatment of COVID-19.

Bruton's Tyrosine Kinase Inhibitors

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

Recommendation

- The Panel **recommends against** the use of **BTK inhibitors** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Acalabrutinib

Acalabrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat B-cell malignancies (i.e., chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma). It has a better toxicity profile than first-generation BTK inhibitors (e.g., ibrutinib) because it has less off-target activity for other kinases.[23] Acalabrutinib is proposed for use in patients with COVID-19 because it can modulate signaling that promotes inflammation.

Clinical Data for COVID-19

Data regarding acalabrutinib are limited to the results from a prospective case series of 19 patients with severe COVID-19.[24] Evaluation of the data to discern any clinical benefit is limited by the study's small sample size and lack of a control group.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of acalabrutinib for the treatment of COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies[25] and to prevent chronic graft-versus-host disease in stem cell transplant recipients.[26] 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.[27]

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.[27] Evaluation of the data for any clinical benefit is limited by the series' small sample size and lack of a control group.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of ibrutinib for the treatment of COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.[28] 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.[29] Zanubrutinib is proposed to benefit patients with COVID-19 by modulating signaling that promotes inflammation.

Clinical Data for COVID-19

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

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of zanubrutinib for the treatment of COVID-19.

Adverse Effects and Monitoring

Hemorrhage and cardiac arrhythmia have occurred in patients who received BTK inhibitors.

Considerations in Pregnancy

There is a paucity of data on human pregnancy and BTK inhibitor use. In animal studies, acalabrutinib

and ibrutinib in doses exceeding the therapeutic human dose were associated with interference with embryofetal development.[25,30] 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 4e. Characteristics of Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: October 19, 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 on using the drugs listed in this table, please refer to the drug-specific sections of the Guidelines and to Therapeutic Management of Hospitalized Adults With COVID-19.

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Colchicine					
Colchicine	**Dose for COVID-19 in COLCORONA Trial:** • Colchicine 0.5 mg twice daily for 3 days and then once daily for 27 days[1]	• Diarrhea • Nausea • Vomiting • Cramping • Abdominal pain • Bloating • Loss of appetite • Neuromyotoxicity (rare)[2] • 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	• Use of 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:** • In the COLCORONA trial, 0.5 mg colchicine tablets were used for dosing; in the United States, colchicine is available as 0.6 mg tablets.

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Corticosteroids					
Budesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials:** • Budesonide 800 mcg inhaled twice daily until symptom resolution or for up to 14 days[3,4]	• Secondary infections • Oral thrush • Systemic adverse effects (less common)	• Signs of adverse effects involving the oral mucosa or throat including thrush • Signs of systemic corticosteroid effects (e.g., adrenal suppression)	• CYP3A4 substrate • **Do not use** with strong CYP3A4 inhibitors.	• A list of clinical trials is available: Inhaled Budesonide
Dexamethasone (Systemic)	**Dose for COVID-19:** • Dexamethasone 6 mg IV or PO once daily for up to 10 days or until hospital discharge, whichever comes first[5]	• Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Avascular necrosis • Adrenal insufficiency • Increased BP • Peripheral edema • Myopathy (particularly if used with neuromuscular blocking agents)	• Blood glucose • BP • Signs and symptoms of new infection • Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with corticosteroids and tocilizumab. Prophylactic treatment for strongyloidiasis (e.g., with IVM) should be considered for persons from areas where *Strongyloides* is endemic.[6]	• 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

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Fluvoxamine					
Fluvoxamine	**Dose for COVID-19 in Clinical Trials:** • Various dosing regimens used	• Nausea • Diarrhea • Dyspepsia • Asthenia • Insomnia • Somnolence • Sweating • Suicidal ideation (rare)	• Hepatic function • Drug interactions • Monitor for withdrawal symptoms when tapering dose.	• 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**. • A list of clinical trials is available: Fluvoxamine
Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors					
Lenzilumab	**Dose for COVID-19 in Clinical Trial:** • Lenzilumab 600 mg IV infusion every 8 hours times 3 doses[7]	• No treatment-emergent SAEs were reported in clinical trials.	• CBC with differential • Liver enzymes • Infusion reactions • HSR	• Data not available	• A list of clinical trials is available: Lenzilumab
Mavrilimumab	**Dose for COVID-19 in Clinical Trial:** • Mavrilimumab 6 mg/kg IV infusion once[8]	• No treatment-emergent SAEs were reported in clinical trials.	• CBC with differential • Liver enzymes • Infusion reactions • HSR	• Data not available	• A list of clinical trials is available: Mavrilimumab
Otilimab	**Dose for COVID-19 in Clinical Trial:** • Otilimab 90 mg IV infusion once[9]	• No treatment-emergent SAEs were reported in clinical trials.	• CBC with differential • Liver enzymes • Infusion reactions • HSR	• Data not available	• A list of clinical trials is available: Otilimab

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interferons					
Interferon Alfa	**Peg-IFN Alfa-2a** *Dose for MERS:* • Peg-IFN alfa-2a 180 µg SQ once weekly for 2 weeks[10,11] **IFN Alfa-2b** *Dose for COVID-19 in Clinical Trial:* • Nebulized IFN alfa-2b 5 million international units twice daily (no duration listed in the study methods)[12]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[13] • 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** use if Child-Pugh Score >6. • Renal function; reduce dose if CrCl <30 mL/min. • Depression, psychiatric symptoms	• 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.

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	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[11] *Dose for COVID-19:* • Dose and duration unknown **IFN Beta-1b** *Dose for COVID-19 in Clinical Trial:* • IFN beta-1b 8 million international units SQ every other day, up to 7 days total[14]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[15] • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (elevation of ALT > of AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity	• CBC with differential • Liver enzymes • 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 IFN-beta products are available in the United States; product doses differ. *IFN Beta-1a Products:* • Avonex, Rebif *IFN Beta-1b Products:* • Betaseron, Extavia

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-1 Inhibitors					
Anakinra	**Dose for Rheumatoid Arthritis:** • Anakinra 100 mg SQ once daily **Dose for COVID-19 in Clinical Trials:** • 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 and angioedema • Headache • Nausea • Diarrhea • Sinusitis • Arthralgia • Flu-like symptoms • Abdominal pain • Injection site reactions • Liver enzyme elevations	• CBC with differential • Liver enzymes • Renal function; reduce dose if CrCl <30 mL/min.	• Use with TNF-blocking agents **is not recommended** due to increased risk of infection. • **Avoid** concomitant administration of live vaccines.	• A list of clinical trials is available: Anakinra • Anakinra for IV administration is not an approved formulation in the United States.[16]
Canakinumab	**Dose for Systemic Juvenile Idiopathic Arthritis:** • Canakinumab 4 mg/kg (maximum 300 mg) SQ every 4 weeks[17] **Dose for COVID-19 in Clinical Trials:** • Dose and duration vary by study *CAN-COVID Trial:* • Single weight-based dose of canakinumab in 250 mL of 5% dextrose by IV infusion over 2 hours:[18] • 40 to <60 kg: 450 mg • 60–80 kg: 600 mg • >80 kg: 750 mg	• HSR • Neutropenia • Nasopharyngitis • Diarrhea • Respiratory tract infections • Bronchitis • Gastroenteritis • Pharyngitis • Musculoskeletal pain • Vertigo • Abdominal pain • Injection site reactions • Liver enzyme elevations	• HSR • CBC with differential • Liver enzymes	• Binding of canakinumab to IL-1 may increase formation of CYP450 enzymes and alter metabolism of drugs that are CYP450 substrates. • Use with TNF-blocking agents **is not recommended** due to potential increased risk of infection. • **Avoid** concomitant administration of live vaccines.	• A list of clinical trials is available: Canakinumab • Canakinumab for IV administration is not an approved formulation in the United States.[17]

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors					
Anti-Interleukin-6 Receptor Monoclonal Antibodies					
Sarilumab[19]	**Dose for COVID-19 in Clinical Trials:** • Single dose of sarilumab 400 mg IV[20] • The only FDA-approved route of administration for sarilumab is SQ. In the REMAP-CAP trial, an SQ formulation of sarilumab 400 mg (in a prefilled syringe) was reconstituted in 100 mL 0.9% NaCl and given as an IV infusion over 1 hour. • Sarilumab infusion should be used within 4 hours of preparation; it can be stored at room temperature until administered.[21]	• Neutropenia, thrombocytopenia • GI perforation • HSR • Increased liver enzymes • HBV reactivation • Infusion-related reaction	• HSR • Infusion reactions • Neutrophils • Platelets • Liver enzymes	• Elevated IL-6 may downregulate CYP450 enzymes; thus, use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. • The effects of sarilumab on CYP450 enzymes may persist for weeks after the drug is stopped.	• Treatment with sarilumab may mask signs of acute inflammation or infection 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. • In the REMAP-CAP trial, SQ formulations of sarilumab were reconstituted for IV administration.[21]

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors, continued					
Anti-Interleukin-6 Receptor Monoclonal Antibodies, continued					
Tocilizumab[22]	**EUA Dose for COVID-19** *For Hospitalized Patients Aged ≥2 Years Based on Body Weight:* • Weighing <30 kg: Tocilizumab 12 mg/kg administered by IV infusion over 1 hour • Weighing ≥30 kg: Tocilizumab 8 mg/kg (maximum dose 800 mg) administered by IV infusion over 1 hour • Per the EUA, if clinical signs or symptoms worsen or do not improve following the first infusion, 1 additional dose of tocilizumab may be administered at least 8 hours after the first dose.	• Infusion-related reaction • HSR • GI perforation • Hepatotoxicity • Treatment-related changes on laboratory tests for neutrophils, platelets, lipids, and liver enzymes • HBV reactivation • Secondary infections	• HSR • Infusion reactions • Neutrophils • Platelets • Liver enzymes • Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids. Prophylactic treatment for strongyloidiasis (e.g., with IVM) should be considered for persons from areas where *Strongyloides* is endemic.[6]	• Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • The effects of tocilizumab on CYP450 enzymes may persist for weeks after the drug is stopped.	• Tocilizumab use **should be avoided** in patients who are significantly immunocompromised. The safety of using tocilizumab plus a corticosteroid in immunocompromised patients is unknown. • The SQ formulation of tocilizumab **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab **Availability:** • IV tocilizumab, which has been approved for non-COVID-19 indications, is available commercially and through an FDA EUA for the treatment of COVID-19 in hospitalized adults and pediatric patients aged ≥2 years who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive mechanical ventilation, IMV, or ECMO. The EUA does not authorize the use of tocilizumab for SQ administration for the treatment of COVID-19.[23]

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	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[24] **Dose for COVID-19:** • Dose and duration unknown	• Infusion-related reaction • HSR • GI perforation • Neutropenia • HTN • Dizziness • Rash • Pruritus • Hyperuricemia	• Neutrophils • HSR • Infusion reactions	• 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.	• Treatment with siltuximab 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 (i.e., 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) • Cardiac arrhythmias • 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 antagonists should be administered 2 hours after acalabrutinib.	• **Avoid** use in patients with severe hepatic impairment. • Patients with underlying cardiac risk factors, HTN, or acute infections may be predisposed to atrial fibrillation. • A list of clinical trials is available: Acalabrutinib

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors, continued					
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 • Cytopenia (i.e., thrombocytopenia, neutropenia, anemia) • HTN • Diarrhea • Musculoskeletal pain • Rash	• CBC with differential • BP • Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) • Cardiac arrhythmias • 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 (i.e., neutropenia, thrombocytopenia, anemia, leukopenia) • Atrial fibrillation and flutter • Infection • Rash • Bruising • Diarrhea • Cough • Musculoskeletal pain	• CBC with differential • Signs and symptoms of bleeding • Cardiac arrhythmias • 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

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Janus Kinase Inhibitors					
Baricitinib[25]	**EUA Dose for COVID-19**[26] *For Adults and Children Aged ≥9 Years Based on eGFR:* • ≥60 mL/min/1.73 m^2: Baricitinib 4 mg PO once daily • 30 to <60 mL/min/1.73 m^2: Baricitinib 2 mg PO once daily • 15 to <30 mL/min/1.73 m^2: Baricitinib 1 mg PO once daily • eGFR <15 mL/min/1.73 m^2: **Not recommended** *For Children Aged 2 to <9 Years Based on eGFR:* • ≥60 mL/min/1.73m^2: Baricitinib 2 mg PO once daily • 30 to <60 mL/min/1.73m^2: Baricitinib 1 mg PO once daily • <30 mL/min/1.73m^2: N**ot recommended** **Duration of Therapy:** • For up to 14 days or until hospital discharge	• Lymphoma and other malignancies • Thrombosis • GI perforation • Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes • HSV reactivation • Herpes zoster • Serious heart-related events (e.g., heart attack, stroke)	• CBC with differential • Renal function • Liver enzymes • New infections	• Dose modification is recommended when administering concurrently with a strong OAT3 inhibitor. • **Avoid** concomitant administration of live vaccines.	• Baricitinib for the treatment of COVID-19 is available through an FDA EUA. See the EUA for dosing guidance for patients with: • ALC <200 cells/μL • ANC <500 cells/μL • If increases in ALT or AST are observed and DILI is suspected, interrupt baricitinib treatment until the diagnosis of DILI is excluded. • A list of clinical trials is available: Baricitinib **Availability:** • Baricitinib, which has been approved for non-COVID-19 indications, is available commercially and through an EUA for the treatment of hospitalized patients with COVID-19 aged ≥2 years.[26]

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	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[27]	• Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster	• CBC with differential • Liver enzymes • New infections	• Dose modification required when administered with strong CYP3A4 inhibitor. • **Avoid** use with fluconazole dose >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 COVID-19 in Clinical Trial:** • Tofacitinib 10 mg PO twice daily for up to 14 days[28]	• Thrombotic events (e.g., PE, DVT, arterial thrombosis) • Anemia • Risk of infection • GI perforation • Diarrhea • Headache • Herpes zoster • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies • Serious heart-related events (e.g., heart attack, stroke)	• CBC with differential • Liver enzymes • 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. • Coadministration with strong CYP3A4 inducers **is not recommended**. • **Avoid** concomitant 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

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	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.	• Transfusion-related reactions • Vital signs at baseline and during and after infusion • Renal function; discontinue treatment if function deteriorates.	• 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; BP = blood pressure; CBC = complete blood count; CHF = congestive heart failure; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P450; DILI = drug-induced liver injury; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; 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; IVM = ivermectin; MAOI = monoamine oxidase inhibitor; MERS = Middle East respiratory syndrome; NaCl = sodium chloride; OAT = organic anion transporter; the Panel = the COVID-19 Treatment Guidelines Panel; PE = pulmonary embolism; Peg-IFN = pegylated interferon; P-gp= P-glycoprotein; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; RDV = remdesivir; SAE = serious adverse event; SQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

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