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-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 • Fluvoxamine • Granulocyte-macrophage colony-stimulating factor inhibitors for hospitalized patients • Inhaled corticosteroids 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 nonhospitalized patients **(BIIa)** • **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)** The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19: • **Colchicine** for hospitalized patients **(AI)**
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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Colchicine

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

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **colchicine** for the treatment of nonhospitalized patients with COVID-19, except in a clinical trial **(BIIa)**.
- 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

COLCORONA, a large randomized placebo-controlled trial that evaluated colchicine in outpatients with COVID-19, did not reach its primary efficacy endpoint of reducing hospitalizations and death.[4] However, 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, a slight reduction in hospitalizations was observed among those who received colchicine.

PRINCIPLE, another randomized, open-label, adaptive-platform trial that evaluated colchicine versus usual care, was stopped for futility when no significant difference in time to first self-reported recovery from COVID-19 between the colchicine and usual care recipients was found.[5]

The PRINCIPLE trial showed no benefit of colchicine, and the larger COLCORONA trial failed to reach its primary endpoint, found only a very modest effect of colchicine in the subgroup of patients with positive SARS-CoV-2 PCR results, and reported more gastrointestinal adverse events in those receiving colchicine. Therefore, the Panel **recommends against** the use of **colchicine** for the treatment of COVID-19 in nonhospitalized patients, except in a clinical trial **(BIIa)**.

For Hospitalized Patients With COVID-19

In the RECOVERY trial, a large randomized trial in hospitalized patients with COVID-19, colchicine demonstrated no benefit with regard to 28-day mortality or any secondary outcomes.[6] Based on the results from this large trial, the Panel **recommends against** the use of **colchicine** for the treatment of COVID-19 in hospitalized patients **(AI)**.

Clinical Data for COVID-19

Colchicine in Nonhospitalized Patients With COVID-19

The COLCORONA Trial

The COLCORONA trial was a contactless, double-blind, placebo-controlled, randomized trial in

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outpatients who received a diagnosis of COVID-19 within 24 hours of enrollment. Participants were aged ≥70 years or aged ≥40 years with at least 1 of the following risk factors for COVID-19 complications: 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. Participants reported by telephone the occurrence of any study endpoints at 15 and 30 days after randomization; in some cases, clinical data were confirmed or obtained 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 participants in the colchicine arm experienced gastrointestinal adverse events, including diarrhea which occurred in 13.7% of colchicine recipients versus 7.3% of placebo recipients ($P < 0.0001$). 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.

The PRINCIPLE Trial

PRINCIPLE is a randomized, open-label, platform trial that evaluated colchicine in symptomatic, nonhospitalized patients with COVID-19 who were aged ≥65 years or aged ≥18 years with comorbidities or shortness of breath, and who had symptoms for ≤14 days. Participants were randomized to receive colchicine 0.5 mg daily for 14 days or usual care. The coprimary endpoints, which included time to first self-reported recovery or hospitalization or death due to COVID-19 by Day 28, were analyzed using a Bayesian model. Participants were followed through symptom diaries that they completed online daily; those who did not complete the diaries were contacted by telephone on Days 7, 14, and 29. The investigators developed a prespecified criterion for futility, specifying a clinically meaningful benefit in time to first self-reported recovery as a hazard ratio ≥1.2, corresponding to about 1.5 days of faster recovery in the colchicine arm.

Results

- The study enrolled 4,997 participants: 212 participants were randomized to receive colchicine;

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2,081 to receive usual care alone; and 2,704 to receive other treatments.

- The prespecified primary analysis included participants with SARS-CoV-2 positive test results (156 in the colchicine arm; 1,145 in the usual care arm; and 1,454 in the other treatments arm).
- The trial was stopped early because the criterion for futility was met; the median time to self-reported recovery was similar in the colchicine arm and the usual care arm (HR 0.92; 95% CrI, 0.72–1.16).
- Analyses of self-reported time to recovery and hospitalizations or death due to COVID-19 among concurrent controls also showed no significant differences between the colchicine and usual care arms.
- There were no statistically significant differences in the secondary outcomes between the colchicine and usual care arms in both the primary analysis population and in subgroups, including subgroups based on symptom duration, baseline disease severity, age, or comorbidities.
- The occurrence of adverse events was similar in the colchicine and usual care arms.

Limitations

- The design of the study was open-label treatment.
- The sample size of the colchicine arm was small.

Colchicine in Hospitalized Patients With COVID-19

The RECOVERY Trial

In the RECOVERY trial, hospitalized patients with COVID-19 were randomized to receive colchicine (1 mg loading dose, followed by 0.5 mg 12 hours later, and then 0.5 mg twice daily for 10 days or until discharge) or usual care.[6]

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 mechanical ventilation or death.
- The incidence of new cardiac arrhythmias, bleeding events, and thrombotic events was similar in the 2 arms. Two serious adverse events were attributed to colchicine: 1 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.

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.[7]

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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 2 points on a 7-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% of participants in the colchicine arm vs. 18.0% in the standard of care arm; $P = 0.003$).

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.[8-11] 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 findings of these studies are difficult to interpret due to significant design or methodological limitations, including small sample sizes, 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.[12,13] 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.[12,14]

Considerations in Children

Colchicine is most commonly used in children to treat periodic fever syndromes and autoinflammatory conditions. Although colchicine is generally considered safe and well tolerated in children, there are no data on the use of the drug to treat pediatric acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C).

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References

1. van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. *Cochrane Database Syst Rev*. 2014(8):CD006190. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25123076.
2. Xia M, Yang X, Qian C. Meta-analysis evaluating the utility of colchicine in secondary prevention of coronary artery disease. *Am J Cardiol*. 2021;140:33-38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33137319.
3. Reyes AZ, Hu KA, Teperman J, et al. Anti-inflammatory therapy for COVID-19 infection: the case for colchicine. *Ann Rheum Dis*. 2021 May;80(5):550-557. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33293273.
4. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med*. 2021;9(8):924-932. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34051877.
5. PRINCIPLE Trial Collaborative Group, Dorward J, Yu L, et al. Colchicine for COVID-19 in adults in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.09.20.21263828v1.
6. RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Respir Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34672950.
7. Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. *JAMA Netw Open*. 2020;3(6):e2013136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32579195.
8. Brunetti L, Diawara O, Tsai A, et al. Colchicine to weather the cytokine storm in hospitalized patients with COVID-19. *J Clin Med*. 2020;9(9). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32937800.
9. Sandhu T, Tieng A, Chilimuri S, Franchin G. A case control study to evaluate the impact of colchicine on patients admitted to the hospital with moderate to severe COVID-19 infection. *Can J Infect Dis Med Microbiol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33133323.
10. Lopes MI, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. *RMD Open*. 2021;7(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33542047.
11. Salehzadeh F, Pourfarzi F, Ataei S. The impact of colchicine on the COVID-19 patients; a clinical trial. *Research Square*. 2020;Preprint. Available at: https://www.researchsquare.com/article/rs-69374/v1.
12. Colchicine (Colcrys) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022352s017lbl.pdf.
13. American College of Cardiology. AHA statement on drug-drug interactions with statins. 2016. Available at: https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2016/10/20/21/53/recommendations-for-management-of-clinically-significant-drug. Accessed November 2, 2021.
14. Indraratna PL, Virk S, Gurram D, Day RO. Use of colchicine in pregnancy: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2018;57(2):382-387. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29029311.

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Corticosteroids

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Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen,[1] presumably by mitigating the COVID-19-induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. There is no observed benefit of systemic corticosteroids in hospitalized patients with COVID-19 who do not require supplemental oxygen.[2] The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the use of corticosteroids in hospitalized patients with COVID-19 are based on results from these clinical trials (see Tables 4a and 4b for more information). There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19.

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

Systemic Corticosteroids in Patients With COVID-19

Nonhospitalized Patients

There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19. Therefore, the safety and efficacy of systemic corticosteroids in this population have not been established. Generally, systemic corticosteroids are associated with adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting (see General Management of Nonhospitalized Patients With Acute COVID-19 for further information). Patients with COVID-19 who are receiving **dexamethasone** or **another corticosteroid** for an underlying condition should continue this therapy as directed by their health care provider **(AIII)**.

Hospitalized Patients

The RECOVERY trial was a multicenter, open-label trial in the United Kingdom that randomly assigned 6,425 hospitalized patients to receive up to 10 days of dexamethasone plus standard care or standard care alone. Mortality at 28 days was lower among the patients who received dexamethasone than among those who received standard care alone.[2] This benefit of dexamethasone was observed in patients who were mechanically ventilated or who required supplemental oxygen at enrollment; in contrast, no benefit

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was seen in patients who did not require supplemental oxygen at enrollment.[2] For additional information on the RECOVERY trial, see Table 4a.

The CoDEX trial was a multicenter, open-label trial in Brazil that evaluated dexamethasone in patients who were mechanically ventilated due to acute respiratory distress syndrome (ARDS) induced by COVID-19. Although the trial was terminated early, the study results support the RECOVERY trial finding that systemic corticosteroids are beneficial in hospitalized patients with COVID-19. The trial randomly assigned 299 patients to receive either standard care plus intravenous (IV) dexamethasone 20 mg once daily for 5 days and then dexamethasone 10 mg once daily for 5 days or standard care alone. The mean number of days alive and free from mechanical ventilation over 28 days was greater in the dexamethasone arm than in the standard care alone arm. However, there were no differences between the arms in 28-day mortality, ICU-free days over 28 days, or duration of mechanical ventilation at 28 days.[3] See Table 4a for additional information.

Systemic corticosteroids used in combination with other agents, including other immunomodulators such as tocilizumab (see Interleukin-6 Inhibitors)[4,5] or baricitinib (see Kinase Inhibitors),[6] have demonstrated clinical benefit in subsets of hospitalized patients with COVID-19, especially those with early critical illness and/or with signs of systemic inflammation. For the Panel's recommendations on when to use dexamethasone with another immunomodulator, see Therapeutic Management of Hospitalized Adults With COVID-19.

Please see Tables 4a and 4b for data from clinical trials evaluating corticosteroid use for COVID-19.

Systemic Corticosteroids Other Than Dexamethasone

Systemic corticosteroids other than dexamethasone, including hydrocortisone[7,8] and methylprednisolone,[9,10] have been studied for the treatment of COVID-19 in several randomized trials. Some of these trials were stopped early due to under enrollment following the release of the RECOVERY trial results. Consequently, the sample size of many these trials was insufficient to assess efficacy (i.e., there were too few events to definitively confirm or exclude an effect, although many point estimates, if true, suggested a beneficial effect). Therefore, evidence to support the use of hydrocortisone or methylprednisolone for the treatment of COVID-19 is not as strong as evidence supporting the use of dexamethasone. Based on the available evidence, the Panel has concluded the following:

- 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 IV)[11] 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 2 divided doses daily.
  - *Short-acting corticosteroid:* Hydrocortisone; half-life 8 to 12 hours, administer in 2 to 4 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

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with ARDS, dexamethasone lacks mineralocorticoid activity and thus has minimal effect on sodium balance and fluid volume.[12]

Inhaled Corticosteroids in Patients With COVID-19

Inhaled corticosteroids have been identified as potential COVID-19 therapeutic agents because of their targeted anti-inflammatory effects on the lungs. In addition, certain inhaled corticosteroids have been shown to impair viral replication of SARS-CoV-2[13] and downregulate expression of the receptors used for cell entry.[14,15] Two open-label randomized controlled trials and 2 double-blind placebo-controlled trials provide additional insights regarding the role of inhaled corticosteroids 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 corticosteroids for the treatment of COVID-19.

Rationale

Inhaled budesonide was studied in 2 open-label randomized controlled trials in outpatients with mild symptoms of COVID-19.[16,17] The small STOIC trial suggested that initiation of inhaled budesonide in adult outpatients with mild COVID-19 may reduce the need for urgent care or emergency department assessment or hospitalization.[16] PRINCIPLE, a larger, open-label trial in nonhospitalized patients with COVID-19 at high risk of disease progression, found that use of inhaled budesonide did not affect the rate of hospitalization or death but did reduce the time to self-reported recovery.[18] The findings from these trials should be interpreted with caution given the open-label design of the studies and other limitations.

Inhaled ciclesonide was studied in 2 double-blind randomized placebo-controlled trials in outpatients with mild COVID-19. The primary endpoint in 1 study was time to alleviation of COVID-19-related symptoms. In this study, the use of inhaled ciclesonide did not reduce the time to self-reported recovery, but the therapy did reduce the number of subsequent COVID-related emergency department visits or hospitalizations. The robustness of this conclusion is uncertain given the small number of events, which is likely due to the relatively small number of participants with comorbidities.[19] In the smaller CONTAIN study, the combined use of inhaled and intranasal ciclesonide did not improve the resolution of fever and/or respiratory symptoms by Day 7.[20]

The above-described studies of inhaled corticosteroid therapy for outpatients with mild COVID-19 have identified inconsistent effects of the therapy on subsequent hospitalization, and similar placebo-controlled trials have not demonstrated that this therapy results in improvements in symptom resolution. The placebo-controlled studies did not enroll enough patients at high risk of disease progression, and therefore, further studies in this population are needed. For additional information on these trials, see Table 4b.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for certain adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Patients who are receiving inhaled corticosteroids may develop oral candidiasis.
- 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 infection, herpesvirus infections, strongyloidiasis, tuberculosis).[21-25]

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- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[26,27] Many clinicians would initiate empiric antiparasitic treatment (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).[28]
- Using 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. Therefore, it could reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should review a patient's medication regimen to assess the potential for drug-drug interactions.
- Using a CYP3A4 inhibitor with inhaled budesonide may lead to increased systemic absorption of budesonide, which may result in systemic adverse effects of the corticosteroid.

Considerations in Pregnancy

A short course of betamethasone or dexamethasone, which are both known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.[29,30]

A short course of dexamethasone for the treatment of COVID-19 during pregnancy offers the potential benefit of decreased maternal mortality and a low risk of fetal adverse effects. Therefore, the Panel recommends using **dexamethasone** in hospitalized pregnant patients with COVID-19 who are mechanically ventilated **(AIII)** or who require supplemental oxygen but 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, 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) but could be considered on a case-by-case basis. The 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 if the benefit is perceived to outweigh the risks. 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. There is insufficient evidence to recommend for or against the use of inhaled corticosteroids for pediatric patients with COVID-19. Corticosteroids are second to IV immunoglobulin as the most used therapy for the treatment of multisystem inflammatory syndrome in children (MIS-C).[31,32] See 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 underway or in development. Please see ClinicalTrials.gov for the latest information.

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References

1. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330-1341. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876694.
2. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
3. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307-1316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876695.
4. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33933206.
5. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
6. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled Phase 3 trial. *Lancet Respir Med*. 2021; Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34480861.
7. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298-1306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876689.
8. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324(13):1317-1329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876697.
9. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: an open-label randomized trial (GLUCOCOVID). *Wien Klin Wochenschr*. 2021;133(7-8):303-311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33534047.
10. Tang X, Feng YM, Ni JX, et al. Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial. *Respiration*. 2021;100(2):116-126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33486496.
11. Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet*. 2005;44(1):61-98. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15634032.
12. Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32043986.
13. Matsuyama S, Kawase M, Nao N, et al. The inhaled steroid ciclesonide blocks SARS-CoV-2 RNA replication by targeting the viral replication-transcription complex in cultured cells. *J Virol*. 2020;95(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33055254.
14. Finney LJ, Glanville N, Farne H, et al. Inhaled corticosteroids downregulate the SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. *J Allergy Clin Immunol*. 2021;147(2):510-519 e515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33068560.
15. Peters MC, Sajuthi S, Deford P, et al. COVID-19-related Genes in Sputum Cells in Asthma. Relationship to Demographic Features and Corticosteroids. *Am J Respir Crit Care Med*. 2020;202(1):83-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32348692.

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16. Ramakrishnan S, Nicolau DV Jr, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a Phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9(7):763-772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33844996.
17. PRINCIPLE Collaborative Group, Yu L, Bafadhel M, et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.10.21254672v1.
18. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021;398(10303):843-855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34388395.
19. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34807241.
20. Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN Phase II randomised controlled trial. *BMJ*. 2021;375:e068060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34728476.
21. Garg D, Muthu V, Sehgal IS, et al. Coronavirus disease (COVID-19) associated mucormycosis (CAM): case report and systematic review of literature. *Mycopathologia*. 2021;186(2):289-298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33544266.
22. Moorthy A, Gaikwad R, Krishna S, et al. SARS-CoV-2, uncontrolled diabetes and corticosteroids—an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis. *J Maxillofac Oral Surg*. 2021:1-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33716414.
23. Machado M, Valerio M, Alvarez-Uria A, et al. Invasive pulmonary aspergillosis in the COVID-19 era: An expected new entity. *Mycoses*. 2021;64(2):132-143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33210776.
24. Chauvet P, Mallat J, Arumadura C, et al. Risk Factors for invasive pulmonary aspergillosis in critically ill patients with coronavirus disease 2019-induced acute respiratory distress syndrome. *Crit Care Explor*. 2020;2(11):e0244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33205046.
25. Liu J, Wang T, Cai Q, et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic hepatitis B virus infection. *Hepatol Res*. 2020;50(11):1211-1221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761993.
26. Lier AJ, Tuan JJ, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020;103(4):1590-1592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32830642.
27. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2021;49(3):539-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32910321.
28. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020;324(7):623-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761166.
29. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics*. 1972;50(4):515-525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4561295.
30. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*. 2016;374(14):1311-1320. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26842679.
31. Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA*.

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2021;325(9):855-864. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33523115.

32. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children - initial therapy and outcomes. *N Engl J Med*. 2021;385(1):23-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133855.

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Table 4a. Systemic Corticosteroids: Selected Clinical Data

Last Updated: December 16, 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. Unless stated otherwise, the clinical trials listed below included participants aged 18 years or older.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Dexamethasone in Hospitalized Patients With COVID-19 in the United Kingdom[1]		

Key Inclusion Criterion:
• Hospitalized with suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criterion:
• Physician determination that risks of participation too great based on patient's medical history or an indication for corticosteroid therapy outside of the study
Interventions:
• DEX 6 mg IV or PO once daily plus SOC for up to 10 days or until discharge (n = 2,104)
• SOC alone (n = 4,321)
Primary Endpoint:
• All-cause mortality at 28 days
	Participant Characteristics:
	• Mean age 66 years; 64% men
	• 56% had ≥1 comorbidity; 24% with diabetes
	• 89% with laboratory-confirmed SARS-CoV-2 infection
	• Median duration of DEX therapy: 7 days
	• At randomization: 16% received MV or ECMO, 60% required supplemental oxygen but not MV, 24% required no supplemental oxygen
	• Received RDV: <1% in each arm
	• Received tocilizumab or sarilumab: 2% in DEX arm vs. 3% in SOC arm
	Primary Outcome:
	• Mortality at 28 days
	  • All participants: 23% in DEX arm vs. 26% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; P < 0.001).
	  • Participants who required MV or ECMO at randomization: 29% in DEX arm vs. 41% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81).
	  • Participants who required supplemental oxygen but not MV at randomization: 23% in DEX arm vs. 26% in SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94).
	  • Participants who did not require supplemental oxygen at randomization: 18% in DEX arm vs. 14% in SOC arm (rate ratio 1.19, 95% CI, 0.91–1.55).
		Key Limitations:
		• Open-label study
		• Published data did not include results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), AEs, and key subgroups (e.g., patients with comorbidities)
		• Participants who required supplemental oxygen (but not MV) had variable severity. It is unclear whether all patients in this group benefited from DEX or whether benefit is restricted to those requiring higher levels of supplemental oxygen
		• Patients >80 years were preferentially assigned to supplemental oxygen therapy (and not MV)
		• High mortality of this patient population may limit generalizability of results to populations with a lower baseline mortality
		Interpretation:
		• In hospitalized patients with severe COVID-19 who required supplemental oxygen, DEX reduced mortality at 28 days, with greatest benefit in those with MV at randomization.
		• No survival benefit of DEX in patients who did not require supplemental oxygen at baseline.

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Methods	Results	Limitations and Interpretation
CoDEX: Open-Label RCT of Dexamethasone in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19 in Brazil[2]		
Key Inclusion Criteria: • Confirmed or suspected COVID-19 • Received MV within 48 hours of meeting criteria for moderate to severe ARDS (PaO_2/FiO_2 ≤200 mm Hg) **Key Exclusion Criteria:** • Immunosuppressive drugs in past 21 days • Expected death within 24 hours **Interventions:** • DEX 20 mg IV daily for 5 days, then DEX 10 mg IV daily for 5 days or until ICU discharge (n = 151) • SOC alone (n = 148) **Primary Endpoint:** • Days alive and free from MV by Day 28 **Key Secondary Endpoints:** • All-cause mortality at Day 28 • ICU-free days by Day 28 • Duration of MV by Day 28 • Score on 6-point ordinal scale at Day 15 • SOFA score at 7 days	**Participant Characteristics:** • Mean age: 60 years in DEX arm vs. 63 years in SOC arm • Women: 40% in DEX arm vs. 35% in SOC arm • Obesity: 31% in DEX arm vs. 24% in SOC arm; DM: 38% in DEX arm vs. 47% in SOC arm • Vasopressor use: 66% in DEX arm vs. 68% in SOC arm; mean PaO_2/FiO_2: 131 mm Hg in DEX arm vs. 133 mm Hg in SOC arm • Median duration of DEX therapy: 10 days • None received RDV or tocilizumab • 35% in SOC arm received corticosteroids for indications such as bronchospasm or septic shock **Primary Outcome:** • Mean number of days alive and free from MV by Day 28: 7 days in DEX arm vs. 4 days in SOC arm ($P = 0.04$). **Secondary Outcomes:** • No differences in arms for Day 28 all-cause mortality (56.3% vs. 61.5%), ICU-free days, and duration of MV, or for Day 15 score on 6-point ordinal scale. • Mean SOFA score at 7 days: 6.1 in DEX arm vs. 7.5 in SOC arm ($P = 0.004$). **Other Outcome:** • Post hoc analysis of probability of death or MV by Day 15: 68% in DEX arm vs. 80% in SOC arm (OR 0.46; $P = 0.01$).	**Key Limitations:** • Open-label study • Underpowered; enrollment stopped after release of data from the RECOVERY trial • Patients discharged before 28 days were not followed for rehospitalization or mortality • High mortality in this study may limit generalizability to populations with a lower baseline mortality • More than one-third of those randomized to SOC also received corticosteroids **Interpretation:** • Compared with SOC alone, DEX increased the number of days alive and free of MV over 28 days in patients with COVID-19 and moderate to severe ARDS.

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Methods	Results	Limitations and Interpretation
COVID STEROID 2: Multinational Blinded RCT of Dexamethasone 12 mg Versus 6 mg in Adults With COVID-19 and Severe Hypoxemia[3]		

Key Inclusion Criteria:
• Confirmed SARS-CoV-2 infection
• Requiring oxygen ≥10 L/min, NIV, CPAP, or MV
Key Exclusion Criteria:
• Treated with DEX >6 mg (or equivalent)
• Treated with corticosteroid ≥5 days
• Invasive fungal infection
• Active TB
Interventions:
• DEX 12 mg IV once daily for up to 10 days (n = 503)
• DEX 6 mg IV once daily for up to 10 days (n = 497)
Primary Endpoint:
• Days alive without life support (MV, circulatory support, or kidney replacement therapy) at 28 days
Key Secondary Endpoints:
• Days alive without life support at 90 days
• Days alive and out of hospital at 90 days
• Mortality at 90 days
• Mortality at 28 days
• SAEs at 28 days
	Participant Characteristics:
	• Median age 65 years; 31% women
	• DM: 27% in 12 mg arm vs. 34% in 6 mg arm
	• Median onset of symptoms to hospitalization: 7 days
	• ICU care: 78% in 12 mg arm vs. 81% in 6 mg arm
	• Oxygen requirements: 54% on oxygen via nasal cannula or face mask (median flow rate 23 L/min); 25% via NIV; 21% via MV
	• 63% received RDV; 12% received IL-6 inhibitors or JAK inhibitors
	• Median duration of DEX treatment: 7 days in both arms
	Primary Outcome:
	• Median days alive without life support: 22 days in 12 mg arm vs. 20 days in 6 mg arm (adjusted mean difference 1.3 days; 95% CI, 0.0–2.6; $P = 0.07$).
	Secondary Outcomes:
	• At 90 days:
	  • Median days alive without life support: 84 days in 12 mg arm vs. 80 days in 6 mg arm.
	  • Median days alive and out of hospital: 62 days in 12 mg arm vs. 48 days in 6 mg arm.
	  • Mortality: 32% in 12 mg arm vs. 38% in 6 mg arm (adjusted relative risk 0.87; 99% CI, 0.70–1.07).
	• Mortality at 28 days: 27% in 12 mg arm vs. 32% in 6 mg arm (adjusted relative risk 0.86; 99% CI, 0.68–1.08).
	• SAEs, including septic shock and invasive fungal infections: 11% in 12 mg arm vs. 13% in 6 mg arm (adjusted relative risk 0.83; 99% CI, 0.54–1.29).
		Key Limitation:
		• The randomized intervention was <10 days in some patients because the trial allowed up to 5 days of DEX before enrollment
		Interpretation:
		• Among patients with COVID-19 and severe hypoxemia, DEX 12 mg once daily did not result in more days alive without life support at 28 days than DEX 6 mg once daily.

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Methods	Results	Limitations and Interpretation
CAPE COVID: Double-Blind RCT of Hydrocortisone Among Critically Ill Patients With COVID-19 in France[4]		

Key Inclusion Criteria:
• Confirmed SARS-CoV-2 infection or radiographically suspected COVID-19 with ≥1 of the following:
  • MV with PEEP ≥5 cm H_2O
  • PaO_2/FiO_2 <300 mm Hg and FiO_2 ≥50% on HFNC
  • PaO_2/FiO_2 <300 mm Hg on reservoir mask oxygen
  • Pulmonary severity index >130
Key Exclusion Criteria:
• Septic shock
• Do-not-intubate orders
Interventions:
• Continuous infusion of hydrocortisone 200 mg/day for 7 days, then 100 mg/day for 4 days, then 50 mg/day for 3 days; if improvement by Day 4, then 200 mg/day for 4 days, then 100 mg/day for 2 days, then 50 mg/day for 2 days (n = 76)
• Placebo (n = 73)
Primary Endpoint:
• Treatment failure (death or dependency on MV or high-flow oxygen) by Day 21
Key Secondary Endpoints:
• Need for MV, prone positioning, ECMO, inhaled nitric oxide
• Nosocomial infection by Day 28
• Clinical status on Day 21
	Participant Characteristics:
	• Mean age 62 years; 70% men; median BMI 28
	• 96% with confirmed SARS-CoV-2 infection
	• Median symptom duration: 9–10 days
	• Required MV: 81% at baseline
	• Received vasopressors: 24% in hydrocortisone arm vs. 18% in placebo arm
	• Received RDV and tocilizumab: <3%
	• Median duration of treatment with study drug: 11 days in hydrocortisone arm vs. 13 days in placebo arm ($P = 0.25$)
	Primary Outcome:
	• Treatment failure by Day 21: 42% in hydrocortisone arm vs. 51% in placebo arm ($P = 0.29$).
	Secondary Outcomes:
	• No difference in need for intubation or prone positioning (too few patients received ECMO or inhaled nitric oxide for comparisons).
	• Among patients who did not require MV at baseline, 50% in hydrocortisone arm vs. 75% in placebo arm required subsequent MV.
	• No difference in proportion with nosocomial infection by Day 28
	• Clinical status on Day 21: no difference in arms, but 15% deaths in hydrocortisone arm vs. 27% deaths in placebo arm ($P = 0.06$).
	• Discharged from ICU by Day 21: 57% in hydrocortisone arm vs. 44% in placebo arm; 23% in both arms still required MV.
		Key Limitations:
		• Underpowered; enrollment stopped after release of data from the RECOVERY trial
		• Limited information about comorbidities
		Interpretation:
		• Hydrocortisone did not reduce treatment failure at Day 21 in patients with COVID-19 and acute respiratory failure, although early termination limited power to detect difference between study arms.

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Methods	Results	Limitations and Interpretation
REMAP-CAP: Randomized, Open-Label, Adaptive Trial of Hydrocortisone in Patients With Severe COVID-19[5]		

Key Inclusion Criteria:
• Presumed or confirmed SARS-CoV-2 infection
• ICU admission for respiratory support
Key Exclusion Criteria:
• Presumed imminent death
• Systemic corticosteroid use
• >36 hours since ICU admission
Interventions:
• Hydrocortisone 50 mg IV 4 times daily for 7 days (n = 137)
• Septic shock-based hydrocortisone 50 mg IV 4 times daily for duration of shock (n = 146)
• No hydrocortisone (n = 101)
Primary Endpoint:
• Days free of respiratory and cardiovascular support up to Day 21
Key Secondary Endpoint:
• In-hospital mortality
	Participant Characteristics:
	• Mean age 60 years; 71% men
	• Mean BMI 29.7–30.9
	• 50% to 64% required MV
	Primary Outcomes:
	• No difference in organ support–free days at Day 21 (median 0 days in each group).
	• Median adjusted ORs for primary outcome for hydrocortisone arms compared to no hydrocortisone arm:
	  • OR 1.43 (95% CrI, 0.91–2.27) with 93% Bayesian probability of superiority for fixed-dose hydrocortisone arm.
	  • OR 1.22 (95% CrI, 0.76–1.94) with 80% Bayesian probability of superiority for septic shock-based hydrocortisone arm.
	Key Secondary Outcome:
	• No differences in mortality: 30% in fixed-dose hydrocortisone arm, 36% in septic shock-based hydrocortisone arm, 33% in no hydrocortisone arm.
		Key Limitations:
		• Open-label study
		• Early termination following release of RECOVERY trial results
		Interpretation:
		• Hydrocortisone did not increase support-free days in either the fixed-dose or the shock-dependent group, although early termination limited power to detect differences between study arms.

Single-Blind RCT of Methylprednisolone in Hospitalized Patients With COVID-19 Pneumonia in China[6]		
Key Inclusion Criteria: • Laboratory-confirmed SARS-CoV-2 infection • Chest CT-confirmed pneumonia • Hospitalized on general ward **Key Exclusion Criteria:** • Severe immunosuppression • Corticosteroid use for other diseases **Interventions:** • Methylprednisolone 1 mg/kg/day IV for 7 days (n = 43) • Saline (n = 43)	**Participant Characteristics:** • Mean age 56 years; 48% men • Median 8 days from symptom onset to randomization • At randomization, 71% received oxygen via nasal cannula **Primary Outcome:** • Clinical deterioration at 14 days: 5% in each arm (OR 1.0; 95% CI, 0.134–7.442; $P = 1.00$). **Secondary Outcomes:** • No difference (all $P > 0.05$) between methylprednisolone arm and saline arm for: • Clinical cure at 14 days: 51% vs. 58%	**Key Limitations:** • Small sample size • Terminated early because of decreasing incidence of COVID-19 pneumonia at study sites **Interpretation:** • The incidence of clinical deterioration did not differ between the methylprednisolone and control arms.

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Methods	Results	Limitations and Interpretation
Single-Blind RCT of Methylprednisolone in Hospitalized Patients With COVID-19 Pneumonia in China[6], continued		
Primary Endpoint: • Clinical deterioration at 14 days **Key Secondary Endpoints:** • Clinical cure at 14 days • Time to clinical cure • ICU admission • In-hospital mortality • Days hospitalized	• Time to clinical cure: 14 days vs. 12 days • ICU admission: 5% each • In-hospital mortality: 0% vs. 2% • Days hospitalized: 17 days vs. 13 days	

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; BMI = body mass index; CPAP = continuous positive airway pressure; CT = computed tomography; DEX = dexamethasone; DM = Diabetes mellitus; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PEEP = positive end-expiratory pressure; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SOFA = sequential organ failure assessment; TB = tuberculosis

References

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
2. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307-1316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876695.
3. COVID Steroid Trial Group, Munch MW, Myatra SN, et al. Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia: the COVID STEROID 2 randomized trial. *JAMA*. 2021;326(18):1807-1817. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34673895.
4. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298-1306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876689.
5. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324(13):1317-1329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876697.
6. Tang X, Feng YM, Ni JX, et al. Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial. *Respiration*. 2021;100(2):116-126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33486496.

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Table 4b. Inhaled Corticosteroids: Selected Clinical Data

Last Updated: December 16, 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 • Contraindication to inhaled budesonide **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 time from symptom onset to randomization: 6 days **Primary Outcomes:** • Percentage of patients who were hospitalized or died due to COVID-19 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 time to reported recovery: 11.8 days in budesonide arm vs. 14.7 days 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 participant self-report **Interpretation:** • Inhaled budesonide reduced time to reported recovery but not COVID-19-related hospitalization or death. • The clinical significance of self-reported time to recovery in an open-label study is unclear.
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)	**Participant Characteristics:** • Mean age 45 years; 58% women • 9% with CVD, 5% with DM • 95% with positive SARS-CoV-2 RT-PCR result • Median time from symptom onset to randomization: 3 days	**Key Limitations:** • Small, open-label trial • Early termination after statistical analysis determined that additional participants would not alter study outcome

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Methods	Results	Limitations and Interpretation
STOIC: Open-Label, Phase 2 RCT of Inhaled Budesonide in Nonhospitalized Adults with Early COVID-19[2], continued		
• Usual care (n = 73) **Primary Endpoint:** • COVID-19-related urgent care visit, including ED visit or hospitalization	**Primary Outcomes:** • Median duration of budesonide use: 7 days. • Percentage of patients with COVID-19-related urgent care visit or hospitalization: 1% in budesonide arm vs.14% in usual care arm (relative risk reduction 91%).	**Interpretation:** • In adult outpatients with mild COVID-19, inhaled budesonide may reduce the need for urgent care or ED assessment and/or hospitalization.
Phase 3, Double-Blind RCT of Inhaled Ciclesonide in Nonhospitalized Patients With COVID-19[3]		

Key Inclusion Criteria:
• Aged ≥12 years
• Positive SARS-CoV-2 molecular or antigen diagnostic test result in previous 72 hours
• ≥1 symptom of fever, cough, or dyspnea
Key Exclusion Criteria:
• Taken inhaled or intranasal corticosteroid within 14 days of enrollment or systemic corticosteroid within 90 days of enrollment
• Unable to use an inhaler
Interventions:
• Ciclesonide MDI 160 µg/actuation, 2 actuations twice a day for 30 days (n = 197)
• Placebo MDI twice a day for 30 days (n = 203)
Primary Endpoint:
• Time to alleviation of all COVID-19-related symptoms by Day 30
Key Secondary Endpoints:
• Alleviation of COVID-19-related symptoms by Day 30
• ED visit or hospital admission for COVID-19 by Day 30
• Hospital admission or death by Day 30
	Participant Characteristics:
	• Mean age 43.3 years; 55.3% women; 86.3% White
	• Mean BMI 29.4
	• 22.3% with HTN, 7.5% with type 2 DM
	• Higher rates of DM and asthma in ciclesonide arm
	Primary Outcome:
	• Median time to alleviation of all COVID-19-related symptoms: 19.0 days in ciclesonide arm vs. 19.0 days in placebo arm (HR 1.08; 95% CI, 0.84–1.38).
	Secondary Outcomes:
	• By Day 30, percentage of patients in whom the following outcomes occurred:
	  • Alleviation of COVID-19-related symptoms: 70.6% in ciclesonide arm vs. 63.5% in placebo arm.
	  • Subsequent ED visit or hospital admission for COVID-19: 1.0% in ciclesonide arm vs. 5.4% in placebo arm (OR 0.18; 95% CI, 0.04–0.85).
	  • Hospital admission or death: 1.5% in ciclesonide arm vs. 3.4% in placebo arm (OR 0.45; 95% CI, 0.11–1.84).
	• No deaths by Day 30 in either arm.
		Key Limitations:
		• ED or hospitalization outcome based on small number of events
		• Primary endpoint of time to alleviation of all symptoms based on participant self-report
		Interpretation:
		• Inhaled ciclesonide did not reduce time to reported recovery.
		• The robustness of the conclusion that inhaled ciclesonide reduced COVID-19-related ED visits or hospitalization is uncertain; there were only a small number of events, which is most likely due to the relatively low rate of comorbidities in the study population.

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Methods	Results	Limitations and Interpretation
CONTAIN: Double-Blind RCT of Inhaled and Intranasal Ciclesonide in Nonhospitalized Patients With COVID-19[4]		
Key Inclusion Criteria: • Aged ≥18 years • Positive SARS-CoV-2 molecular diagnostic test result • ≥1 symptom of fever, cough, or shortness of breath • Symptom duration ≤6 days **Key Exclusion Criteria:** • Already taking an inhaled corticosteroid or taken PO or IM corticosteroids within 7 days of enrollment • Unable to use an inhaler • No respiratory symptoms • Use of oxygen at home • COVID-19 vaccinated **Interventions:** • Ciclesonide MDI 600 µg/actuation and intranasal ciclesonide 100 µg, both twice a day for 14 days (n = 105) • Saline placebo MDI and intranasal saline, both twice a day for 14 days (n = 98) **Primary Endpoint:** • Resolution of fever and all respiratory symptoms at Day 7 **Key Secondary Endpoints:** • Resolution of fever and all respiratory symptoms at Day 14 • Hospital admission by Day 14	**Participant Characteristics:** • Median age 35 years; 54% women; 61% White • 20% with comorbid condition **Primary Outcome:** • Percentage of patients with resolution of fever and all respiratory symptoms at Day 7: 40% in ciclesonide arm vs. 35% in placebo arm (adjusted risk difference 5.5%; 95% CI, -7.8% to 18.8%). **Secondary Outcomes:** • Percentage of patients with resolution of fever and all respiratory symptoms at Day 14: 66% in ciclesonide arm vs. 58% in placebo arm (adjusted risk difference 7.5%; 95% CI, -5.9% to 20.8%). • Percentage of patients who were admitted to the hospital by Day 14: 6% in ciclesonide arm vs. 3% in placebo arm (adjusted risk difference 2.3%; 95% CI, -3.0% to 7.6%).	**Key Limitation:** • Small study with a relatively young, healthy population **Interpretation:** • The use of inhaled ciclesonide plus intranasal ciclesonide did not improve resolution of fever and respiratory symptoms in nonhospitalized patients with COVID-19.

Key: BMI = body mass index; CVD = cardiovascular disease; DM = diabetes mellitus; ED = emergency department; HTN = hypertension; IM = intramuscular; MDI = metered dose inhaler; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = oral; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction

References

1. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021;398(10303):843-855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34388395.

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2. Ramakrishnan S, Nicolau DV, Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a Phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9(7):763-772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33844996.
3. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34807241.
4. Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of COVID-19 in adult outpatients: CONTAIN Phase II randomised controlled trial. *BMJ*. 2021;375:e068060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34728476.

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Fluvoxamine

Last Updated: December 16, 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 on 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] Ongoing studies are establishing whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans and are clinically relevant in the setting of COVID-19.

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of fluvoxamine for the treatment of COVID-19.

Rationale

Three randomized trials have studied the use of fluvoxamine for the treatment of nonhospitalized patients with COVID-19. In STOP COVID, a contactless, double-blind randomized placebo-controlled trial conducted in the United States among nonhospitalized adults with mild COVID-19 diagnosed within 7 days of symptom onset, fluvoxamine (100 mg up to 3 times daily for 15 days) reduced clinical deterioration at Day 15.[3] Clinical deterioration was defined as shortness of breath plus oxygen saturation (SpO_2) <92% or hospitalization plus SpO_2 <92%. This was a small study (≤80 participants per arm) with limited cases of clinical deterioration and a short follow-up period. In addition, 24% of participants stopped responding to surveys prior to Day 15.

The subsequent STOP COVID 2, a Phase 3 randomized controlled trial (ClinicalTrials.gov Identifier NCT04668950) that enrolled >700 participants in the United States and Canada, was stopped for futility by a data safety monitoring board after lower than expected case rates and treatment effect were observed.[4]

TOGETHER is an adaptive platform, double-blind randomized placebo-controlled trial conducted in Brazil.[5] Nonhospitalized adults with COVID-19 and a known risk factor for progression to severe disease were randomized to fluvoxamine 100 mg twice daily (n = 741) or placebo (n = 756) for 10 days. Fluvoxamine use was associated with a lower risk of the primary composite outcome of retention in the emergency department for >6 hours or admission to a tertiary hospital (79 of 741 participants [11%] in the fluvoxamine arm vs. 119 of 756 participants [16%] in the placebo arm [relative risk 0.68; 95% CrI, 0.52–0.88]). Of note, 87% of the primary outcome events were hospitalizations. There was no statistically significant difference between study arms for the secondary outcomes of need for hospitalization or time to symptom resolution. There was no significant difference in mortality between study arms in the intention-to-treat (ITT) population (17 of 741 participants [2%] in the fluvoxamine arm vs. 25 of 756 participants [3%] in the placebo arm [OR 0.69; 95% CI, 0.36–1.27]). In a secondary, per-protocol analysis of participants who received >80% of possible doses, death was the outcome for 1 of 548 participants (<1%) in the fluvoxamine arm versus 12 of 618 participants (2%) in the placebo arm (OR 0.09; 95% CI, 0.01–0.47). Participants in the fluvoxamine arm were less likely to present to an emergency setting for COVID-19 for any duration, although this analysis was not prespecified.

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Compared with those in the placebo arm, participants who received fluvoxamine were less adherent to therapy and discontinued therapy due to intolerance more often.

While fluvoxamine treatment significantly reduced the primary composite outcome in the TOGETHER trial (i.e., retention in the emergency department for >6 hours or admission to a tertiary hospital), the difference in hospitalizations between arms was not significant.[5] Defining the clinical relevance of the >6 hour emergency department observation time endpoint is difficult, especially its applicability to practice settings in different countries. Moreover, the endpoint has not been used in other studies of interventions for nonhospitalized patients at high risk for hospitalization and death. While a per-protocol analysis found a significant treatment effect for mortality in patients taking >80% of possible doses (assessed by patient self-report), no such benefit was found in the primary ITT analysis. The 80% threshold has no clear justification, and only 74% of participants in the fluvoxamine arm reached this level of adherence. Since per-protocol analyses are not randomized comparisons, they can introduce bias when adherence is associated with factors that influence the outcome; this bias cannot be excluded in this study. Notably, mortality in the placebo arm was substantially higher in those with ≤80% adherence than in those with >80% adherence, suggesting that factors other than adherence differed in the per-protocol population. Finally, including only participants who could tolerate fluvoxamine does not reflect the actual effectiveness of the drug, since intolerance and adherence appeared to be related.

Additional studies are needed to provide more specific, evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19. Further details of the studies discussed are provided in Table 4c.

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, anxiety, headache), and rarely suicidal ideation.

Fluvoxamine is a cytochrome P450 (CYP) 2D6 substrate and a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9, CYP2D6, and CYP3A4.[6] Fluvoxamine can enhance the serotonergic effects of other SSRIs or monoamine oxidase inhibitors (MAOIs), resulting in serotonin syndrome; therefore, it should not be used within 2 weeks of receipt of other SSRIs or MAOIs. Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants; therefore, patients receiving these drugs should be closely monitored.

Considerations in Pregnancy

Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnancy are limited.[7,8] The association of SSRI use in the late third trimester with a small, increased risk of primary persistent pulmonary hypertension in newborns has not been excluded, although the absolute risk is likely low.[9] 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.[10] 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.[11] There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in children.

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Clinical Trials

See ClinicalTrials.gov for the latest information on studies of fluvoxamine and COVID-19.

References

1. Rosen DA, Seki SM, Fernandez-Castaneda A, et al. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. *Sci Transl Med*. 2019;11(478). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30728287.
2. Rafiee L, Hajhashemi V, Javanmard SH. Fluvoxamine inhibits some inflammatory genes expression in LPS/stimulated human endothelial cells, U937 macrophages, and carrageenan-induced paw edema in rat. *Iran J Basic Med Sci*. 2016;19(9):977-984. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27803785.
3. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. 2020;324(22):2292-2300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33180097.
4. Lenze E. Fluvoxamine for early treatment of COVID-19: the STOP COVID clinical trials. 2021. Available at: https://rethinkingclinicaltrials.org/news/august-20-2021-fluvoxamine-for-early-treatment-of-covid-19-the-stop-covid-clinical-trials-eric-lenze-md/. Accessed December 8, 2021.
5. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34717820.
6. Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab*. 2002;3(1):13-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11876575.
7. Einarson A, Choi J, Einarson TR, Koren G. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry*. 2009;54(4):242-246. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19321030.
8. Furu K, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. *BMJ*. 2015;350:h1798. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25888213.
9. Huybrechts KF, Bateman BT, Palmsten K, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA*. 2015;313(21):2142-2151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26034955.
10. Fluvoxamine maleate tablets [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021519s012lbl.pdf.
11. Safer DJ, Zito JM. Treatment-emergent adverse events from selective serotonin reuptake inhibitors by age group: children versus adolescents. *J Child Adolesc Psychopharmacol*. 2006;16(1-2):159-169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16553536.

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Table 4c. Fluvoxamine: Selected Clinical Data

Last Updated: December 16, 2021

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

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1]		
Key Inclusion Criteria: • Aged ≥50 years or aged ≥18 years with comorbidities • Laboratory-confirmed SARS-CoV-2 infection • ≤7 days of symptoms **Key Exclusion Criteria:** • Use of an SSRI • Severe mental illness • Cirrhosis, recent seizures, severe ventricular cardia arrythmia **Interventions:** • Fluvoxamine 100 mg PO twice daily for 10 days (n = 741) • Placebo (route, dosing frequency, and duration for some patients may have differed from fluvoxamine) (n = 756) **Primary Endpoint:** • Composite endpoint of emergency setting observation for >6 hours or hospitalization due to progression of COVID-19 within 28 days after randomization **Key Secondary Endpoints:** • Occurrence of COVID-19-related hospitalizations • Time to symptom resolution • Proportion of patients who were adherent to study drugs, defined as receiving >80% of possible doses	**Participant Characteristics:** • Median age 50 years; 58% women; 95% self-identified as mixed race • 13% with uncontrolled HTN; 13% with type 2 DM; 50% with BMI ≥30 kg/m^2 • Mean of 3.8 days from symptom onset to randomization **Primary Outcome:** • Proportion of patients who met the primary composite endpoint: 11% in fluvoxamine arm vs. 16% in placebo arm (relative risk 0.68; 95% CrI, 0.52–0.88) **Secondary Outcomes:** • 87% of clinical events were hospitalizations. • No difference between arms in COVID-19-related hospitalizations: 10% in fluvoxamine arm vs. 13% in placebo arm (OR 0.77; 95% CI, 0.55–1.05) • No difference between arms in time to symptom resolution. • Adherence: 74% in fluvoxamine arm vs. 82% in placebo arm (OR 0.62; 95% CI, 0.48–0.81). 11% in fluvoxamine arm vs. 8% in placebo arm stopped drug due to issues of tolerability. • Mortality (ITT): 2% in fluvoxamine arm vs. 3% in placebo arm (OR 0.68; 95% CI, 0.36–1.27)	**Key Limitations:** • The >6-hour emergency setting observation endpoint has not been used in other studies of interventions for nonhospitalized patients who are at high risk for hospitalization and death • As this was an adaptive platform trial where multiple investigational treatments or placebos were being evaluated simultaneously, not all patients in the placebo arm received a placebo that was matched to fluvoxamine by route of administration, dosing frequency, or duration of therapy • PP analyses are not randomized comparisons, and they introduce bias when adherence is associated with factors that influence the outcome • Adherence was self-reported and not verified **Interpretation:** • Fluvoxamine reduced the proportion of patients who met the composite endpoint of COVID-19-related hospitalization or retention in an emergency setting for >6 hours. • The use of fluvoxamine did not impact the incidence of COVID-19-related hospitalizations.

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Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1], continued		
• Mortality in both the primary ITT population and a PP population that included patients who took >80% of the study medication doses	• Mortality (PP): <1% in fluvoxamine arm vs. 2% in placebo arm (OR 0.09; 95% CI, 0.01–0.47)	• It is difficult to define the clinical relevance of the >6-hour emergency setting observation endpoint and apply it to practice settings in different countries. • Fluvoxamine did not have a consistent impact on mortality. • Fluvoxamine did not impact time to symptom resolution.
STOP COVID: Double-Blind RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in the United States[2]		

Key Inclusion Criteria:
• Aged ≥18 years
• Positive SARS-CoV-2 PCR result
• ≤7 days of symptoms
Key Exclusion Criteria:
• Immunocompromised
• Unstable medical comorbidities
Interventions:
• Fluvoxamine 50 mg PO for 1 dose, then fluvoxamine 100 mg twice daily, then fluvoxamine 100 mg 3 times daily through Day 15 (n = 80)
• Placebo (n = 72)
Primary Endpoint:
• Clinical deterioration within 15 days of randomization. Clinical deterioration was defined as:
  • Having dyspnea or being hospitalized for dyspnea or pneumonia; *and*
  • Having SpO_2 <92% on room air or requiring supplemental oxygen to attain SpO_2 ≥92%
Key Secondary Endpoint:
• Hospitalization
	Participant Characteristics:
	• Mean age 46 years; 72% women; 25% Black
	• 56% with obesity; 20% with HTN; 17% with asthma
	• Median of 4 days from symptom onset to randomization
	Primary Outcome:
	• Clinical deterioration: 0% in fluvoxamine arm vs. 8.3% in placebo arm (absolute difference 8.7%; 95% CI, 1.8% to 16.4%)
	Secondary Outcome:
	• No patients in fluvoxamine arm and 4 patients in placebo arm were hospitalized.
		Key Limitations:
		• Small sample size
		• Short follow-up period
		• Ascertaining clinical deterioration was challenging because all assessments were done remotely
		• 24% of patients stopped responding to follow-up prior to Day 15 but were included in the final analysis
		Interpretation:
		• Fluvoxamine reduced the proportion of patients who experienced clinical deterioration.
		• Due to significant limitations, it is difficult to draw definitive conclusions about the efficacy of using fluvoxamine to treat COVID-19.

Key: BMI = body mass index; DM = diabetes; HTN = hypertension; ITT = intention-to-treat; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = oral; PP = per protocol; RCT = randomized controlled trial; SpO_2 = oxygen saturation; SSRI = selective serotonin reuptake inhibitor

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References

1. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34717820.
2. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. 2020;324(22):2292-2300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33180097.

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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 4d.

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.

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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.

References

1. Mehta P, Porter JC, Manson JJ, et al. Therapeutic blockade of granulocyte macrophage colony-stimulating factor in COVID-19-associated hyperinflammation: challenges and opportunities. *Lancet Respir Med*. 2020;8(8):822-830. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32559419.
2. Thwaites RS, Sanchez Sevilla Uruchurtu A, Siggins MK, et al. Inflammatory profiles across the spectrum of disease reveal a distinct role for GM-CSF in severe COVID-19. *Sci Immunol*. 2021;6(57). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33692097.
3. Hamilton JA. GM-CSF in inflammation and autoimmunity. *Trends Immunol*. 2002;23(8):403-408. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12133803.
4. Lotfi N, Thome R, Rezaei N, et al. Roles of GM-CSF in the pathogenesis of autoimmune diseases: an update. *Front Immunol*. 2019;10:1265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31275302.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31986264.
6. Zhou Y, Fu B, Zheng X, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. *biorxiv*. 2020. Available at: https://www.biorxiv.org/content/10.1101/2020.02.12.945576v1.
7. De Luca G, Cavalli G, Campochiaro C, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol*. 2020;2(8):e465-e473. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32835256.
8. Lang FM, Lee KM, Teijaro JR, Becher B, Hamilton JA. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. *Nat Rev Immunol*. 2020;20(8):507-514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32576980.
9. Temesgen Z, Assi M, Shweta FNU, et al. GM-CSF Neutralization with lenzilumab in severe COVID-19 pneumonia: a case-cohort study. *Mayo Clin Proc*. 2020;95(11):2382-2394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33153629.
10. Burmester GR, Feist E, Sleeman MA, Wang B, White B, Magrini F. Mavrilimumab, a human monoclonal antibody targeting GM-CSF receptor-alpha, in subjects with rheumatoid arthritis: a randomised, double-blind, placebo-controlled, Phase I, first-in-human study. *Ann Rheum Dis*. 2011;70(9):1542-1549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21613310.
11. Patel J, Beishuizen A, Ruiz XB, et al. A randomized trial of otilimab in severe COVID-19 pneumonia (OSCAR). *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.14.21255475v1.

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12. Temesgen Z, Burger CD, Baker J, et al. Lenzilumab efficacy and safety in newly hospitalized COVID-19 subjects: results from the live-air Phase 3 randomized double-blind placebo-controlled trial. *medRxiv*. 2021;Preprint. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33972949.
13. Cremer PC, Abbate A, Hudock K, et al. Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Rheumatol*. 2021;3(6):e410-e418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33754144.
14. Chaulagain CP, Pilichowska M, Brinckerhoff L, Tabba M, Erban JK. Secondary pulmonary alveolar proteinosis in hematologic malignancies. *Hematol Oncol Stem Cell Ther*. 2014;7(4):127-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25300566.

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Table 4d. 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.

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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.

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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.

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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

References

1. Patel J, Beishuizen A, Ruiz XB, et al. A randomized trial of otilimab in severe COVID-19 pneumonia (OSCAR). *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.14.21255475v1.
2. Temesgen Z, Burger CD, Baker J, et al. Lenzilumab efficacy and safety in newly hospitalized COVID-19 subjects: results from the live-air Phase 3 randomized double-blind placebo-controlled trial. *medRxiv*. 2021;Preprint. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33972949.
3. Cremer PC, Abbate A, Hudock K, et al. Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Rheumatol*. 2021;3(6):e410-e418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33754144.

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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 acute 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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References

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

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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)**.

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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

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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

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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]

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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)**.

References

1. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior Phase III trial. *Crit Care Med*. 2016;44(2):275-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26584195.
2. Monteagudo LA, Boothby A, Gertner E. Continuous intravenous anakinra infusion to calm the cytokine storm in macrophage activation syndrome. *ACR Open Rheumatol*. 2020;2(5):276-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32267081.
3. Anakinra (Kineret) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf.
4. Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34480127.
5. CORIMUNO-19 Collaborative Group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. *Lancet Respir Med*. 2021;9(3):295-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33493450.
6. The REMAP-CAP Investigators, Derde LPG. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.
7. Caricchio R, Abbate A, Gordeev I, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. *JAMA*. 2021;326(3):230-239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34283183.
8. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis*. 2020;79(10):1381-1382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32376597.
9. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(6):e325-e331. Available at: https://pubmed.ncbi.nlm.nih.gov/32501454/.
10. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol*. 2020;2(7):e393-e400. Available at: https://pubmed.ncbi.nlm.nih.gov/32835245/.
11. Kooistra EJ, Waalders NJB, Grondman I, et al. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. *Crit Care*. 2020;24(1):688. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33302991.

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12. Fisher CJ, Jr., Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA*. 1994;271(23):1836-1843. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8196140.
13. Fisher CJ, Jr., Slotman GJ, Opal SM, et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med*. 1994;22(1):12-21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8124953.
14. Opal SM, Fisher CJ Jr, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a Phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med*. 1997;25(7):1115-1124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9233735.
15. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbiol Infect*. 2018;24 Suppl 2:S21-S40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29447987.
16. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumato*l. 2020;72(4):529-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32090480.
17. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-part II: analgesics and other drugs used in rheumatology practice. *Rheumatology (Oxford)*. 2016;55(9):1698-1702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26750125.
18. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653-661. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32593339.
19. Derespina KR, Kaushik S, Plichta A, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. *J Pediatr*. 2020;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32681989.
20. Dove ML, Jaggi P, Kelleman M, et al. Multisystem inflammatory syndrome in children: survey of protocols for early hospital evaluation and management. *J Pediatr*. 2021;229:33-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33075369.
21. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 2. *Arthritis Rheumatol*. 2021;73(4):e13-e29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33277976.
22. Harwood R, Allin B, Jones CE, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Adolesc Health*. 2021;5(2):133-141. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32956615.

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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 2 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 (NIV), or 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 **(BIII)**.

Additional Considerations

- Tocilizumab and sarilumab **should be used with caution** in patients with COVID-19 who have not been adequately represented in clinical trials. This includes patients who are significantly immunosuppressed, particularly those who have recently received other biologic immunomodulating drugs, and patients with any of the following:
  - 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 tocilizumab or sarilumab
- 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 assess the patient's clinical response to dexamethasone before deciding whether tocilizumab or sarilumab is needed.
- In both the REMAP-CAP and the RECOVERY trials, 29% of patients received a second dose of tocilizumab at the discretion of their treating physician. However, there is currently insufficient evidence to recommend either for or against a second dose of tocilizumab.[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 the antiparasitic drug 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]

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Rationale

The results of the RECOVERY and REMAP-CAP trials provide consistent evidence that tocilizumab, when coadministered 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 of efficacy for tocilizumab is more extensive than 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 an 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 4e.

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).[12-16]

Subsequently, in the setting of background corticosteroid therapy, the 2 largest randomized controlled trials evaluating tocilizumab, REMAP-CAP and RECOVERY, both reported a mortality benefit of tocilizumab in certain patients, including patients exhibiting rapid respiratory decompensation associated with an inflammatory response. REMAP-CAP enrolled critically ill patients who were within 24 hours of receiving respiratory support in an intensive care unit. The participants were randomized to receive open-label tocilizumab or usual care. In-hospital mortality was 28% in the tocilizumab arm and 36% in the usual care arm.[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 had hypoxemia and CRP levels ≥75 mg/L were offered enrollment into a second randomization that evaluated tocilizumab versus usual care. In this subgroup, the 28-day mortality was 31% in the tocilizumab arm and 35% in the usual care arm. For 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, see Therapeutic Management of Hospitalized Adults With COVID-19.

In contrast to the REMAP-CAP and RECOVERY trials, the REMDACTA trial did not find a mortality benefit of tocilizumab. The trial randomized hospitalized COVID-19 patients, most of whom required NIV or high-flow oxygen support, to receive tocilizumab or placebo. All the participants received

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remdesivir and most received corticosteroids. Tocilizumab use did not reduce 28-day mortality (18% in the tocilizumab arm and 20% in the placebo arm).[17]

Despite this conflicting evidence, the Panel's recommendations for using tocilizumab are based on the collective evidence from the clinical trials reported to date (see Table 4e).

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 control patients. Additional adverse effects of tocilizumab, such as serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation, have been reported.[18]

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 the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy.[19] Whether to use tocilizumab during pregnancy should be a joint decision between the pregnant individual and their health care provider, 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 on the effectiveness of tocilizumab for the treatment of acute COVID-19 in pediatric patients 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.[20] 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, NIV, 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, 1 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 4e.

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An adaptive Phase 2 and 3 double-blind randomized (2:2:1) placebo-controlled 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 in the United States in patients with severe and critical COVID-19 also failed to show a benefit of sarilumab. In this placebo-controlled trial, there was a reduction in mortality among the sarilumab recipients with critical COVID-19 pneumonia who required mechanical ventilation and received corticosteroids at baseline. However, due to the small sample size, this 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 in the sarilumab arm (n = 485) had more organ support-free days (OR 1.50; 95% CrI, 1.13–2.00) and a greater likelihood of survival 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 those in the sarilumab arm: randomization closed on November 2020 for the standard of care arm and continued through April 2021 for the sarilumab arm.[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 the exposed fetus.

Considerations in Children

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

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 1 hour.[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.

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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 the exposed fetus.

Considerations in Children

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

References

1. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2009;83(7):3039-3048. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19004938.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32171076.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31986264.
4. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020;71(15):769-777. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32176772.
5. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
6. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33933206.
7. Lier AJ, Tuan JJ, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020;103(4):1590-1592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32830642.
8. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2021;49(3):539-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32910321.
9. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-

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related strongyloides hyperinfection. *JAMA*. 2020;324(7):623-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761166.

10. The REMAP-CAP Investigators, Derde LPG. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.
11. Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist*. 2018;23(8):943-947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29622697.
12. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med*. 2020;383(24):2333-2344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33085857.
13. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med*. 2021;181(1):41-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080002.
14. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):32-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080017.
15. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;384(1):20-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33332779.
16. Rosas IO, Brau N, Waters M, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. *N Engl J Med*. 2021;384(16):1503-1516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631066.
17. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med*. 2021;47(11):1258-1270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34609549.
18. Charan J, Dutta S, Kaur R, et al. Tocilizumab in COVID-19: a study of adverse drug events reported in the WHO database. *Expert Opin Drug Saf*. 2021;20(9):1125-1136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34162299.
19. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol*. 2020;72(4):529-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32090480.
20. Food and Drug Administration. Letter of authorization: EUA for tocilizumab (Actemra) for the treatment of coronavirus disease 2019 (COVID-19). 2021. Available at: https://www.fda.gov/media/150319/download.
21. Lescure FX, Honda H, Fowler RA, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet Respir Med*. 2021;9(5):522-532. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33676590.
22. Sivapalasingam S, Lederer DJ, Bhore R, et al. A randomized placebo-controlled trial of sarilumab in hospitalized patients with COVID-19. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.05.13.21256973v3.
23. Gritti G, Raimondi F, Ripamonti D, et al. IL-6 signalling pathway inactivation with siltuximab in patients with COVID-19 respiratory failure: an observational cohort study. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v4.

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

Last Updated December 16, 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 within 28 days
• Among those not on MV at enrollment, receipt of MV or death within 28 days
	Participant Characteristics:
	• Mean age 63.6 years; 67% men; 76% White
	• 95% had PCR-confirmed SARS-CoV-2 infection
	• At baseline:
	  • 45% on conventional oxygen
	  • 41% on HFNC oxygen or NIV
	  • 14% on MV
	  • 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 MV 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 than usual care arm (57% vs. 50%; rate ratio 1.22; 95% CI, 1.12–1.33; $P < 0.0001$).
	• Proportion of patients not on MV at baseline who died or required MV within 28 days 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 COVID-19 patients with hypoxemia and elevated CRP, tocilizumab was associated with reduced all-cause mortality and shorter time to discharge.

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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 MV, NIV, 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 IV and possible second dose in 12–24 hours, 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.
Primary Endpoint:
• Composite ordinal endpoint of in-hospital mortality and organ support-free days to Day 21
	Participant Characteristics:
	• Mean age 60 years; 69% men; 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 oxygen or NIV
	  • 33% on MV
	  • 67% on corticosteroids in SOC 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 according to oxygen requirement at baseline.
	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 according to 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.

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Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive-Platform RCT of Tocilizumab and Sarilumab in Patients With COVID-19[2,3], continued		
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 (ordinal score) **Key Secondary Endpoints:** • Time to discharge • ICU LOS • Day 28 mortality	**Participant Characteristics:** • Mean age 61 years; 70% men; 58% White • 30% on HFNC oxygen or NIV • 14% on MV • 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 LOS 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 arm).	**Key Limitations:** • Modest power to detect differences in Day 28 clinical status • More patients in placebo arm than tocilizumab arm received corticosteroids • Few patients on MV **Interpretation:** • There was no difference between arms in Day 28 clinical status or survival. • The median times for recovery and ICU LOS were shorter in the tocilizumab arm than in the placebo arm.

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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:
• NIV or MV
Interventions:
• Single dose of tocilizumab 8 mg/kg plus SOC, possible second dose (n = 249)
• Placebo plus SOC (n = 128)
Primary Endpoint:
• MV, ECMO, or death by Day 28
Key Secondary Endpoints:
• Time to hospital discharge or readiness for discharge (ordinal score)
• All-cause mortality by Day 28
	Participant Characteristics:
	• Mean age 56 years; 59% men; 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 MV or ECMO or 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).
	Secondary Outcomes:
	• Median time to hospital discharge or readiness for discharge was 6.0 days in tocilizumab arm and 7.5 days in placebo arm (HR 1.16; 95% CI, 0.91–1.48).
	• All-cause mortality by Day 28 was 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 MV, ECMO, or death by Day 28 but provided no benefit for 28-day all-cause 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% men; 45% Hispanic/Latinx
	• 50% with BMI ≥30; 49% with HTN; 31% with DM
	• 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 rate of Day 28 MV 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 MV 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.

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Methods	Results	Limitations and Interpretation
BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[6], continued		
Key Exclusion Criteria: • Requiring supplemental oxygen at rate >10 L/min • Recent use of biologic agents or small molecule immunosuppressive therapy that investigators believe place the patient at a higher risk for infection **Interventions:** • Tocilizumab 8 mg/kg plus usual care (n = 161) • Placebo plus usual care (n = 81) **Primary Endpoint:** • MV or death, according to a time to event analysis; data censored at Day 28 **Key Secondary Endpoints:** • Clinical worsening by Day 28 (ordinal score) • Discontinuation of supplemental oxygen among patients receiving it at baseline	**Secondary Outcomes:** • No difference between arms in proportion of patients who had 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: • 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	**Participant Characteristics:** • Median age 59 years; 63% men; 77% White; 36% Hispanic/Latinx • 39% on HFNC oxygen, MV, or NIV • 42% with BMI ≥30; 43% with HTN; 26% with type 2 DM • 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). **Secondary Outcome:** • No difference among the arms in survival rate 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.

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Methods	Results	Limitations and Interpretation
Double-Blind, RCT of Sarilumab in Hospitalized Patients With Severe or Critical COVID-19[7], continued		
Key Secondary Endpoint: • Survival at Day 29		
REMDACTA: Double-Blind RCT of Tocilizumab and Remdesivir in Hospitalized Patients With Severe COVID-19 Pneumonia[8]		

Key Inclusion Criteria:
• PCR-confirmed SARS-CoV-2 infection
• Hospitalized with pneumonia confirmed by CXR or CT and requiring supplemental oxygen >6 L/min
Key Exclusion Criteria:
• eGFR <30 mL/min
• ALT or AST >5 times ULN
• Infection other than SARS-CoV-2
• Treatment with antivirals, CP, CQ, HCQ, JAK inhibitors
Interventions:
• Up to 10 days RDV plus:
  • Tocilizumab 8 mg/kg IV, with second dose within 8–24 hours if indicated (n = 434)
  • Placebo (n = 215)
Primary Endpoint:
• Time to discharge or "ready for discharge" through Day 28
Key Secondary Endpoints:
• Time to MV or death through Day 28
• Day 14 clinical status (ordinal score)
• Time to death through Day 28
	Participant Characteristics:
	• Mean age 59 years; 40% in tocilizumab arm and 34% in placebo arm aged ≥65 years
	• 63% men; 67% White
	• Respiratory support:
	  • 78% in tocilizumab arm and 83% in placebo arm on NIV or high-flow oxygen
	  • 15% in tocilizumab arm and 11% in placebo arm required MV or ECMO
	• Corticosteroid use:
	  • 83% in tocilizumab arm and 86% in placebo arm at baseline
	  • 88% in each arm during the trial
	Primary Outcome:
	• No difference between arms in time to discharge or "ready for discharge" through Day 28 (14 days in each arm; HR 0.97; 95% CI, 0.78–1.19; $P = 0.74$).
	Secondary Outcomes:
	• There was no difference between the arms in key secondary outcomes:
	  • Proportion of patients in each arm who required MV or died by Day 28 was 29%; time to death was non-evaluable (HR 0.98; 95% CI, 0.72–1.34; $P = 0.90$).
	  • Mean ordinal score for clinical status at Day 14 was 2.8 in tocilizumab arm and 2.9 in placebo arm ($P = 0.72$).
	  • 18% of patients in tocilizumab arm and 20% in placebo arm died by Day 28; time to death was non-evaluable (HR 0.95; 95% CI, 0.65–1.39; $P = 0.79$).
		Key Limitations:
		• During the trial, primary outcome changed from clinical status on Day 28 to time to discharge or "ready for discharge" to Day 28
		• Imbalances in patient characteristics at baseline between arms
		• Possible underrepresentation of patients with rapidly progressive disease
		Interpretation:
		• Compared with placebo plus RDV, tocilizumab plus RDV did not shorten the time to discharge or "ready for discharge" in patients with severe COVID-19 pneumonia.
		• There was no difference in mortality between the arms.

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Key: ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CP = convalescent plasma; CQ = chloroquine; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; LDH = lactate dehydrogenase; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; 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

References

1. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33933206.
2. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
3. The REMAP-CAP Investigators, Derde LPG. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.
4. Rosas IO, Brau N, Waters M, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. *N Engl J Med*. 2021;384(16):1503-1516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631066.
5. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;384(1):20-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33332779.
6. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med*. 2020;383(24):2333-2344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33085857.
7. Lescure FX, Honda H, Fowler RA, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet Respir Med*. 2021;9(5):522-532. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33676590.
8. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med*. 2021;47(11):1258-1270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34609549.

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

Last Updated: December 16, 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 certain hospitalized patients who require oxygen supplementation.
- 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 mechanical ventilation. However, a key limitation of the ACTT-2 trial is that corticosteroids were not used as the 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 1 elevated inflammatory marker at enrollment who were not on 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 antitumor necrosis factor inhibitors in people with rheumatoid arthritis found that tofacitinib was associated with additional serious adverse

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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 dose (2 mg once daily) 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, 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

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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 8-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 1 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 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, 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). However, subgroup analyses did not identify a statistically significant benefit of baricitinib versus placebo among patients receiving low-flow oxygen at baseline. The occurrence of adverse events, serious adverse events, serious infections, and venous thromboembolic events was comparable in the baricitinib and placebo arms.[6]

The COV-BARRIER trial added a critically ill cohort to the original study. In this cohort, participants on mechanical ventilation or ECMO at baseline (n = 101) were randomly assigned to baricitinib 4 mg (n = 51) or placebo (n = 50) for up to 14 days in combination with the standard of care. At baseline, 86% of participants were receiving corticosteroids and 2% were receiving remdesivir. Baricitinib significantly reduced the prespecified endpoint of 28-day all-cause mortality when compared with placebo (39.2% vs. 58.0%; HR 0.54; 95% CI, 0.31–0.96; $P = 0.03$). Significant reductions were also reported with baricitinib versus placebo in 60-day mortality (45% vs. 62%; $P = 0.027$) and hospital days (23.7 vs. 26.1 days; $P = 0.05$). The implications of these findings are limited due to the very small sample size of this addendum trial population.[19]

The collective data from these studies have informed the Panel's recommendations on the use of baricitinib in hospitalized patients with COVID-19. The specific recommendations and additional information on the rationale 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.

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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, 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.[20] Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.[21]

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.[22] 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, Phase 2 randomized controlled 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 2-point improvement on a 7-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.[23] A Phase 3 trial of ruxolitinib in patients with COVID-19-associated acute respiratory distress syndrome is currently in progress (ClinicalTrials.gov Identifier NCT04377620).

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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.[24] 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.[25] 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[26] and to prevent chronic graft-versus-host disease in stem cell transplant recipients.[27] 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.[28]

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of 6 patients with COVID-19 who were receiving the drug for a condition other than COVID-19.[28] 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.[29] 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.[30] Zanubrutinib is proposed to benefit patients with COVID-19 by modulating signaling that promotes inflammation.

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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.[26,31] Based on these data, use of BTK inhibitors that occurs during organogenesis may be associated with fetal malformations. The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.

Considerations in Children

The safety and efficacy of BTK inhibitors have not been evaluated in pediatric patients with COVID-19, and data on the use of the drugs in children with other conditions are extremely limited. Use of BTK inhibitors for the treatment of COVID-19 in pediatric patients **is not recommended**, except in a clinical trial.

References

1. Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN. The molecular regulation of Janus kinase (JAK) activation. *Biochem J*. 2014;462(1):1-13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25057888.
2. Bousoik E, Montazeri Aliabadi H. "Do we know jack" about JAK? A closer look at JAK/STAT signaling pathway. *Front Oncol*. 2018;8:287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30109213.
3. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clin Immunol.* 2020;214:108393. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32222466.
4. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20(4):400-402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32113509.
5. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Me*d. 2021;384(9):795-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33306283.
6. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled Phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407-1418. Available at: https://pubmed.ncbi.nlm.nih.gov/34480861/.
7. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;385(5):406-415. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133856.
8. Food and Drug Administration. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. 2021. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death. Accessed December 2, 2021.
9. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization (EUA) of baricitinib. 2021. Available at: https://www.fda.gov/media/143823/download.
10. Baricitinib (Olumiant) [package insert]. Food and Drug Administration. 2019. Available at:

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.

11. Posada MM, Cannady EA, Payne CD, et al. Prediction of transporter-mediated drug-drug interactions for baricitinib. *Clin Transl Sci*. 2017;10(6):509-519. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28749581.
12. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol*. 2020;72(4):529-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32090480.
13. Clowse ME, Feldman SR, Isaacs JD, et al. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf*. 2016;39(8):755-762. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27282428.
14. Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis*. 2018;24(12):2494-2500. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29982686.
15. Wieringa JW, van der Woude CJ. Effect of biologicals and JAK inhibitors during pregnancy on health-related outcomes in children of women with inflammatory bowel disease. *Best Pract Res Clin Gastroenterol*. 2020;44-45:101665. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32359679.
16. McInnes IB, Byers NL, Higgs RE, et al. Comparison of baricitinib, upadacitinib, and tofacitinib mediated regulation of cytokine signaling in human leukocyte subpopulations. *Arthritis Res Ther*. 2019;21(1):183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31375130.
17. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30-e31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32032529.
18. Hoang TN, Pino M, Boddapati AK, et al. Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. *Cell*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33278358.
19. Ely EW, Ramanan AV, Kartman CE, et al. Baricitinib plus standard of care for hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: results of a randomised, placebo-controlled trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.10.11.21263897v2.
20. Migita K, Izumi Y, Jiuchi Y, et al. Effects of Janus kinase inhibitor tofacitinib on circulating serum amyloid A and interleukin-6 during treatment for rheumatoid arthritis. *Clin Exp Immunol*. 2014;175(2):208-214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24665995.
21. Tofacitinib (Xeljanz) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s024,208246s010lbl.pdf.
22. Ruxolitinib (JAKAFI) [package insert]. 2020. Available at: https://www.jakafi.com/pdf/prescribing-information.pdf.
23. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32470486.
24. Owen C, Berinstein NL, Christofides A, Sehn LH. Review of Bruton tyrosine kinase inhibitors for the treatment of relapsed or refractory mantle cell lymphoma. *Curr Oncol*. 2019;26(2):e233-e240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31043832.
25. Roschewski M, Lionakis MS, Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol*. 2020;5(48). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32503877.
26. Ibrutinib (Imbruvica) [package insert]. Food and Drug Administration. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf.
27. Food and Drug Administration. FDA expands ibrutinib indications to chronic GVHD. 2017. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-ibrutinib-indications-chronic-

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gvhd. Accessed December 2, 2021.

28. Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. *Blood*. 2020;135(21):1912-1915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32302379.
29. Zanubrutinib (Brukinsa) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf.
30. Tam C, Grigg AP, Opat S, et al. The BTK inhibitor, Bgb-3111, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: initial report of a Phase 1 first-in-human trial. *Blood*. 2015;126(23):832. Available at: https://ashpublications.org/blood/article/126/23/832/136525/The-BTK-Inhibitor-Bgb-3111-Is-Safe-Tolerable-and.
31. Acalabrutinib (Calquence) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf.

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Table 4f. Characteristics of Immunomodulators

Last Updated: December 16, 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 drug interaction information, please refer to product labels and visit the Liverpool COVID-19 Drug Interactions website.
- 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 Nonhospitalized Adults With COVID-19, and Therapeutic Management of Hospitalized Adults With COVID-19.

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Colchicine *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
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 who receive the drug 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.

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Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Corticosteroids (Inhaled) *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Budesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials:** • Budesonide 800 mcg oral inhalation twice daily until symptom resolution or for up to 14 days[3,4]	• Secondary infections • Oral thrush • Systemic AEs (less common)	• Signs of AEs 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
Ciclesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials:** • Ciclesonide 160 mcg: 2 MDI inhalations twice daily for 30 days[5]	• Secondary infections • Oral thrush • Systemic AEs (less common)	• Signs of AEs involving the oral mucosa or throat including thrush • Signs of systemic corticosteroid effects (e.g., adrenal suppression)	• CYP3A4 substrate • Effect of strong CYP3A4 inhibitors on ciclesonide exposure is not expected to be as significant as that on budesonide.	• A list of clinical trials is available: Ciclesonide
Corticosteroid (Systemic) *Recommended by the Panel for the treatment of COVID-19 in certain nonhospitalized and hospitalized patients.*					

Dexamethasone (Systemic)	**Dose for COVID-19:**
	• DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge, whichever comes first[6]
		• 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.[7]
				• Moderate CYP3A4 inducer
				• CYP3A4 substrate
				• Although coadministration of RDV and DEX has not been formally studied, a clinically significant PK interaction is not predicted (Gilead, written communication, August 2020).
					• If DEX is not available, an alternative corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
					• The approximate total daily dose equivalencies for these glucocorticoids to DEX 6 mg (PO or IV) are:
					  • Prednisone 40 mg
					  • Methylprednisolone 32 mg
					  • Hydrocortisone 160 mg
					• A list of clinical trials is available: Dexamethasone

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Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Fluvoxamine *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Fluvoxamine	**Dose for COVID-19 in Clinical Trials:** • Various dosing regimens used, including: • Fluvoxamine 50 mg twice daily • Fluvoxamine 100 mg twice daily • Fluvoxamine 100 mg 3 times daily	• 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 CYP 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

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Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-1 Inhibitors *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Anakinra	**FDA-Approved 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 when used concomitantly with 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.	• Anakinra for IV administration is not an approved formulation in the United States.[8] • A list of clinical trials is available: Anakinra

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Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-1 Inhibitors, continued					

Canakinumab	**FDA-Approved Dose for Systemic Juvenile Idiopathic Arthritis:**
	• Canakinumab 4 mg/kg (maximum 300 mg) SQ every 4 weeks[9]
	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:[10]
	  • 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 CYP enzymes and alter metabolism of drugs that are CYP substrates.
				• Use with TNF-blocking agents **is not recommended** due to potential increased risk of infection.
				• **Avoid** concomitant administration of live vaccines.
					• Canakinumab for IV administration is not an approved formulation in the United States.[9]
					• A list of clinical trials is available: Canakinumab

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Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with 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 *Recommended by the Panel for the treatment of COVID-19 in certain nonhospitalized and hospitalized patients.*					
Sarilumab[11]	**Dose for COVID-19 in Clinical Trials:** • Single dose of sarilumab 400 mg IV[12] • 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.[13]	• 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 CYP enzymes; thus, use of sarilumab may lead to increased metabolism of drugs that are CYP substrates. • The effects of sarilumab on CYP 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.[13]
Tocilizumab[14]	**EUA Dose for COVID-19** *For Hospitalized Patients Aged ≥2 Years Based on Body Weight:* • <30 kg: Tocilizumab 12 mg/kg administered by IV infusion over 1 hour • ≥30 kg: Tocilizumab 8 mg/kg (maximum dose 800 mg) administered by IV infusion over 1 hour	• Infusion-related reaction • HSR • GI perforation • Hepatotoxicity • Treatment-related changes on laboratory tests for neutrophils, platelets, lipids, and liver enzymes • HBV reactivation	• 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.	• Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP substrates. • The effects of tocilizumab on CYP 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

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Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with 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[14], continued	• 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.	• Secondary infections	Prophylactic treatment for strongyloidiasis (e.g., with IVM) should be considered for persons from areas where *Strongyloides* is endemic.[7]		**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, NIV, MV, or ECMO. The EUA does not authorize the use of tocilizumab for SQ administration for the treatment of COVID-19.[15]
Anti-Interleukin-6 Monoclonal Antibody *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Siltuximab	**FDA-Approved Dose for Multicentric Castleman Disease:** • Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks[16] **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 CYP substrates. • The effects of siltuximab on CYP enzymes may persist for weeks after therapy is stopped.	• Treatment with siltuximab may mask signs of acute inflammation or infection by suppressing fever and CRP levels. • A list of clinical trials is available: Siltuximab

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Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors					
Janus Kinase Inhibitors *Baricitinib and Tofacitinib: Recommended by the Panel for the treatment of COVID-19 in certain nonhospitalized and hospitalized patients.* *Ruxolitinib: Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					

Baricitinib[17]	**EUA Dose for COVID-19**[18]
	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/1.73 m^2: Baricitinib 2 mg PO once daily
	• 30 to <60 mL/min/1.73 m^2: Baricitinib 1 mg PO once daily
	• <30 mL/min/1.73 m^2: **Not 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 cardiac-related events (e.g., MI, 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.[18]

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Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors, continued					
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[19]	• 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 doses >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 or until hospital discharge[20]	• 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 cardiac-related events (e.g., MI, 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

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Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Non-SARS-CoV-2 Specific Immunoglobulin *Primarily used for the treatment of multi-system inflammatory syndrome in children (MIS-C). Currently under investigation in clinical trials.*					
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; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P450; DEX = dexamethasone; 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; IL = interleukin; IV = intravenous; IVIG = intravenous immunoglobulin; IVM = ivermectin; MAOI = monoamine oxidase inhibitor; MDI = metered dose inhaler; MI= myocardial infarction; MV = mechanical ventilation; NaCl = sodium chloride; NIV = noninvasive ventilation; OAT = organic anion transporter; the Panel = the COVID-19 Treatment Guidelines Panel; PE = pulmonary embolism; P-gp= P-glycoprotein; PK = pharmacokinetic; PO = orally; RDV = remdesivir; SQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury

References

1. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a Phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med*. 2021;9(8):924-932. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34051877.

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2. Colchicine (Colcrys) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022352s017lbl.pdf.
3. Ramakrishnan S, Nicolau DV, Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a Phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9(7):763-772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33844996.
4. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021 Sep 4;398(10303):843-855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34388395.
5. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults With symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34807241.
6. Randomised Evaluation of COVID-19 Therapy (RECOVERY). Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. 2020. Available at: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19. Accessed February 9, 2021.
7. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020;324(7):623-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761166.
8. Anakinra (Kineret) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf.
9. Canakinumab (Ilaris) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125319s100lbl.pdf.
10. Caricchio R, Abbate A, Gordeev I, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. *JAMA*. 2021;326(3):230-239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34283183.
11. Sarilumab (Kevzara) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf.
12. Regeneron and Sanofi provide update on U.S. Phase 2/3 adaptive-designed trial of KEVZARA® (sarilumab) in hospitalized COVID-19 patients [press release]. 2020.
13. The REMAP-CAP Investigators, Derde LPG. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.
14. Tocilizumab (Actemra) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125276s131lbl.pdf.
15. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for actemra (tocilizumab). 2021. Available at: https://www.fda.gov/media/150321/download.
16. Siltuximab (Sylvant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125496s018lbl.pdf.

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 12/23/2021

17. Baricitinib (Olumiant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.
18. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization (EUA) of baricitinib. 2021. Available at: https://www.fda.gov/media/143823/download.
19. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32470486.
20. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;385(5):406-415. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133856.

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