

Immune-Based Therapy Under Evaluation for Treatment of COVID-19

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Given the hyperactive inflammatory effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), agents that modulate the immune response are being explored as adjunctive treatments for the management of moderate to critical COVID-19.¹ These agents include human blood-derived products and immunomodulatory therapies.

Some human blood-derived products are obtained from individuals who have recovered from SARS-CoV-2 infection (e.g., convalescent plasma, immunoglobulin products).^{2,3} These heterogeneous products are postulated to have either direct antiviral properties, such as with convalescent plasma, and/or immunomodulatory effects like those noted with mesenchymal stem cells.⁴ Additionally, neutralizing monoclonal antibodies directed against SARS-CoV-2 have been developed and are under investigation in clinical trials.⁵

Other agents in this group include therapeutics currently approved for the treatment of other immune and/or inflammatory syndromes. These agents include corticosteroids (e.g., glucocorticoids),⁶ which as a class possess a broad array of mechanisms to abrogate systemic inflammation, and more targeted anti-inflammatory treatments such as interleukin inhibitors,^{7,8} interferons,⁹ kinase inhibitors,¹⁰ and others.

In the following sections of the COVID-19 Treatment Guidelines, different blood-derived products and immunomodulators under investigation for the management of COVID-19 are discussed. Items discussed include the proposed rationale for use of these therapies, the clinical safety and efficacy data to date, and the COVID-19 Treatment Guidelines Panel's recommendations for their use.

References

1. Zhong J, Tang J, Ye C, Dong L. The immunology of COVID-19: is immune modulation an option for treatment? *Lancet Rheumatology*. 2020;2(7):e438-e436. Available at: [https://www.theLancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30120-X/fulltext#seccesstitle10](https://www.theLancet.com/journals/lanrhe/article/PIIS2665-9913(20)30120-X/fulltext#seccesstitle10).
2. Wang X, Guo X, Xin Q, et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.15.20065623v3>.
3. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis*. 2015;211(1):80-90. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25030060>.
4. Shetty AK. Mesenchymal stem cell infusion shows promise for combating coronavirus (COVID-19)-induced pneumonia. *Aging Dis*. 2020;11(2):462-464. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32257554>.
5. Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32539093>.
6. Horby P, Shen Lim W, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1>.
7. 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>.

8. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32350134>.
9. Zhou Q, Wei X, Xiang X, et al. Interferon-a2b treatment for COVID-19. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.06.20042580v1>.
10. 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;146(1):137-146. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32470486>.

Blood-Derived Products Under Evaluation for the Treatment of COVID-19

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Summary Recommendations
<ul style="list-style-type: none">• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:<ul style="list-style-type: none">• COVID-19 convalescent plasma• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins• The Panel recommends against the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial:<ul style="list-style-type: none">• Mesenchymal stem cells (All)• Non-SARS-CoV-2-specific intravenous immunoglobulins (IVIg) (AIII). This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion</p>

Convalescent Plasma

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Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.¹

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and nonrandomized studies, observational cohorts, and animal experiments—met the criteria for Emergency Use Authorization (EUA) issuance.^{2,3} Despite meeting the “may be effective” criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of convalescent plasma due to the lack of a randomized, untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population.^{4,5} Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing.

The Panel's assessment of the EAP data is consistent with the FDA statements in the convalescent plasma EUA documents.^{3,6,7}

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Adverse Effects

Before administering convalescent plasma to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank.

The available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications. These risks include transfusion-transmitted infections (e.g., human immunodeficiency

virus [HIV], hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.⁷

Additional risks include a theoretical risk of antibody-dependent enhancement and a theoretical risk of suppressed long-term immunity.

Considerations in Pregnancy

The safety and effectiveness of COVID-19 convalescent plasma during pregnancy have not been evaluated. Several ongoing clinical trials that are evaluating COVID-19 convalescent plasma include pregnant individuals.

Considerations in Children

The safety and effectiveness of COVID-19 convalescent plasma have not been evaluated in pediatric patients. Clinical trials of COVID-19 convalescent plasma in children are ongoing.

Product Availability

On August 23, 2020, the FDA authorized the use of convalescent plasma for the treatment of hospitalized patients with COVID-19.³ Both High Titer (i.e., Ortho VITROS SARS-CoV-2 IgG tested with signal-to-cutoff ratio ≥ 12) and Low Titer COVID-19 Convalescent Plasma are authorized for use.^{6,7} Access to convalescent plasma is no longer available through the Mayo Clinic EAP, which was discontinued on August 28, 2020. Please refer to the [FDA's Recommendations for Investigational COVID-19 Convalescent Plasma website](#) for guidance on the transfusion of investigational convalescent plasma while blood establishments develop the necessary operating procedures to manufacture COVID-19 convalescent plasma in accordance with the Conditions of Authorization set forth in the EUA.

People who have been fully recovered from COVID-19 for ≥ 2 weeks and who are interested in donating plasma can contact their local blood donation or plasma collection center or refer to the FDA's [Donate COVID-19 Plasma website](#).

Clinical Trials

Randomized clinical trials that are evaluating convalescent plasma for the treatment of COVID-19 are underway; a list is available at [ClinicalTrials.gov](#).

Clinical Data to Date

Open-Label Randomized Clinical Trial of Convalescent Plasma in Hospitalized Patients With Severe or Life-Threatening COVID-19

An open-label randomized clinical trial of convalescent plasma versus standard of care for patients with severe or life-threatening laboratory-confirmed COVID-19 was conducted in Wuhan, China, from February 14 to April 1, 2020. The primary outcome was time to clinical improvement within 28 days. Only plasma units with a SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer of at least 1:640 were transfused. The median time from symptom onset to study randomization was 27 days in the treatment group and 30 days in the control group.⁸

Due to the decreasing incidence of COVID-19 in Wuhan, the trial was terminated early after 103 of the planned 200 patients were enrolled. There was no significant difference between the treatment and control groups in time to clinical improvement within 28 days (HR 1.40; 95% CI, 0.79–2.49; $P = 0.26$). Among

those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference of 23%; OR 1.34; 95% CI, 0.98–1.83; $P = 0.07$). Among those with life-threatening disease, the proportion of patients who showed clinical improvement was similar between the treatment (21%) and control (24%) groups. There was no significant difference in mortality (16% vs. 24% of patients in the treatment and control groups, respectively; $P = 0.30$). At 24 hours, the rates of negative SARS-CoV-2 viral polymerase chain reaction were significantly higher in the convalescent plasma group (45%) than in the control group (15%; $P = 0.003$), and differences persisted at 72 hours.

Limitations

The study was not blinded, and, on average, convalescent plasma was administered approximately 1 month into the disease course. Also, the study was terminated early, and thus lacked sufficient power to detect differences in clinical outcomes between the study groups.

Open-Label Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (ConCOVID Study)

This study has not been peer reviewed.

An open-label randomized clinical trial of convalescent plasma versus standard of care for hospitalized patients with COVID-19 was conducted in 14 hospitals in the Netherlands from April 8 to July 1, 2020. Only plasma confirmed to have anti-SARS-CoV-2 neutralizing antibodies by a SARS-CoV-2 plaque reduction neutralization test (PRNT) and a PRNT50 titer $\geq 1:80$ was transfused. The primary endpoint was in-hospital mortality up to 60 days after admission.

The trial was halted prematurely by the investigators and the study's data safety monitoring board when the baseline SARS-CoV-2 neutralizing antibody titers of participant and convalescent plasma were found to be comparable, challenging the potential benefit of convalescent plasma for the study patient population. Fifty-three of 66 participants had anti-SARS-CoV-2 antibodies at baseline despite being symptomatic for a median time of only 10 days. Among 56 participants whose blood was tested using SARS-CoV-2 plaque reduction neutralization testing, 44 (79%) had neutralizing antibody levels that were comparable to those of 115 donors (median titers of 1:160 vs. 1:160, respectively, $P = 0.40$). When the trial was halted, 86 participants had been enrolled. No differences in mortality ($P = 0.95$), length of hospital stay ($P = 0.68$), or disease severity at Day 15 ($P = 0.58$) were observed between the study arms.⁴

Limitations

The study was terminated early, and thus lacked sufficient power to detect differences in clinical outcomes between the study groups.

Open-Label Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (PLACID Trial)

This study has not been peer reviewed.

An open-label, randomized clinical trial of convalescent plasma versus standard of care for hospitalized patients with COVID-19 was conducted in 39 tertiary care centers in India from April 22 to July 14, 2020. Patients with confirmed COVID-19 and signs of severe disease with hypoxia were eligible if matched donor plasma was available at the time of enrollment. Critically ill patients (those with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [$\text{PaO}_2/\text{FiO}_2$] < 200 mmHg or shock) were excluded. The primary outcome was time to disease progression through 28 days (i.e., to $\text{PaO}_2/\text{FiO}_2 < 100$ mmHg) or all-cause mortality at 28 days. Participants in the intervention arm received two doses of 200 mL plasma, transfused 24 hours apart. Antibody testing to assess titers of donated plasma was not available when the trial started.

Four-hundred and sixty-four participants were randomized; 235 were randomized into the convalescent plasma arm and 229 were randomized into the standard of care arm. The arms were well-balanced with regard to age (median of 52 years in both arms) and days from symptom onset to enrollment (median of 8 days in both arms). There was no difference in the primary outcome (time to disease progression and 28-day mortality) across the trial arms. The composite outcome occurred in 44 patients (18.7%) in the convalescent plasma arm and 41 (17.9%) in the control arm. Thirty-four participants (14.5%) in the convalescent plasma arm and 31 patients in the control arm (13.6%) died. In each arm, 17 participants progressed to severe disease (7.2% in the convalescent plasma arm vs. 7.4% in the standard of care arm).⁵

Limitations

SARS-CoV-2 antibody testing was not used to select donated convalescent plasma units; therefore, many participants may have received units with low titers of SARS-CoV-2 neutralizing antibodies. Additionally, the study was not blinded.

Prospective Safety Analyses and Retrospective Exploratory Analyses of Outcomes Among Tens of Thousands of Patients Receiving Open-Label COVID-19 Convalescent Plasma Through the Mayo Clinic Expanded Access Program

The [Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19](#) program was an open-label, nonrandomized EAP that was primarily designed to provide adult patients who have severe or life-threatening (critical) COVID-19 with access to convalescent plasma. Secondary objectives were to obtain data on the safety of the intervention. Exploratory objectives included assessment of 7-day and 28-day mortality. The program was sponsored by the Mayo Clinic and included a diverse range of clinical sites. SARS-CoV-2 antibody testing of plasma donors and assessment of SARS-CoV-2 neutralization potential were not mandated. Patients were transfused with 1 or 2 units (200–500 mL) of convalescent plasma. The main outcomes for the safety analysis were serious adverse events (SAEs), including death; SAEs were reported at 4 hours and at 7 days after transfusion, or as they occurred.^{3,6,9,10}

A peer-reviewed publication described the safety outcomes for the first 20,000 EAP plasma recipients, enrolled between April 3 and June 2, 2020.⁹ One-third of the participants were aged ≥ 70 years, 60% were men, and 71% had severe or life-threatening COVID-19. Twenty percent of the participants were African American, 35% were Hispanic/Latino, and 5% were Asian. Thirteen deaths were assessed as possibly or probably related to the convalescent plasma treatment. The 83 nonfatal SAEs that were assessed as possibly or probably related to the convalescent plasma treatment included 37 TACO events, 20 TRALI events, and 26 severe allergic reactions. The life-threatening events that were reported up to 7 days after transfusion included 87 thrombotic/thromboembolic complications, 406 sustained hypotension events, and 643 cardiac events. The overall mortality rate was 8.6% at 7 days.

Both the FDA and the Mayo Clinic performed retrospective, indirect evaluations of the efficacy of COVID-19 convalescent plasma by using subsets of EAP data, hypothesizing that patients who received plasma units with higher titers of neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower titers of antibodies. This analytic approach was not prespecified in the Mayo Clinic EAP protocol.

The FDA analysis included 4,330 patients, and donor neutralizing antibody titers were measured by the Broad Institute using a pseudovirus assay.⁶ The analysis revealed no difference in 7-day mortality between the patients who received high-titer plasma and those who received low-titer plasma, in the patient population overall, or in the subset of patients who were intubated. However, among nonintubated patients (approximately two-thirds of those analyzed), mortality within 7 days of transfusion was 11% for those who received high-titer plasma and 14% for those who received low-titer plasma ($P = 0.03$).³ In a post hoc analysis of patients aged < 80 years who were not intubated and who

were treated within 72 hours of COVID-19 diagnosis, 7-day mortality was lower among the patients who received high-titer plasma than among those who received low-titer plasma (6.3% vs. 11.3%, respectively; $P = 0.0008$).⁶

A similar efficacy analysis by the Mayo Clinic, which has not been peer reviewed, included 3,082 participants who received a single unit of plasma out of the 35,322 participants who had received plasma through the EAP by July 4, 2020. Antibody titers were measured by using the Ortho Clinical Diagnostics COVID-19 IgG assay, and outcomes in patients transfused with low- (lowest 18%), medium-, and high- (highest 17%) titer plasma were compared. After adjusting for baseline characteristics, the 30-day mortality in the low-titer group was 29% and 25% in the high-titer group. This difference did not reach statistical significance. Similar to the FDA analyses, post hoc subgroup analyses suggested a benefit of high-titer plasma in patients aged <80 years who received plasma within 3 days of COVID-19 diagnosis and who were not intubated.¹⁰

Limitations

- The lack of an untreated control arm limits interpretation of the safety and efficacy data. For example, the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded.
- The EAP data may be subject to multiple confounders, including regional differences and temporal trends in the management of COVID-19.
- There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers in convalescent plasma from patients who have recovered from COVID-19 are highly variable.
- The efficacy analyses rely on a subset of EAP patients who only represent a fraction of the patients who received convalescent plasma through the EAP.
- The subgroup that demonstrated the largest estimated effect between high-titer and low-titer convalescent plasma—patients aged <80 years who were not intubated and who were transfused within 3 days of COVID-19 diagnosis—was selected post hoc by combining several subset rules which favored subgroups that showed a trend toward benefit of high-titer plasma. This approach tends to overestimate the treatment effect.
- The FDA analysis relied on 7-day mortality, which may not be clinically meaningful in the context of the prolonged disease course of COVID-19. Because participants in this observational study were not rigorously followed after they were discharged from the hospital, the 30-day mortality estimates are uncertain.

Other Clinical Studies of COVID-19 Convalescent Plasma

The results of retrospective case-controlled studies that evaluated outcomes among COVID-19 convalescent plasma recipients have been published.¹¹ In one such study of patients who were hospitalized between March 24 and April 8, 2020, at Mount Sinai Hospital in New York City, outcomes among 39 consecutive patients who received convalescent plasma with a SARS-CoV-2 anti-spike antibody titer of 1:320 were compared to outcomes among 156 propensity-score-matched controls. As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died ($P = 0.04$, log-rank test), and 72% and 67% of the transfused patients and control patients, respectively, had been discharged from the hospital. Subgroup analyses suggested a benefit of convalescent plasma among patients who were not intubated, had a shorter duration of symptoms, and received therapeutic anticoagulation.

Another study compared convalescent plasma with standard of care in patients with COVID-19 who were hospitalized between March 28 and July 6, 2020, at eight Houston Methodist hospitals. Outcomes for the

first 136 convalescent plasma recipients who reached Day 28 post-transfusion were compared with the outcomes for two sets of propensity-score matched controls at 28 days after admission. The analyses suggested a trend towards benefit of convalescent plasma, with larger differences in mortality seen primarily among subgroups of patients who were transfused early (i.e., within 72 hours of admission) with high-titer plasma (i.e., anti-spike protein receptor binding domain titer $\geq 1:1350$).¹²

Other smaller, uncontrolled case series that describe clinical outcomes in patients with COVID-19 have been reported and also suggest that SAEs are uncommon following COVID-19 convalescent plasma treatment.^{1,13-18}

Clinical Data for Other Viral Infections

The use of convalescent plasma has been evaluated for other viral diseases, such as SARS, with some suggestion of potential benefit.¹⁹⁻²¹ The only randomized controlled trial that demonstrated efficacy of convalescent plasma for an infectious disease was conducted more than 40 years ago, for treating Argentine hemorrhagic fever.²² No convalescent plasma products are currently approved by the FDA for the treatment of COVID-19.

References

1. Wang X, Guo X, Xin Q, et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32497196>.
2. Food and Drug Administration. Convalescent plasma letter of authorization. 2020. Available at: <https://www.fda.gov/media/141477/download>. Accessed August 31, 2020.
3. Food and Drug Administration. EUA 26382: Emergency Use Authorization (EUA) decision memo. 2020 Available at: <https://www.fda.gov/media/141480/download>. Accessed August 31, 2020.
4. Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Convalescent plasma for COVID-19: a randomized clinical trial. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1>.
5. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate COVID-19 in India: an open-label parallel-arm phase II multicentre randomized controlled trial (PLACID Trial). *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.09.03.20187252v2>.
6. Food and Drug Administration. EUA 26382: emergency use authorization (EUA) request. 2020. Available at: <https://www.fda.gov/media/141481/download>.
7. Food and Drug Administration. EUA of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients: fact sheet for health care providers. 2020. Available at: <https://www.fda.gov/media/141478/download>. Accessed September 22, 2020.
8. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32492084>.
9. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clinical Proceedings*. 2020. Available at: https://mayoclinicproceedings.org/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp_ft95_6_8.pdf. Accessed June 26, 2020.
10. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medRxiv*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32817978>.
11. Liu STH, Lin HM, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. *Nat Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32934372>.
12. Salazar E, Christensen PA, Graviss EA, et al. Treatment of coronavirus disease 2019 patients with

- convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32795424>.
13. Salazar E, Perez KK, Ashraf M, et al. Treatment of COVID-19 patients with convalescent plasma in Houston, Texas. *medRxiv*. 2020;Preprint. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32511574>.
 14. Ahn JY, Sohn Y, Lee SH, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. *J Korean Med Sci*. 2020;35(14):e149. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32281317>.
 15. Pei S, Yuan X, Zhang Z, et al. Convalescent plasma to treat COVID-19: Chinese strategy and experiences. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.07.20056440v1>.
 16. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32293713>.
 17. Zeng Q, Yu Z, Gou J, et al. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *The Journal of Infectious Diseases*. 2020;In press. Available at: <https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa228/5826985>.
 18. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci US*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32253318>.
 19. Burnouf T, Radosевич M. Treatment of severe acute respiratory syndrome with convalescent plasma. *Hong Kong Med J*. 2003;9(4):309; author reply 310. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12904626>.
 20. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis*. 2005;24(1):44-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15616839>.
 21. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis*. 2015;211(1):80-90. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25030060>.
 22. Maiztegui JI, Fernandez NJ, de Damián AJ. Efficacy of immune plasma in treatment of Argentine haemorrhagic fever and association between treatment and a late neurological syndrome. *Lancet*. 1979;2(8154):1216-1217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/92624>.

Immunoglobulins: SARS-CoV-2 Specific

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Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins** for the treatment of COVID-19.

Rationale

Currently, there are no clinical data on the use of SARS-CoV-2 immunoglobulins. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants.

Proposed Mechanism of Action and Rationale for Use in Patients with COVID-19

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response. The use of virus-specific immunoglobulins for other viral infections (e.g., cytomegalovirus [CMV] immunoglobulin for the prevention of post-transplant CMV infection and varicella zoster immunoglobulin for postexposure prophylaxis of varicella in individuals at high-risk) has proven to be safe and effective; however, there are currently no clinical data on the use of such products for COVID-19. Potential risks may include transfusion reactions. Theoretical risks may include antibody-dependent enhancement of infection.

Clinical Data

There are no clinical data on the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

Considerations in Pregnancy

Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children

Hyperimmunoglobulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data on their use for other respiratory viruses is limited.

Immunoglobulins: Non-SARS-CoV-2 Specific

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Recommendation

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

Rationale for Recommendation

Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, it is unknown whether products derived from the plasma of donors without confirmed SARS-CoV-2 infection contain high titer of SARS-CoV-2 neutralizing antibodies. Furthermore, although other blood components in IVIG may have general immunomodulatory effects, it is unclear whether these theoretical effects will benefit patients with COVID-19.

Clinical Data for COVID-19

This study has not been peer reviewed.

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

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

Considerations in Pregnancy

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

Considerations in Children

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

References

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

Mesenchymal Stem Cells

Last Updated: October 9, 2020

Mesenchymal stem cells are investigational products that have been studied extensively for broad clinical applications in regenerative medicine¹ and for their immunomodulatory properties.² It is hypothesized that mesenchymal stem cells could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **mesenchymal stem cells** for the treatment of COVID-19, except in a clinical trial (**AII**).

Rationale for Recommendation

No mesenchymal stem cells are approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. There are insufficient data to assess the role of mesenchymal stem cells for the treatment of COVID-19.

The FDA has recently issued several warnings about patients being potentially vulnerable to stem cell treatments that are illegal and potentially harmful.³ Several cord blood-derived products are currently licensed by the FDA for indications such as the treatment of cancer (e.g., stem cell transplant) or rare genetic diseases, and as scaffolding for cartilage defects and wound beds. None of these products are approved for the treatment of COVID-19 or any other viral disease.⁴ In the United States, mesenchymal stem cells **should not be used** for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access programs, or an Emergency Investigational New Drug application (**AII**).

Rationale for Use in COVID-19

Mesenchymal stem cells are multipotent adult stem cells that are present in most human tissues, including the umbilical cord. Mesenchymal stem cells can self-renew by dividing and can differentiate into multiple types of tissues, including osteoblasts, chondroblasts, adipocytes, hepatocytes, and others, which has led to a robust clinical research agenda in regenerative medicine. It is hypothesized that mesenchymal stem cells could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-CoV-2. Furthermore, mesenchymal stem cells lack the angiotensin-converting enzyme 2 receptor that SARS-CoV-2 uses for viral entry into cells; therefore, mesenchymal stem cells are resistant to infection.^{5,6}

Clinical Data

Data supporting the use of mesenchymal stem cells in patients with viral infections, including SARS-CoV-2 infection, are limited to case reports and small, open-label studies.

Clinical Data for COVID-19

- A pilot study of intravenous mesenchymal stem cell transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as critical, severe, or common type. Seven patients (one with critical illness, four with severe illness, and two with common-type illness) received mesenchymal stem cells; three patients with severe illness received placebo. All seven patients who received mesenchymal stem cells recovered. Among the three severely ill control patients, one died, one developed acute respiratory distress syndrome (ARDS), and one remained stable with severe disease.⁷

- A small clinical trial evaluated human umbilical cord mesenchymal stem cell (hUC-MSC) infusion in patients with severe COVID-19 who had not responded to standard of care therapies after 7 to 10 days of treatment. The standard of care therapies included supplemental oxygen, umifenovir/oseltamivir, antibiotics if indicated, and glucocorticosteroids. The study was intended as a randomized controlled trial; however, due to the lack of sufficient hUC-MSCs, it was not possible to randomize the participants as originally planned. Among the 41 patients eligible to participate in the study, 12 received hUC-MSC infusion and 29 received standard of care therapies only. The study arms were well balanced with regard to demographic characteristics, laboratory test results, and disease severity. All 12 participants who received hUC-MSC infusion recovered without requiring mechanical ventilation and were discharged to home, whereas four patients who received only standard of care therapies progressed to critical illness requiring mechanical ventilation, and three of these patients died. These results are not statistically significant and interpretation of the study is limited by its lack of randomization and small sample size.⁸

Clinical Data for Other Viral Infections

- In an open-label study of mesenchymal stem cells for the treatment of H7N9 influenza in China, 17 patients received mesenchymal stem cell treatment plus standard of care, and 44 patients received standard of care only. In the mesenchymal stem cell group, three patients (17.6%) died; in the control group, 24 patients (54.5%) died. The 5-year follow-up was limited to five patients in the mesenchymal stem cell group. No safety concerns were identified.⁹

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) for a list of clinical trials evaluating mesenchymal stem cells for the treatment of COVID-19, COVID-19-related ARDS, and COVID-19-associated multiorgan system inflammatory syndrome in children (MIS-C).

Adverse Effects

Risks associated with mesenchymal stem cell transfusion appear to be uncommon. The potential risks include failure of the cells to work as expected, potential for mesenchymal stem cells to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions.¹⁰

Considerations in Pregnancy

There are insufficient data to assess the risk of mesenchymal stem cell use during pregnancy.

Considerations in Children

There are insufficient data on the efficacy and safety of mesenchymal stem cell use in children.

References

1. Samsonraj RM, Raghunath M, Nurcombe V, Hui JH, van Wijnen AJ, Cool SM. Concise review: multifaceted characterization of human mesenchymal stem cells for use in regenerative medicine. *Stem Cells Transl Med.* 2017;6(12):2173-2185. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29076267>.
2. Li N, Hua J. Interactions between mesenchymal stem cells and the immune system. *Cell Mol Life Sci.* 2017;74(13):2345-2360. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28214990>.
3. Food and Drug Administration. FDA warns about stem cell therapies. 2019. Available at: <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>. Accessed June 26, 2020.

4. Food and Drug Administration. Approved cellular and gene therapy products. 2019. Available at: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>. Accessed June 26, 2020.
5. Lukomska B, Stanaszek L, Zuba-Surma E, Legosz P, Sarzynska S, Drela K. Challenges and controversies in human mesenchymal stem cell therapy. *Stem Cells Int*. 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31093291>.
6. Shetty AK. Mesenchymal stem cell infusion shows promise for combating coronavirus (COVID-19)-induced pneumonia. *Aging Dis*. 2020;11(2):462-464. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32257554>.
7. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2(-) mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis*. 2020;11(2):216-228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32257537>.
8. Shu L, Niu C, Li R, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. *Stem Cell Res Ther*. 2020;11(1):361. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32811531>.
9. Chen J, Hu C, Chen L, et al. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment. *Engineering (Beijing)*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32292627>.
10. Centers for Disease Control and Prevention. Stem cell and exosome products. 2019. Available at: <https://www.cdc.gov/hai/outbreaks/stem-cell-products.html>. Accessed June 26, 2020.

Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: August 27, 2020

Summary Recommendations
<p>Dexamethasone</p> <ul style="list-style-type: none">• On the basis of the preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated (AI) and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated (BI).• The Panel recommends against using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen (AI).• If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone (see Additional Considerations in the Corticosteroids section for dosing recommendations) (AIII). <p>Other Immunomodulators</p> <p>There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19:</p> <ul style="list-style-type: none">• Interleukin (IL)-1 inhibitors (e.g., anakinra)• Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. <p>The Panel recommends against the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial:</p> <ul style="list-style-type: none">• Anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab) (BI).• Interferons (alfa or beta) for the treatment of severely or critically ill patients with COVID-19 (AIII).• Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib) and Janus kinase inhibitors (e.g., baricitinib, ruxolitinib, tofacitinib) (AIII).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion</p>

Corticosteroids

Last Updated: August 27, 2020

Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, randomized, open-label trial in hospitalized patients with COVID-19, showed that the mortality rate was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care.¹ This benefit was observed in patients who required supplemental oxygen at enrollment. No benefit of dexamethasone was seen in patients who did not require supplemental oxygen at enrollment. Details of the RECOVERY trial are discussed in Clinical Data to Date below.¹

Recommendations for Patients With COVID-19

- On the basis of the preliminary report from the RECOVERY trial, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated (**AI**) and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated (**BI**).
- The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen (**AI**).
- If **dexamethasone** is not available, the Panel recommends using alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** (see Additional Considerations below for dosing recommendations) (**AIII**).

Rationale for Use in Patients With COVID-19

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

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus infections, strongyloidiasis, tuberculosis).

- The risk of reactivation of latent infections for a 10-day course of dexamethasone (6 mg once daily) is not well-defined. When initiating dexamethasone, appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in patients at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities) or fulminant reactivations of HBV should be considered.¹⁶⁻¹⁹
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. As such, it may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should review a patient's medication regimen to assess potential interactions.
- Coadministration of remdesivir and dexamethasone has not been formally studied, but a clinically significant pharmacokinetic interaction is not predicted.
- Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first.

Additional Considerations

- Whether use of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) for the treatment of COVID-19 provides the same benefit as dexamethasone is unclear. The total daily dose equivalencies for these drugs to dexamethasone 6 mg (oral or intravenous [IV])²⁰ are:
 - Prednisone 40 mg
 - Methylprednisolone 32 mg
 - Hydrocortisone 160 mg
- Half-life, duration of action, and frequency of administration vary among corticosteroids.
 - *Long-acting corticosteroid*: dexamethasone; half-life: 36 to 72 hours, administer once daily.
 - *Intermediate-acting corticosteroids*: prednisone and methylprednisolone; half-life: 12 to 36 hours, administer once daily or in two divided doses daily.
 - *Short-acting corticosteroid*: hydrocortisone; half-life: 8 to 12 hours, administer in two to four divided doses daily.
- Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; please refer to the [Critical Care](#) section for more information. Unlike other corticosteroids previously studied in ARDS, dexamethasone lacks mineralocorticoid activity and thus has minimal effect on sodium balance and fluid volume.¹⁰

Considerations in Pregnancy

A short course of betamethasone and dexamethasone, which are known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.^{21,22}

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

Considerations in Children

The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Importantly, the RECOVERY trial did not include a significant number of pediatric patients, and mortality rates are significantly lower among pediatric patients with COVID-19 than among adult patients with the disease. Thus, caution is warranted when

extrapolating the results of this trial to patients aged <18 years. Dexamethasone may be beneficial in pediatric patients with COVID-19 respiratory disease who require mechanical ventilation. Use of dexamethasone in patients who require other forms of supplemental oxygen support should be considered on a case-by-case basis and is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only). Additional studies are needed to evaluate the use of steroids for the treatment of COVID-19 in pediatric patients, including for multisystem inflammatory syndrome in children (MIS-C).

Clinical Data to Date

Multicenter, Randomized, Controlled Trial of Dexamethasone Versus Standard of Care in Hospitalized Patients

Study Design

The RECOVERY study is an ongoing, multicenter, open-label, adaptive trial sponsored by the National Health Service in the United Kingdom. Eligible participants were randomized to receive one of several potential treatments for COVID-19 plus the standard of care or standard of care alone. In one of the study arms, dexamethasone 6 mg daily was administered either orally or intravenously for up to 10 days or until hospital discharge, whichever came first. The primary study endpoint was all-cause mortality at 28 days after randomization. Secondary endpoints included time to hospital discharge, cause-specific mortality, need for renal replacement, major cardiac arrhythmia, and receipt and duration of ventilation.¹

Study Population

Hospitalized patients in the United Kingdom with clinically suspected COVID-19 or laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were eligible for enrollment. Patients were not enrolled into the dexamethasone study arm (or included in the analysis) if their physicians determined that the risks of participation were too great based on their medical history or that corticosteroid therapy was indicated. Recruitment into the dexamethasone arm was stopped by the study steering committee on June 8, 2020, when enough participants were enrolled to assess the benefit of dexamethasone therapy.

Preliminary Results

Participant characteristics:

- The preliminary analysis included 6,425 participants: 2,104 participants in the dexamethasone arm and 4,321 in the standard of care alone arm.
- SARS-CoV-2 infection was confirmed by laboratory testing in 89% of the participants.
- The mean age of the participants was 66.1 years, 64% of participants were male, and 56% had at least one major comorbidity, including 24% who had diabetes.
- At enrollment, 16% of participants required invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% had received supplemental oxygen but not invasive ventilation, and 24% required no oxygen supplementation.
- Few participants received remdesivir, hydroxychloroquine, lopinavir/ritonavir, or tocilizumab (0% to 3% of participants in both arms); approximately 8% of participants in the standard of care alone arm received dexamethasone after randomization. Use of azithromycin was balanced in both arms (24% in the dexamethasone arm vs. 25% in the standard of care alone arm).

Study endpoint analyses:

- Overall, 22.9% of participants in the dexamethasone arm and 25.7% in the standard of care alone arm died within 28 days of study enrollment (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; $P < 0.001$).

- There was an interaction between baseline severity of COVID-19 and the treatment effect of dexamethasone.
 - Survival benefit appeared greatest among participants who required invasive mechanical ventilation at randomization: 29.3% of participants in the dexamethasone arm died within 28 days of enrollment compared with 41.4% in the standard of care alone arm (rate ratio 0.64; 95% CI, 0.51–0.81).
 - Among patients who required supplemental oxygen but not mechanical ventilation at enrollment, 23.3% of participants in the dexamethasone arm and 26.2% in the standard of care alone arm died within 28 days of enrollment (rate ratio 0.82; 95% CI, 0.72–0.94).
 - No survival benefit was seen among participants who did not require oxygen therapy at enrollment; 17.8% of participants in the dexamethasone arm and 14.0% in the standard of care alone arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55).
- The risk of progression to invasive mechanical ventilation was lower in the dexamethasone group than in the standard of care alone group (rate ratio 0.77; 95% CI, 0.62–0.95).
- Results for several secondary endpoints (e.g., cause-specific mortality, need for renal replacement, major cardiac arrhythmia) have not yet been reported.

Limitations

- The study was randomized, but open label.
- In this preliminary report, the results for key secondary endpoints, potential adverse events, and efficacy of dexamethasone in key subgroups (e.g., patients with comorbidities) have not been reported.
- Study participants with COVID-19 who, according to their providers, required oxygen but not mechanical ventilation were a heterogeneous group of patients with respect to their severity of illness; it is unclear whether use of dexamethasone will be beneficial for other participant subsets (e.g., those who require lower rather than higher levels of supplemental oxygen). There were also no standardized or objective criteria for oxygen supplementation.
- The age distribution of participants differed by respiratory status at randomization. The participants who received mechanical ventilation were more likely to be aged <70 years. Among the participants who were aged >80 years, only 1% were mechanically ventilated, while 62% and 37% were in the oxygen group and no oxygen group, respectively. Therefore, the survival benefit of dexamethasone for mechanically ventilated patients aged >80 years is unknown.
- Remdesivir was used in only five patients in the RECOVERY trial; therefore, the safety and efficacy of coadministering remdesivir and dexamethasone are not known.
- Very few pediatric or pregnant patients with COVID-19 were included in the RECOVERY trial; therefore, the safety and efficacy of dexamethasone for the treatment of COVID-19 in children or in pregnant individuals are unknown.

Interpretation

In patients with severe COVID-19 who required oxygen support, the use of dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days in a preliminary analysis. The benefit of dexamethasone was most apparent in hospitalized patients who were mechanically ventilated. There was no observed benefit of dexamethasone in patients who did not require oxygen support. Further clarity on the mortality benefit of dexamethasone by baseline levels of oxygenation, age, sex, comorbidities, and/or duration of symptoms would better inform application of these findings. More details regarding the safety of dexamethasone and longer follow-up would assist in interpretation of this study.

Other Clinical Studies of Corticosteroid Use in COVID-19

Smaller retrospective cohort and case series studies have yielded conflicting results on the efficacy of corticosteroids for the treatment of COVID-19.²³ Several studies demonstrated the clinical benefit of using low-dose methylprednisolone early in the course of infection, including more rapid resolution of hypoxia, less need for mechanical ventilation, fewer intensive care unit transfers, and shorter hospital stays.²⁴ Additionally, other studies suggest a benefit of corticosteroids in lowering overall mortality in patients with moderate disease, severe disease, and ARDS,²⁵⁻²⁹ which is consistent with results from the RECOVERY study.

Conversely, results reported for other studies, including a meta-analysis of 15 studies in patients with coronavirus infections (e.g., COVID-19, SARS, MERS)³⁰ and a retrospective review of critically ill patients with COVID-19, suggest an increased risk of multiorgan dysfunction and no mortality benefit (and potentially an increased risk of death) with use of corticosteroids.³¹

These study results should be interpreted with caution, as the studies are retrospective and have methodological problems.

Clinical Trials

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

References

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
2. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990;323(21):1451-1457. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2233917>.
3. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29161116>.
4. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16968120>.
5. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26950335>.
6. Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med*. 2016;42(5):829-840. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26508525>.
7. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest*. 2007;131(4):954-963. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17426195>.
8. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354(16):1671-1684. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16625008>.
9. Liu L, Li J, Huang YZ, et al. [The effect of stress dose glucocorticoid on patients with acute respiratory

- distress syndrome combined with critical illness-related corticosteroid insufficiency]. *Zhonghua Nei Ke Za Zhi*. 2012;51(8):599-603. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23158856>.
10. Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32043986>.
 11. Rezk NA, Ibrahim AM. Effects of methyl prednisolone in early ARDS. *Egypt J Chest Dis Tuberc*. 2013;62(1):167-172. Available at: <https://www.sciencedirect.com/science/article/pii/S0422763813000265>.
 12. Tongyoo S, Permpikul C, Mongkolpun W, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care*. 2016;20(1):329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27741949>.
 13. Zhao WB, Wan SX, Gu DF, Shi B. Therapeutic effect of glucocorticoid inhalation for pulmonary fibrosis in ARDS patients. *Medical J Chinese People's Liberation Army*. 2014;39(9):741-745. Available at: <http://www.plamj.org/index.php/plamj/article/view/1009>.
 14. Mammen MJ, Aryal K, Alhazzani W, Alexander PE. Corticosteroids for patients with acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials. *Pol Arch Intern Med*. 2020;130(4):276-286. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32186831>.
 15. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32224769>.
 16. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761166>.
 17. Liu J, Wang T, Cai Q, et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic HBV infection. *Hepatol Res*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761993>.
 18. Centers for Disease Control and Prevention. Parasites—strongyloides: resources for health professionals. 2020. Available at: https://www.cdc.gov/parasites/strongyloides/health_professionals/index.html. Accessed August 14, 2020.
 19. Lier AJ, Tuan JL, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020. Available at: <http://www.ajtmh.org/content/journals/10.4269/ajtmh.20-0699>.
 20. 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>.
 21. 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>.
 22. 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>.
 23. Keller MJ, Kitsis EA, Arora S, et al. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19. *J Hosp Med*. 2020;15(8):489-493. Available at: <https://pubmed.ncbi.nlm.nih.gov/32804611>.
 24. Wang Y, Jiang W, He Q, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. *Signal Transduct Target Ther*. 2020;5(1):57. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32341331>.
 25. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):1-11.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32167524>.

26. Nelson BC, Laracy J, Shoucri S, et al. Clinical outcomes associated with methylprednisolone in mechanically ventilated patients with COVID-19. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32772069>.
27. Corral L, Bahamonde A, Arnaiz delas Revillas F, et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. *medRxiv*. 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.06.17.20133579v1>.
28. Fadel R, Morrison AR, Vahia A, et al. Early short course corticosteroids in hospitalized patients with COVID-19. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32427279>.
29. Fernandez-Cruz A, Ruiz-Antoran B, Munoz-Gomez A, et al. A retrospective controlled cohort study of the impact of glucocorticoid treatment in SARS-CoV-2 infection mortality. *Antimicrob Agents Chemother*. 2020;64(9):e01168-20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32571831>.
30. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. *J Infect*. 2020;81(1):e13-e20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32283144>.
31. Lu X, Chen T, Wang Y, Wang J, Yan F. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. *Crit Care*. 2020;24(1):241. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32430057>.

Interferons (Alfa, Beta)

Last Updated: August 27, 2020

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

Recommendation

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

Rationale

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

Clinical Data for COVID-19

Interferon Beta-1a

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

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

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

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

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

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

Interferon Alfa-2b

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

Clinical Data for SARS and MERS

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

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

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

Clinical Trials

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

Adverse Effects

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

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

Drug-Drug Interactions

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

Considerations in Pregnancy

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

Considerations in Children

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

References

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

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

Interleukin-1 Inhibitors

Last Updated: July 17, 2020

Recommendation

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

Rationale

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

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

Rationale for Use in Patients with COVID-19

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

Clinical Data for COVID-19

- A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra and 44 historical controls. The patients in both groups were all admitted to the same hospital in Paris, France. Case patients were consecutive admissions from March 24 to April 6, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia ($\text{SpO}_2 \leq 93\%$ with $\geq 6\text{L}/\text{min O}_2$) or worsening hypoxia ($\text{SpO}_2 \leq 93\%$ with $>3\text{L}/\text{min O}_2$ and a loss of $\geq 3\%$ of O_2 saturation on room air in the previous 24 hours). The historic controls were patients who fulfilled the same eligibility criteria and admitted to the hospital during the same period. As standard of care for both groups, some patients received hydroxychloroquine, azithromycin, or parenteral beta-lactam antibiotics. Anakinra was dosed as 100 mg subcutaneous (SQ) twice daily for 72 hours, followed by anakinra 100 mg SQ daily for 7 days. Clinical characteristics were similar between the groups, except that the cases had a lower mean body mass index than the controls (25.5 kg/m² vs. 29.0 kg/m², respectively), longer duration of symptoms (mean of 8.4 days for cases vs. 6.2 days for controls), and a higher frequency of hydroxychloroquine use (90% for cases vs. 61% for controls) and azithromycin use (49% for cases vs. 34% for controls). The primary outcome of admission to the intensive care unit for mechanical ventilation or death occurred among 13 case patients (25%) and 32 control patients (73%) (hazard ratio 0.22; 95% confidence interval, 0.11 to 0.41). However, within the first 2 days of follow up, in the control group, six patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. C-reactive protein (CRP) levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) who received anakinra and in five control patients (11%). The clinical implications of these findings are uncertain due to limitations in the

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

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

Clinical Trials

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

Adverse Effects

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

Considerations in Pregnancy

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

Considerations in Children

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

Drug Availability

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

References

1. Anakinra (kineret) [package insert]. Food and Drug Administration. 2012. Available at: <https://www.fda.gov/oc/ohrt/kineret.pdf>.

accessdata.fda.gov/drugsatfda_docs/label/2012/103950s51361bl.pdf. Accessed April 8, 2020.

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

Interleukin-6 Inhibitors

Last Updated: August 27, 2020

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

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

Recommendation

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

Rationale

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

Anti-Interleukin-6 Receptor Monoclonal Antibodies

Sarilumab

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

Clinical Data for COVID-19

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

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

Adverse Effects

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

Considerations in Pregnancy

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

Drug Availability

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

Tocilizumab

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

Clinical Data for COVID-19

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

Published Study

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

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

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

Clinical Trials

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

Adverse Effects

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

Considerations in Pregnancy

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

Considerations in Children

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

Drug Availability

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

Anti-Interleukin-6 Monoclonal Antibody

Siltuximab

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

Clinical Data in COVID-19

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

Clinical Trials

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

Adverse Effects

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

Considerations in Pregnancy

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

Drug Availability

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

References

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

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

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

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

Last Updated: July 17, 2020

Recommendation

The COVID-19 Treatment Guidelines Panel **recommends against** the use of **Bruton's tyrosine kinase (BTK) inhibitors**, such as **acalabrutinib**, **ibrutinib**, and **zanubrutinib**; and **Janus kinase (JAK) inhibitors**, such as **baricitinib**, **ruxolitinib**, and **tofacitinib**; for the treatment of COVID-19, except in a clinical trial (AIII).

Rationale

BTK inhibitors and JAK inhibitors have broad immunosuppressive effects. Ongoing clinical trials should help clarify their role in the treatment of COVID-19.

BTK inhibitors are licensed by the Food and Drug Administration (FDA) for the treatment of B-cell malignancies.¹ BTK is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion.²

JAK inhibitors are potent immunosuppressive agents that are FDA approved for the treatment of rheumatoid arthritis, psoriatic arthritis, polycythemia vera, myelofibrosis, ulcerative colitis, and graft-versus-host disease. JAK inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins^{3,4} that are involved in vital cellular functions, including signaling, growth, and survival. Phosphorylation of STAT proteins involved in these pathways can increase or decrease their function, and aberrant activation of these proteins has been associated with autoimmune disorders and cancers.⁵ JAKs transmit cytokine signaling by pairing with another JAK (e.g., JAK1/JAK2, JAK1/JAK3); however, whether inhibition of specific JAKs is relevant to therapeutic effectiveness is unknown.

Rationale for Use in Patients With COVID-19

The kinase inhibitors are proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).⁶ This immunosuppression could potentially reduce the inflammation and associated immunopathologies that have been observed in patients with COVID-19. Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells.⁷

Adverse Effects

Most of the data on adverse effects of BTK and JAK inhibitors refer to chronic use of the agents. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses. Additional toxicities include myelosuppression and transaminase elevations. Hemorrhage and cardiac arrhythmia have occurred in patients who received BTK inhibitors. Thrombotic events and gastrointestinal perforation have occurred in patients who received JAK inhibitors.

Considerations in Pregnancy

- BTK inhibitors: There is a paucity of data on human pregnancy and BTK inhibitor use. In

animal studies, in doses exceeding the therapeutic human dose, acalabrutinib and ibrutinib were associated with interference with embryofetal development.^{8,9} Based on these data, BTK inhibitors may be associated with fetal malformations when use occurs during organogenesis. The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.

- JAK inhibitors: There is a paucity of data on the use of JAK inhibitors in pregnancy. Fetal risk cannot be ruled out. Pregnancy registries provide some outcome data on tofacitinib used during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general pregnant population.¹⁰⁻¹² Risks of use should be balanced against potential benefits.

Bruton's Tyrosine Kinase Inhibitors

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) due to less off-target activity for other kinases.¹³ 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 a retrospective case series of 19 patients with severe COVID-19.¹⁴ However, data interpretation to discern any clinical benefit is limited by the study's small sample size and lack of a control group.

Clinical Trials

Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information on studies of acalabrutinib and COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies⁹ and prevent chronic graft-versus-host disease in stem cell transplant recipients.¹⁵ Based on results from a small case series, ibrutinib has been theorized to improve inflammation and protect against ensuing lung injury in patients with COVID-19.¹⁶

Clinical Data for COVID-19

Data regarding ibrutinib are limited to an uncontrolled, retrospective case series of six patients with COVID-19 who were receiving ibrutinib for a condition other than COVID-19.¹⁶ However, evaluation of the data for any clinical benefit is limited by the series's small sample size and lack of a control group.

Clinical Trials

Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information on studies of ibrutinib and COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.¹⁷ It has been shown to have fewer toxicities than first-generation BTK inhibitors (e.g., ibrutinib) due to less off-target activity for other kinases.¹⁸ Zanubrutinib is proposed to be of use in patients with COVID-19 by modulating signaling that promotes inflammation.

Clinical Data for COVID-19

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

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of zanubrutinib and COVID-19.

Janus Kinase Inhibitors

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and FDA approved for the treatment of rheumatoid arthritis.¹⁹ Among the JAK inhibitors studied, baricitinib has been postulated to have the greatest theoretical antiviral efficacy in inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from entering and infecting lung cells because of its affinity for adaptor-associated kinase-1 (AAK1), a regulator of viral endocytosis in pulmonary alveolar type 2 (AT2) epithelial cells.²⁰ In addition, baricitinib can modulate downstream inflammatory responses via inhibition of JAK1/JAK2 kinase and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.²¹

Clinical Data for COVID-19

This study has not been peer-reviewed.

A small, nonrandomized study in patients with moderate COVID-19 pneumonia compared combination therapy with baricitinib and lopinavir/ritonavir to standard of care (SOC) therapy (i.e., combination lopinavir/ritonavir and hydroxychloroquine). Both study groups included 12 patients. Compared to SOC therapy, combination therapy with baricitinib and lopinavir/ritonavir demonstrated a statistically significant shorter time to improvement of clinical and respiratory symptoms and a greater reduction of C-reactive protein levels.²²

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of baricitinib and COVID-19.

Ruxolitinib

Ruxolitinib is an oral JAK inhibitor selective for JAK1 and JAK2 and is currently approved for myelofibrosis, polycythemia vera, and acute graft-versus-host disease.²³ Like baricitinib, it is theorized to have antiviral properties through inhibition of AAK1, which may prevent viral entry and infection of pulmonary AT2 epithelial cells.⁷

Clinical Data for COVID-19

A small, prospective, single-blind, randomized controlled Phase 2 trial in patients with COVID-19 in China compared ruxolitinib 5 mg orally twice daily (n = 20) with placebo (administered as vitamin C 100 mg; n = 21), both given in combination with SOC therapy. The median age of the patients was 63 years. There were no significant demographic differences between the two arms. Treatment with ruxolitinib was associated with a nonsignificant reduction in the median time to clinical improvement (12 days for ruxolitinib vs. 15 days for placebo; $P = 0.15$), defined as a two-point improvement on a seven-category ordinal scale or as hospital discharge. There was no difference between the groups in the median time to discharge (17 days for ruxolitinib vs. 16 days for placebo; $P = 0.94$). More patients in the ruxolitinib group than in the placebo group had radiographic improvement on computerized tomography scans of the chest at Day 14 (90% for ruxolitinib vs. 61.9% for placebo; $P = 0.05$) and a shorter time to recovery from initial lymphopenia (5 days for ruxolitinib vs. 8 days for placebo; $P = 0.03$), when it was present. The use of ruxolitinib was not associated with an increased risk of adverse events or mortality (no deaths in the ruxolitinib group vs. three deaths [14%] in the control group). Despite the theoretical antiviral properties of JAK inhibitors, there was no significant difference in the time to viral clearance among the patients who had detectable viral loads at the time of randomization to ruxolitinib treatment

(n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of ventilated patients at study entry, and the frequent concomitant use (among 70% of patients) of antivirals and steroids.²⁴

A small, retrospective, single-arm study in Germany reported no safety concerns in 14 patients with severe COVID-19 who received a brief course of ruxolitinib therapy (with a median of 9 days of treatment).²⁵

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of ruxolitinib and COVID-19.

Tofacitinib

Tofacitinib is the prototypical JAK inhibitor, predominantly selective for JAK1 and JAK3, with modest activity against JAK2, and, as such, can block signaling from gamma-chain cytokines (e.g., IL-2, IL-4) and gp 130 proteins (e.g., IL-6, IL-11, interferons). It is an oral agent first approved for the treatment of rheumatoid arthritis and has been shown to decrease levels of IL-6 in patients with this disease.²⁶ Tofacitinib is also FDA approved for the treatment of psoriatic arthritis and ulcerative colitis.²⁷

Clinical Data for COVID-19

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

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of tofacitinib and COVID-19.

References

1. Wang Y, Zhang LL, Champlin RE, Wang ML. Targeting Bruton's tyrosine kinase with ibrutinib in B-cell malignancies. *Clin Pharmacol Ther.* 2015;97(5):455-468. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25669675>.
2. Chen SS, Chang BY, Chang S, et al. BTK inhibition results in impaired CXCR4 chemokine receptor surface expression, signaling and function in chronic lymphocytic leukemia. *Leukemia.* 2016;30(4):833-843. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26582643>.
3. 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>.
4. 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>.
5. Fragoulis GE, McInnes IB, Siebert S. JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. *Rheumatology (Oxford).* 2019;58(Suppl 1):i43-i54. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30806709>.
6. 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>.
7. 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>.
8. Acalabrutinib (Calquence) [Package Insert]. Food and Drug Administration. November 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf.
9. Ibrutinib (Imbruvica) [package insert]. Food and Drug Administration. April 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205552s030,210563s006lblPI.pdf.
10. 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.

11. 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>.
12. 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>.
13. 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>.
14. 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>.
15. Food and Drug Administration. FDA expands ibrutinib indications to chronic GVHD. 2017. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-ibrutinib-indications-chronic-gvhd>. Accessed July 14, 2020.
16. 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>.
17. Zanubrutinib (Brukinsa) [package insert]. Food and Drug Administration. November 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf.
18. 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. Available at: <https://ashpublications.org/blood/article/126/23/832/136525/The-BTK-Inhibitor-Bgb-3111-Is-Safe-Tolerable-and>.
19. Baricitinib (Olumiant) [package insert]. Food and Drug Administration. October 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.
20. 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>.
21. 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>.
22. Cantini F, Niccoli L, Matarrese D, Nicastrì E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. *J Infect*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32333918>.
23. J Ruxolitinib (Jakafi) [package insert]. Food and Drug Administration. January 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202192Orig1s019Rpllbl.pdf.
24. 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;146(1):137-146. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32470486>.
25. La Rosee F, Bremer HC, Gehrke I, et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. *Leukemia*. 2020;34(7):1805-1815. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32518419>.
26. 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>.
27. Tofacitinib (Xeljanz) [package insert]. Food and Drug Administration. July 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s024_208246s010lbl.pdf.

Table 3a. Immune-Based Therapy Under Evaluation for the Treatment of COVID-19: Clinical Data to Date

Last Updated: October 9, 2020

Information presented in this table may include data from preprint/non-peer reviewed articles. This table will be updated as new information becomes available.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products			
COVID-19 Convalescent Plasma	<ul style="list-style-type: none"> Convalescent plasma is not approved by the FDA. It has received an EUA from the FDA for the treatment of hospitalized patients with COVID-19.¹ Both High Titer (i.e., Ortho VITROS SARS-CoV-2 IgG tested with signal-to-cutoff ratio ≥ 12) and Low Titer COVID-19 Convalescent Plasma are authorized for use.^{2,3} Please refer to the FDA's Recommendations for Investigational COVID-19 Convalescent Plasma website for guidance on the transfusion of investigational convalescent plasma while blood establishments develop the necessary operating procedures 	<ul style="list-style-type: none"> Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2.⁴ Thousands of U.S. patients have received convalescent plasma through clinical trials, expanded access treatment trials, and EIND applications. However, the standards and methods for screening donated plasma for SARS-CoV-2 binding and neutralizing antibodies have not been established. The variability in SARS-CoV-2 antibody levels in donor plasma may impact the product's efficacy. Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. 	<p>For COVID-19:</p> <ul style="list-style-type: none"> <i>Open-Label, Randomized Clinical Trial of Convalescent Plasma in 103 Hospitalized Patients With Severe or Life-Threatening COVID-19:</i> Investigators conducted an open-label, randomized clinical trial of convalescent plasma versus SOC for patients with severe or life-threatening laboratory-confirmed COVID-19 in 7 medical centers in Wuhan, China, from February 14–April 1, 2020. The primary outcome was time to clinical improvement within 28 days, which was defined as patient discharged alive or a reduction of 2 points on a 6-point disease severity scale. Only plasma units with SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer $\geq 1:640$ were transfused. The median dose of ABO-compatible convalescent plasma was 200 mL. The time from symptom onset to randomization was 27 days in the treatment group and 30 days in the control group. Due to control of the COVID-19 outbreak in Wuhan, the trial was terminated early after 103 of the planned for 200 patients were enrolled. The convalescent plasma and control groups were well balanced by age (median age of 70 years vs. 69 years, respectively), but the control group had a higher proportion of men (65%) than the convalescent plasma group (52%). Baseline severity scores (45 patients had severe disease and 58 had life-threatening disease) and use of concomitant therapies were similar between the 2 groups. There was no significant difference between the groups in the primary outcome of time to clinical improvement within 28 days (HR 1.40; 95% CI, 0.79–2.49; $P = 0.26$). Among those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference 23%; OR 1.34; 95% CI, 0.98–1.83; $P = 0.07$). Among those with life-threatening disease, 21% of the convalescent plasma recipients and 24% of the control patients improved by Day 28 (difference -3.4%; OR 0.86; 95% CI, 0.33–2.24; $P = 0.75$). There was no significant difference in 28-day mortality between the groups (16% vs. 24% for the treatment and control groups, respectively; OR 0.65; 95% CI, 0.29–1.46; $P = 0.30$). At 24, 48, and 72 hours, the rates of negative SARS-CoV-2 viral PCR were significantly higher in the convalescent plasma group than in the control group (45% vs. 15%, $P = 0.003$ at 24 hours; 68% vs. 33%, $P = 0.001$ at 48 hours; and 87% vs.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products , continued			
COVID-19 Convalescent Plasma , continued	to manufacture COVID-19 convalescent plasma in accordance with the Conditions of Authorization set forth in the EUA.		<p>38%, $P < 0.001$ at 72 hours). Two transfusion-related events were reported, including 1 severe event; both events resolved with supportive care. The study's primary limitations were its open-label design and that, on average, the convalescent plasma was transfused approximately 1 month into the disease course. In addition, the study was terminated early, and thus the sample size was insufficient to detect differences in clinical outcomes.⁵</p> <ul style="list-style-type: none"> • <i>Open-Label, Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (ConCOVID Study)</i>: An open-label, randomized clinical trial of convalescent plasma versus SOC for hospitalized patients with COVID-19 was conducted in 14 hospitals in the Netherlands from April 8–July 1, 2020. Only plasma confirmed to have anti-SARS-CoV-2 neutralizing antibodies by a SARS-CoV-2 PRNT and a PRNT50 titer $\geq 1:80$ was transfused. The primary endpoint was in-hospital mortality up to 60 days after admission. The trial was halted prematurely by the investigators and the study's data safety monitoring board when the baseline SARS-CoV-2 neutralizing antibody titers of participant and convalescent plasma were found to be comparable, challenging the potential benefit of convalescent plasma for the study patient population. Fifty-three of 66 participants had anti-SARS-CoV-2 antibodies at baseline despite being symptomatic for a median time of only 10 days. Among 56 participants whose blood was tested using SARS-CoV-2 PRNT, 44 (79%) had neutralizing antibody levels that were comparable to those of 115 donors (median titers of 1:160 vs. 1:160, respectively, $P = 0.40$). When the trial was halted, 86 participants had been enrolled. No differences in mortality ($P = 0.95$), length of hospital stay ($P = 0.68$), or disease severity at Day 15 ($P = 0.58$) were observed between the study arms. The study was terminated early, and thus lacked sufficient power to detect differences in clinical outcomes between the study groups.⁶ • <i>Open-Label, Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (PLACID Trial): Not Peer Reviewed</i>. An open-label, randomized clinical trial of convalescent plasma versus SOC for hospitalized patients with COVID-19 was conducted in 39 tertiary care centers in India from April 22–July 14, 2020. Patients with confirmed COVID-19 and signs of severe disease with hypoxia were eligible if matched donor plasma was available at the time of enrollment. Critically ill patients (those with $\text{PaO}_2/\text{FiO}_2 < 200$ mmHg or shock) were excluded. The primary outcome was time to disease progression through 28 days (i.e., to $\text{PaO}_2/\text{FiO}_2 < 100$ mmHg) or all-cause mortality at 28 days. Participants in the intervention arm received 2 doses of 200 mL plasma, transfused 24 hours apart. Antibody testing to assess titers of donated plasma was not available when the trial started. Four-hundred and sixty-four participants were randomized; 235 were randomized into the convalescent plasma arm and 229 were randomized into the SOC arm. The arms were well-balanced with regard to age

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Blood-Derived Products , continued			
COVID-19 Convalescent Plasma , continued			<p>(median of 52 years in both arms) and days from symptom onset to enrollment (median of 8 days in both arms). There was no difference in the primary outcome (time to disease progression and 28-day mortality) across the trial arms. The composite outcome occurred in 44 patients (18.7%) in the convalescent plasma arm and 41 (17.9%) in the control arm. Thirty-four participants (14.5%) in the convalescent plasma arm and 31 patients in the control arm (13.6%) died. In each arm, 17 participants progressed to severe disease (7.2% in the convalescent plasma arm vs. 7.4% in the SOC arm). SARS-CoV-2 antibody testing was not used to select donated convalescent plasma units; therefore, many participants may have received units with low titers of SARS-CoV-2 neutralizing antibodies. Additionally, the study was not blinded.⁷</p> <ul style="list-style-type: none"> • <i>Preliminary Safety Analysis of the First Consecutive 5,000 Patients to Receive Open-Label COVID-19 Convalescent Plasma Through a National Expanded Access Program.</i>⁸ The Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19 program was an open-label, nonrandomized protocol primarily designed to provide patients with severe or life-threatening (critical) COVID-19 with access to convalescent plasma, which is an investigational product in the United States. Secondary objectives were to obtain safety data on the product. The protocol was sponsored by the Mayo Clinic and included a diverse range of clinical sites. Plasma donors were required to have documented COVID-19, with complete resolution of symptoms for at least 14 days prior to donation, and be either male, female without history of pregnancy, or female with history of pregnancy and negative HLA testing after the most recent pregnancy. SARS-CoV-2 antibody testing of donors was not mandated. ABO-compatible convalescent plasma was transfused preferentially, but in the absence of ABO-compatible plasma, patients could receive either Group A plasma or low anti-A titer Group O plasma, as available. The Mayo Clinic EAP was discontinued on August 28, 2020. This safety analysis describes the first 5,000 patients, enrolled between April 7–May 3, 2020. Participants were adults with a median age of 62 years; 63% were male and 81% had severe or life-threatening COVID-19. The main safety outcomes for the safety analysis were SAEs including death; SAEs were reported at 4 hours and at 7 days after transfusion, or as they occurred. SAEs were reported in 36 patients (<1%) within 4 hours of transfusion; SAEs included 15 deaths, including 4 possibly or probably related to the convalescent plasma treatment. The 21 nonfatal SAEs included 7 TACO events, 11 TRALI events, and 3 severe allergic reactions. The overall 7-day mortality rate was 14.9%. In this study, COVID-19 convalescent plasma therapy was associated with a low rate (<1%) of serious transfusion-related events. The study design, which does not include a control arm, precludes an assessment of efficacy or ADE. • <i>Retrospective Exploratory Analyses of Outcomes Among Tens of Thousands of Patients Receiving Open-Label COVID-19 Convalescent Plasma Through the Mayo Clinic EAP:</i>

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products , continued			
COVID-19 Convalescent Plasma , continued			<p>Both the FDA and the Mayo Clinic performed retrospective, indirect evaluations of the efficacy of COVID-19 convalescent plasma by using subsets of EAP data, hypothesizing that patients who received plasma units with higher titers of neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower titers of antibodies. This analytic approach was not prespecified in the Mayo Clinic EAP protocol.</p> <ul style="list-style-type: none"> • <i>FDA Efficacy Analysis:</i> This analysis included 4,330 patients, and donor neutralizing antibody titers were measured by the Broad Institute using a pseudovirus assay.² The analysis revealed no difference in 7-day mortality between the patients who received high-titer plasma and those who received low-titer plasma, in the patient population overall, or in the subset of patients who were intubated. However, among nonintubated patients (approximately two-thirds of those analyzed), mortality within 7 days of transfusion was 11% for those who received high-titer plasma and 14% for those who received low-titer plasma ($P = 0.03$).¹ In a post hoc analysis of patients aged <80 years who were not intubated and who were treated within 72 hours of COVID-19 diagnosis, 7-day mortality was lower among the patients who received high-titer plasma than among those who received low-titer plasma (6.3% vs. 11.3%, respectively; $P = 0.0008$).² • <i>Mayo Clinic Efficacy Analysis: Not Peer Reviewed.</i> This analysis included 3,082 participants who received a single unit of plasma out of the 35,322 participants who had received plasma through the EAP by July 4, 2020. Antibody titers were measured by using the Ortho Clinical Diagnostics COVID-19 IgG assay, and outcomes in patients transfused with low- (lowest 18%), medium-, and high- (highest 17%) titer plasma were compared. After adjusting for baseline characteristics, the 30-day mortality in the low-titer group was 29% and 25% in the high-titer group. This difference did not reach statistical significance. Similar to the FDA analyses, post hoc subgroup analyses suggested a benefit of high-titer plasma in patients aged <80 years who received plasma within 3 days of COVID-19 diagnosis and who were not intubated.⁹ • <i>Limitations of the EAP Analyses:</i> The lack of an untreated control arm limits interpretation of the safety and efficacy data. For example, the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded. In addition: <ul style="list-style-type: none"> • The EAP data may be subject to multiple confounders, including regional differences and temporal trends in the management of COVID-19. • There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers in convalescent plasma from patients who have recovered from COVID-19 are highly variable.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products , continued			
COVID-19 Convalescent Plasma , continued			<ul style="list-style-type: none"> • The efficacy analyses rely on a subset of EAP patients who only represent a fraction of the patients who received convalescent plasma through the EAP. • The subgroup that demonstrated the largest estimated effect between high-titer and low-titer convalescent plasma-patients aged <80 years who were not intubated and who were transfused within 3 days of COVID-19 diagnosis was selected post hoc by combining several subset rules which favored subgroups that showed a trend toward benefit of high-titer plasma. This approach tends to overestimate the treatment effect. • The FDA analysis relied on 7-day mortality, which may not be clinically meaningful in the context of the prolonged disease course of COVID-19. Because participants in this observational study were not rigorously followed after they were discharged from the hospital, the 30-day mortality estimates are uncertain. • <i>Retrospective, Single-Center, Case-Control Study Evaluating Convalescent Plasma Plus SOC Versus SOC Without Convalescent Plasma:</i>¹⁰ <i>Not Peer Reviewed.</i> This case-control study reports clinical outcomes among 39 consecutive patients who received COVID-19 convalescent plasma through the FDA's single patient EIND program while hospitalized at Mount Sinai Hospital in New York City during the period of March 24–April 8, 2020. Recipients were transfused with 2 units of ABO-compatible convalescent plasma from donors with a SARS-CoV-2 anti-spike antibody titer of 1:320 dilution. The control group (n = 156) was identified retrospectively from the hospital's EHR database. The control patients were hospitalized during the same period as the patients in the convalescent plasma group and had confirmed COVID-19 but did not receive convalescent plasma. They were matched 4:1 to the convalescent plasma recipients using propensity scores to correct for measured confounders. Convalescent plasma recipients had a mean age of 55 years and 64% were male. At the time of transfusion, 87% of the recipients required supplemental oxygen through noninvasive ventilation and 10% through invasive mechanical ventilation. By Day 14, the clinical condition had worsened in 18% of the convalescent plasma patients and 24% of the control patients ($P = 0.17$). As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died ($P = 0.04$, log-rank test) and 72% of the transfused patients and 67% of the control patients had been discharged. Interpretation of the study results is limited by the lack of randomization and the potential for unmeasured patient selection bias. • <i>Retrospective Case-Controlled Study Evaluating Outcomes Among COVID-19 Convalescent Plasma Recipients:</i> In this study of patients who were hospitalized between March 24 and April 8, 2020, at Mount Sinai Hospital in New York City, outcomes among 39 consecutive patients who received convalescent plasma with a SARS-CoV-2 anti-spike antibody titer of 1:320 were compared to outcomes among 156 propensity-score-

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products , continued			
COVID-19 Convalescent Plasma , continued			<p>matched controls. As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died ($P = 0.04$, log-rank test), and 72% and 67% of the transfused patients and control patients, respectively, had been discharged from the hospital. Subgroup analyses suggested a benefit of convalescent plasma among patients who were not intubated, had a shorter duration of symptoms, and received therapeutic anticoagulation.¹⁰</p> <ul style="list-style-type: none"> • <i>Retrospective Case-Controlled Study of COVID-19 Convalescent Plasma Versus SOC:</i> This study compared convalescent plasma with SOC in patients with COVID-19 who were hospitalized between March 28 and July 6, 2020, at 8 Houston Methodist hospitals. Outcomes for the first 136 convalescent plasma recipients who reached Day 28 post-transfusion were compared with the outcomes for two sets of propensity-score matched controls at 28 days after admission. The analyses suggested a trend towards benefit of convalescent plasma, with larger differences in mortality seen primarily among subgroups of patients who were transfused early (i.e., within 72 hours of admission) with high-titer plasma (i.e., anti-spike protein receptor binding domain titer $\geq 1:1350$).¹¹ • Other smaller, uncontrolled case series describing clinical outcomes in patients with COVID-19 have been reported and also suggest that SAEs are uncommon following COVID-19 convalescent plasma treatment.¹²⁻¹⁷
SARS-CoV-2-Specific Immunoglobulins	<ul style="list-style-type: none"> • Not approved by the FDA 	<ul style="list-style-type: none"> • Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response. 	<ul style="list-style-type: none"> • No clinical data for COVID-19, SARS, or MERS
Non-SARS-CoV-2-Specific Intravenous Immunoglobulins	<ul style="list-style-type: none"> • Primary immune disorders • Thrombocytopenic purpura • Kawasaki disease • Motor neuropathy 	<ul style="list-style-type: none"> • Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors without confirmation of SARS-CoV-2 infection are not likely to 	<p>For COVID-19:</p> <ul style="list-style-type: none"> • <i>Not Peer Reviewed.</i> A retrospective, nonrandomized cohort study of IVIG for the treatment of COVID-19 was conducted across 8 treatment centers in China between December 2019 and March 2020. The study found no difference in 28-day or 60-day mortality between 174 patients who were treated with IVIG and 151 patients who were not treated with IVIG. Patients who received IVIG were hospitalized for longer (median stay of 24 days for IVIG group vs. 16 days for no IVIG group) and experienced longer duration of disease (median of 31 days for IVIG group vs. 23 days for no IVIG group).

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products , continued			
Non-SARS-CoV-2-Specific Intravenous Immunoglobulins , continued	<ul style="list-style-type: none"> Prophylaxis of various bacterial and viral infections 	<p>contain SARS-CoV-2 antibodies. Furthermore, although IVIG contains other blood components that may have general immunomodulatory effects, it is unclear whether these theoretical immunomodulatory effects will benefit patients with COVID-19.</p>	<p>More IVIG-treated patients 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). 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 are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive 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 no IVIG group. The IVIG group also had more patients with severe COVID-19 disease at study entry. Also, patients in both groups received many concomitant therapies for COVID-19.¹⁸</p>
Mesenchymal Stem Cells	<ul style="list-style-type: none"> Not approved by the FDA 	<ul style="list-style-type: none"> Multipotent adult stem cells that are present in most human tissues including the umbilical cord It is hypothesized that MSCs could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-COV-2. MSCs lack the ACE2 receptor that SARS-COV-2 uses for viral entry into cells; therefore, MSCs are resistant to infection.^{19,20} 	<p>For COVID-19:</p> <ul style="list-style-type: none"> A pilot study of IV MSC transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as critical, severe, or common-type disease. Seven patients (1 with critical illness, 4 with severe illness, and 2 with common-type illness) received MSCs; 3 patients with severe illness received placebo. All 7 patients who received MSCs recovered. Among the 3 severely ill control patients, 1 died, 1 developed ARDS, and 1 remained stable with severe disease.²¹ A small clinical trial evaluated human umbilical cord MSC (hUC-MSc) infusion in patients with severe COVID-19 who had not responded to SOC therapies after 7 to 10 days of treatment. The SOC therapies included supplemental oxygen, umifenovir/oseltamivir, antibiotics if indicated, and glucocorticosteroids. The study was intended as a randomized controlled trial; however, due to the lack of sufficient hUC-MSCs, it was not possible to randomize the participants as originally planned. Among the 41 patients eligible to participate in the study, 12 received hUC-MSc infusion and 29 received SOC therapies only. The study arms were well balanced with regard to demographic characteristics, laboratory test results, and disease severity. All 12 participants who received hUC-MSc infusion recovered without requiring mechanical ventilation and were discharged to home, whereas 4 patients who received only SOC therapies progressed to critical illness requiring mechanical ventilation, and 3 of these patients died. These results are not statistically significant and interpretation of the study is limited by its lack of randomization and small sample size.²² <p>For Other Viruses:</p> <ul style="list-style-type: none"> In an open-label study of MSCs for the treatment of H7N9 influenza in China, 17 patients received MSC treatment plus SOC, and 44 patients received SOC only. In the MSC group, 3 patients (17.6%) died; in the control group, 24 patients (54.5%) died.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products , continued			
Mesenchymal Stem Cells , continued			The 5-year follow-up was limited to 5 patients in the MSC group. No safety concerns were identified. ²³
Immunomodulators			
<i>Corticosteroids</i>			
Dexamethasone	FDA-Approved Indications: <ul style="list-style-type: none"> • Allergic states (e.g., severe or incapacitating asthma, dermatitis, drug HSRs) • Dermatologic diseases (e.g., bullous dermatitis, Stevens-Johnson syndrome) • Endocrine disorders (e.g., adrenocortical insufficiency) • Gastrointestinal diseases (e.g., ulcerative colitis) • Hematologic disorders (e.g., hemolytic anemia, idiopathic thrombocytopenia purpura, pure red cell aplasia) • Neoplastic diseases (e.g., palliative treatment of leukemia, lymphoma) 	<ul style="list-style-type: none"> • Long-acting potent synthetic glucocorticoid with minimal mineralocorticoid activity. Glucocorticoid activity includes anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects.²⁵ • Potent anti-inflammatory effects may mitigate or prevent the systemic inflammatory response associated with severe COVID-19. 	For COVID-19: <ul style="list-style-type: none"> • Preliminary results from the RECOVERY study, a large, multicenter, randomized, open-label trial in patients hospitalized with suspected or confirmed COVID-19 in the United Kingdom, showed that fewer patients randomized to dexamethasone 6 mg daily (n = 2,104) died within 28 days of enrollment than those who received the SOC (n = 4,321) (22.9% vs. 25.7%; age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; <i>P</i> < 0.001). The survival benefit was greatest among participants who required invasive mechanical ventilation at randomization: 29.3% of participants in the dexamethasone group died within 28 days of enrollment compared with 41.4% in the SOC group (rate ratio 0.64; 95% CI, 0.51–0.81). Among patients who required supplemental oxygen but not invasive mechanical ventilation at enrollment, 23.3% in the dexamethasone arm died within 28 days of enrollment compared with 26.2% in the SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94). No survival benefit was seen among participants who did not require oxygen therapy at enrollment; 17.8% of dexamethasone participants died within 28 days of enrollment compared with 14.0% in the SOC arm (rate ratio 1.19; 95% CI, 0.91–1.55). Interpretation of these results is limited by several factors: full analysis of the trial is ongoing; results for key secondary endpoints, potential AEs, and dexamethasone efficacy in key subgroups have not been reported; there were no standardized or objective criteria for oxygen supplementation; and the age distribution of patients differed by respiratory status at randomization (patients who received invasive mechanical ventilation were more likely to be aged <70 years).²⁶ • Small, retrospective cohort studies and case series have yielded conflicting results regarding corticosteroids, with some suggesting benefits associated with short courses of corticosteroids²⁷⁻³⁰ and others showing potential harm.^{31,32} • Conversely, results reported for other studies, including a meta-analysis of 15 studies in patients with coronavirus infections (e.g., COVID-19, SARS, MERS)³² and a retrospective review of critically ill patients with COVID-19 suggest an increased risk of multiorgan dysfunction, no mortality benefit, and possibly an increased risk of death with use of corticosteroids.³³

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Immunomodulators			
<i>Corticosteroids</i>			
Dexamethasone , continued	<ul style="list-style-type: none"> Nervous system disorders (e.g., multiple sclerosis, cerebral edema) Ophthalmic diseases (e.g., temporal arteritis, uveitis) Renal diseases (e.g., to induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome) Respiratory diseases (e.g., eosinophilic pneumonia) Rheumatic disorders (e.g., ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus)²⁴ 		
<i>Interferon Alfa and Interferon Beta</i>			
Interferon Alfa	<ul style="list-style-type: none"> IFN alfa-2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C IFN alfa-1b is not available in the United States. 	<ul style="list-style-type: none"> Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types³⁴⁻³⁶ 	<p>For COVID-19:</p> <ul style="list-style-type: none"> <i>Not Peer Reviewed.</i> In a retrospective cohort study of 77 adults with moderate COVID-19 in China, those who used nebulized IFN alfa-2b with or without umifenovir (Arbidol) achieved viral clearance in the upper respiratory tract faster and had lower systemic inflammation than those who used only umifenovir. However, results are difficult to interpret because participants in the IFN alfa-2b group were substantially younger than those in the umifenovir-only group (mean age 40 years vs. 65 years) and had fewer comorbidities (15% vs. 54%) at study entry. The nebulized formulation of IFN alfa-2b is not FDA approved for use in the United States.³⁷ <i>Press Release.</i> A double-blind, placebo-controlled trial conducted in the United Kingdom evaluated inhaled IFN beta-1a (once daily for up to 14 days) in nonventilated patients hospitalized with COVID-19. Compared to the patients receiving placebo (n = 50), the patients receiving inhaled IFN beta-1a (n = 48) were more likely to recover to ambulation without restrictions (HR 2.19; 95% CI, 1.03–4.69; P = 0.04), had decreased odds of developing severe disease (OR 0.21; 95% CI, 0.04–0.97; P = 0.046),
Interferon Beta	<ul style="list-style-type: none"> Multiple sclerosis (IFN beta-1a, IFN beta-1b) 	<ul style="list-style-type: none"> Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function)^{34,41} Among IFN subtypes, IFN beta-1b shows greatest <i>in vitro</i> inhibition of MERS-CoV.^{42,43} <i>In vitro</i> activity against MERS-CoV in lung cells.⁴⁴ 	

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
<i>Interferon Alfa and Interferon Beta, continued</i>			
Interferon Alfa	<ul style="list-style-type: none"> • IFN alfa-2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C • IFN alfa-1b is not available in the United States. 	<ul style="list-style-type: none"> • Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types³⁴⁻³⁶ 	<p>and had less breathlessness. Additional detail is required to fully evaluate these findings and their implications. Note that the inhaled IFN beta-1a formulation used in this study is not commercially available in the United States.³⁸</p> <ul style="list-style-type: none"> • An open-label, randomized trial at a single center in Iran evaluated SQ IFN beta-1a (3 times weekly for 2 weeks) in patients with severe COVID-19. There was no difference in the primary outcome of time to clinical response between the IFN beta-1a group (n = 42) and the control group (n = 39), and there was no difference between the groups in overall length of hospitalization, length of ICU stay, or duration of mechanical ventilation. The reported 28-day overall mortality was lower in the IFN beta-1a group, but 4 patients in that group who died before receiving the fourth dose of IFN beta-1a were excluded from the analysis, which makes it difficult to interpret these results.³⁹
Interferon Beta	<ul style="list-style-type: none"> • Multiple sclerosis (IFN beta-1a, IFN beta-1b) 	<ul style="list-style-type: none"> • Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function)^{34,41} • Among IFN subtypes, IFN beta-1b shows greatest <i>in vitro</i> inhibition of MERS-CoV.^{42,43} • <i>In vitro</i> activity against MERS-CoV in lung cells.⁴⁴ 	<ul style="list-style-type: none"> • An open-label, Phase 2 clinical trial randomized 127 participants (median age 52 years) 2:1 to combination antiviral therapy or LPV/r. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants admitted within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (IFN beta-1b 8 million international units SQ every other day for up to 7 days total, LPV/r, and ribavirin); those admitted ≥7 days after symptom onset (n = 51) were randomized to double therapy (LPV/r and ribavirin) because of concerns regarding potential inflammatory effects of IFN. All participants in the control group received LPV/r alone regardless of time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed SARS-CoV-2 infection who were hospitalized regardless of disease severity until they had 2 negative NP swabs. The median time to a negative SARS-CoV-2 PCR on an NP swab (the primary endpoint) was shorter for the combination group than for the control group (7 days vs. 12 days, <i>P</i> = 0.001). The combination group had more rapid clinical improvement as assessed by NEWS2 and SOFA score and a shorter hospital stay (9 days for combination group vs. 14.5 days for control group, <i>P</i> = 0.016). There was no difference in oxygen use between the groups. The antiviral and clinical effect was more pronounced in the patients hospitalized within 7 days of symptom onset suggesting that IFN beta-1b with or without ribavirin was the critical component of the combination therapy. The study provides no information about the effect of IFN beta-1b administered ≥7 days after symptom onset.⁴⁰

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
<i>Interleukin-1 Inhibitor</i>			
Anakinra	<ul style="list-style-type: none"> Rheumatoid arthritis Cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease⁴⁵ IV formulation is not approved for use in the United States. 	<ul style="list-style-type: none"> Competitively inhibits IL-1 binding to the IL-1 type I receptor 	<p>For COVID-19:</p> <ul style="list-style-type: none"> A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra to outcomes in 44 historical controls. The patients in both groups were admitted to the same hospital system in Paris, France. Cases were consecutive admissions from March 24–April 6, 2020, with laboratory-confirmed SARS-CoV-2 infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia ($SpO_2 \leq 93\%$ with ≥ 6 L/min O_2) or worsening hypoxia ($SpO_2 \leq 93\%$ with >3 L/min O_2 and a loss of $\geq 3\%$ of O_2 saturation on room air in the previous 24 hours). Historic controls were patients fulfilling the same eligibility criteria and admitted to the hospital from March 18–March 24, 2020. SOC for both groups entailed use of HCQ, AZM, and parenteral beta-lactam antibiotics. Patients in the anakinra group received anakinra 100 mg SQ twice daily for 72 hours, followed by anakinra 100 mg daily for 7 days. Clinical characteristics were similar between the groups, except that the case patients had a lower mean BMI (25.5 kg/m² for cases vs. 29.0 kg/m² for controls), longer duration of symptoms (8.4 days for cases vs. 6.2 days for controls), and a higher frequency of HCQ use (90% for cases vs. 61% for controls) and AZM use (49% for cases vs. 34% for controls). The primary outcome of either admission to the ICU for invasive mechanical ventilation or death occurred among 13 cases (25%) and 32 controls (73%) (HR 0.22; 95% CI, 0.11–0.41). However, within the first 2 days of follow up in the control group, 6 patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. CRP levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) in the case group and 5 patients (11%) in the control group. The clinical implications of these findings are uncertain, due to limitations in the study design related to unmeasured confounding combined with the very high early event rate among the retrospective controls.⁴⁶ A single-center case series reported on open-label use of anakinra in 9 hospitalized patients with COVID-19, presenting with 4–12 days of symptoms, requiring oxygen ≤ 6 L/min, and serum CRP ≥ 50 mg/L. Anakinra was administered SQ, 100 mg every 12 hours for 3 days followed by 100 mg daily for up to 7 more days. Two patients also received HCQ plus AZM; the other 7 patients received no specific additional treatments. Anakinra was discontinued in 1 patient who progressed to acute respiratory failure after

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
<i>Interleukin-1 Inhibitor, continued</i>			
Anakinra , continued			<p>the first dose of the drug. Good clinical outcomes were observed in the other 8 patients as assessed by oxygen flow, decline in CRP, and no progression in infiltrates on serial CT scans. Three patients had elevated liver transaminase levels. Results are difficult to interpret because of the low number of patients in the case series, the short follow-up, and the absence of a comparison group.⁴⁷</p> <ul style="list-style-type: none"> • A single-center, retrospective, cohort study in Italy compared outcomes in 29 patients following open-label anakinra use with outcomes in 16 historical controls. All patients had COVID-19 with moderate to severe ARDS requiring noninvasive ventilation and evidence of hyperinflammation. High-dose IV anakinra 5 mg/kg twice daily was administered for a median of 9 days, followed by SQ administration (anakinra 100 mg twice daily) for 3 days to avoid inflammatory relapses. Both the anakinra and control (standard treatment) groups received HCQ and LPV/r. In the high-dose anakinra group, reductions in CRP levels were noted following anakinra initiation. The 21-day survival rate was 90% in the anakinra group and 56% in the control group ($P = 0.009$); however, the patients in the anakinra group were younger (median age of 62 years in anakinra group vs. 70 years in control group), and fewer patients had chronic kidney disease. High-dose anakinra was discontinued in 7 patients (24%) due to AEs (bacteremia in 4 patients, elevated liver enzymes in 3 patients); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of 7 patients received low-dose SQ anakinra (100 mg twice daily); however, treatment in this group was stopped after 7 days because of lack of clinical or anti-inflammatory effects.⁴⁸

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
<p><i>Interleukin-6 Inhibitors</i></p> <p>Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in some patients with COVID-19; IL-6 inhibition may reduce these effects.</p>			
Sarilumab	<ul style="list-style-type: none"> Rheumatoid arthritis⁴⁹ 	<ul style="list-style-type: none"> Human recombinant monoclonal antibody IL-6 receptor antagonist⁵⁰ 	<p>For COVID-19:</p> <ul style="list-style-type: none"> <i>Press Release:</i> In a Phase 2 and 3 clinical trial (ClinicalTrials.gov Identifier NCT04315298), patients hospitalized with COVID-19 were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Randomization was stratified by severity of illness (i.e., severe, critical, multisystem organ dysfunction) and use of systemic corticosteroids for COVID-19. The Phase 2 component of the trial verified that sarilumab (at either dose) reduced CRP levels. The primary outcome for Phase 3 of the trial was change on a 7-point scale, and this phase was modified to focus on the dose of sarilumab 400 mg among the patients in the critically ill group. During the conduct of the trial, there were numerous amendments that increased the sample size and modified the dosing strategies being studied, and multiple interim analyses were performed. The trial findings to date do not support a clinical benefit of sarilumab for any of the disease severity subgroups or dosing strategies studied. Additional detail (as would be included in a published manuscript) is required to fully evaluate the implications of these study findings.⁵¹
Siltuximab	<ul style="list-style-type: none"> Multicentric Castleman disease 	<ul style="list-style-type: none"> Recombinant human-mouse chimeric monoclonal antibody IL-6 antagonist⁵² 	<p>For COVID-19:</p> <ul style="list-style-type: none"> <i>Not Peer Reviewed.</i> In a single-center observational study of 21 patients with COVID-19 who developed pneumonia and ARDS and received treatment with IV siltuximab, some patients experienced decreased CRP levels (16 of 21 patients) and improved clinical condition (7 of 21 patients) following siltuximab treatment. Other patients experienced no clinically relevant change in condition (9 of 21 patients) or worsening condition (5 of 21 patients). Among the 5 patients with worsening condition, there was 1 death and 1 cerebrovascular event (median follow-up of 8 days).⁵³

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
<i>Interleukin-6 Inhibitors, continued</i>			
Tocilizumab	<ul style="list-style-type: none"> • Cytokine release syndrome (induced by CAR T-cell therapy) • Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis⁵⁴ 	<ul style="list-style-type: none"> • Recombinant humanized monoclonal antibody • IL-6 receptor antagonist 	<p>For COVID-19:</p> <ul style="list-style-type: none"> • <i>Press Release:</i> The industry-sponsored Phase 3 COVACTA trial (<i>ClinicalTrials.gov</i> Identifier NCT04320615), randomized 450 adults hospitalized with severe COVID-19-related pneumonia to receive tocilizumab or placebo. The trial failed to meet its primary endpoint or several key secondary endpoints. The primary outcome was improved clinical status, which was measured using a 7-point ordinal scale to assess clinical status based on the need for intensive care and/or ventilator use and the requirement for supplemental oxygen over a 4-week period. Key secondary outcomes included 4-week mortality. Differences in the primary outcome between the tocilizumab and placebo groups were not statistically significant (OR 1.19; 95% CI, 0.81–1.76; <i>P</i> = 0.36). At Week 4, mortality rates did not differ between the tocilizumab and placebo groups (19.7% vs. 19.4%; difference of 0.3%; 95% CI, -7.6% to 8.2%; <i>P</i> = 0.94). The difference in median number of ventilator-free days between the tocilizumab and placebo groups did not reach statistical significance (22 days for tocilizumab group vs. 16.5 days for placebo group; difference of 5.5 days; 95% CI, -2.8 to 13.0 days; <i>P</i> = 0.32). Infection rates at Week 4 were 38.3% in the tocilizumab group and 40.6% in the placebo group; serious infection rates were 21.0% and 25.9% in the tocilizumab and placebo groups, respectively.⁵⁵ • <i>Press Release.</i> Early results were reported for the CORIMUNO-TOCI trial (<i>ClinicalTrials.gov</i> Identifier NCT04331808), an open-label, randomized trial of hospitalized patients with COVID-19 (<i>n</i> = 129) at 7 sites in France. The patients, who had moderate or severe disease at study entry, were randomized to receive tocilizumab plus SOC (<i>n</i> = 65) or SOC alone (<i>n</i> = 64). The dosing strategy was tocilizumab 8 mg/kg on Day 1; if there was no response (i.e., no decrease of oxygen requirement), a second infusion was repeated on Day 3. In this preliminary report, the proportion of participants who died or needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group than in the SOC alone group. Detailed results of the trial have not been reported. • Sixty-three adults hospitalized with COVID-19 were enrolled in a prospective open-label study of tocilizumab for severe COVID-19. All patients received off-label ARV PIs. Patients received either tocilizumab 8 mg/kg IV or tocilizumab 324 mg SQ; within 24 hours, a second dose of tocilizumab was administered to 52 of the 63 patients. Following tocilizumab administration, fevers resolved in all but 1 patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO₂/FIO₂ ratio

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
<i>Interleukin-6 Inhibitors, continued</i>			
Tocilizumab , continued			<p>increased between admission (152 +/-53 mm Hg) and Day 7 (284 +/-116 mm Hg). No moderate or severe AEs attributable to tocilizumab were reported. Overall mortality rate was 11% (7 deaths among the 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association between earlier use of tocilizumab and reduced mortality, but provide no details regarding a comparison group or specify an a priori comparison, which limits interpretation of this result.⁵⁶</p> <ul style="list-style-type: none"> • An uncontrolled, retrospective cohort study of 21 hospitalized COVID-19 patients who received tocilizumab reported improvement in oxygenation and systemic inflammation. At study entry, among the 21 patients (mean age 56 years; range 25 to 88 years), 17 had severe disease and 4 had critical disease. All patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (2 required mechanical ventilation). Mean CRP level was 75 mg/L, mean IL-6 expression level was 153 pg/mL, mean D-dimer level was 0.80 µg/mL, and mean lymphocyte percentage was 15.5%. Eighteen patients were given tocilizumab IV infusion once, and within 12 hours, 3 patients received a second infusion for indication of fever. Following tocilizumab administration, fevers normalized, lymphocyte percentages improved, and CRP levels declined. By Day 5, oxygen requirements were reduced in 15 of 20 participants (75%). There were no serious AEs attributed to tocilizumab, and no concurrent bacterial, fungal, or viral infections were observed during the treatment. The interpretability of this retrospective case series is limited due to its small sample size and lack of control group.⁵⁷ • Additional data supporting the use of tocilizumab for COVID-19 include a small retrospective cohort study, a case series, and a case-control study.⁵⁸⁻⁶⁰
Kinase Inhibitors			
<i>Bruton's Tyrosine Kinase Inhibitors</i>			
Acalabrutinib	<ul style="list-style-type: none"> • Chronic lymphocytic leukemia/small lymphocytic lymphoma • Mantle cell lymphoma⁶¹ 	<ul style="list-style-type: none"> • Second-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm⁶² 	<p>For COVID-19:</p> <ul style="list-style-type: none"> • Data regarding acalabrutinib are limited to a retrospective case series in 19 patients with severe COVID-19. However, data interpretation to discern any clinical benefit is limited by the study's small sample size and lack of a control group.⁶³

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
<i>Bruton's Tyrosine Kinase Inhibitors, continued</i>			
Ibrutinib	<ul style="list-style-type: none"> Chronic lymphocytic leukemia/ small lymphocytic lymphoma Mantle cell lymphoma Marginal zone lymphoma Waldenström macroglobulinemia Chronic graft-versus-host disease in stem cell transplant recipients⁶⁴ 	<ul style="list-style-type: none"> First-generation oral BTK inhibitor Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways Potential modulation of signaling that promotes inflammation and cytokine storm⁶⁵ 	<p>For COVID-19:</p> <ul style="list-style-type: none"> Data regarding ibrutinib are limited to an uncontrolled, retrospective case series of 6 patients with COVID-19 who were receiving ibrutinib for a condition other than COVID-19. However, evaluation of the data for any clinical benefit is limited by the study's small sample size and lack of control group.⁶⁵
Zanubrutinib	<ul style="list-style-type: none"> Mantle cell lymphoma⁶⁶ 	<ul style="list-style-type: none"> Second-generation oral BTK inhibitor Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways Potential modulation of signaling that promotes inflammation and cytokine storm⁶² 	<ul style="list-style-type: none"> No clinical data for COVID-19, SARS, or MERS
<i>Janus Kinase Inhibitors</i>			
Baricitinib	<ul style="list-style-type: none"> Rheumatoid arthritis⁶⁷ 	<ul style="list-style-type: none"> JAK inhibitor selective for JAK1, JAK2, and TYK2, relative to JAK3 Theoretical direct antiviral activity through inhibition of kinases (AAK1 and cyclin G-associated kinase) that regulate viral endocytosis in pulmonary AT2 epithelial cells, which may prevent SARS-CoV-2 entry into and infection of susceptible cells. Dose-dependent inhibition of IL-6 induced STAT3 phosphorylation⁶⁸ 	<p>For COVID-19:</p> <ul style="list-style-type: none"> <i>Not Peer Reviewed.</i> A small, nonrandomized study of 12 patients with moderate COVID-19 pneumonia compared therapy with baricitinib and LPV/r with SOC alone (i.e., combination LPV/r and HCQ). Baricitinib and LPV/r therapy demonstrated a statistically significant time to improvement in clinical and respiratory symptoms and reduction in measured CRP.⁶⁹

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
<i>Janus Kinase Inhibitors, continued</i>			
Ruxolitinib	<ul style="list-style-type: none"> • Myelofibrosis • Polycythemia vera • Steroid-refractory acute graft-versus-host disease⁷⁰ 	<ul style="list-style-type: none"> • JAK inhibitor selective for JAK1 and JAK2 • Theoretical antiviral properties through inhibition of AAK1 which may prevent viral entry into and infection of pulmonary AT2 alveolar epithelial cells^{71,72} • Inhibition of IL-6 via JAK1/JAK2 pathway inhibition 	<p>For COVID-19:</p> <ul style="list-style-type: none"> • A small, prospective, single-blind randomized controlled Phase 2 trial in patients with COVID-19 in China compared ruxolitinib 5 mg PO twice daily (n = 20) to placebo (vitamin C 100 mg; n = 21), both given in combination with SOC therapy. The median age of the patients was 63 years. There were no significant demographic differences between the 2 arms. Treatment with ruxolitinib was associated with a nonsignificant reduction in median time to clinical improvement (12 days for ruxolitinib vs. 15 days for placebo; <i>P</i> = 0.15), defined as a 2-point improvement on a 7-category ordinal scale or hospital discharge. There was no difference between the groups in the median time to discharge (17 days for ruxolitinib vs. 16 days for placebo; <i>P</i> = 0.94). More patients in the ruxolitinib group than in the placebo group had radiographic improvement on CT scans of the chest at Day 14 (90% for ruxolitinib vs. 61.9% for placebo; <i>P</i> = 0.05), and a shorter time to recovery from initial lymphopenia when present (5 days for ruxolitinib vs. 8 days for placebo; <i>P</i> = 0.03). The use of ruxolitinib was not associated with an increased risk of AEs or mortality (no deaths in the ruxolitinib group vs. 3 deaths [14% of patients] in the control group). Despite the theoretical antiviral properties of JAK inhibitors, there was no significant difference in time to viral clearance among patients who had detectable viral loads at randomization to ruxolitinib (n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of patients who required invasive mechanical ventilation at study entry, and the concomitant use of antivirals and steroids by 70% of patients.⁷³ • A small, retrospective, single-arm study in Germany reported no safety concerns in 14 patients with severe COVID-19 who received a brief course of ruxolitinib therapy (median 9 days).⁷⁴
Tofacitinib	<ul style="list-style-type: none"> • Rheumatoid arthritis • Psoriatic arthritis • Ulcerative colitis⁷⁵ 	<ul style="list-style-type: none"> • JAK inhibitor selective for JAK1 and JAK3 with modest activity against JAK2 • Blocks signaling from gamma-chain cytokines (IL-2, IL-4) and gp130 proteins (IL-6, IL-11, IFNs) • Shown to decrease levels of IL-6 in rheumatoid arthritis⁷⁶ 	<ul style="list-style-type: none"> • No clinical data for COVID-19, SARS, or MERS

Key: AAK1 = Adaptor-associated kinase 1; ADE = antibody-dependent enhancement; AE = adverse event; ARDS = acute respiratory distress syndrome; ARV = antiretroviral; AT2 = alveolar type 2; AZM = azithromycin; BTK = Bruton's tyrosine kinase; CAR = chimeric antigen receptor; CRP = C-reactive protein; CI = confidence interval; CT = computerized tomography; EHR = electronic health record; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GAK = cyclin G-associated kinase; HCQ = hydroxychloroquine; HR = hazard ratio; HSR = hypersensitivity reaction; ICU = intensive care unit; IDMC = independent data monitoring committee; IFN = interferon; IL = interleukin; IND = Investigational New Drug application; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; JAK = Janus kinase inhibitor; MERS = Middle East respiratory syndrome; MERS-CoV = Middle East respiratory syndrome coronavirus; MSC = mesenchymal stem cells; NP = nasopharyngeal; NEWS2 = National Early Warning Score 2; OR = odds ratio; PaO₂/FiO₂ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PI = protease inhibitor; PRNT = plaque reduction neutralization test; RR = age-adjusted rate ratio; SAE = adverse event; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SOFA = sequential organ failure assessment; SQ = subcutaneous; STAT3 = signal transducer and activator of transcription 3; TACO = transfusion-associated circulatory overload, TRALI = transfusion-related acute lung injury

References

1. Food and Drug Administration. EUA 26382: Emergency Use Authorization (EUA) Decision Memo. 2020. Available at: <https://www.fda.gov/media/141480/download>. Accessed August 31, 2020.
2. Food and Drug Administration. EUA 26382: emergency use authorization (EUA) request. 2020. Available at: <https://www.fda.gov/media/141481/download>.
3. Food and Drug Administration. EUA of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients: fact sheet for health care providers. 2020. Available at: <https://www.fda.gov/media/141478/download>. Accessed September 22, 2020.
4. Wang X, Guo X, Xin Q, et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32497196>.
5. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32492084>.
6. Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Convalescent plasma for COVID-19: a randomized clinical trial. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1>.
7. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate COVID-19 in India: an open-label parallel-arm Phase II multicentre randomized controlled trial (PLACID Trial). *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.09.03.20187252v2>.
8. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. *J Clin Invest*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32525844>.
9. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medRxiv*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32817978>.
10. Liu STH, Lin HM, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. *Nat Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32934372>.
11. Salazar E, Christensen PA, Graviss EA, et al. Treatment of coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly

- decreased mortality. *Am J Pathol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32795424>.
12. Salazar E, Perez KK, Ashraf M, et al. Treatment of COVID-19 patients with convalescent plasma in Houston, Texas. *medRxiv*. 2020;Preprint. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32511574>.
 13. Ahn JY, Sohn Y, Lee SH, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. *J Korean Med Sci*. 2020;35(14):e149. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32281317>.
 14. Pei S, Yuan X, Zhang Z, et al. Convalescent plasma to treat COVID-19: Chinese strategy and experiences. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.07.20056440v1>.
 15. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32293713>.
 16. Zeng Q, Yu Z, Gou J, et al. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *The Journal of Infectious Diseases*. 2020; In press. Available at: <https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa228/5826985>.
 17. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci USA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32253318>.
 18. 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>.
 19. Lukomska B, Stanaszek L, Zuba-Surma E, Legosz P, Sarzynska S, Drela K. Challenges and controversies in human mesenchymal stem cell therapy. *Stem Cells Int*. 2019;2019:9628536. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31093291>.
 20. Shetty AK. Mesenchymal stem cell infusion shows promise for combating coronavirus (COVID-19)-induced pneumonia. *Aging Dis*. 2020;11(2):462-464. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32257554>.
 21. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2(-) mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis*. 2020;11(2):216-228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32257537>.
 22. Shu L, Niu C, Li R, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. *Stem Cell Res Ther*. 2020;11(1):361. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32811531>.
 23. Chen J, Hu C, Chen L, et al. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment. *Engineering (Beijing)*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32292627>.
 24. Dexamethasone (DECADRON) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/011664s064lbl.pdf.
 25. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9(1):30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23947590>.
 26. Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
 27. Kolilekas L, Loverdos K, Giannakaki S, et al. Can steroids reverse the severe COVID-19 induced ‘cytokine storm’? *J Med Virol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32530507>.
 28. Fadel R, Morrison AR, Vahia A, et al. Early short course corticosteroids in hospitalized patients with COVID-19. *Clin Infect Dis*. 2020. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32427279>.

29. So C, Ro S, Murakami M, Imai R, Jinta T. High-dose, short-term corticosteroids for ARDS caused by COVID-19: a case series. *Respirol Case Rep*. 2020;8(6):e00596. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32514354>.
30. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32167524>.
31. Yuan M, Xu X, Xia D, et al. Effects of corticosteroid treatment for non-severe COVID-19 pneumonia: a propensity score-based analysis. *Shock*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32496422>.
32. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. *J Infect*. 2020;81(1):e13-e20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32283144>.
33. Lu X, Chen T, Wang Y, Wang J, Yan F. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. *Crit Care*. 2020;24(1):241. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32430057>.
34. Spiegel M, Pichlmair A, Muhlberger E, Haller O, Weber F. The antiviral effect of interferon-beta against SARS-coronavirus is not mediated by MxA protein. *J Clin Virol*. 2004;30(3):211-213. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15135736>.
35. Interferon alfa-2b (INTRON A) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103132Orig1s5199lbl.pdf. Accessed April 8, 2020.
36. Peginterferon alfa-2a (PEGASYS) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103964s5270lbl.pdf. Accessed April 8, 2020.
37. Zhou Q, Chen V, Shannon CP, et al. Interferon-alpha2b Treatment for COVID-19. *Front Immunol*. 2020;11:1061. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32574262>.
38. Synairgen announces positive results from trial of SNG001 in hospitalised COVID-19 patients [press release]. July 20, 2020.
39. Davoudi-Monfared E, Rahmani H, Khalili H, et al. Efficacy and safety of interferon beta-1a in treatment of severe COVID-19: a randomized clinical trial. *Antimicrob Agents Chemother*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32661006>.
40. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, Phase 2 trial. *Lancet*. 2020;395(10238):1695-1704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32401715>.
41. Haji Abdolvahab M, Mofrad MR, Schellekens H. Interferon beta: from molecular level to therapeutic effects. *Int Rev Cell Mol Biol*. 2016;326:343-372. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27572132>.
42. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clin Infect Dis*. 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31925415>.
43. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. *Antimicrob Agents Chemother*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32152082>.
44. Schofield A. Synairgen to start trial of SNG001 in COVID-19. 2020. Available at: https://pharmafield.co.uk/pharma_news/synairgen-to-start-trial-of-sng001-in-covid-19/. Accessed April 8, 2020.

45. Anakinra (Kineret) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf. Accessed April 8, 2020.
46. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatology*. 2020. Available at: [https://www.thelancet.com/pdfs/journals/lanrhe/PIIS2665-9913\(20\)30164-8.pdf](https://www.thelancet.com/pdfs/journals/lanrhe/PIIS2665-9913(20)30164-8.pdf).
47. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32376597>.
48. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatology*. 2020. Available at: [https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30127-2/fulltext](https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30127-2/fulltext).
49. Sarilumab (KEVZARA) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf. Accessed April 8, 2020.
50. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32176772>.
51. 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.
52. Siltuximab (SYLVANT) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125496s018lbl.pdf. Accessed April 8, 2020.
53. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. *medRxiv*. 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1>.
54. Tocilizumab (ACTEMRA) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125276s127,125472s040lbl.pdf. Accessed April 8, 2020.
55. Roche. Roche provides an update on the Phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. 2020. Available at: <https://www.roche.com/investors/updates/inv-update-2020-07-29.htm>. Accessed August 10, 2020.
56. Sciascia S, Apra F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol*. 2020;38(3):529-532. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32359035>.
57. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32350134>.
58. Morena V, Milazzo L, Oreni L, et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. *Eur J Intern Med*. 2020;76:36-42. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32448770>.
59. Capra R, De Rossi N, Mattioli F, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *Eur J Intern Med*. 2020;76:31-35. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32405160>.
60. Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med*. 2020;76:43-49. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32482597>.
61. Acalabrutinib (CALQUENCE) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/

[label/2017/210259s000lbl.pdf](#). Accessed June 26, 2020.

62. 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>.
63. 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>.
64. Ibrutinib (IMBRUVICA) [package insert]. Food and Drug Administration. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf. Accessed May 28, 2020.
65. 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>.
66. Zanubrutinib (BRUKINSA) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf. Accessed May 20, 2020.
67. Baricitinib (OLUMIANT) [package Insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf. Accessed April 8, 2020.
68. 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>.
69. Cantini F, Niccoli L, Matarrese D, Nicastrì E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. *J Infect*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32333918>.
70. Ruxolitinib (JAKAFI) [package Insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202192s017lbl.pdf.
71. 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>.
72. 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>.
73. 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>.
74. La Rosee F, Bremer HC, Gehrke I, et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. *Leukemia*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32518419>.
75. Tofacitinib (XELJANZ) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s024,208246s010lbl.pdf. Accessed May 28, 2020.
76. 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>.

Table 3b. Characteristics of Immune-Based Therapy Under Evaluation for the Treatment of COVID-19

Last Updated: August 27, 2020

- The information in this table is derived from data on the use of these drugs and biologic products for FDA-approved indications or in investigational trials; it is supplemented with data on their use in patients with COVID-19 where available.
- The effective dosing of these agents for the treatment of COVID-19 is unknown. Therefore, the doses listed below are primarily derived from FDA-approved indications or from clinical trials investigating therapies for COVID-19.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- Treatment-related AEs associated with immune-based therapy in patients with COVID-19 are not well defined. Whether the frequency and severity of AEs associated with use of these agents for FDA-approved indications are the same in patients with COVID-19, especially in critically ill patients, is unknown. AEs associated with long-term use of these drugs (i.e., months to years) are not included in this table because treatment for COVID-19 is not long term. 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 additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of 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 labeling and visit the Liverpool [COVID-19 Drug Interactions website](#).
- For information on drugs that prolong the QTc interval, please visit [CredibleMeds.org](#).

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood-Derived Products					
COVID-19 Convalescent Plasma	1 or more transfusions based on patient response	<ul style="list-style-type: none"> • TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens¹ • Thrombotic events 	<ul style="list-style-type: none"> • Monitor for transfusion-related reactions. • Vital signs at baseline and during and after transfusion 	Drug products should not be added to the IV infusion line for the blood product.	<ul style="list-style-type: none"> • There are insufficient data for the Panel to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immunoglobulins for the treatment of COVID-19. • A list of clinical trials is available: Convalescent Plasma
Immunoglobulins: SARS-CoV-2 Specific	Doses vary by clinical trial.	<ul style="list-style-type: none"> • TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens 	<ul style="list-style-type: none"> • Monitor for transfusion-related reactions. • Vital signs at baseline and during and after transfusion 	Drug products should not be added to the IV infusion line for the blood product.	<ul style="list-style-type: none"> • There are insufficient data for the Panel to recommend either for or against the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. • A list of clinical trials is available: Immunoglobulin

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood-Derived Products, continued					
Immunoglobulins: Non-SARS-CoV-2 Specific	Doses vary based on indication and formulation.	<ul style="list-style-type: none"> • Allergic reactions including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens 	<ul style="list-style-type: none"> • Monitor for transfusion-related reactions. • Vital signs at baseline and during and after infusion • Discontinue if renal function deteriorates during treatment. 	IVIG may interfere with immune response to certain vaccines.	<ul style="list-style-type: none"> • The Panel recommends against the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in a clinical trial (All). This recommendation should not preclude the use of IVIG when otherwise indicated for treatment of complications that arise during COVID-19. • AEs may vary by formulation. • AEs may be precipitated by high-dose, rapid infusion, or underlying conditions. • A list of clinical trials is available: Intravenous Immunoglobulin
Mesenchymal Stem Cells	Doses vary by clinical trial. In the United States, mesenchymal stem cells should not be used in the United States for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access protocol, or EIND process.	<ul style="list-style-type: none"> • Failure of the cells to work as expected² • Potential for mesenchymal stem cells to multiply or change into inappropriate cell types • Product contamination • Growth of tumors • Infections • Thrombus formation³ • Administration site reactions^{4,5} 	<ul style="list-style-type: none"> • Monitor for administration site reactions. 	Drug products should not be added to the IV infusion line for the mesenchymal stem cell product.	<ul style="list-style-type: none"> • The Panel recommends against the use of mesenchymal stem cells for the treatment of COVID-19, except in a clinical trial (All). • The FDA has issued several warnings about patients being potentially vulnerable to stem cell treatments that are illegal and potentially harmful.⁴ A number of cord blood-derived products are currently licensed by the FDA for various indications such as the treatment of cancer (stem cell transplant) and rare genetic diseases. These products are not FDA approved for the treatment of COVID-19. • A list of clinical trials is available: Mesenchymal Stem Cells

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Immunomodulators					
<i>Corticosteroids</i>					
Dexamethasone	<p>For COVID-19:</p> <ul style="list-style-type: none"> • Dexamethasone 6 mg daily IV or PO, for up to 10 days⁶ • Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first. 	<ul style="list-style-type: none"> • Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Avascular necrosis • Adrenal insufficiency • Increased blood pressure • Peripheral edema • Myopathy (particularly if used with neuromuscular blocking agents) • When used during outbreaks of other novel coronavirus infections (i.e., MERS and SARS), corticosteroid therapy was associated with delayed virus clearance.^{7,8} 	<ul style="list-style-type: none"> • Blood glucose • Blood pressure • Sign and symptoms of new infection • When initiating dexamethasone, appropriate screening and treatment to reduce the risk of <i>Strongyloides</i> hyperinfection in patients at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm temperate regions or who engage in agricultural activities) or fulminant reactivations of HBV should be considered.⁹⁻¹¹ 	<ul style="list-style-type: none"> • Moderate CYP3A4 inducer • CYP3A4 substrate • Although coadministration of RDV and dexamethasone has not been formally studied, a clinically significant PK interaction is not predicted (Gilead, written communication, August 2020). 	<ul style="list-style-type: none"> • On the basis of the preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, the Panel recommends using dexamethasone 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated (AI) and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated (BI). • The Panel recommends against using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen (AI). • If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone (AIII). • The approximate daily dose equivalencies for these glucocorticoids to dexamethasone 6 mg (PO or IV) are: prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. • In the RECOVERY trial, only 5 patients received RDV; therefore, the safety and efficacy of coadministering RDV and dexamethasone are not known. • In the United States, dexamethasone is available in the following formulations: oral tablet, oral solution, oral elixir, and IV solution. • A list of clinical trials is available: Dexamethasone

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons					
Interferon Alfa	<ul style="list-style-type: none"> Peginterferon alfa-2a 180 mcg SQ once weekly for 2 weeks for MERS^{12,13} <p>IFN Alfa-2b: <i>COVID-19 Clinical Trial Dosing:</i></p> <ul style="list-style-type: none"> Nebulized IFN alfa-2b 5 million international units twice daily (no duration listed in the study)¹⁴ 	<ul style="list-style-type: none"> Flu-like symptoms (e.g., fever, fatigue, myalgia)¹⁵ Injection site reactions Liver function abnormalities Decreased blood counts Worsening depression Insomnia Irritability Nausea Vomiting Hypertension Induction of autoimmunity 	<ul style="list-style-type: none"> CBC with differential Liver enzymes; avoid if Child-Pugh Score >6 Depression, psychiatric symptoms Reduce dose in patients with CrCl <30 mL/min. 	<ul style="list-style-type: none"> Low potential for drug interactions Inhibition of CYP1A2 	<ul style="list-style-type: none"> The Panel recommends against the use of IFNs for the treatment of patients with severe and critical COVID-19, except in a clinical trial (AIII). For COVID-19, IFN alfa has primarily been used as nebulization and usually as part of a combination regimen. Nebulized IFN alfa-2b is not approved by the FDA for use in the United States. IFN alfa-1b is not approved by the FDA for use in the United States. Use with caution with other hepatotoxic agents. Reduce dose if ALT >5 times ULN; discontinue if accompanied by increase in bilirubin. Reduce dose or discontinue if neutropenia or thrombocytopenia occur. A list of clinical trials is available: Interferon

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons, continued					
Interferon Beta	<p>IFN Beta-1a:</p> <ul style="list-style-type: none"> • IFN beta-1a 44 mcg SQ 3 times weekly for MERS¹³ • Duration for COVID-19 unknown <p>IFN Beta-1b:</p> <ul style="list-style-type: none"> • IFN beta-1b 8 million international units SQ, every other day, up to 7 days total for COVID-19¹⁶ 	<ul style="list-style-type: none"> • Flu-like symptoms (e.g., fever, fatigue, myalgia)¹⁷ • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity 	<ul style="list-style-type: none"> • Liver enzymes • CBC with differential • Worsening CHF • Depression, suicidal ideation 	Low potential for drug interactions	<ul style="list-style-type: none"> • The Panel recommends against the use of IFNs for the treatment of patients with severe and critical COVID-19, except in a clinical trial (AIII). • There are insufficient data to recommend either for or against the use of IFN beta for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • A list of clinical trials is available: Interferon <p>Availability:</p> <ul style="list-style-type: none"> • Several products are available in the United States; product doses differ. <p><i>IFN Beta-1a Products:</i></p> <ul style="list-style-type: none"> • Avonex, Rebif <p><i>IFN Beta-1b Products:</i></p> <ul style="list-style-type: none"> • Betaseron, Extavia

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-1 Inhibitor					
Anakinra	<ul style="list-style-type: none"> Standard adult dose is anakinra 100 mg SQ once daily Has also been used IV Duration unknown 	<ul style="list-style-type: none"> Neutropenia (particularly in combination with other agents that can cause neutropenia) Anaphylaxis Headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, and abdominal pain Injection site reactions Liver enzyme elevations 	<ul style="list-style-type: none"> CBC with differential Renal function (reduce dose in patients with CrCl <30 mL/min) Liver enzymes 	Use with TNF-blocking agents is not recommended due to increased risk of infection.	<ul style="list-style-type: none"> There are insufficient data for the Panel to recommend either for or against the use of IL-1 inhibitors (e.g., anakinra) for the treatment of COVID-19. A list of clinical trials is available: Anakinra
Interleukin-6 Inhibitors					
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies</i>					
Sarilumab¹⁸	<p>Clinical Trial Dosing (See ClinicalTrials.gov Identifier NCT04315298):</p> <ul style="list-style-type: none"> Sarilumab 400 mg IV (single dose)¹⁹ <p>Note: The only FDA-approved sarilumab product is an SQ formulation.</p>	<ul style="list-style-type: none"> Neutropenia, thrombocytopenia Gastrointestinal perforation HSR Increased liver enzymes HBV reactivation Infusion reaction possible 	<ul style="list-style-type: none"> Monitor for HSR Monitor for infusion reaction Neutrophils Platelets Liver enzymes 	<ul style="list-style-type: none"> Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> The Panel recommends against the use of sarilumab for the treatment of COVID-19, except in a clinical trial (BI). May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) A list of clinical trials is available: Sarilumab

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies, continued</i>					
Tocilizumab ²⁰	Clinical Trial Dosing: <ul style="list-style-type: none"> • Tocilizumab 8 mg/kg IV once • Dose should not exceed tocilizumab 800 mg. • Dose may be repeated once, 12 hours later, if clinical symptoms worsen or show no improvement (see <i>ClinicalTrials.gov</i> Identifier NCT04320615). 	<ul style="list-style-type: none"> • Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and liver enzymes • HBV reactivation 	<ul style="list-style-type: none"> • Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets • Liver enzymes 	<ul style="list-style-type: none"> • Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> • The Panel recommends against the use of tocilizumab for the treatment of COVID-19, except in a clinical trial (BI). • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • The SQ formulation of tocilizumab is not intended for IV administration. • A list of clinical trials is available: Tocilizumab
<i>Anti-Interleukin-6 Monoclonal Antibody</i>					
Siltuximab	<ul style="list-style-type: none"> • Siltuximab 11 mg/kg IV over 1 hour every 3 weeks for multicentric Castleman disease²¹ • Dose and duration for COVID-19 unknown 	<ul style="list-style-type: none"> • Infusion-related reaction • HSR • Gastrointestinal perforation • Neutropenia • Hypertension • Dizziness • Rash • Pruritus • Hyperuricemia 	<ul style="list-style-type: none"> • Monitor for HSR • Monitor for infusion reaction • Neutrophils 	<ul style="list-style-type: none"> • Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> • The Panel recommends against the use of siltuximab for the treatment of COVID-19, except in a clinical trial (BI). • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • A list of clinical trials is available: Siltuximab

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors					
<i>Bruton's Tyrosine Kinase Inhibitors</i>					
Acalabrutinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> • Acalabrutinib 100 mg PO every 12 hours • Dose and duration for COVID-19 unknown 	<ul style="list-style-type: none"> • Hemorrhage • Cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia) • Atrial fibrillation and flutter • Infection • Headache • Diarrhea • Fatigue • Myalgia 	<ul style="list-style-type: none"> • CBC with differential • Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) • Monitor for cardiac arrhythmias • Monitor for new infections 	<ul style="list-style-type: none"> • Avoid concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors. • Avoid concomitant PPI use. • H2-receptor antagonist should be administered 2 hours after acalabrutinib. 	<ul style="list-style-type: none"> • The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). • Avoid use in patients with severe hepatic impairment. • Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to atrial fibrillation. • A list of clinical trials is available: Acalabrutinib
Ibrutinib	Doses for FDA-Approved Indications: <ul style="list-style-type: none"> • Ibrutinib 420 mg or 560 mg PO once daily • Dose and duration for COVID-19 unknown 	<ul style="list-style-type: none"> • Hemorrhage • Cardiac arrhythmias • Serious infections • Cytopenias (thrombocytopenia, neutropenia, anemia) • Hypertension • Diarrhea • Musculoskeletal pain • Rash 	<ul style="list-style-type: none"> • CBC with differential • Blood pressure • Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) • Monitor for cardiac arrhythmias • Monitor for new infections 	<ul style="list-style-type: none"> • Avoid concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors. 	<ul style="list-style-type: none"> • The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). • Avoid in patients with severe baseline hepatic impairment. Dose modifications required in patients with mild or moderate hepatic impairment. • Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to cardiac arrhythmias. • A list of clinical trials is available: Ibrutinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
<i>Bruton's Tyrosine Kinase Inhibitors, continued</i>					
Zanubrutinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily Dose and duration for COVID-19 unknown 	<ul style="list-style-type: none"> Hemorrhage Cytopenias (neutropenia, thrombocytopenia, anemia, leukopenia) Atrial fibrillation and flutter Infection Rash Bruising Diarrhea Cough Musculoskeletal pain 	<ul style="list-style-type: none"> CBC with differential Signs and symptoms of bleeding Monitor for cardiac arrhythmias Monitor for new infections 	<ul style="list-style-type: none"> Avoid concomitant use with moderate or strong CYP3A inducers. Dose reduction required with moderate and strong CYP3A4 inhibitors. 	<ul style="list-style-type: none"> The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). Dose reduction required in patients with severe hepatic impairment. A list of clinical trials is available: Zanubrutinib
Janus Kinase Inhibitors					
Baricitinib²²	For Rheumatoid Arthritis: <ul style="list-style-type: none"> Baricitinib 2 mg PO once daily Doses for COVID-19 in Clinical Trials: <ul style="list-style-type: none"> Baricitinib 2 mg–4 mg PO once daily for 7–14 days 	<ul style="list-style-type: none"> Lymphoma and other malignancies Thrombosis Gastrointestinal perforation Treatment-related changes in lymphocytes, neutrophils, hemoglobin, liver enzymes Herpes simplex Herpes zoster 	<ul style="list-style-type: none"> CBC with differential Renal function Liver enzymes Monitor for new infections 	Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor.	<ul style="list-style-type: none"> The Panel recommends against the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). Baricitinib is not recommended in patients with severe hepatic or renal impairment. A list of clinical trials is available: Baricitinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Janus Kinase Inhibitors , continued					
Ruxolitinib	<ul style="list-style-type: none"> Doses for FDA-approved indications range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily. Doses in COVID-19 clinical trials range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily, for 14 days. 	<ul style="list-style-type: none"> Thrombocytopenia Anemia Neutropenia Liver enzyme elevations Risk of infection Dizziness Headache Diarrhea CPK elevation Herpes zoster 	<ul style="list-style-type: none"> CBC with differential Liver enzymes Monitor for new infections 	<ul style="list-style-type: none"> Dose modifications required when administered with strong CYP3A4 inhibitors. Avoid use with fluconazole doses >200 mg. 	<ul style="list-style-type: none"> The Panel recommends against the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). Dose modification may be required in patients with moderate or severe renal impairment, hepatic impairment, or thrombocytopenia. A list of clinical trials is available: Ruxolitinib
Tofacitinib	<p>Doses for FDA-Approved Indications:</p> <ul style="list-style-type: none"> Tofacitinib 5 mg PO twice daily (rheumatoid and psoriatic arthritis) Tofacitinib 10 mg PO twice daily (ulcerative colitis) Dose and duration for COVID-19 is unknown; a planned COVID-19 clinical trial will be evaluating tofacitinib 10 mg twice daily for 14 days. 	<ul style="list-style-type: none"> Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) Anemia Risk of infection Gastrointestinal perforation Diarrhea Headache Herpes zoster reactivation Lipid elevations Liver enzyme elevations Lymphoma and other malignancies 	<ul style="list-style-type: none"> CBC with differential Liver enzymes Monitor for new infections 	<ul style="list-style-type: none"> Dose modifications required when administered with strong CYP3A4 inhibitors, or when used with a moderate CYP3A4 inhibitor coadministered with a strong CYP2C19 inhibitor. Avoid live vaccines. 	<ul style="list-style-type: none"> The Panel recommends against the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). Avoid use in patients with ALC <500 cells/mm³, ANC <1,000 cells/mm³, or Hgb <9 grams/dL. Dose modification may be required in patients with moderate or severe renal impairment or moderate hepatic impairment. A list of clinical trials is available: Tofacitinib

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

References

1. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus.* 2016;14(2):152-157. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26674811>.
2. Giordano A, Galderisi U, Marino IR. From the laboratory bench to the patient's bedside: an update on clinical trials with mesenchymal stem cells. *J Cell Physiol.* 2007;211(1):27-35. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17226788>.
3. Tatsumi K, Ohashi K, Matsubara Y, et al. Tissue factor triggers procoagulation in transplanted mesenchymal stem cells leading to thromboembolism. *Biochem Biophys Res Commun.* 2013;431(2):203-209. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23313481>.
4. Food and Drug Administration. FDA warns about stem cell therapies. 2019. Available at: <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>. Accessed June 26, 2020.
5. Centers for Disease Control and Prevention. Stem cell and exosome products. 2019. Available at: <https://www.cdc.gov/hai/outbreaks/stem-cell-products.html>. Accessed June 26, 2020.
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 June 23, 2020.
7. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med.* 2018;197(6):757-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29161116>.
8. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med.* 2006;3(9):e343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16968120>.
9. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761166>.
10. Liu J, Wang T, Cai Q, et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic HBV infection. *Hepatology Res.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761993>.
11. Centers for Disease Control and Prevention. Parasites—strongyloides: resources for health professionals. 2020. Available at: https://www.cdc.gov/parasites/strongyloides/health_professionals/index.html. Accessed August 14, 2020.
12. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis.* 2014;14(11):1090-1095. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25278221>.

13. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alpha2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother.* 2015;70(7):2129-2132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25900158>.
14. Zhou Q, Chen V, Shannon CP, et al. Interferon-alpha2b Treatment for COVID-19. *Front Immunol.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32574262>.
15. Peginterferon alpha-2a (PEGASYS) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103964s5270lbl.pdf.
16. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, Phase 2 trial. *Lancet.* 2020;395(10238):1695-1704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32401715>.
17. Interferon beta-1a [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103780s5204lbl.pdf.
18. Sarilumab (KEVZARA) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf.
19. Regeneron and Sanofi provide update on U.S. Phase 2/3 adaptive-designed trial of KEVZARA® (sarilumab) in hospitalized COVID-19 patients. News release. PRNewswire. April 27, 2020. Available at: <https://investor.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-us-phase-23-adaptive>.
20. Tocilizumab (ACTEMRA) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125276s127,125472s040lbl.pdf.
21. Siltuximab (SYLVANT) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125496s018lbl.pdf.
22. Baricitinib (OLUMIANT) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.