

# Interleukin-6 Inhibitors

---

Last Updated: February 29, 2024

Interleukin (IL)-6 is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells.<sup>1</sup> COVID-19–associated systemic inflammation and hypoxemic respiratory failure can be associated with heightened cytokine release, as indicated by elevated levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin in the blood.<sup>2-4</sup>

The recombinant humanized anti-IL-6 receptor monoclonal antibodies (mAbs) tocilizumab and sarilumab have been evaluated in hospitalized patients with COVID-19 who had systemic inflammation. Tocilizumab is approved by the Food and Drug Administration (FDA) for use in patients with rheumatologic disorders and in patients with cytokine release syndrome induced by chimeric antigen receptor T cell therapy. On December 21, 2022, the FDA approved the use of intravenous (IV) tocilizumab for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive ventilation (NIV), mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).<sup>5,6</sup> Tocilizumab can be administered as an IV infusion or a subcutaneous (SUBQ) injection; however, only the IV formulation of tocilizumab should be used for the treatment of COVID-19.

Sarilumab is approved by the FDA for use in patients with rheumatoid arthritis. It is available as a SUBQ formulation and is not approved for the treatment of cytokine release syndrome or COVID-19.

## Recommendations

- See [Therapeutic Management of Hospitalized Adults With COVID-19](#) for the COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations on the use of tocilizumab in combination with dexamethasone in hospitalized patients who require conventional oxygen, high-flow nasal cannula (HFNC) oxygen, NIV, or mechanical ventilation.

## Additional Considerations

- If none of the recommended immunomodulatory therapies discussed in [Therapeutic Management of Hospitalized Adults With COVID-19](#) are available or feasible to use, **IV sarilumab** can be used in combination with dexamethasone (**CIIa**). Sarilumab is only commercially available as a SUBQ injection; see [Table 5e](#) for information regarding the preparation of an IV infusion using the SUBQ product.
- Tocilizumab and sarilumab should be used with caution in patients with COVID-19 who belong to populations that have not been adequately represented in clinical trials. This includes patients who are significantly immunosuppressed, such as those who have recently received other biologic immunomodulators, and patients with any of the following:
  - Alanine transaminase levels >5 times the upper limit of normal
  - A high risk for gastrointestinal perforation
  - An uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infection
  - Absolute neutrophil counts <500 cells/ $\mu$ L
  - Platelet counts <50,000 cells/ $\mu$ L

- Known hypersensitivity to tocilizumab or sarilumab
- In both the REMAP-CAP and RECOVERY trials, 29% of patients received a second dose of tocilizumab at the discretion of their treating physician.<sup>7,8</sup> However, there is insufficient evidence for the Panel to recommend either for or against the use of a second dose of tocilizumab for the treatment of COVID-19.
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.<sup>9,10</sup> Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin), with or without serologic testing, in patients from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).<sup>11</sup>

## Rationale

The results of the RECOVERY and REMAP-CAP trials provide consistent evidence that tocilizumab, when administered as a second immunomodulatory agent in combination with a corticosteroid, offers a survival benefit in certain patients with COVID-19.<sup>7,8</sup> Specifically, the patients who may benefit are those who are severely ill and require HFNC oxygen or NIV, those who are rapidly deteriorating and have increasing oxygen needs, or those who are having a significant inflammatory response. In the REMAP-CAP trial, a long-term follow-up through 180 days confirmed that treatment with an anti-IL-6 receptor mAb improved survival among patients with severe to critical COVID-19.<sup>12</sup> However, the Panel found it challenging to determine which patients with COVID-19 who are receiving low-flow oxygen would benefit from receiving tocilizumab or sarilumab plus dexamethasone.

If none of the recommended immunomodulatory therapies are available or feasible to use, sarilumab may be used because the REMAP-CAP trial demonstrated that the use of tocilizumab and the use of sarilumab improved survival and reduced the duration of organ support.<sup>12,13</sup> Sarilumab is currently only approved for use in the United States as a SUBQ injection.

## Monitoring and Adverse Effects

The primary laboratory abnormalities reported in people receiving tocilizumab and sarilumab are elevated liver enzyme levels that appear to be dose dependent and rare occurrences of neutropenia or thrombocytopenia.<sup>5,14</sup> In randomized trials, no excess secondary infections were seen among patients who received tocilizumab plus corticosteroids when compared with control patients.<sup>15-17</sup> Additional adverse effects of tocilizumab, such as serious infections (e.g., tuberculosis, bacterial or fungal infections) and bowel perforation, have been reported. These adverse effects may occur with long-term use of sarilumab as well.

## Considerations in Pregnant and Lactating People

See [Pregnancy, Lactation, and COVID-19 Therapeutics](#) for the Panel's guidance regarding the use of tocilizumab during pregnancy and lactation.

There are insufficient data to determine whether the use of sarilumab is associated with an increased risk for major birth defects or miscarriage. As pregnancy progresses, mAbs are actively transported across the placenta (with the greatest transfer occurring during the third trimester), and immune responses in the exposed fetus may be affected.

## Considerations in Children

See [Therapeutic Management of Hospitalized Children With COVID-19](#) for the Panel's

recommendations regarding the use of tocilizumab and sarilumab in children.

## Drug Availability

On December 21, 2022, the FDA approved the use of IV tocilizumab for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, NIV, mechanical ventilation, or ECMO.<sup>5</sup> In June 2021, the FDA issued an Emergency Use Authorization for the use of tocilizumab in combination with corticosteroids for the treatment of COVID-19 in hospitalized children aged  $\geq 2$  years who require supplemental oxygen, NIV, mechanical ventilation, or ECMO.<sup>6</sup> If a patient's clinical signs or symptoms worsen or do not improve after the first dose of tocilizumab, 1 additional IV infusion of tocilizumab may be administered at least 8 hours after the initial infusion.

The IV administration of sarilumab is not approved by the FDA, but in clinical trials, single SUBQ sarilumab doses were modified to enable IV administration. See [Table 5e](#) for additional details.

## Clinical Data

Two large randomized controlled trials, REMAP-CAP and RECOVERY, evaluated the use of tocilizumab in combination with standard of care corticosteroids.<sup>7,8</sup> Both studies reported a statistically significant survival benefit from the use of tocilizumab in certain patients, including patients who exhibited rapid respiratory decompensation associated with an inflammatory response.

REMAP-CAP enrolled critically ill patients who were within 24 hours of receiving respiratory support in an intensive care unit.<sup>7</sup> At baseline, 29% of these patients were receiving HFNC oxygen, 42% were receiving NIV, and 29% were receiving mechanical ventilation. The patients were randomized to receive open-label tocilizumab or usual care. In-hospital mortality was 28% in the tocilizumab arm and 36% in the usual care arm. A follow-up analysis confirmed these findings.<sup>12</sup> At 180 days, mortality was 36% in the tocilizumab arm and 40% in the usual care arm.

The RECOVERY trial enrolled hospitalized patients with COVID-19 into an open-label platform trial that included several treatment options.<sup>8</sup> A subset of all trial participants who had hypoxemia and CRP levels  $\geq 75$  mg/L were offered enrollment into a second randomization that compared the use of tocilizumab to usual care. In this subgroup, the 28-day mortality was 31% in the tocilizumab arm and 35% in the usual care arm.

In contrast to the REMAP-CAP and RECOVERY trials, other randomized trials, including the REMDACTA and EMPACTA trials, found that tocilizumab did not reduce all-cause mortality.<sup>18,19</sup> In those trials,  $>80\%$  of participants received corticosteroids as part of standard care, and most participants in the REMDACTA trial required NIV or HFNC oxygen.<sup>18</sup>

In the REMAP-CAP trial, the efficacy results for sarilumab were similar to those for tocilizumab.<sup>13</sup> When compared with patients in the standard of care arm ( $n = 406$ ), patients in the sarilumab arm ( $n = 485$ ) had more organ support-free days (OR 1.50; 95% CrI, 1.13–2.00) and a greater likelihood of survival while hospitalized (OR 1.51; 95% CrI, 1.06–2.20). In-hospital mortality was 33% for the sarilumab arm and 37% for the standard of care arm, and mortality at 180 days was 33% for the sarilumab arm and 40% for the standard of care arm.<sup>12</sup> A notable limitation to the sarilumab findings in the REMAP-CAP trial is that patients in the standard of care arm were enrolled earlier in the pandemic than those in the sarilumab arm.<sup>13</sup> Randomization closed in November 2020 for the standard of care arm and continued through April 2021 for the sarilumab arm.

An adaptive, multinational, double-blind, randomized (2:2:1) trial compared the efficacy and safety of sarilumab 400 mg IV and sarilumab 200 mg IV to placebo in hospitalized patients with COVID-19.<sup>20</sup>

This trial did not show a clinical benefit of sarilumab in hospitalized patients who were receiving supplemental oxygen.

A similar adaptive study conducted in the United States in patients with severe and critical COVID-19 also failed to show a benefit of sarilumab.<sup>21</sup> In this placebo-controlled trial, mortality by Day 22 was reduced among the sarilumab recipients with critical COVID-19 pneumonia who required mechanical ventilation and received corticosteroids at baseline. However, due to the small sample size, this result was not statistically significant.

The clinical data on the use of tocilizumab and sarilumab for the treatment of COVID-19, including data from several randomized trials and large observational studies, are summarized in [Table 5c](#).

## References

1. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CTK. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2009;83(7):3039-3048. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19004938>.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32171076>.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31986264>.
4. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020;71(15):769-777. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32176772>.
5. Tocilizumab (Actemra) [package insert]. Food and Drug Administration. 2022. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/125276s138lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125276s138lbl.pdf).
6. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization for Actemra (tocilizumab). 2021. Available at: <https://www.fda.gov/media/150321/download>.
7. REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33631065>.
8. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33933206>.
9. Lier AJ, Tuan JJ, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020;103(4):1590-1592. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32830642>.
10. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2021;49(3):539-542. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32910321>.
11. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related Strongyloides hyperinfection. *JAMA*. 2020;324(7):623-624. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761166>.
12. Writing Committee for the REMAP-CAP Investigators. Long-term (180-day) outcomes in critically ill patients with COVID-19 in the REMAP-CAP randomized clinical trial. *JAMA*. 2023;329(1):39-51. Available at: <https://pubmed.ncbi.nlm.nih.gov/36525245>.
13. REMAP-CAP Investigators. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2>.

14. Sarilumab (Kevzara) [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/761037s001lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf).
15. Charan J, Dutta S, Kaur R, et al. Tocilizumab in COVID-19: a study of adverse drug events reported in the WHO database. *Expert Opin Drug Saf.* 2021;20(9):1125-1136. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34162299>.
16. Peng J, Fu M, Mei H, et al. Efficacy and secondary infection risk of tocilizumab, sarilumab and anakinra in COVID-19 patients: a systematic review and meta-analysis. *Rev Med Virol.* 2022;32(3):e2295. Available at: <https://pubmed.ncbi.nlm.nih.gov/34558756>.
17. Shah R, Shah J, Gohil J, Revathi G, Surani S. Secondary infections in patients with COVID-19 pneumonia treated with tocilizumab compared to those not treated with tocilizumab: a retrospective study at a tertiary hospital in Kenya. *Int J Gen Med.* 2022;2022(15):2415-2425. Available at: <https://pubmed.ncbi.nlm.nih.gov/35264878>.
18. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med.* 2021;47(11):1258-1270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34609549>.
19. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med.* 2021;384(1):20-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33332779>.
20. Lescure FX, Honda H, Fowler RA, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet Respir Med.* 2021;9(5):522-532. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33676590>.
21. Sivapalasingam S, Lederer DJ, Bhore R, et al. Efficacy and safety of sarilumab in hospitalized patients with COVID-19: a randomized clinical trial. *Clin Infect Dis.* 2022;75(1):e380-e388. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35219277>.