Interleukin-6 Inhibitors

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. COVID-19–associated systemic inflammation and hypoxemic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.

The anti–IL-6 receptor monoclonal antibodies (mAbs) tocilizumab and sarilumab have been evaluated in hospitalized patients with COVID-19 who had systemic inflammation.

On December 21, 2022, the Food and Drug Administration (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).

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 hospitalized patients who require conventional oxygen, high-flow nasal canula (HFNC) oxygen, NIV, or mechanical ventilation.

• The Panel recommends the use of sarilumab for the treatment of COVID-19 only when tocilizumab is not available or feasible to use (BIIa).

Additional Considerations

• 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 immunomodulating drugs, and patients with any of the following:
  • Alanine transaminase levels >5 times the upper limit of normal
  • A high risk for gastrointestinal perforation
  • An uncontrolled serious bacterial, fungal, or non–SARS-CoV-2 viral infection
  • Absolute neutrophil counts <500 cells/µL
  • Platelet counts <50,000 cells/µL
  • Known hypersensitivity to tocilizumab or sarilumab

• In both the REMAP-CAP and RECOVERY trials, 29% of patients received a second dose of tocilizumab at the discretion of their treating physician. 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. Many clinicians would empirically initiate treatment for strongyloidiasis (e.g., with ivermectin), with or without serologic testing, in patients from areas where Strongyloides is endemic (i.e., tropical, subtropical, or warm temperate areas).
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. Specifically, the patients who may benefit are those who are severely ill and require HFNC oxygen or NIV, those who are rapidly deteriorating with 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. However, the Panel found it challenging to define which patients receiving low-flow oxygen would benefit from a COVID-19 treatment of tocilizumab or sarilumab combined with a corticosteroid such as dexamethasone.

If tocilizumab is not available, sarilumab may be used as an alternative because the REMAP-CAP trial demonstrated that the use of tocilizumab and the use of sarilumab had similar clinical benefits of improved survival and reduced duration of organ support. However, sarilumab should only be used when tocilizumab is not available or feasible to use because the evidence of efficacy is more extensive for tocilizumab than for sarilumab. In addition, sarilumab is currently only approved for use as a subcutaneous (SUBQ) injection in the United States.

Tocilizumab

Tocilizumab is a recombinant humanized anti–IL-6 receptor mAb approved by the FDA for use in certain hospitalized adults with COVID-19. It is also approved for use in patients with rheumatologic disorders and in patients with cytokine release syndrome induced by chimeric antigen receptor T cell therapy. Tocilizumab can be administered as an IV infusion or a SUBQ injection. Only the IV formulation of tocilizumab should be used for the treatment of COVID-19.

Clinical Data for COVID-19

Clinical data on the use of tocilizumab for the treatment of COVID-19, including data from several randomized trials and large observational studies, are summarized in Table 5c.

Two large randomized controlled trials, REMAP-CAP and RECOVERY, evaluated the use of tocilizumab in combination with standard-of-care corticosteroids. Both studies reported a statistically significant survival benefit from the use of tocilizumab in certain patients, including in 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. 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. 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. A subset of all trial participants who had hypoxemia and CRP levels ≥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.
those trials, >80% of participants received corticosteroids as part of standard care, and most participants in the REMDACTA trial required NIV or HFNC oxygen. For additional findings from the REMAP-CAP and RECOVERY trials and the rationale for using tocilizumab in certain hospitalized patients who are exhibiting rapid respiratory decompensations due to COVID-19, see Therapeutic Management of Hospitalized Adults With COVID-19.

**Adverse Effects**

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

**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.

**Considerations in Children**

See Therapeutic Management of Hospitalized Children With COVID-19 for the Panel’s recommendations regarding the use of tocilizumab 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. 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 ≥2 years who require supplemental oxygen, NIV, mechanical ventilation, or ECMO. 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. If there is a local or regional shortage of tocilizumab, sarilumab can be used as an alternative (see Therapeutic Management of Hospitalized Adults With COVID-19).

**Sarilumab**

Sarilumab is a recombinant humanized anti–IL-6 receptor mAb that is approved by the FDA for use in patients with rheumatoid arthritis. It is available as a SUBQ formulation and is not approved for the treatment of cytokine release syndrome.

**Clinical Data for COVID-19**

Clinical data on the use of sarilumab as a treatment for COVID-19 are summarized in Table 5c.

An adaptive, Phase 2 and 3, 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. This trial did not show a clinical benefit of sarilumab in hospitalized patients who were receiving supplemental oxygen.

A similar adaptive design study conducted in the United States in patients with severe and critical COVID-19 also failed to show a benefit of sarilumab. In this placebo-controlled trial, 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.

In the REMAP-CAP trial, the efficacy results for sarilumab were similar to those for tocilizumab.\textsuperscript{13} 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 for the sarilumab arm and the standard of care arm was 33% and 37%, respectively, and mortality at 180 days was 33% and 40%, respectively.\textsuperscript{12}

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.\textsuperscript{13} Randomization closed on November 2020 for the standard of care arm and continued through April 2021 for the sarilumab arm. If tocilizumab is not available, sarilumab may be used as an alternative because the REMAP-CAP trial demonstrated that the use of tocilizumab and the use of sarilumab had similar clinical benefits of improved survival and reduced duration of organ support.\textsuperscript{12}

**Adverse Effects**

The primary laboratory abnormalities are transient or reversible elevations in liver enzyme levels that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia.\textsuperscript{21} Additional adverse effects, such as serious infections (e.g., tuberculosis, bacterial or fungal infections) and bowel perforation have been reported, but only with long-term use of sarilumab.

**Considerations in Pregnancy**

There are insufficient data to determine whether sarilumab is associated with 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 sarilumab in children.

**Drug Availability**

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.

**References**


