Interleukin-6 Inhibitors

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Interleukin (IL)-6 is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells. 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. It is hypothesized that modulating IL-6 levels or the effects of IL-6 may reduce the duration and/or severity of COVID-19.

There are 2 classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (mAbs) (e.g., tocilizumab, sarilumab) and anti-IL-6 mAbs (i.e., siltuximab). These drugs have been evaluated in patients with COVID-19 who have systemic inflammation.

Recommendations

• See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations on the use of tocilizumab and sarilumab in hospitalized patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation.

• The Panel recommends against the use of anti-IL-6 mAb therapy (i.e., siltuximab) for the treatment of COVID-19, except in a clinical trial (BIII).

Additional Considerations

• Tocilizumab and sarilumab should be used with caution in patients with COVID-19 who belong to populations that have not been adequately represented in clinical trials. This includes patients who are significantly immunosuppressed, particularly those who have recently received other biologic immunomodulating drugs, and patients with any of the following:
  • Alanine transaminase levels >5 times the upper limit of normal
  • A high risk for gastrointestinal perforation
  • An uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infection
  • Absolute neutrophil counts <500 cells/µL
  • Platelet counts <50,000 cells/µL
  • Known hypersensitivity to tocilizumab or sarilumab

• Tocilizumab and sarilumab should only be given in combination with a course of dexamethasone or an alternative corticosteroid at a dose that is equivalent to dexamethasone 6 mg. See Corticosteroids for more information.

• Some clinicians would assess the patient’s clinical response to dexamethasone before deciding whether tocilizumab or sarilumab is needed.

• In both the REMAP-CAP and the RECOVERY trials, 29% of patients received a second dose of tocilizumab at the discretion of their treating physician. However, there is insufficient evidence for the Panel to recommend either for or against a second dose of tocilizumab.

• Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids. Many clinicians would initiate empiric
treatment (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients who are from areas where Strongyloides is endemic (i.e., tropical, subtropical, or warm temperate areas).  

Rationale

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

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

Anti-Interleukin-6 Receptor Monoclonal Antibodies

Tocilizumab

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

Clinical Data for COVID-19

Clinical data on the use of tocilizumab (and other IL-6 inhibitors) for the treatment of COVID-19, including data from several randomized trials and large observational studies, are summarized in Table 5c.

The initial studies that evaluated the use of tocilizumab for the treatment of COVID-19 produced conflicting results. Many of these trials were limited by low power, heterogenous populations, and/or a low frequency of concomitant use of corticosteroids (now the standard of care for patients with severe COVID-19). Subsequently, patients in the 2 largest randomized controlled trials that evaluated the use of tocilizumab, REMAP-CAP and RECOVERY, received corticosteroids as part of standard of care. Both studies reported a survival benefit 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. 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. 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. For additional findings from the REMAP-CAP and RECOVERY trials and the rationale for using tocilizumab in certain hospitalized patients who are exhibiting rapid respiratory decompensations due to COVID-19, see Therapeutic Management of Hospitalized Adults With COVID-19.
In contrast to the REMAP-CAP and RECOVERY trials, the REMDACTA trial did not find a survival benefit of tocilizumab. The trial randomized hospitalized patients with COVID-19, most of whom required NIV or high-flow oxygen support, to receive tocilizumab or placebo. All the patients received remdesivir and most received corticosteroids. Tocilizumab use did not reduce 28-day mortality among these patients (18% of patients died in the tocilizumab arm vs. 20% in the placebo arm).¹⁸

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

Adverse Effects
The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. In randomized trials, no excess secondary infections were seen among patients who received combination therapy compared to control patients. Additional adverse effects of tocilizumab, such as serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation, have been reported.¹⁹

Considerations in Pregnancy
There are insufficient data to determine whether there is a tocilizumab-associated 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 this may affect immune responses in the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy.²⁰ Whether to use tocilizumab during pregnancy should be a joint decision between the pregnant individual and their health care provider, and the decision-making process should include a discussion of the potential risks and benefits.

Considerations in Children
See Therapeutic Management of Hospitalized Children With COVID-19 for the Panel’s recommendations regarding the use of tocilizumab in children.

Drug Availability
On June 24, 2021, the FDA issued an Emergency Use Authorization (EUA) for the use of tocilizumab in combination with corticosteroids in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, NIV, mechanical ventilation, or extracorporeal membrane oxygenation.²¹ Per this EUA, 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).¹⁰

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

Clinical Data for COVID-19
The clinical data on the use of sarilumab as a treatment for COVID-19 are summarized in Table 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.
(ClinicalTrials.gov Identifier NCT04315298). 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, there was a reduction in mortality by Day 22 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. Compared to the patients in the standard of care arm (n = 418), those in the sarilumab arm (n = 485) had more organ support-free days (OR 1.50; 95% CrI, 1.13–2.00) and a greater likelihood of survival while hospitalized (OR 1.51; 95% CrI, 1.06–2.20). A notable limitation to the sarilumab findings in the REMAP-CAP trial is that patients in the standard of care arm were enrolled earlier in the pandemic than those in the sarilumab arm. Randomization closed on November 2020 for the standard of care arm and continued through April 2021 for the sarilumab arm.

**Clinical Trials**

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

**Adverse Effects**

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

**Considerations in Pregnancy**

There are insufficient data to determine whether there is a sarilumab-associated risk for major birth defects or miscarriage. As pregnancy progress, mAbs are actively transported across the placenta (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus.

**Considerations in Children**


**Drug Availability**

The IV formulation of sarilumab is not approved by the FDA. In the REMAP-CAP trial, a single SQ dose of sarilumab 400 mg was reconstituted in 100 cc 0.9% NaCl and given as an IV infusion over 1 hour.

**Anti-Interleukin-6 Monoclonal Antibody**

**Siltuximab**

Siltuximab is a recombinant human-mouse chimeric mAb that binds IL-6 and is approved by the FDA for use in patients with multicentric Castleman disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors, inhibiting IL-6 signaling. Siltuximab is administered as an IV infusion.
Clinical Data for COVID-19
There are limited data on the efficacy of siltuximab in patients with COVID-19. There is no information on clinical experiences with using siltuximab for patients with other novel coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]).

Clinical Trials
See ClinicalTrials.gov for a list of clinical trials evaluating the use of siltuximab for the treatment of COVID-19.

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

Considerations in Pregnancy
There are insufficient data to determine whether there is a siltuximab-associated risk for major birth defects or miscarriage. As pregnancy progresses, mAbs are transported across the placenta (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus.

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

References
9. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-


