The COVID-19 Treatment Guidelines Panel's Statement on the Use of Tocilizumab for the Treatment of COVID-19

Last Updated: March 5, 2021

Tocilizumab is a recombinant humanized anti-interleukin (IL)-6 receptor monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of certain rheumatologic disorders and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR-T cell) therapy. It is hypothesized that modulating the levels of proinflammatory IL-6 or its effects may reduce the duration and/or severity of COVID-19 illness. To date, no IL-6 inhibitor is FDA-approved or authorized for the treatment of COVID-19.

On February 3, 2021, the COVID-19 Treatment Guidelines Panel (the Panel) issued a statement on the use of tocilizumab that included recommendations based on a preliminary report of results from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP). Since the statement was issued, the Panel has reviewed published results of REMAP-CAP[1] and the preliminary results of the open-label, pragmatic Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial,[2] released on February 11, 2021. Based on this review, the Panel has updated its recommendations on the use of tocilizumab in certain populations of patients with COVID-19.

Recommendations

Based on the collective evidence from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Randomized Evaluation of COVID-19 Therapy (RECOVERY) trials, the COVID-19 Treatment Guidelines Panel (the Panel) has determined the following:
• The Panel recommends the use of **tocilizumab**[a] (single intravenous dose of 8 mg/kg of actual body weight, up to 800 mg) **in combination with dexamethasone** (6 mg daily for up to 10 days)[b] in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19.[c] The patients included in this population are:
  • Recently hospitalized patients[d] who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV), or high-flow nasal canula (HFNC) oxygen (>0.4 FiO_2/30 L/min of oxygen flow) **(BIIa)**; *or*
  • Recently hospitalized patients[d] (not in the ICU) with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation **(BIIa)** (**Note:** The RECOVERY trial inclusion criterion for inflammation was C-reactive protein [CRP] ≥75 mg/L; see details below).
• For hospitalized patients with hypoxemia who require conventional oxygen supplementation, the Panel recommends using one of the following options: **remdesivir (BIIa)**, **dexamethasone plus remdesivir (BIII)**, or **dexamethasone alone (BI)** (see Therapeutic Management of Adults With COVID-19).
  • There is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also give tocilizumab to patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥75 mg/L but who do not yet require NIV or HFNC, as described above.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] Use of tocilizumab **should be avoided** in patients with any of the following: (1) significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs; (2) alanine transaminase >5 times the upper limit of normal; (3) high risk for gastrointestinal perforation; (4) an uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection; (5) absolute neutrophil count <500 cells/mL; or (6) platelet count <50,000 cells/mL.

[b] As an alternative to dexamethasone, corticosteroids at a dose equivalent to dexamethasone 6 mg are acceptable (see Corticosteroids).

[c] Respiratory decompensation should be due to progressive COVID-19 and not due to alternative causes, such as volume overload or asthma exacerbation.

[d] For example, within 3 days. Median days of hospitalization until randomization was 1.2 days (IQR 0.8–2.8 days) in REMAP-CAP and 2 days (IQR 1–5 days) in the RECOVERY trial.

Additional Considerations

- Tocilizumab should be given only in combination with dexamethasone (or another corticosteroid at an equivalent dose).
- Some clinicians may assess a patient's clinical response to dexamethasone first, before deciding whether tocilizumab is needed.
- Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of treating physicians, there are insufficient data to determine which patients, if any, would benefit from an additional dose of the drug.
- Cases of severe and disseminated strongyloidiasis have been reported with the use of tocilizumab and corticosteroids in patients with COVID-19.[3,4] Prophylactic treatment with ivermectin should be considered for persons who are from areas where strongyloidiasis is endemic.[5]
- Tocilizumab use **should be avoided** in patients who are significantly immunocompromised. The basis for this precaution is that the REMAP-CAP and RECOVERY trials enrolled very few severely immunocompromised patients, and thus the safety of using tocilizumab plus a corticosteroid in such patients is unknown.
- There are insufficient data to recommend either for or against tocilizumab for the treatment of hospitalized children with COVID-19 or multisystem inflammatory syndrome of children (MIS-C). In children, tocilizumab has been used to treat cytokine release syndrome associated with CAR-T cell therapy and systemic and polyarticular juvenile idiopathic arthritis.
- Health systems are encouraged to ensure that an adequate supply of tocilizumab is available for patients who need the drug for FDA-approved indications.

Rationale for the Panel's Recommendations

The results of the RECOVERY and REMAP-CAP trials provide consistent evidence that tocilizumab, when added to corticosteroid therapy, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill and exhibit rapid clinical deterioration with increasing oxygen needs and a significant inflammatory response to the virus. However, the Panel found it challenging to define the specific population(s) that would benefit from this intervention. See an overview of the clinical trial data on the use of tocilizumab in patients with COVID-19 below.

For patients with severe to critical COVID-19 who are exhibiting rapid respiratory decompensation, the Panel found that the evidence for a benefit of tocilizumab in combination with dexamethasone was strongest for those who recently started high-flow nasal canula (HFNC) oxygen or noninvasive mechanical ventilation (NIV). REMAP-CAP reported a mortality benefit in their overall study population of patients admitted to the ICU within the prior 24 hours who required invasive mechanical ventilation (IMV), NIV, or HFNC. The RECOVERY trial also suggested a mortality benefit of tocilizumab plus dexamethasone in patients requiring NIV or HFNC. However, it was unclear whether there was a benefit of tocilizumab for patients who received IMV >24 hours after ICU admission.

Although several trials reported before REMAP-CAP and RECOVERY did not show a mortality benefit in patients on HFNC, NIV, or IMV, most of these studies were much smaller; enrolled patients who may not have exhibited rapid clinical progression, patients who received oxygen support >24 hours after ICU admission, and patients later in their ICU course of stay; and included only a minority of patients who were receiving corticosteroids. The concomitant use of corticosteroids is likely an important factor

for treatment outcomes, as the RECOVERY trial showed no benefit of tocilizumab in the subset of participants who were not receiving dexamethasone. Overall, these data provide the basis for the Panel's recommendations on the use of tocilizumab with corticosteroids for certain patients who exhibit rapid respiratory decompensation.

For patients with severe COVID-19 on conventional oxygen therapy who are typically admitted to general medical wards, the Panel found that the evidence was insufficient to identify which patients would benefit from adding tocilizumab to treatment with corticosteroids. Specifically, most previous trials with a high proportion of patients receiving conventional oxygen therapy did not show a treatment effect from tocilizumab, though many were under-powered and had low use of corticosteroids.[6-10] Although a mortality benefit of tocilizumab was observed in the RECOVERY trial, the study did not identify a particular subgroup of hospitalized patients on conventional oxygen therapy who benefited most from the drug. Among 21,550 participants randomized in the RECOVERY platform trial, only 4,116 (19%) of the participants underwent a second randomization to the tocilizumab intervention, suggesting that the study results are generalizable only to a restricted subset of hospitalized patients. The consort diagram for the RECOVERY trial suggests that patients with clinical evidence of progressive COVID-19 were preferentially selected for the tocilizumab study. The lack of clearly defined clinical criteria and the application of an arbitrary C-reactive protein (CRP) threshold to define inflammation and expected heterogeneity of CRP measurements between assays also influenced the Panel's recommendations. The Panel recognizes that there may be some hospitalized patients who are receiving conventional oxygen therapy who may have progressive hypoxemia and significant systemic inflammation. The addition of tocilizumab to their standard treatment may provide modest benefit. Nevertheless, at present, there is insufficient evidence to fully define and clearly characterize subgroups within this patient population.

Clinical Trial Data Among Hospitalized Patients With COVID-19

Initial studies that evaluated the use of tocilizumab for the treatment of COVID-19 produced conflicting results. Many trials were limited by low statistical power, heterogenous study populations with varying degrees of disease severity, and/or a low frequency of concomitant use of corticosteroids, which has become the standard of care for patients with severe or critical COVID-19.[8,10,11] These trials failed to demonstrate a reduction in mortality within 1 month of tocilizumab treatment. However, two studies conducted prior to the REMAP-CAP and RECOVERY trials did demonstrate a benefit of tocilizumab. A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA) found that tocilizumab treatment lowered the incidence or duration of ICU and hospital stays.[12] The Evaluating Minority Patients With Actemra (EMPACTA) showed that tocilizumab treatment lowered the composite rate of mechanical ventilation or death.[7] The COVACTA trial primarily enrolled participants who were receiving higher than conventional levels of oxygen therapy (more than two-thirds of the participants were receiving HFNC, NIV, or IMV), and EMPACTA had a very high proportion of concurrent corticosteroid use (80% of participants), which suggests that these factors may contribute to the differences in the treatment effect seen in trials reported prior to REMAP-CAP and RECOVERY.

REMAP-CAP and RECOVERY, the two largest, randomized controlled tocilizumab trials, have reported a mortality benefit of tocilizumab in selected populations. REMAP-CAP enrolled a narrowly defined population of critically ill patients requiring respiratory support who were admitted to an ICU and randomized to receive open-label tocilizumab (n = 353) or usual care (n = 402). Participants were enrolled within 24 hours of ICU admission, and within a median of 1.2 days (IQR 0.8–2.8 days) of hospitalization. Corticosteroids were given to 92.7% and 93.9% of the patients in the tocilizumab and usual care arms, respectively. Compared to usual care, tocilizumab use reduced both in-hospital mortality (28% of the tocilizumab recipients vs. 36% of the usual care recipients died) and time to hospital discharge (HR 1.41; 95% credible interval [CrI], 1.18–1.70) and increased the number of organ support-free days (10 days in the tocilizumab arm vs. 0 days in the usual care arm; OR 1.64; 95% CrI, 1.25–2.14).

Limitations of the REMAP-CAP trial include the open-label design of the study, the limited collection of data on adverse events, and the lack of subgroup analyses by oxygen requirement at enrollment.[1]

The RECOVERY trial enrolled hospitalized patients with COVID-19 into an open-label, platform trial of several treatment options. A subset of participants with hypoxemia (i.e., SpO_2 <92% or need for supplemental oxygen) and CRP level ≥75 mg/L were offered enrollment into a second randomization (1:1) to tocilizumab (8 mg/kg once, with possible second dose) versus usual care. Across the tocilizumab arm (n = 2,022) and the usual care arm (n = 2,094), the median duration of hospitalization was 2 days, and 82% of the participants were receiving concomitant corticosteroids. At baseline, 45% of the participants were on conventional oxygen, 41% on HFNC or NIV, and 14% on IMV. The study reported that tocilizumab reduced all-cause mortality through 28 days (29% of tocilizumab recipients vs. 33% of usual care recipients died by Day 28; RR 0.86; 95% CI, 0.77–0.96), as well as the median time to being discharged alive (20 days for the tocilizumab recipients vs. >28 days for the usual care recipients). In the subgroup analysis, the mortality benefit was restricted to participants who were also receiving corticosteroids (RR 0.80; 95% CI, 0.70–0.90); no benefit was seen among those receiving tocilizumab without corticosteroids. Limitations of the RECOVERY trial include its open-label design, the broad eligibility criteria for patients who were offered the second randomization to tocilizumab, the fact that a high proportion of those randomized to tocilizumab did not receive the treatment (17%), and the limited collection of data on adverse events. The study has not yet been published in a peer-reviewed journal.[2]

References

1. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
2. RECOVERY Collaborative Group, Horby PW, Pessoa-Amorim G, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *medRxiv*. 2021;preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1.
3. 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/docserver/fulltext/10.4269/ajtmh.20-0699/tpmd200699.pdf?expires=1598276702&id=id&accname=guest&checksum=D8AA596942F31C34007E0FE065AF1F5F.
4. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32910321.
5. 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.
6. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ*. 2021;372:n84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33472855.
7. 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.
8. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med*. 2020;383(24):2333-2344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33085857.
9. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):24-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080005.
10. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*.

2021;181(1):32-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080017.

11. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med*. 2021;181(1):41-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080002.
12. Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. *medRxiv*. 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.08.27.20183442v2.