



# Infliximab

Last Updated: October 10, 2023

Infliximab is a tumor necrosis factor–alpha (TNF-alpha) inhibitor that has been evaluated for the treatment of hospitalized patients with moderate to severe COVID-19. TNF-alpha is a pleiotropic proinflammatory cytokine mainly generated by activated macrophages, lymphocytes, and natural killer cells that plays a significant role in immune-mediated inflammatory diseases. Early in the COVID-19 pandemic, increased levels of interleukin (IL)-6 and TNF-alpha were identified as independent predictors of disease severity and death.<sup>1</sup> Furthermore, several cohort studies and registries noted that people with immune-mediated inflammatory diseases who were receiving TNF-alpha inhibitors were at lower risk for COVID-19–related hospitalizations and severe disease than people with immune-mediated inflammatory diseases who were receiving non–TNF-alpha biologic products.<sup>2,3</sup> It has been hypothesized that modulating levels of TNF-alpha or its effects may reduce the duration or severity of COVID-19.

## Recommendation

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

## Rationale

The ACTIV-1 immune modulator trial was a double-blind, multi-arm, placebo-controlled, randomized trial in moderately to severely ill adults hospitalized with COVID-19.<sup>4</sup> The trial separately evaluated treatment with abatacept, cenicriviroc, and infliximab versus placebo. All arms received standard care, and the separate analyses included data from a shared placebo arm. One substudy compared the use of a single dose of intravenous infliximab 5 mg/kg to placebo. The primary endpoint was time to recovery by Day 28. Key secondary endpoints included clinical status at Day 14 and mortality through Days 28 and 60.

The study concluded that use of infliximab in patients with COVID-19 did not have a significant effect on the time to recovery. A reduction in 28-day mortality, a secondary endpoint, was found. Patients who required mechanical ventilation or extracorporeal membrane oxygenation (ECMO) did not benefit from the use of infliximab.

## Clinical Data

In the ACTIV-1 trial, the modified intention-to-treat analysis for the infliximab substudy included 517 patients in the infliximab arm and 516 patients in the placebo arm. At baseline, 52% of the patients required conventional oxygen supplementation, and 33% required HFNC oxygen or NIV. As part of their standard care before or during the study, 93% of the patients received remdesivir, and 92% received corticosteroids.

## Results

- The use of infliximab did not reduce the median time to recovery, which was the primary endpoint. The median time to recovery was 8 days in the infliximab arm versus 9 days in the

placebo arm (recovery rate ratio 1.12; 95% CI, 0.99–1.28;  $P = 0.08$ ), and there was no differential effect across subgroups based on disease severity (interaction  $P = 0.36$ ).

- Mortality by Day 28 was lower among patients who received infliximab (52 of 517 patients [10.1%]) than among those who received placebo (75 of 516 patients [14%]; OR 0.59; 95% CI, 0.39–0.90).
- Subgroup analyses showed reduced mortality only among patients in the infliximab arm who required HFNC oxygen or NIV (OR 0.52; 95% CI, 0.29–0.91).
- Among patients who required mechanical ventilation or ECMO, there was no difference in mortality by Day 28 (OR 1.11; 95% CI, 0.45–2.72).
- There were no differences in secondary infections or in the number or severity of serious adverse events between the infliximab and placebo arms.

### **Limitations**

- Each of the 3 active agents was compared to a shared placebo group without adjustment for multiple comparisons.
- Mortality was a secondary endpoint. Although the treatment difference found for mortality by Day 28 was nominally significant, no adjustment was made for having considered multiple outcomes (primary outcome and mortality).
- The study was not powered to analyze differences within disease severity subgroups.

### **Adverse Effects and Monitoring**

Most of the data on adverse effects of infliximab come from the chronic use of the agent for the treatment of autoimmune diseases. Adverse effects include serious infections (including invasive fungal infections), infusion-related reactions and hypersensitivity, cytopenias, hepatotoxicity, and, rarely, cardiovascular and cerebrovascular events. Because of infliximab's immunosuppressive effects, all patients who receive it should be monitored for new infections. In the ACTIV-1 trial, data on the safety of short-term use of infliximab in patients with COVID-19 did not reveal significant safety concerns.

### **Considerations in Pregnant and Lactating People**

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

### **Considerations in Children**

Infliximab is approved for the treatment of inflammatory bowel disease in children and is often used to treat juvenile idiopathic arthritis. The Food and Drug Administration has not approved the use of infliximab for the treatment of COVID-19 in children, and there are no published reports on the efficacy of infliximab in this population. No patients aged <18 years were included in the ACTIV-1 trial.

See [Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A](#) for the Panel's recommendations regarding the use of infliximab in pediatric patients with multisystem inflammatory syndrome in children (MIS-C).

### **References**

1. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med.* 2020;26(10):1636-1643. Available at: <https://pubmed.ncbi.nlm.nih.gov/32839624>.

2. Curtis JR, Zhou X, Rubin DT, et al. Characteristics, comorbidities, and outcomes of SARS-CoV-2 infection in patients with autoimmune conditions treated with systemic therapies: a population-based study. *J Rheumatol*. 2022;49(3):320-329. Available at: <https://pubmed.ncbi.nlm.nih.gov/34782447>.
3. Izadi Z, Brenner EJ, Mahil SK, et al. Association between tumor necrosis factor inhibitors and the risk of hospitalization or death among patients with immune-mediated inflammatory disease and COVID-19. *JAMA Netw Open*. 2021;4(10):e2129639. Available at: <https://pubmed.ncbi.nlm.nih.gov/34661663>.
4. O'Halloran JA, Ko ER, Anstrom KJ, et al. Abatacept, cenicriviroc, or infliximab for treatment of adults hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA*. 2023;330(4):328-339. Available at: <https://pubmed.ncbi.nlm.nih.gov/37428480>.