Infliximab

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Tumor necrosis factor–alpha (TNF-alpha) is a pleiotropic proinflammatory cytokine that is mainly generated by activated macrophages, lymphocytes, and natural killer cells. TNF-alpha plays a significant role in immune-mediated inflammatory diseases. Early in the COVID-19 pandemic, increased levels of interleukin-6 and TNF-alpha were identified as independent predictors of disease severity and death.[1] 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.[2,3] It has been hypothesized that modulating levels of TNF-alpha or its effects may reduce the duration or severity of COVID-19. Infliximab is a TNF-alpha inhibitor that has been evaluated for the treatment of hospitalized patients with moderate to severe 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 immunomodulator trial was a double-blind, multi-arm, randomized trial in moderately to severely ill adults who were hospitalized with COVID-19.[4] 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 did not benefit from the use of infliximab.

Monitoring and Adverse Effects

Because of infliximab's immunosuppressive effects, all patients who receive it should be monitored for new infections. In the ACTIV-1 trial, the use of a single dose of infliximab in patients with COVID-19 did not reveal significant safety concerns.

Most of the data on the 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.[5]

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 using 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).

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 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 patients received remdesivir, and 92% received corticosteroids.

Results

- 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 extracorporeal membrane oxygenation, 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 adjusting for multiple comparisons.
- Mortality was a secondary endpoint. Although the treatment difference for mortality by Day 28 was nominally significant, no adjustment was made to the analysis to assess multiple outcomes (primary outcome and mortality).
- The study was not powered to analyze differences within disease severity subgroups.

References

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