Immune Modulator Drugs Improved Survival for People Hospitalized With COVID-19

Two drugs widely used to treat certain autoimmune diseases substantially improved clinical status and reduced deaths.

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A large randomized, placebo-controlled clinical trial led by the National Institutes of Health (NIH) shows that treating adults hospitalized with COVID-19 with infliximab or abatacept – drugs widely used to treat certain autoimmune diseases – did not significantly shorten time to recovery but did substantially improve clinical status and reduce deaths.

Some COVID-19 patients experience an immune response in which the immune system unleashes excessive amounts of proteins that trigger inflammation that can lead to acute respiratory distress syndrome, multiple organ failure and other life-threatening complications. As part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private initiative, NIH launched the ACTIV-1 Immune Modulators clinical trial to determine if certain drugs that help minimize the effects of an overactive immune response could speed recovery and reduce deaths in adults hospitalized with moderate to severe COVID-19.

The ACTIV-1 master protocol included three sub-studies; each one tested an immune modulator drug as compared to a placebo. This approach allowed for coordinated and efficient evaluation of multiple investigational agents simultaneously.

NIH's National Center for Advancing Translational Sciences (NCATS) coordinated and oversaw the trial with funding from the Biomedical Advanced Research and Development Authority (BARDA) of the U.S. Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response.

"These promising ACTIV-1 results demonstrate the collaborative power of public-private partnerships to accelerate therapeutic answers during this unprecedented global health crisis," said Acting NIH Director Lawrence A. Tabak, DDS, PhD. "Working together, NIH and our ACTIV partners have brought to bear the best tools and clinical trial designs in our research arsenals. The innovative ACTIV model is bringing greater clarity to the search for effective, evidence-based COVID-19 treatments."

ACTIV-1 participants were randomly assigned to one of the immune modulator drugs or placebo in addition to the standard of care, which may include remdesivir (Veklury) supplied by Gilead Sciences, Inc. About 90% received remdesivir, and about 85% received dexamethasone.

Investigators monitored participants and recorded their clinical status daily while hospitalized according to an eight-point scale ranging from not hospitalized with no limitations on activities to death. The full report on these data in a peer-reviewed scientific journal is expected in fall of 2022, and a preprint will be available sooner.

The topline results showed:

- Compared to placebo, participants receiving infliximab (Remicade) displayed a strong but not statistically significant improvement in the primary endpoint of time to recovery as measured by day of discharge from hospital. Substantial improvements for both key secondary endpoints of mortality and clinical status at 28 days were observed. The 518 participants receiving infliximab had a death rate of 10.0%, compared to 14.5% for the 519 participants receiving placebo, resulting in 40.5% lower adjusted odds of dying. The relative improvement in mortality was similar in both moderately and severely ill participants. People in the infliximab group had 43.8% better odds of clinical improvement than those in the placebo group. Infliximab, which was given as a single dose, was developed and is marketed by Janssen Biotech, Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson.
- Compared to placebo, participants receiving abatacept (Orencia) displayed a strong but not statistically significant improvement in the primary endpoint of time to recovery as measured by day of discharge from hospital. Substantial improvements for both key secondary endpoints of mortality and clinical status at 28 days were observed. The 509 participants receiving abatacept had a death rate of 11.0%, compared to 15.0% for the 513 participants receiving placebo, resulting in 37.4% lower adjusted odds of dying. The relative improvement in mortality was similar in both moderately and severely ill participants. People in the abatacept group had 34.2% better odds of clinical improvement than those in the placebo group. Abatacept, which was given as a single dose, was developed and is marketed by Bristol Myers Squibb.
- Enrollment into the third sub-study evaluating the investigational medicine cenicriviroc was stopped in September 2021 after an independent data and safety monitoring board (DSMB)

recommended closing it due to lack of efficacy. Cenicriviroc was provided by AbbVie.

The results will be made available to treatment guideline groups and regulatory bodies.

“When given in addition to standard of care treatments, like remdesivir and dexamethasone, infliximab and abatacept each offered a substantial reduction in mortality,” said the trial’s protocol chair, William G. Powderly, MD, director of the Institute for Clinical and Translational Sciences and co-director of the Division of Infectious Diseases at Washington University School of Medicine in St. Louis. “These drugs could potentially add to the therapeutic options available for the treatment of patients hospitalized with COVID-19.”

From October 2020 through December 2021, the ACTIV-1 Immune Modulators clinical trial enrolled 1,971 participants at 46 medical facilities in the United States and 23 medical facilities in Latin America. The study was reviewed periodically by an independent DSMB, and no safety concerns were noted during the conduct of the trial.

NCATS’ Clinical and Translational Science Awards (CTSA) Program and the Trial Innovation Network played a key role in enrolling participants in the United States.

“More than half of the CTSA Program sites contributed their infrastructure and expertise to speed completion of this trial,” said Joni L. Rutter, PhD, acting director of NCATS. “This collaborative and efficient multinational platform trial design streamlined our ability to urgently and robustly test promising therapies for treating people hospitalized with COVID-19.”

For more information about the trial, please visit clinicaltrials.gov and search identifier NCT04593940.

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