Drug reduces deaths for subset of COVID-19 patients in trial

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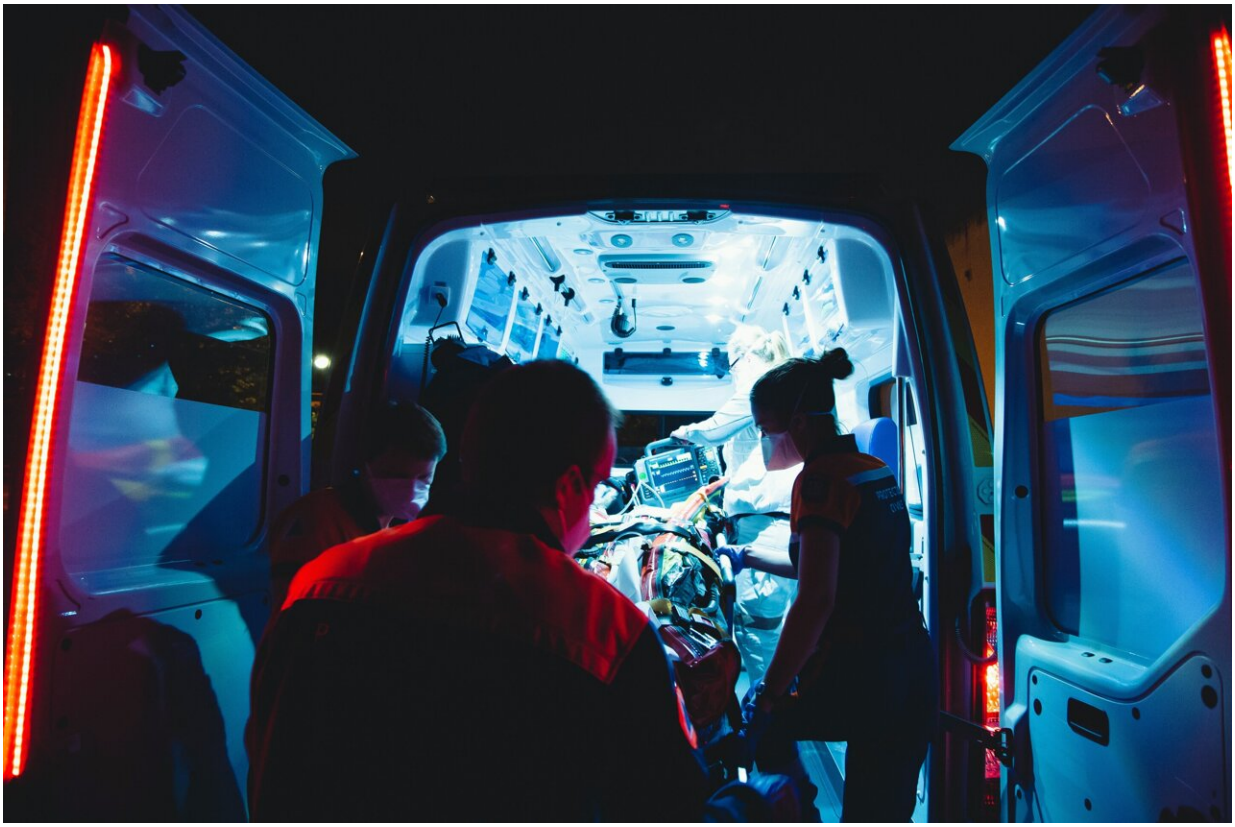

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Preliminary RECOVERY trial results find a monoclonal antibody (MAB) drug by Regeneron reduces the risk of death in a subset of patients with severe COVID-19.

The RECOVERY trial has demonstrated that in patients who have not mounted a natural antibody response of their own, the investigational antibody combination developed by Regeneron reduces the risk of death when given to patients hospitalized with severe COVID-19.

The RECOVERY trial was established as a randomized clinical trial to test a range of potential treatments for patients hospitalized with COVID-19.

It is funded by the Medical Research Council (MRC) and National Institute for Health Research (NIHR) as part of their COVID-19 rapid research response (National Archives).

To provide real-time information in the pandemic, the preliminary results are available as a preprint on medRxiv on 16 June 2021. Full results will be submitted to a peer-reviewed journal.

Monoclonal antibody treatment

The treatment uses a combination of two monoclonal antibodies, casirivimab and imdevimab, known as REGEN-COV in the US. They bind specifically to two different sites on the COVID-19 spike protein, neutralizing the ability of the virus to infect cells.

Previous studies in non-hospitalized COVID-19 patients have shown that the treatment:

- reduces viral load
- shortens the time to resolution of symptoms
- significantly reduces the risk of hospitalization or death.

In a previous small trial in hospitalized patients, preliminary evidence (Regeneron) suggested a clinical benefit in patients who had not

mounted a natural antibody response of their own when they entered the trial. That is, they were 'seronegative."

RECOVERY is the first trial large enough to determine definitively whether this treatment reduces mortality in patients hospitalized with severe COVID-19.

Reduced mortality

Between 18 September 2020 and 22 May 2021, 9785 patients hospitalized with COVID-19 were randomly allocated to receive usual care plus the antibody combination treatment or usual care alone as part of the RECOVERY trial. Of these:

- about one-third were seronegative at baseline, for example, they had not mounted a natural antibody response of their own,
- one-half were seropositive, for example, they had already developed natural antibodies), and
- one-sixth had unknown serostatus.

Among patients who received usual care alone, 28-day mortality was twice as high in those who were seronegative (30%) compared to those who were seropositive (15%) at study entry. Follow-up is complete for 99% of participants.

Among patients who were seronegative at baseline, which was the primary analysis population for this comparison, the antibody combination significantly reduced the primary outcome of 28-day mortality by one-fifth. This was compared with usual care alone where 24% of patients in the antibody combination group died, comparative to 30% of patients in the usual care group.

Thus, for every 100 such patients treated with the antibody combination,

there would be six fewer deaths.

Difference by serostatus

There was clear evidence that the effect of treatment in seronegative patients differed from that in seropositive patients. When combining the larger seropositive group, as well as those with unknown status, with the seronegative patients, there was no longer a significant effect on 28-day mortality. The results showed overall 20% of patients in the antibody combination group died compared with 21% of patients in the usual care group.

For the seronegative patients, the duration of hospital stay was four days shorter among those allocated to the antibody combination than the usual care group. The median was 13 days compared with 17 days. The proportion of patients discharged alive by day 28 was greater, 64% compared with 58%.

Among the seronegative patients not on invasive mechanical ventilation at baseline, the risk of progressing to the composite endpoint of invasive mechanical ventilation or death was lower among those allocated to the antibody combination than the usual care group. The results showed 30% compared with 37%, respectively.

No such benefits were seen in the overall study population, combining patients with negative, positive, or unknown serostatus.

Ground-breaking treatment

Professor Sir Peter Horby (Nuffield Department of Medicine), University of Oxford, and joint chief investigator for the trial, said:

"These results are very exciting. The hope was that by giving a combination of antibodies targeting the SARS-CoV-2 virus we would be able to reduce the worst manifestations of COVID-19. There was, however, great uncertainty about the value of antiviral therapies in late-stage COVID-19 disease.

"It is wonderful to learn that even in advanced COVID-19 disease, targeting the virus can reduce mortality in patients who have failed to mount an antibody response of their own."

Professor Sir Martin Landray (Nuffield Department of Population Health), University of Oxford, and joint chief investigator, said: "We now know that this antibody combination is not only bad for the virus but it is also good for the sickest patients who have failed to mount a natural immune response of their own. That is excellent news. It is the first time that any antiviral treatment has been shown to save lives in hospitalized COVID-19 patients. We are incredibly grateful to the many NHS staff and patients who have contributed to today's discovery."

RECOVERY participant, Kimberley Featherstone (37), was treated at Huddersfield Royal Infirmary and Calderdale Royal Hospital and randomly allocated to the monoclonal antiviral antibody combination. She said:

"I was certainly glad to take part in the RECOVERY trial. I feel very lucky that the trial was up and running by the time I was taken to hospital with COVID-19, and I was able to receive this ground-breaking treatment. I'm happy that by participating, I played a part in finding out this treatment is successful."

Professor Fiona Watt, Executive Chair, MRC, said: "The flagship RECOVERY trial once again leads the way in showing the importance of well-designed clinical trials to identify life-saving treatments. This

very important finding means, for patients hospitalized with COVID-19 who do not make their own antibodies to the virus, being treated with antibody-based drugs to the spike protein can reduce their risk of death and time spent in hospital.

"Patients who have made their own antibodies to the virus do not benefit from the new treatment, which is also important information given the cost of drugs."

Professor Nick Lemoine, Medical Director at the NIHR Clinical Research Network, said: "It is fantastic news that the RECOVERY trial has provided evidence to establish another lifesaving treatment against COVID-19 through this monoclonal antiviral antibody combination. The incredible impact the trial continues to have is testament to the scientists and healthcare professionals, but equally the tens of thousands of patients who have taken part. We sincerely want to thank every single one of them for their contribution."

Previously, in June 2020, the RECOVERY trial found that the inexpensive and widely available steroid dexamethasone reduces death for patients with severe COVID-19. This rapidly became part of standard-of-care given to all such patients.

Provided by Medical Research Council