The BMJ

Cite this as: *BMJ* 2021;373:n1570
http://dx.doi.org/10.1136/bmj.n1570
Published: 17 June 2021

Covid-19: Regeneron's antibody combination cuts deaths in seronegative patients, trial finds

Elisabeth Mahase

Regeneron's antibody combination treatment cut deaths in seronegative patients—meaning those who had not mounted their own antibody response to covid-19—by one fifth, the Recovery trial has found.[1]

The researchers found that for every 100 seronegative patients treated with the combination of casirivimab and imdevimab, there were six fewer deaths. They said patients admitted to hospital should now be routinely tested for antibodies to determine whether the treatment could benefit them.

The two virus neutralising antibodies work by binding non-competitively to the critical receptor binding domain of SARS-CoV-2's spike protein, thereby stopping the virus from binding to and entering human cells.

Recovery, which is being carried out in 177 UK hospitals, has been evaluating potential covid-19 treatments for patients admitted to hospital. It discovered the first effective treatment for reducing mortality—dexamethasone—while also discounting others including hydroxychloroquine and convalescent plasma.

As part of the trial, 9785 covid-19 patients admitted to hospital were randomised to receive either usual care plus the antibody combination treatment or usual care alone between September 2020 and May 2021. Of these, about one third were seronegative at baseline, half were seropositive (they had 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 with those who were seropositive (15%) at study entry. For those who were seronegative at baseline, however, the antibody combination reduced deaths by 25% (from 30% in the usual care group to 24% in the antibody combination group; rate ratio 0.80; 95% confidence interval 0.70 to 0.91; P=0.001). The treatment also reduced the duration of hospital stay by four days in this group (median 13 days *v* 17 days with usual care only.)

The treatment did not have an effect on those who were seropositive at baseline.

Belt and braces approach

In the preprint of the study researchers said that while they did not specifically look at variants, the major variants circulating in the UK throughout the trial, such as alpha, remained sensitive to the treatment.

They added that although spike glycoprotein mutations in the beta and delta variants have been associated with a reduction of neutralisation activity of casirivimab, the treatment remains potent because of the inhibitory activity of imdevimab. The researchers described the treatment as having a "belt and braces approach" so that if one fails the other should still work.

Convalescent plasma

One question raised in light of the positive results is why this antibody treatment works while convalescent plasma—which contains antibodies to covid-19 from people who've recovered from the virus—does not.

Speaking at the Science Media Centre briefing, Recovery trial chief investigator Peter Hornby, professor of emerging infectious diseases and global health at the University of Oxford, said it comes down to the dose and quality of antibodies.

"The monoclonal antibodies are selected to be highly potent—the best they can find. And we give a very high dose. Whereas with convalescent plasma you've got a mix of high quality and low quality antibodies and much lower quantities. It's just a much less potent product, I think," he said.

The study was funded by UK Research and Innovation and the National Institute of Health Research. One author on the study was an employee of Regeneron Pharmaceuticals and holds shares or share options in the company. All other authors had no conflict of interest or relevant financial relationships.

1 Horby PW, Mafham M, Peto L, et al. Casirivimab and imdevimab in patients admitted to hospital with covid-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv 2021.06.15.21258542v1 [Preprint]. 2021. www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.