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RECOVERY trial finds Regeneron's monoclonal antibody combination reduces deaths for hospitalised COVID-19 patients who have not mounted their own immune response

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

The treatment uses a combination of two monoclonal antibodies (casirivimab and imdevimab, known as REGEN-COV in the US) that bind specifically to two different sites on the coronavirus spike protein, neutralising the ability of the virus to infect cells.

Previous studies in non-hospitalised COVID-19 patients have shown that the treatment reduces viral load, shortens the time to resolution of symptoms, and significantly reduces the risk of hospitalisation or death. In a small trial in hospitalised patients, preliminary evidence suggested a clinical benefit in patients who had not mounted a natural antibody response of their own when they entered the trial (were seronegative).[1] RECOVERY is the first trial large enough to determine definitively whether this treatment reduces mortality in patients hospitalised with severe COVID-19.

Between 18 September 2020 and 22 May 2021, 9785 patients hospitalised with COVID-19 were randomly allocated to receive usual care plus the antibody combination treatment (casirivimab 4g with imdevimab 4g by intravenous infusion) or usual care alone as part of the RECOVERY trial. Of these, about one-third were seronegative at baseline (ie they had not mounted a natural antibody response of their own), one-half were seropositive (ie 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%) vs. those who were seropositive (15%) at study entry. Follow-up is complete for 99% of participants and preliminary results are announced today.

Among patients who were seronegative at baseline (the primary analysis population for this comparison), the antibody combination significantly reduced the primary outcome of 28-day mortality by one-fifth compared with usual care alone (24% of patients in the antibody combination group died vs 30% of patients in the usual care group; rate ratio 0·80; 95% confidence interval 0·70–0·91; p=0·001). Thus, for every 100 such patients treated with the antibody combination, there would be six fewer deaths.

There was clear evidence that the effect of treatment in seronegative patients differed from that in seropositive patients (test for heterogeneity p=0·001). 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 (overall 20% of patients in the antibody combination group died vs 21% of patients in the usual care group; rate ratio 0·96; 95% confidence interval 0·86–1·03; p=0·17).

For the seronegative patients, the duration of hospital stay was four days shorter (median 13 days vs. 17 days) among those allocated to the antibody combination than the usual care group, and the proportion of patients discharged alive by day 28 was greater (64% vs. 58%; rate ratio 1·19, 95% confidence interval 1·08 to 1·30). 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 (30% vs. 37%; risk ratio 0·83, 95% confidence interval 0·75 to 0·92). No such benefits were seen in the overall study population (combining patients with negative, positive, or unknown serostatus).

Sir Peter Horby, Professor of Emerging Infectious Diseases in the Nuffield Department of Medicine, University of Oxford, and Joint Chief Investigator for the RECOVERY 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.'

Sir Martin Landray, Professor of Medicine and Epidemiology at the 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 hospitalised 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.'

The preliminary results of this evaluation of the monoclonal antibody combination will be available as a pre-print on medRxiv later on 16 June 2021 and will be submitted to a leading peer-reviewed medical journal.

Professor Fiona Watt, Executive Chair, Medical Research Council, which helped fund the study, said 'The flagship RECOVERY trial once again leads the way in showing the importance of well-designed clinical trials to identify lifesaving treatments. This very important finding means, for patients hospitalised 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.'

Notes

For **further information or interviews** with the chief investigators or participant case studies, please contact Dr Caroline Wood, caroline.wood@ndph.ox.ac.uk or Anne Whitehouse, anne.whitehouse@ndph.ox.ac.uk.

[1] Regeneron press release, 29 December 2020: Regeneron announces encouraging initial data from covid-19 antibody cocktail trial in hospitalized patients on low-flow oxygen

Full details of the **study protocol** and related materials are available at www.recoverytrial.net.

The **RECOVERY trial** is conducted by the registered clinical trials units with the Nuffield Department of Population Health in partnership with the Nuffield Department of Medicine. The trial is supported by a grant to the University of Oxford from UK Research and Innovation/ the National Institute for Health Research (NIHR), and by core funding provided by the Bill and Melinda Gates Foundation, the Foreign, Commonwealth & Development Office, Health Data Research UK, the Medical Research Council Population Health Research Unit, the NIHR Oxford Biomedical Research Centre, NIHR Clinical Trials Unit Support Funding, and Wellcome. Funding for RECOVERY outside the UK is provided by Wellcome through the COVID-19 Therapeutics Accelerator. Regeneron Pharmaceuticals Inc., Tarrytown, New York, USA provided all supplies of the monoclonal antibody combination (casirivimab and imdevimab).

The RECOVERY trial currently involves many thousands of doctors, nurses, pharmacists, and research administrators at 177 hospitals across the whole of the UK. In the UK, the trial is supported by staff at the NIHR Clinical Research Network, NHS DigiTrials, Public Health England, Department of Health & Social Care, the Intensive Care National Audit & Research Centre, Public Health Scotland, the Secure Anonymised Information Linkage at the University of Swansea, and the NHS in England, Scotland, Wales and Northern Ireland.

Statistical note: In accordance with the statistical analysis plan, no hypothesis testing of the secondary outcomes was performed since the comparison of the effects of antibody combination vs. usual care on 28-day mortality among the overall population (regardless of serostatus) was not significant at $P<0.05$.

The **investigational antibody combination** (casirivimab and imdevimab) was invented by Regeneron and consists of two monoclonal antibodies designed specifically to block infectivity of SARS-CoV-2, the virus that causes COVID-19. The two potent, virus-neutralizing antibodies bind non-competitively to the critical receptor binding domain of the virus's spike protein. By using a combination of antibodies that bind to non-overlapping locations on the receptor binding domain, the likelihood of viral variants to escape treatment is diminished. Regeneron and Roche are collaborating to increase global supply of the monoclonal antibody combination. Regeneron is responsible for development and distribution of the treatment in the US (under the brand name REGEN-COV™), and Roche is primarily responsible for development and distribution outside the US.