Tocilizumab reduces deaths in patients hospitalised with COVID-19

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial has demonstrated that an anti-inflammatory treatment, tocilizumab, reduces the risk of death when given to hospitalised patients with severe COVID-19. The study also showed that tocilizumab shortens the time until patients are successfully discharged from hospital and reduces the need for a mechanical ventilator.

The RECOVERY trial has been testing a range of potential treatments for COVID-19 since March 2020. Tocilizumab, an intravenous drug used to treat rheumatoid arthritis, was added to the trial in April 2020 for patients with COVID-19 who required oxygen and had evidence of inflammation. Recruitment to the tocilizumab arm stopped on 24 January 2021 since, in the view of the trial Steering Committee, sufficient patients had been enrolled to establish whether or not the drug had a meaningful benefit.

A total of 2022 patients were randomly allocated to receive tocilizumab by intravenous infusion and were compared with 2094 patients randomly allocated to usual care alone. 82% of patients were taking a systemic steroid such as dexamethasone.

Treatment with tocilizumab significantly reduced deaths: 596 (29%) of the patients in the tocilizumab group died within 28 days compared with 694 (33%) patients in the usual care group (rate ratio 0.86; [95% confidence interval [CI] 0.77 to 0.96]; p=0.007), an absolute difference of 4%. This means that for every 25 patients treated with tocilizumab, one additional life would be saved. Tocilizumab also increased the probability of discharge alive within 28 days from 47% to 54% (rate ratio 1.23, [95% CI 1.12 to 1.34], p<0.0001). These benefits were seen in all patient subgroups, including those requiring oxygen via a simple face mask through to those requiring mechanical ventilators in an intensive care unit.

Among patients not on invasive mechanical ventilation when entered into the trial, tocilizumab significantly reduced the chance of progressing to invasive mechanical ventilation or death from 38% to 33% (risk ratio 0.85, [95% CI 0.78 to 0.93], p=0.0005). However, there was no evidence that tocilizumab had any effect on the chance of successful cessation of invasive mechanical ventilation.

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. The benefits of tocilizumab were clearly seen to be in addition to those of steroids.

The data suggest that in COVID-19 patients with hypoxia (requiring oxygen) and significant inflammation, treatment with the combination of a systemic corticosteroid (such as dexamethasone) plus tocilizumab reduces mortality by about one third for patients requiring simple oxygen and nearly one half for those requiring invasive mechanical ventilation.
Peter Horby, Professor of Emerging Infectious Diseases in the Nuffield Department of Medicine, University of Oxford, and Joint Chief Investigator for RECOVERY, said 'Previous trials of tocilizumab had shown mixed results, and it was unclear which patients might benefit from the treatment. We now know that the benefits of tocilizumab extend to all COVID patients with low oxygen levels and significant inflammation. The double impact of dexamethasone plus tocilizumab is impressive and very welcome.'

Martin Landray, Professor of Medicine and Epidemiology at the Nuffield Department of Population Health, University of Oxford, and Joint Chief Investigator, said 'The results from the RECOVERY trial clearly show the benefits of tocilizumab and dexamethasone in tackling the worst consequences of COVID-19 – improving survival, shortening hospital stay, and reducing the need for mechanical ventilators. Used in combination, the impact is substantial. This is good news for patients and good news for the health services that care for them in the UK and around the world. We simply would not know this if it wasn’t for the incredible support of NHS patients and staff in the most challenging of circumstances.'

Wendy Coleman (62) received tocilizumab through the RECOVERY trial last year when she was admitted to Chesterfield Royal Hospital with severe COVID-19. ‘I was struggling to breathe quite badly and on the verge of being placed in an intensive care unit when I was asked if I wanted to take part in the RECOVERY trial. After I was given tocilizumab, my condition stabilised and I didn’t get any worse. Up until then, it was quite scary as I didn’t know if I was going to make it or not.’

‘I’d like to thank those who run the RECOVERY trial, besides all the staff at the Royal Hospital at Chesterfield. You never think about clinical trials, until you are in need of these treatments and then you realise what happens behind the scenes to find out if they work.’

Professor Nick Lemoine, Medical Director of the National Institute for Health Research (NIHR) Clinical Research Network said ‘Through our programme of urgent public research – working closely with the RECOVERY team and NHS hospital staff right across the UK – the NIHR has helped over 35,000 patients take part in this flagship treatment study. In doing so, the RECOVERY trial has been able to provide data which has now given the world two life-saving treatments against this dreadful disease.’

Professor Fiona Watt, Executive Chair of the Medical Research Council, which funded the study with the NIHR, said ‘It’s incredibly encouraging that doctors now have an additional COVID-19 treatment that can save lives and reduce the length of hospital stays. We’ve been funding the RECOVERY trial since early last year and were delighted when the RECOVERY team identified the first drug to substantially reduce COVID-19 deaths, dexamethasone. Importantly, the benefits from tocilizumab are in addition to those provided by dexamethasone - patients receiving both drugs do even better than patients on dexamethasone alone. This world-leading study shows the power of well-designed clinical trials to discover which drugs can help patients.’

The preliminary results will be made available via medRxiv shortly and submitted to a peer-reviewed medical journal. For this preliminary report, information on the primary outcome was available for 92% of patients.
About the RECOVERY trial

In March 2020, the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial was established as a randomised clinical trial to test a range of potential treatments for COVID-19, including tocilizumab (an anti-inflammatory used to treat rheumatoid arthritis). Over 35,000 patients have been enrolled so far from 177 NHS hospitals in the UK.

Patients eligible for the tocilizumab comparison in RECOVERY were required to have an oxygen saturation less than 92% on room air or requiring oxygen (with or without other forms of respiratory support), and a C-reactive protein (a marker of inflammation) level of at least 75mg/L.

In June 2020, the RECOVERY trial demonstrated that the inexpensive and widely available steroid, dexamethasone, reduced the risk of death by one-third for patients on an invasive mechanical ventilator and by one-fifth for those requiring oxygen. This was the first treatment for COVID-19 shown to save lives and was rapidly adopted as part of standard hospital treatment around the world.

The trial has previously announced results showing that hydroxychloroquine, lopinavir-ritonavir, azithromycin, and convalescent plasma have no benefits for patients hospitalised with COVID-19.

The RECOVERY trial is continuing to investigate the following treatments:

- aspirin (commonly used to thin the blood)
- baricitinib (an anti-inflammatory used to treat rheumatoid arthritis)
- colchicine (a commonly used anti-inflammatory drug)
- Regeneron’s antibody cocktail (a combination of monoclonal antibodies directed against coronavirus)

The RECOVERY trial involves many thousands of doctors, nurses, pharmacists, and research administrators at 177 hospitals across the whole of the UK, supported by staff at the NIHR Clinical Research Network, NHS DigiTrials, Public Health England, Public Health Scotland, Department of Health & Social Care, and the NHS in England, Scotland, Wales and Northern Ireland.

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/National Institute for Health Research (NIHR) and by core funding provided by NIHR Oxford Biomedical Research Centre, Wellcome, the Bill and Melinda Gates Foundation, the Foreign, Commonwealth & Development Office, Health Data Research UK, the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding. Roche Products Ltd supported the RECOVERY trial through the provision of tocilizumab.
About tocilizumab

- Tocilizumab is an anti-intereukin (IL)-6 receptor therapy.
- IL-6 is a cellular messenger in the body, known as a cytokine, involved in the regulation of the immune system, inflammation, bone formation and blood cell development (among other functions).
- IL-6 is believed to play a key role in activating the inflammatory pathway that contributes to the signs and symptoms of rheumatoid arthritis. Tocilizumab binds to IL-6 receptors, blocking the pro-inflammatory effect of IL-6.
- In the UK, tocilizumab is approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and chimeric antigen receptor T cell-induced cytokine release syndrome.

About Oxford University

Oxford University has been placed number 1 in the Times Higher Education World University Rankings for the third year running, and at the heart of this success is our ground-breaking research and innovation. Oxford is world-famous for research excellence and home to some of the most talented people from across the globe. Our work helps the lives of millions, solving real-world problems through a huge network of partnerships and collaborations. The breadth and interdisciplinary nature of our research sparks imaginative and inventive insights and solutions. Through its research commercialisation arm, Oxford University Innovation, Oxford is the highest university patent filer in the UK and is ranked first in the UK for university spinouts, having created more than 170 new companies since 1988. Over a third of these companies have been created in the past three years.