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Arthritis drugs may reduce mortality and time in ICU for sickest COVID patients

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Treating critically ill COVID-19 patients with drugs typically used for rheumatoid arthritis may significantly improve survival, a landmark study has found.

The findings, which were announced in January and have now been peer-reviewed and published in the *New England Journal of Medicine*, come from the REMAP-CAP trial, which evaluates the effect of treatments on a combination of survival and length of time patients need support in an intensive care unit (ICU).

Initial findings reported in November showed that tocilizumab, a drug used to treat arthritis, was likely to improve outcomes among critically ill COVID-19 patients. But the impact on patient survival and length of time on organ support in ICU was not clear at that time.

The full, peer-reviewed analysis shows that tocilizumab and a second drug called sarilumab—both types of immune modulators called IL-6 receptor antagonists—have a significant impact on patient survival, reducing mortality by 8.5%.

Furthermore, the treatment also improved recovery so that on average patients were able to be discharged from the intensive care unit (ICU) about a week earlier.

"We are delighted that our full results are now published after peer review. This confirms the robustness of our findings, that tocilizumab

and sarilumab can reduce deaths by nearly a quarter, in the sickest patients with COVID," said Professor Anthony Gordon, Chair in Anaesthesia and Critical Care at Imperial College London and a Consultant in Intensive Care Medicine at Imperial College Healthcare NHS Trust.

"We also saw that it helped speed up recovery, so that on average patients were discharged from ICU a week earlier and leave hospital two weeks earlier. It is great news to know that several thousand patients have already benefited from these drugs being used within the NHS. Other studies have now confirmed our results and so even more patients will continue to benefit.

"We are hugely grateful to all the NHS staff who helped make the trial happen and to all patients and their families who agreed to take part in this trial. Together we are all helping to tackle this dreadful disease."

Tocilizumab and sarilumab are immunosuppressive drugs used to treat rheumatoid arthritis. They were two of several immune modulation treatments included in the REMAP-CAP trial.At the end of last year, positive early findings on tocilizumab were released before the full data had been collected. With the full analysis now available, researchers are confident the findings will continue to bring clinical benefit for the sickest patients with COVID-19.

Full findings

At the time of full analysis 353 patients had been assigned to tocilizumab, 48 to sarilumab and 402 to control. The majority of patients were also treated with corticosteroids and were receiving respiratory support.

The trial data yielded an odds ratio of 1.64 for a better outcome with

tocilizumab, and 1.76 for sarilumab, compared to no immune modulation, with a high degree of statistical certainty (>99.5% probability that both treatments are superior to no immune modulation).

Hospital mortality was 27.3% among patients receiving IL-6 receptor agonists (28.0% for tocilizumab, 22.2% for sarilumab) compared with 35.8% for control group. This means for every 12 patients treated, one life would be saved.

Professor Gordon added: "Previous trials using IL-6 receptor agonists have showed no clear benefit on either disease progression or survival in COVID-19 patients, but those studies included less severely ill patients and started treatment at different stages in the disease course.

"A crucial difference may be that in our study, critically ill patients were enrolled within 24 hours of starting organ support. This highlights a potential early window for treatment where the sickest patients may gain the most benefit from immune modulation treatment."

Study co-author Christopher Seymour, M.D., associate professor of critical care medicine and emergency medicine at the University of Pittsburgh School of Medicine (UPMC), said: "As soon as the immune modulator results hit our statistical trigger, these drugs were immediately incorporated at UPMC and other North American REMAP-CAP partners as our standard treatment for patients critically ill with COVID-19.

"In addition, the overall design of REMAP-CAP allows us to test multiple interventions concurrently and over time. So, while we implement new evidence-based care practices, we continue to test other promising therapies in patients with both moderate and severe COVID-19."

REMAP-CAP study is led by Imperial College London and the Intensive Care National Audit & Research Centre (ICNARC) in the UK and University Medical Center Utrecht in Europe. It began investigating treatments for COVID-19 in March 2020, enrolling hospitalised patients with either moderate or severe (requiring ICU care) COVID-19 disease.

The study design randomises patients to multiple combinations of treatments, enabling researchers to evaluate different treatments for COVID-19, including antivirals, drugs which modulate the immune response, and therapies that modulate or support other vital aspects of the body's response to the virus.

To date, over 5,500 patients in 15 countries have been enrolled at more than 290 hospitals worldwide and randomised to multiple treatment combinations. The effects of interventions are assessed separately for moderate and severely ill patients.

The latest findings on tocilizumab and sarilumab add to REMAP-CAP findings from earlier this year, which found that hydrocortisone steroid treatment improved recovery among critically ill COVID-19 patients.

This study is one of a number of COVID-19 studies that have been given urgent public health research status by the Department of Health and Social Care. As of February 2021 75% of all study participants had been recruited in the UK through the NIHR's Clinical Research Network (CRN).

Provided by Imperial College London