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Tocilizumab, which dampens the immune system, is 100 times more expensive than dexamethasone, another drug that reduces mortality from COVID-19. MARC BRUXELLE/ALAMY STOCK PHOTO

## World's largest COVID-19 drug trial identifies second compound that cuts risk of death

By **Kai Kupferschmidt** | Feb. 11, 2021 , 3:30 PM

**Science's COVID-19 reporting is supported by the Heising-Simons Foundation.**

The world's largest trial of COVID-19 drugs has produced more good news: The anti-inflammatory drug tocilizumab cut the death risk of people hospitalized with the disease, reduced their need for a mechanical ventilator, and shortened time spent in the hospital, investigators of the United Kingdom's Recovery trial announced today at a press conference. A preprint about the data has been **published on medRxiv.**

"This is an incredibly significant result," says Athimalaipet Ramanan, a rheumatologist at the University of Bristol who was not involved in the study but sits on the steering committee of a tocilizumab trial in India. "This is probably only the second drug that has an impact on mortality," he says, after the steroid dexamethasone. If the data pan out, it's "fantastic news," adds Jason Pogue, a pharmacist at the University of Michigan, Ann Arbor, and president of the Society of Infectious Diseases Pharmacists. "I think this will (and I think it

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should) lead to more widespread use in the United States,” Pogue wrote in an email.

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But tocilizumab is about 100 times more expensive than dexamethasone, raising questions once again about how to make sure populations across the world can benefit from scientific progress against COVID-19.

Used to treat rheumatoid arthritis and other autoimmune diseases, tocilizumab is a monoclonal antibody that blocks the protein that serves as receptor for interleukin-6 (IL-6), a signaling molecule in the immune system. That dampens the immune response, which is often overactive in late-stage COVID-19, causing serious disease and sometimes death. Soon after the pandemic started, physicians began to test tocilizumab against COVID-19 in small clinical trials. They were encouraged when Recovery showed in June 2020 that dexamethasone **reduced COVID-19 deaths by up to one-third** in hospitalized patients. That drug quickly became part of the standard of care.

“You might think of corticosteroids like dexamethasone as a very sort of shotgun approach,” to turning down the immune system, Peter Horby, one of Recovery’s principal investigators, said at today’s press conference. “We’re now looking at drugs that are very targeted.”

In the trial, 2022 patients were randomly allocated to receive tocilizumab and compared with 2094 others randomized to receive usual care; 82% of the patients also received dexamethasone. After 28 days, 596 patients in the tocilizumab group had died, compared

with 694 in the control group, a reduction of the mortality rate from 33% to 29%. That means on average 25 patients have to be treated with the drug to save one life.

“ This is going to be one more tool for wealthy countries to add to the mix, but not something that’s going to be widely available for the rest of the world. ”

Ashish Jha, Brown University School of Public Health

That may seem like a small effect compared with that of dexamethasone, but “a 4% absolute reduction in mortality is not marginal,” says physician Ashish Jha, dean of Brown University’s School of Public Health. Dexamethasone’s success may have raised unrealistic expectations about what other drugs can do, Jha says: “Those results were so fantastic that in some ways, it ruined it for people.” The benefit of tocilizumab came on top of the steroid’s, the analysis showed.

The mortality benefits spanned all groups, Martin Landray, another Recovery investigator, said at the press conference: “We saw them in the young and the old, we saw them in men and women, we saw them in different types of ethnicity, we saw them in people who are on invasive ventilators, noninvasive ... ventilators and people on simple oxygen masks on the general ward.” The drug also significantly reduced the likelihood that a COVID-19 patient would progress to invasive mechanical ventilation.

Early COVID-19 trials of tocilizumab had mixed results, but they were smaller than Recovery. Recently released [results from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia](#) (REMAP-CAP) convinced some doctors that the drug was beneficial, Pogue wrote. “Others, given the mixed bag of clinical trial data previously, were waiting for RECOVERY,” he wrote. And although the REMAP-CAP trial only included the sickest patients, the Recovery results suggest the benefit extends to patients with milder disease as well.

The drug comes at a steeper price than dexamethasone, however: about £500 per treatment course in the United Kingdom, versus £5 for the steroid. “This is going to be one more tool for wealthy countries to add to the mix, but not something that’s going to be widely available for the rest of the world,” Jha says. But that can

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change, Horby says: “I would hope that there will be a lot of work going on behind the scenes now and in the next few months, to see what can be done to make sure ... that this drug does become available to everyone, not just to those in rich countries.”

Tocilizumab is not the only available IL-6 inhibitor. Another inhibitor called sarilumab showed a similar effect in the REMAP-CAP trial, but results from two large, completed trials of that drug are yet to be reported. “Publication of results from those trials is now essential to assess whether alternative [interleukin-6] antagonists to tocilizumab are effective,” the Recovery investigators write in their preprint.

The largest trial of COVID-19 therapeutics in the world, Recovery has so far enrolled more than 36,000 patients at about 170 U.K. clinics. In addition to identifying two successful drugs, it helped rule out several others, including the antimalarial hydroxychloroquine, the HIV drug combination lopinavir/ritonavir, and azithromycin, an antibiotic. The trial is still testing aspirin, an anti-inflammatory drug named colchicine, an antibody cocktail from drug company Regeneron, and baricitinib, another drug used to treat rheumatoid arthritis.

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