Repurposed drug shows promise for treating COVID-19 inflammation

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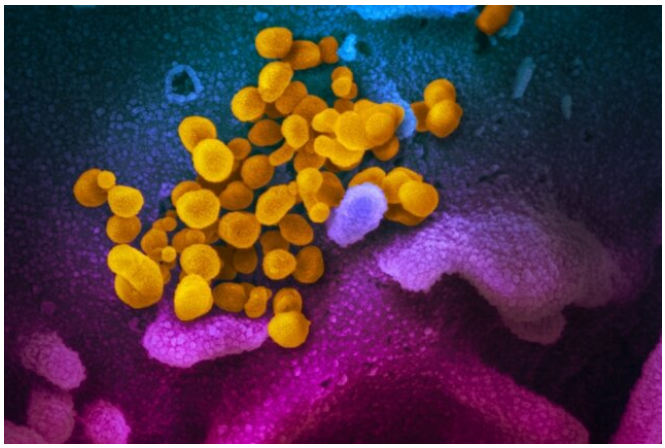

This scanning electron microscope image shows SARS-CoV-2 (yellow)—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient, emerging from the surface of cells (blue/pink) cultured in the lab. Credit: NIAID-RML

Yale clinicians report promising results after treating COVID-19 patients at Yale New Haven Hospital (YNHH) with a drug that reduces hyperinflammation in cancer patients undergoing immunotherapy.

The team initially gave the drug, tocilizumab, to the most severely ill COVID-19 patients—specifically, those experiencing a dangerous immune response known as a "cytokine storm"—and it appeared to improve survival rates, especially among patients requiring mechanical ventilation.

Encouraged, the clinicians began administering the drug to less severely ill COVID-19 patients, with the aim of helping them avoid the need for ventilation. Although the hospital saw a surge in COVID-19 patients during the study period (from March 10 to April 21), there was no parallel surge in ventilator use, suggesting the drug was effective in managing dangerous inflammation associated with the disease, they said.

The clinician-researchers report their results in the June 15 edition of the journal *Chest*.

"Because this was not a randomized control trial, we can't say that patients who were treated with tocilizumab had a survival advantage," said lead author Dr. Christina Price, assistant professor of medicine (immunology), "but compared to other published data on survival and mechanical ventilator outcomes, [patients at Yale] seem to be doing better."

The hyperinflammation that happens in some cancer patients as a result of T-cell immunotherapy resembles the "cytokine storm" in COVID-19, Price said. During the "cytokine storm," or Cytokine Releasex Syndrome (CRS) the body's immune system overreacts, and immune cells and fluid flood into the lungs, Price said. This condition leads to respiratory failure and death in the most severely ill patients.

The researchers hypothesized that tocilizumab could suppress CRS to reduce life-threatening inflammation and prevent patients from needing mechanical ventilation.

"We chose this drug for biologic reasons," said Price. "The combination of reports from small clinical series from other countries suggested that tocilizumab might treat severe inflammatory responses in COVID-19 patients. Our expertise with its use at Yale and with the evolving use of biologics for immune dysregulation plus the drug's availability guided this decision."

The study represents the largest clinical series of COVID-19 patients treated with tocilizumab to date. The research examined the first 239 hospitalized COVID-19 patients at YNHH, 153 of whom were treated with tocilizumab.

The team found that COVID-19 patients with CRS who were treated with tocilizumab showed relatively low mortality rates overall compared to reports from other hospitals, especially those CRS patients who required mechanical ventilation—typically a poor prognostic indicator. The 14-day survival rate for all tocilizumab-treated patients, most of whom met admission criteria for severe COVID-19, was 87%. The 48 tocilizumab-treated patients who required mechanical ventilation spent an average of five and a half days on a ventilator, and their 14-day survival rate was 75%.

"Typically, at least half of the patients who require mechanical ventilation die, but in those treated with tocilizumab here, only 25% did," said Dr. Maricar Malinis, one of the senior authors and associate professor of medicine (infectious diseases).

Across studies, mortality rates for COVID-19 patients requiring ventilation ranges from 40% to 90%.

To determine which patients with COVID-19 would receive the drug, the Yale team designed an algorithm to identify patients who appeared to have CRS, as indicated by required oxygen and inflammatory markers.

"This strategy is quite different—we usually treat the infectious disease rather than the consequence," said Dr. Jeff Topal, an associate clinical professor of medicine and infectious diseases expert who oversees the drug formulary at the hospital.

Use of the algorithm "democratized treatment," said Dr. Frederick L. Altice, professor of medicine (infectious diseases) and public health, "by focusing on the clinical presentation rather than the patient. Consequently," he noted, "unlike elsewhere, people of color had lower mortality than did whites."

The team included doctors and experts across disciplines: rheumatology, allergy and immunology, hematology, oncology, pulmonary, pharmacy, and infectious disease.

As the team observed that tocilizumab was safe and showed promising results among the most severe COVID-19 patients, they began administering it to patients with less severe forms of the disease but who showed signs of hyperinflammation. The goal was to reduce the likelihood of mechanical ventilation.

Dr. Charles Dela Cruz, an associate professor in medicine (pulmonary and critical care) who specializes in respiratory infections, said: "Once a patient needs mechanical ventilation, the patient does poorly. In the absence of clinical trials, it made sense to use a safe medication to prevent the worst consequences of COVID-19."

Despite a surge in new COVID-19 patients entering the hospital during the study period (March and April), the anticipated increase in patients needing mechanical ventilation did not happen in parallel. Use of tocilizumab appeared to keep COVID-19 patients from progressing to mechanical ventilation, and the need for ventilation never exceeded 18% of hospital capacity.

Additional studies and prospective clinical trials at Yale are expected to further validate the impact of tocilizumab on patient outcomes.

More information: Christina C. Price et al. Tocilizumab treatment for Cytokine Release Syndrome in hospitalized COVID-19 patients: survival and clinical outcomes, *Chest* (2020). DOI: 10.1016/j.chest.2020.06.006

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