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COVACTA trial raises questions about tocilizumab's benefit in COVID-19

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For more on the **suspended CORIMUNO-VIRO trial** see https://clinicaltrials.gov/ct2/show/NCT04341870

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To read the **RECOVERY study** see *N Engl J Med* 2020; published online July 17. https:doi.org/10.1056/NEJMoa2021436

Hoffmann-La Roche has announced disappointing results from its much-anticipated phase 3 COVACTA trial of tocilizumab, raising questions about the efficacy of interleukin (IL)-6 blockade in patients with severe COVID-19 pneumonia.

SARS-CoV-2 induces production of inflammatory cytokines, including IL-6, which can contribute to cytokine storm syndromes that damage the lungs and other organs, ultimately killing many patients. Early observational studies have hinted at beneficial effects of drugs that block inflammatory cytokines, including IL-6 and IL-1.

But the randomised controlled COVACTA trial failed to meet its primary endpoint of improved clinical status, the company announced on July 29. Nor did tocilizumab improve patient mortality, although tocilizumab-treated patients spent roughly a week less in hospital compared with those given placebo, which could have a meaningful clinical impact in the face of surging capacity during a pandemic. Full results of the trial have not yet been published.

Another IL-6 antagonist, sarilumab, showed early promise in retrospective studies, only to see a prospective, randomised phase 3 study suspended for futility.

"I'm surprised that the IL-6 studies haven't proven out", said Randy Cron (University of Alabama at Birmingham, Birmingham, AL, USA). "In the large case series, tocilizumab seemed to help. There have been a lot of case series and various studies with tocilizumab and a few other anti-IL-6 or anti-IL-6 receptor agents that really did show, compared to historical controls, evidence that patients were getting better."

But the top-line data from Hoffmann-La Roche are unlikely to provide the full picture and might not be the nail in the coffin for tocilizumab for COVID-19 treatment. Cron and others urge a cautious interpretation of COVACTA, in view of the study's broad patient selection criteria and other study design factors.

The timing of administration is one such consideration. "You want to be sick enough to be hospitalised but not necessarily while the virus is replicating", Cron said. "It is at the point where the virus is on its way out, but the immune response is making the patient sick, that you want to intervene, whether it's with broad immunosuppression with glucocorticoids, or IL-6 blockade."

Because COVACTA assessed patient outcomes on a specified day, at which time different patients will have had different duration and severity of illness and previous treatments, the study might have missed clinically relevant differences between patient groups, cautioned Dario Roccatello (University of Torino, Torino, Italy).

"In the setting of COVID-19-induced cytokine storm, anti-IL-6 treatment might be most helpful earlier in the disease: after the onset of severe disease but before florid respiratory failure", Roccatello said.

Notably, COVACTA's eligibility criteria were broad and did not appear to stratify patients by clinical signs of hyperinflammation. "There are some who have more limited inflammatory responses, and … others who may have full-blown multiorgan system failure, hypotension, and respiratory failure beyond what can be supported on ventilators," noted Joseph Alvarnas (City of Hope, Duarte, CA, USA). "I think we want to be careful about thinking about these patients not as one monomorphic population, but as subpopulations of patients for whom different treatment strategies might be appropriate."

Tocilizumab's potential as a COVID-19 therapy has been controversial from the start, partly because IL-6 has both pro-inflammatory and anti-inflammatory effects and is also involved in antiviral responses. Like glucocorticoids, IL-6 blockade can increase patients' risks of secondary infections. But retrospective studies have suggested an association between tocilizumab and reduced hospital mortality, particularly in patients in intensive care units, as well as evidence that baseline C-reactive protein concentrations (controlled in part by IL-6) predict benefit.

COVACTA's failure raises doubts about these earlier associations, but researchers are awaiting the full trial data, including those on SARS-CoV-2 viral loads and inflammatory marker trends over the entire study period.

For the time being, glucocorticoids will "likely save the day" for the global COVID-19 response because of their ready availability and low expense, Cron said. Dexamethasone is the only drug thus far to have shown a mortality benefit for patients with COVID-19.

But here too, timing could be crucial. "The RECOVERY trial results show a clear benefit of dexamethasone in patients who require respiratory support but not in patients who do not require respiratory support", said Peter Horby, first author of that study. "This suggests that the timing of anti-inflammatory treatments in relation to the stage of disease is important."

Any benefit of anti-inflammatory treatments would likely be observed only in patients who progress to an inflammatory state, which usually happens around one week into illness, Horby noted.

"Tocilizumab continues to be evaluated in RECOVERY", Horby said. "With over 850 patients randomised to tocilizumab versus standard of care, this is almost twice the size of the COVACTA trial and will provide critical data to confirm or refute the COVACTA results."

Bryant Furlow