Small study of patients with severe COVID-19 treated with the arthritis drug anakinra finds clinical improvements

May 8 2020

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The first study to report use of the rheumatoid arthritis drug anakinra to treat COVID-19 patients found that high-dose anakinra was safe and was

associated with respiratory improvements and reduced signs of cytokine storm in 72% (21/29) of patients, according to results from patients studied for 21 days (enrolled from 17 to 27 March 2020) in a Milan hospital, published in *The Lancet Rheumatology* journal.

All 29 patients received standard care (of non-invasive ventilation (CPAP), hydroxychloroquine, and lopinavir/ritonavir) as well as the drug treatment (daily high-dose intravenous infusions of anakinra at 10 mg/kg bodyweight). They were compared to 16 patients who received standard care only. However, the study was not a randomised controlled trial, which is the gold standard for establishing the effectiveness of a treatment.

Prof Lorenzo Dagna, head of the Unit of Immunology, Rheumatology, Allergy and Rare Diseases at San Raffaele Hospital and Vita-Salute San Raffaele University, Italy, says: "Until a vaccine is available, we urgently need to find a way to help people survive the most severe symptoms of COVID-19, and to do that without overwhelming the intensive care capacity of hospitals. A treatment that has already met strict safety tests and that is available in sufficient quantities to meet the needs of the current pandemic is ideal."

Dr. Giulio Cavalli, from the Unit of Immunology, Rheumatology, Allergy and Rare Diseases at San Raffaele Hospital and Vita-Salute San Raffaele University, Italy, says: "Our study is the first to suggest that a high dose of the arthritis drug anakinra may be able to block the overreaction of the immune system caused by COVID-19. The results are interesting and the drug deserves controlled testing in large randomised trials."

Most people with COVID-19 experience only mild symptoms, but in severely affected patients the immune system overreacts, triggering a storm of immune proteins called cytokines. The cytokines contribute to

hyperinflammation, leading to acute respiratory distress syndrome (ARDS) and reducing oxygen levels in the blood. ARDS is the main cause of death from coronavirus disease. Of patients admitted to intensive care units with COVID-19 and ARDS, the estimated death rate ranges from 28% to 78%. Patients' breathing is supported until inflammation recedes, but the number of patients needing ventilation can exceed the number intensive care units with mechanical ventilators. Treatments are urgently needed to improve the prognosis of critically ill patients treated outside of ICUs.

The drug anakinra is already approved by the US Food and Drug Administration and the European Medicines Agency to treat rheumatoid arthritis, Still's disease, and recurrent fever. It works by blocking the proinflammatory cytokine IL-1. A Viewpoint piece, also published in *The Lancet Rheumatology* earlier this week, explains why intravenous anakinra might be effective and safe in treating cytokine storm syndromes generally. The authors of the current study note that compared with other cytokine-blocking agents, anakinra has a strong safety record and a short half-life, making it suitable for critically ill patients.

In the study, at 21 days, treatment with high-dose anakinra was associated with reductions in serum C-reactive protein and with progressive improvements in respiratory function in 21 (72%) of 29 patients. Survival was 90% (26 out of 29). Five of 29 patients (17%) needed mechanical ventilation.

The authors compare these observations with what they saw in a group of 16 patients who received standard treatment before the start of the current study (between 10 and 17 March). Most of the 16 patients experienced persistent or recurrent increases in C-reactive protein. Respiratory function improved for half of the patients (8 patients, 50%), and 56% (nine of 16) survived. One patient received mechanical

ventilation (6%).

The authors report that high-dose anakinra was generally safe. Among adverse effects, four patients (14%) in the high-dose anakinra group had bacteraemia (bacteria in the blood), compared to two patients (13%) in the standard treatment group. Discontinuation of anakinra was not followed by inflammatory relapses. Causes of death in patients receiving high-dose intravenous anakinra were pulmonary thromboembolism, respiratory insufficiency, and multiorgan failure (1 patient per cause of death). Causes of death in the comparison group were respiratory insufficiency (3 patients), multiorgan failure (3 patients), and pulmonary thromboembolism (1 patient).

The authors caution that the retrospective nature of the study and the small number of patients in group make it impossible to draw definitive conclusions. The findings need to be validated with a controlled trial, conducted over a longer period to check for long-term outcomes. A randomised controlled trial of intravenous anakinra to treat COVID-19 is underway, but is assessing lower doses and does not include patients with ARDS.

"The patients in our study were severely ill, had an average age of 62, and underlying health conditions, giving them a high risk of dying from COVID-19. Administration of high-dose intravenous anakinra in these patients, who were managed outside of the ICU in a setting overwhelmed by the COVID-19 pandemic and with a shortage of ICU resources, appeared to dampen systemic inflammation and was associated with progressive improvement in respiratory function. While great attention has been focused so far on viral control, inflammation control might also be as crucial for the treatment of COVID-19. This seems to have allowed us to postpone or avoid intubation in most patients. Based on our promising results, this approach may be considered irrespective of resource availability. Again, results will need

to be confirmed in controlled trials." says Chiara Tassan Din, co-author of this study from the Department of Infectious Diseases at San Raffaele Hospital, Italy.

Writing in a linked Comment, lead author Dr. Scott Canna (who was not involved in the study) from the University of Pittsburgh Medical Center, USA, says: "In view of the biological plausibility of anakinra, the pharmacokinetic and safety profile of the drug, and a growing body of positive experience in autoinflammation and cytokine storm, these data are promising and support prioritising this approach in the planning and enrolment of randomised controlled trials."

More information: Giulio Cavalli et al, Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study, *The Lancet Rheumatology* (2020). DOI: 10.1016/S2665-9913(20)30127-2

Provided by Lancet