Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial

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Summary

Background Infections with SARS-CoV-2 continue to cause significant morbidity and mortality. Interleukin (IL)-1 and IL-6 blockade have been proposed as therapeutic strategies in COVID-19, but study outcomes have been conflicting. We sought to study whether blockade of the IL-6 or IL-1 pathway shortened the time to clinical improvement in patients with COVID-19, hypoxic respiratory failure, and signs of systemic cytokine release syndrome.

Methods We did a prospective, multicentre, open-label, randomised, controlled trial, in hospitalised patients with COVID-19, hypoxia, and signs of a cytokine release syndrome across 16 hospitals in Belgium. Eligible patients had a proven diagnosis of COVID-19 with symptoms between 6 and 16 days, a ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) of less than 350 mm Hg on room air or less than 280 mm Hg on supplemental oxygen, and signs of a cytokine release syndrome in their serum (either a single ferritin measurement of more than 2000 µg/L and immediately requiring high flow oxygen or mechanical ventilation, or a ferritin concentration of more than 1000 µg/L, which had been increasing over the previous 24 h, or lymphopenia below 800/mL with two of the following criteria: an increasing ferritin concentration of more than 700 µg/L, an increasing lactate dehydrogenase concentration of more than 300 international units per L, an increasing C-reactive protein concentration of more than 70 mg/L, or an increasing D-dimers concentration of more than 1000 ng/mL). The COV-AID trial has a 2×2 factorial design to evaluate IL-1 blockade versus no IL-1 blockade and IL-6 blockade versus no IL-6 blockade. Patients were randomly assigned by means of permuted block randomisation with varying block size and stratification by centre. In a first randomisation, patients were assigned to receive subcutaneous anakinra once daily (100 mg) for 28 days or until discharge, or to receive no IL-1 blockade (1:2). In a second randomisation step, patients were allocated to receive a single dose of siltuximab (11 mg/kg) intravenously, or a single dose of tocilizumab (8 mg/kg) intravenously, or to receive no IL-6 blockade (1:1:1). The primary outcome was the time to clinical improvement, defined as time from randomisation to an increase of at least two points on a 6-category ordinal scale or to discharge from hospital alive. The primary and supportive efficacy endpoints were assessed in the intention-to-treat population. Safety was assessed in the safety population. This study is registered online with ClinicalTrials.gov (NCT04330638) and EudraCT (2020-001500-41) and is complete.

Findings Between April 4, and Dec 6, 2020, 342 patients were randomly assigned to IL-1 blockade (n=112) or no IL-1 blockade (n=230) and simultaneously randomly assigned to IL-6 blockade (n=227; 114 for tocilizumab and 113 for siltuximab) or no IL-6 blockade (n=115). Most patients were male (265 [77%] of 342), median age was 65 years (IQR 54–73), and median Systematic Organ Failure Assessment (SOFA) score at randomisation was 3 (2–4). All 342 patients were included in the primary intention-to-treat analysis. The estimated median time to clinical improvement was 12 days (95% CI 10–16) in the IL-1 blockade group versus 12 days (10–15) in the no IL-1 blockade group (hazard ratio [HR] 0·94 [95% CI 0·73–1·21]). For the IL-6 blockade group, the estimated median time to clinical improvement was 11 days (95% CI 10–16) versus 12 days (11–16) in the no IL-6 blockade group (HR 1·00 [0·78–1·29]). 55 patients died during the study, but no evidence for differences in mortality between treatment groups was found. The incidence of serious adverse events and serious infections was similar across study groups.

Interpretation Drugs targeting IL-1 or IL-6 did not shorten the time to clinical improvement in this sample of patients with COVID-19, hypoxic respiratory failure, low SOFA score, and low baseline mortality risk.

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