Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Anakinra in COVID-19: A step closer to the cure

Acute respiratory distress syndrome and cytokine release syndrome are the major complications of coronavirus disease 2019 (COVID-19) associated with increased mortality risk [1]. Apart from dexamethasone and probably tocilizumab in critically ill patients, there are no well-established effective therapies to treat SARS-CoV-2 infection [2,3]. Considering the noticed shortage of intensive care unit (ICU) beds and consequently the increased burden in medical wards [4], identifying additional therapeutic modalities to improve adverse outcomes and prevent ICU admission and death in this population remains a public health emergency.

In this setting, anakinra has been proved an appealing therapeutic option for the management of coronavirus disease 2019 (COVID-19) [5]. A meta-analysis of four observational studies ($n = 184$) provided early evidence indicating that the administration of anakinra was safe and could be associated with a clinical benefit in patients with COVID-19 [6]. This argument was further strengthened by a subsequent meta-analysis with a larger sample (9 cohorts; $n = 1119$) which demonstrated that anakinra reduced both the need for invasive mechanical ventilation (IMV) and mortality risk of hospitalized non-intubated patients with COVID-19 without increasing the risk of adverse effects (Fig. 1) [5]. This notion has been recently confirmed by SAVE-MORE, a double blinded, placebo-controlled, randomized trial [7]. SAVE-MORE evaluated the efficacy and safety of anakinra in 594 patients with COVID-19 at risk of progressing to respiratory failure, as identified by plasma soluble urokinase plasminogen activator receptor (suPAR) ≥6 ng/ml [7]. Based on the assessment of 11-point World Health Organization Clinical Progression Scale (WHO—CPS) at day 28, anakinra was associated with a better clinical outcome compared with placebo (odds ratio, OR: 0.36; 95% confidence interval, CI: 0.26–0.50, $p < 0.001$) [7]. Moreover, treatment with anakinra resulted in a reduced 28-day mortality risk and a non-significant reduction of intubation risk (Fig. 1) [7]. SAVE-MORE also confirmed the safety of anakinra in patients with COVID-19, since it did not increase the risk of bloodstream infections or liver dysfunction compared with placebo (Fig. 1) [7].

The encouraging results of SAVE-MORE towards the use of anakinra in COVID-19 should be considered within the clinical setting of the study design. Patients with critical COVID-19 and severe respiratory failure (PO_2/FiO_2 <150) were excluded. This prompts for an early treatment in

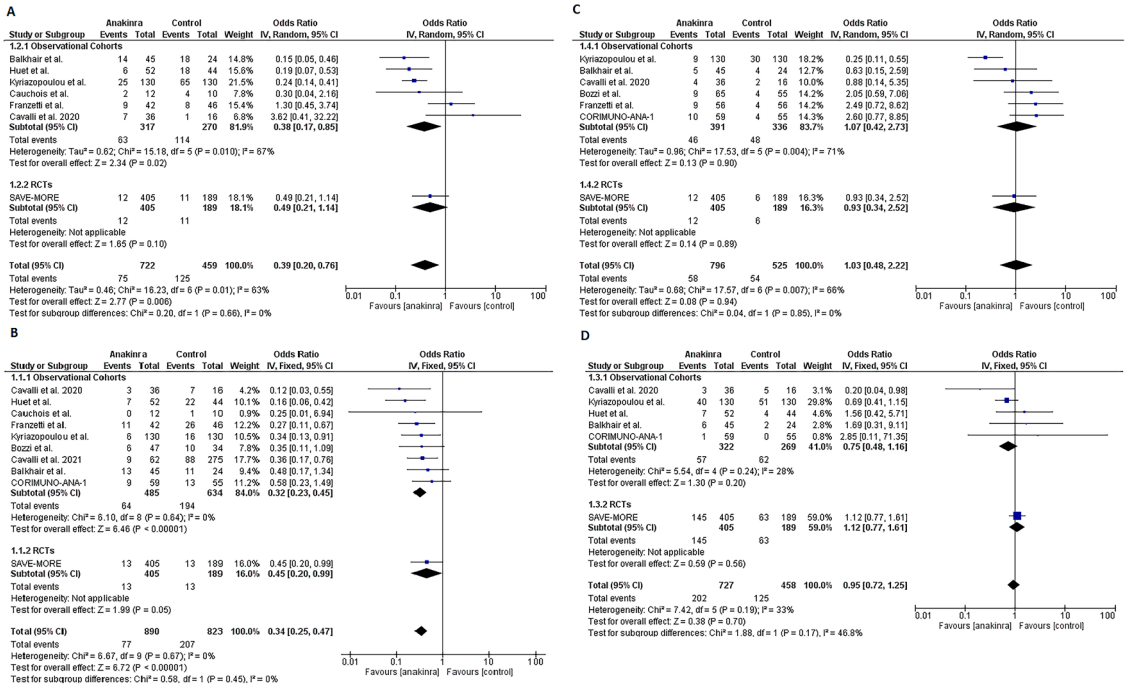

Fig. 1. Effect of anakinra on the risk of (A) invasive mechanical ventilation, (B) mortality, (C) bacteremia and (D) liver enzyme increase in non-intubated patients with COVID-19.

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the initial stages of the disease. Although accumulating evidence indicates that suPAR can reliably be used as a marker of progression to severe respiratory failure or death in patients with COVID-19 [8], its applicability could be problematic if not widely available. To overcome this restriction, commonly inflammatory markers, such as C-reactive protein (CRP) and ferritin, could be enlisted to assess eligible patients to receive the drug [9]. Indeed, a recent patient-level meta-analysis (n = 1185) demonstrated that anakinra was more effective in lowering mortality risk in patients with CRP >100 mg/L (OR: 0.28, 95% CI: 0.17–0.47) or in those with ferritin >1000 ng/ml (OR: 0.36, 95% CI: 0.19–0.69) [10].

Tocilizumab, another humanized antibody which blocks the action of circulating IL-6, has been shown to increase survival in patients with COVID-19 [11]. U.S. FDA (Food and Drug Administration) has recently issued its emergency use authorization for the treatment of hospitalized adult and pediatric patients (≥2 years of age) treated with systemic corticosteroids and requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation [12]. Considering the results derived from the latest anakinra studies, a question arises as to which of these two immunomodulating agents is superior. Although there is no head-to-head randomized clinical trial (RCT) comparing anakinra with tocilizumab available yet, an analysis of three observational studies (n = 237) indicated that anakinra might be superior to tocilizumab in terms of COVID-19 death prevention, since the former was associated with a decreased mortality risk by 40% (relative risk: 0.60, 95% CI: 0.36–0.98, I^2=0%) [13]. However, the small sample size and design flaws of the included studies comprise notable limitations to reach safe conclusions.

Considering that vaccination rates fall behind what was expected, encouraging results from RCTs promote continuously testing for efficacious, safe and tolerable therapeutic interventions in COVID-19.

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Declaration of Competing Interest

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