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.

Interleukin-1 and interleukin-6 inhibition in patients with COVID-19 and hyperinflammation

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We read with interest the study by Giulio Cavalli and colleagues.[1] The Article compares the clinical effectiveness of IL-1 inhibition (anakinra) and IL-6 inhibition (tocilizumab or sarilumab) with standard treatment in a large homogeneous cohort of patients with COVID-19, respiratory insufficiency, and hyperinflammation.

The authors reported a significantly reduced mortality risk in patients who received anakinra (hazard ratio [HR] 0·450, 95% CI 0·204–0·990, p=0·047) but not in those treated with IL-6 inhibition (HR 0·900, 0·412–1·966, p=0·79). However, the dose of anakinra in this study (5 mg/kg twice daily until clinical benefit) was higher than that used by our group[2] and other authors, and raises safety concerns. High doses of anakinra were associated with a 24% rate of severe adverse effects and a 14% rate of infectious complications in one published study.[3] Moreover, several clinical trials of high doses of anakinra in patients with COVID-19 have been stopped because of safety concerns. Our group observed that early treatment with intermediate doses of anakinra in patients with moderate hyperinflammation was associated with a reduced risk of mortality (adjusted HR 0·518, 0·265–0·910; p=0·044). Our, as yet unpublished, clinical experience with more than 100 patients with COVID-19 pneumonia and moderate hyperinflammation treated with intermediate doses of anakinra (100 mg/12 h subcutaneously until sustained improvement in respiratory parameters and serum C-reactive protein, then 100 mg/day subcutaneously for 5–7 days) suggests that this regimen is efficacious in controlling inflammation and reducing mortality without increasing adverse events in patients whose respiratory condition worsened within 24 h after receiving glucocorticoids (methylprednisolone 1 mg/kg per day intravenously). Published studies by Huet and colleagues[4] showed that intermediate doses of anakinra (100 mg twice a day for 72 h, then 100 mg daily for 7 days) reduced both the need for invasive mechanical ventilation in the intensive care unit and mortality among patients with severe forms of COVID-19, without serious side-effects. In another published study,[5] which used intermediate doses of anakinra (a single daily dose of 300 mg intravenously for 5 days, then tapered to 200 mg/day for 2 days, and to 100 mg for 1 day), all patients improved clinically with no deaths and no adverse effects or bacterial infections. In our opinion, the early use of intermediate doses of anakinra in patients with moderate hyperinflammation associated with severe COVID-19 pneumonia could reduce mortality by controlling inflammation, probably with a better safety profile.

The authors declare no competing interests.

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Authors' reply

We thank Juan Salvatierra and colleagues for their interest in our Article.[1] Salvatierra and colleagues pose a critical question: how to select the right treatment and regimen for a patient with severe COVID-19. We posit that cytokine inhibition has a clear rationale in patients with severe COVID-19 with hyperinflammation, a condition caused by excess cytokine production and burdened by considerable mortality.[2] In patients with severe COVID-19 and hyperinflammation, inhibiting excess cytokine production might reduce mortality. Hence, throughout our studies, we did not treat patients with mild or moderate disease or those without evidence of hyperinflammation, as we feel that many of these individuals have an appropriate immune response to the virus.[1,3] Conversely, we selectively and consistently evaluated anakinra in patients with severe COVID-19, respiratory insufficiency, and hyper-inflammation (defined as serum C-reactive protein ≥100 mg/L, ferritin ≥900 ng/mL, or both). In this population of patients with severe COVID-19, we initially evaluated low-dose subcutaneous anakinra (100 mg twice daily). However, we found that treatment with low-dose subcutaneously was neither associated with reductions in serum C-reactive protein nor with meaningful improvements in clinical status at day 7.[3] Although no safety concerns emerged, the lack of marked clinical or anti-inflammatory effects led to early termination of this