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.

transaminases could correspond to haemophagocytic lymphohistiocytosis-like manifestations of COVID-19. Of note, increased liver transaminases might also have been a side-effect of lopinavir–ritonavir treatment in the study by Cavalli and colleagues.[1,4] Moreover, liver injury and increased liver transaminases are associated with COVID-19 severity.[4,5] Discontinuation of anti-IL-1 therapy due to increased liver transaminases could result in a lost opportunity for patients to receive anakinra who need it most, although the withdrawal of anakinra did not shorten the median duration of treatment in the study by Cavalli and colleagues.[1] Thus, we believe that only stronger and continuous increases in liver transaminases, mostly those that appeared after the onset of anakinra, should be considered to avoid premature discontinuation of therapy.

We hope that the ongoing randomised controlled trials will confirm these promising results and provide answers to the outstanding questions.

We declare no competing interests.

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In *The Lancet Rheumatology*, Giulio Cavalli and colleagues[1] report potential beneficial effects of the IL-1 receptor antagonist anakinra in patients with COVID-19, acute respiratory distress syndrome (ARDS), and hyperinflammation. In the study protocol, anakinra was given in combination with a 4-aminoquinoline and, although promising, we suggest that this combination cannot be fully synergistic in the presence of cytokine release syndrome.

4-aminoquinolines impair the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into host cells by inhibiting lysosomal acidification. However, by blocking autophagosome fusion and degradation, 4-aminoquinoline also blocks autophagy, which is not desirable in the presence of hyperinflammation. Autophagy plays a pivotal role in a number of fundamental biological processes, including ageing, immunity, clearance of viral particles and inflammation, by influencing the survival of inflammatory cells and the secretion of cytokines.[2] More importantly, autophagy modulates transcription, processing, and secretion of IL-1β, and might control inflammation in part through the degradation of IL-1β[3]. By contrast, IL-1α and IL-1β have both been shown to induce autophagy, serving as a negative feedback mechanism. Blocking autophagy in patients with the most severe forms of COVID-19 with cytokine release syndrome is probably ineffective, and it could potentially be harmful. Furthermore, recent publications have linked 4-aminoquinolines to an increase in the secretion of IL-1β in some viral infections, in which autophagy serves as a cell-intrinsic mechanism to restrict secretion of IL-1β[4]; nevertheless, this aspect has not been studied in COVID-19 patients.

Notably, induction of autophagy with rapamycin and other stimulators inhibits the secretion of IL-1β via the NLRP3 inflammasome, and thereby decreases inflammation-induced tissue damage. Interestingly, in the context of other coronaviruses, NLRP3 activation has been shown to trigger cytokine storms.[5] This observation suggests that there is an interplay between SARS-CoV2, autophagy, and cytokine release, and we propose that in future trials, combining anakinra with autophagy inhibitors should be avoided in patients with COVID-19 and evidence of hyperinflammation. It is also reasonable to hypothesise that a combination of anakinra and an autophagy activator should be explored. Although the mechanism needs to be studied further, enhancing autophagy might help to decrease IL-1β production and limit inflammatory cell influx and production of other cytokines, thereby working synergistically with immunomodulatory agents in attenuating the cytokine storm.

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Authors' reply

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