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.

Anakinra for patients with COVID-19

We read with interest the Article by Giulio Cavalli and colleagues[1] in *The Lancet Rheumatology* about the use of anakinra for patients with acute respiratory distress syndrome (ARDS) related to COVID-19. Although the study by Cavalli and colleagues was not performed in intensive care units (ICUs), the semantics used by the authors derive from critical care practice and need some precision. First, the definition of ARDS necessitates a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) of less than 200 mm Hg for a diagnosis of moderate ARDS and of less than 100 mm Hg for severe ARDS, assessed on invasive mechanical ventilation with a positive end-expiratory pressure of more than 5 cm H_2O.[2] Individuals included in this study benefited from non-invasive ventilation, which defines the patients as having mild ARDS. Thus, the patients in the study by Cavalli and colleagues had mild ARDS, irrespective of the PaO_2:FiO_2 ratio (provided that PaO_2:FiO_2 is <300 mm Hg), and the authors are incorrect to classify the patients as having moderate-to-severe ARDS.

Second, non-invasive ventilation can be used outside the ICU, but only in specific patients, in specialised units with adequate monitoring and skilled and experienced physicians and nurses,[3] which seems to differ from the care reported by Cavalli and colleagues.[1] Consequently, the COVID-19 pandemic context, with a shortage of ICU resources, and the patient severity raise questions about the use of non-invasive ventilation in general wards, and subsequently about the patient outcomes that were compared.

Third, the evolution of PaO_2:FiO_2 ratio was assessed with a derivative formula based on oxygen saturation.[4] This formula, which is neither recommended nor used in clinical practice, showed a satisfactory ability to assess a range of PaO_2:FiO_2 ratios with the transcutaneous oxygen saturation, but this cannot be used as a surrogate for the PaO_2:FiO_2 ratio.

Finally, despite a high rate of bacteraemia, the authors conclude that anakinra has a remarkable safety profile that makes it especially suitable for use in critically ill patients. This assertion remains questionable without additional data focusing on ICU patients, especially those undergoing invasive mechanical ventilation with moderate-to-severe ARDS. Such patients are at increased risk of nosocomial infections, notably ventilator-associated pneumonia,[5] the diagnosis of which could be more difficult in a patient treated with anakinra due to the drug's immunosuppressive effect. Indeed, decreases in fever and leucocyte count could delay treatment and have important effects on the attributable mortality of such hospital-acquired infections. In conclusion, further studies are necessary to establish the safety and efficacy profile of the recombinant interleukin-1 receptor antagonist anakinra in patients with ARDS who are hospitalised in the ICU setting.

We declare no competing interests.

*Xavier Valette, Damien du Cheyron
valette-x@chu-caen.fr

Department of Medical Intensive Care, CHU de Caen Normandie, Caen 14000, France

1 Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020; **2:** 325–31.
2 ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012; **307:** 2526–33.
3 Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet* 2009; **374:** 250–59.
4 Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO2/FiO2 ratio and the PaO_2/FiO_2 ratio in patients with acute lung injury or ARDS. *Chest* 2007; **132:** 410–17.
5 Vincent J-L, Sakr Y, Singer M, et al. Prevalence and outcomes of infection among patients in intensive care units in 2017. *JAMA* 2020; **323:** 1478–87.

The Article published by Giulio Cavalli and colleagues in *The Lancet Rheumatology*,[1] in combination with our case series of nine patients,[2] supports the targeting of the IL-1 pathway as a safe and promising approach in the various types of lung involvement in patients with COVID-19. These complementary studies that cover the entire spectrum of severity of lung involvement in hospitalised patients with COVID-19, provide the first efficacy and safety data for anakinra, depending on the doses used and the stage of lung injury.

The study by Cavalli and colleagues focused on moderate-to-severe acute respiratory distress syndrome (ARDS) associated with COVID-19, for which low-dose anakinra was ineffective, prompting a significant increase in anakinra dosage that yielded better outcomes.[1] However, in our study,[2] a low-dose regimen, similar to that proposed by Cavalli and colleagues,[1] was associated with good outcomes in patients with moderate-to-severe COVID-19 and oxygen-dependent pneumonia with a high risk of worsening (due to comorbidities, intense inflammatory syndrome, or both).

In a longitudinal transcriptomic cytokine analysis, Ong and colleagues[3] showed that peak expression of IL-1α and IL-1β preceded the nadir of respiratory function in patients with severe COVID-19 pneumonia. Therefore, the early use of anakinra during COVID-associated lung injury might prevent the progression to ARDS and mechanic ventilation.

Because of safety concerns, Cavalli and colleagues chose to stop anakinra as soon as liver transaminases exceeded the upper normal limit by more than three times.[1] However, such an increase in liver transaminases is common in patients COVID-19.[4] We noticed in patients treated with low-dose anakinra, as well as in untreated patients (data not shown), that concentrations of liver transaminases and triglycerides increase, even when C-reactive protein concentrations decreased. Therefore, the increase in triglyceride levels, which is not a classic anakinra side-effect, and in liver

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.

*Nicolas Martin-Silva, Hubert de Boysson, *Achille Aouba*
aouba-a@chu-caen.fr

Department of Internal Medicine and Clinical Immunology, CHU et Université de Caen Normandie, Caen 14000, France

1 Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020; **2:** 325–31.
2 Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis* 2020; published online May 6. DOI:10.1136/annrheumdis-2020-217706.
3 Ong EZ, Chan YFZ, Leong WY, et al. A dynamic immune response shapes COVID-19 progression. *Cell Host Microbe* 2020; published online April 30. DOI:10.1016/j.chom.2020.03.021.
4 Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. *J Hepatol* 2020; published online April 13. DOI:10.1016/j.jhep.2020.04.006.
5 Parohan M, Yaghoubi S, Seraj A. Liver injury is associated with severe coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of retrospective studies. *Hepatol Res* 2020; published online May 9. DOI:10.1111/hepr.13510.

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-1β3. 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-1β4; 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.

We declare no competing interests.

**Omar Maoujoud, Mohammed Asserraji, Samir Ahid, Marouane Belarbi, Nadir Zemraoui*
maoujoud@gmail.com

Department of Nephrology, Avicennes Military Hospital, Faculty of Medicine, Cadi Ayyad University, Marrakech 40000, Morocco (OM, MA, MB, NZ); Research Team of Pharmacoeconomics & Pharmacoepidemiology, Faculty of Medicine & Pharmacy, Mohammed V University, Rabat, Morocco (OM, SA); Methodological Support Unit, Faculty of Pharmacy, Mohammed VI University of Health Sciences, Casablanca, Morocco (SA)

1 Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020; **2:** 325–31.
2 Qian M, Fang X, Wang X. Autophagy and inflammation. *Clin Transl Med* 2017; **6:** 24.
3 Harris J. Autophagy and IL-1 family cytokines. *Front Immunol* 2013; **4:** 83.
4 Zhang J, Zhang W, Ren L, et al. Astragaloside IV attenuates IL-1β secretion by enhancing autophagy in H1N1 infection. *FEMS Microbiol Lett* 2020; **367:** fnaa007.
5 Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? *Aging (Albany NY)* 2020; published online May 29. DOI:10.18632/aging.103344.

Authors' reply

We thank Xavier Valette and Damien du Cheyron, Nicolas Martin-Silva and colleagues, and Omar Maoujoud and colleagues for their interest in our