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.

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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