# Anakinra for severe forms of COVID-19

Marc Laine, Laurent Bonello

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We read the Article by Thomas Huet and colleagues[1] describing the effects of the interleukin-1 receptor antagonist anakinra in patients with severe COVID-19 with great interest. The authors compared a composite endpoint of death or admission to an intensive care unit for invasive ventilation between a group of patients with severe COVID-19 treated with anakinra plus standard of care (anakinra group) with a historical control group that received standard care alone.

Anakinra was found to significantly reduce the need for admission to an intensive care unit and mortality compared with standard care. Complementary analysis confirmed this benefit when adjusted for cofounding factors, including body-mass index and hydroxychloroquine intake. Furthermore, this clinical benefit was supported by a reduction of C-reactive protein in the anakinra group.

The analysis of the benefit of an innovative treatment using a historical cohort as control group has some methodological limitations that authors acknowledged. The presence of factors not included in the statistical analysis might compromise the relevance of the results. COVID-19 has been shown to be associated with a high rate of thrombotic complications, such as pulmonary embolism, in severe cases.[2] Anticoagulant treatment appears to be beneficial in this situation, which has led to changes in clinical practice in many centres that were managing patients with COVID-19.[3] Of note, pulmonary embolism was not systematically investigated by Huet and colleagues.[1] Could the authors provide data on the proportion of patients receiving anticoagulant drugs in the two groups and analyse whether this parameter modifies the results observed on the primary endpoint when considered as a cofounding factor?

We would like to thank and congratulate the authors of this study for the important insight they provide into the treatment of this critical condition.

We declare no competing interests.

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We read with interest the Article by Thomas Huet and colleagues[1] that shows an association between anakinra use and reduced need for invasive mechanical ventilation in an intensive care unit and mortality in patients with severe forms of COVID-19, without serious side-effects.

The authors should be applauded; however, we would like to highlight some important limitations. First, looking at the Kaplan-Meier curves, there is an immediate drop in the historical control group suggesting that some of the patients were either already receiving mechanical ventilation in the intensive care unit when they met the inclusion criteria (one patient was already dead at time zero) or they developed the event on the same day they met the inclusion criteria, thereby biasing the effect estimate in favour of anakinra group.

Second, although authors have stated the time zero for the anakinra group, the same has not been done for the historical group. The historical group was selected retrospectively based on time varying inclusion and exclusion criteria, which could have led to sicker patients in this group.

Third, using oxygen saturation as a criterion for inclusion might not reveal an adequate spectrum of disease severity compared with other variables, such as the partial pressure of arterial oxygen to percentage of inspired oxygen ratio.

Fourth, the 73% of patients in the historical group requiring invasive mechanical ventilation or dying is not consistent with the available literature. Mortality estimates, published in 2020, from various cohorts range between 16% and 45%.[2,3]

Finally, hydroxychloroquine was significantly more commonly used in the anakinra group compared with the historical control group. Although the authors mention that the results remain unchanged after multivariable analysis, the possibility of baseline confounding cannot be ruled out.

We would like the authors to reanalyse the data in the presence of above limitations before any conclusions are drawn from this study.

We declare no competing interests.

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There is an urgent need to seek new therapeutic approaches to combat the infective and post-infective stages of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The Article by Thomas Huet and colleagues[1] on the clinical use of the interleukin-1 (IL-1) receptor antagonist, anakinra, to treat patients with COVID-19 is very interesting. The main hypothesis of the study was based on hyperinflammation caused by an increase in proinflammatory cytokines,