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 severe forms of COVID-19

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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,

such as IL-1β, IL-6, and tumour necrosis factor (TNF), triggered by SARS-CoV-2 infection. The recruited participants in this study did not have any other infection, but what if the patients did have another proinflammatory condition, such as obesity, rheumatoid arthritis, or other autoimmune disease?

The strategy to block peripheral inflammation as a treatment is not new. Humanised antibodies raised against TNF have been very promising for the treatment of inflammation-associated pathologies, such as rheumatoid arthritis.[2] Tocilizumab, another humanised antibody which blocks the action of circulating IL-6, has been shown to increase survival in patients with COVID-19.[3] At the start of the COVID-19 pandemic, there was controversy regarding the use of classic anti-inflammatory drugs, such as glucocorticoids, because these drugs might exacerbate the pathogenesis. However, corticosteroid therapy along with tocilizumab is associated with improved clinical outcome of patients with COVID-19.[4]

Can anakinra and tocilizumab be used as a combination therapy with corticosteroids in the treatment of severe SARS-CoV-2 infection, in the presence of inflammation-associated pathologies? A subgroup of patients with COVID-19 have a cytokine storm, characterised by a large increase in proinflammatory cytokines.[5] Therefore, the use of combination therapy might be justified for improved protection and treatment of patients with severe COVID-19 associated with systemic hyperinflammation. However, one should be careful; corticosteroids exert not only an anti-inflammatory effect but also immunosuppression, and the aforementioned cytokine storm is also followed by an immunosuppression. SARS-CoV-2 infection in patients with obesity is associated with an increased rate of pneumonia, artificial ventilation, and respiratory tract illness. The pathology of obesity is also marked with a cytokine storm, with high concentrations of IL-6 and TNF, largely from inflamed adipocytes. Inflamed adipocytes provide a favourable habitat for infiltrated macrophages and can cause some of the adipocytes to be transformed into macrophage-like cells, which can result in immunosuppression. Obesity with known increased viral shedding and hyperinflammation might lead to life-threatening outcomes in case of SARS-CoV-2 infection. The question regarding the use of anti-inflammatory drugs in patients with COVID-19 patients remains open.

I declare no conflict of interest.

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Authors' reply

We thank Marc Laine and Laurent Bonello, Adil Rashid Khan and colleagues, and Naim Khan for their interest in our Article on treatment of patients with severe forms of COVID-19 with the interleukin (IL)-1 receptor antagonist anakinra.[1]

Our colleagues pointed out (as did we in our Article) that the design of our study was not perfect from a statistical point of view because we compared the patients receiving anakinra with a historical control group. Only high-quality randomised trials can avoid confounding factors, but the urgent context of the COVID-19 pandemic means randomised trials are not always appropriate.

Laine and Bonello underline the significant effect of hypercoagulability in patients with severe COVID-19. At the time our study began, the issue of hypercoagulability was not fully understood. Of note, the proportion of patients who were given anticoagulants for a pre-existing disease before admission for COVID-19 was higher in the historical control group compared with the anakinra group (11 [25%] of 44 *vs* 5 [10%] of 52; p=0·044). The inclusion of this variable in our multivariate analysis did not modify the results. Once the patients were admitted to our hospital, they all received at least a prophylactic treatment with low molecular weight heparin. During the hospital stay, more patients developed a thromboembolic event in the anakinra group (ten [19%] of 52 patients) than in the control group (five [11%] of 44 patients). Therefore, a confounding effect favouring anakinra and related to this kind of complication appears unlikely.

With regards to the questions raised by Adil Rashid Khan and colleagues, it is absolutely true that some patients reached the primary endpoint at day 0, but no patient was on mechanical ventilation at inclusion. When excluding patients who experienced an event at day 0, the hazard ratio (HR) was 0·30 (95% CI 0·14–0·69). When excluding patients with an event on day 0 and day 1, the HR was 0·25 (0·09–0·70). As stated in our Article,[1] the patients in the historical control group had to fulfil the same inclusion and exclusion criteria as those in the anakinra group; however, we should have indicated that the inclusion criteria had to be fulfilled for the first time during hospitalisation, within the 24 h preceding anakinra initiation. Because our patients received standard oxygen therapy in medical wards, we were not able to assess a reliable percentage of inspired oxygen ratio at inclusion. As a result, a partial pressure of arterial

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