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Anakinra in COVID-19—how to interpret elevations of serum liver enzymes: comment on the article by Navarro-Millán et al

To the Editor:

We read with interest the article by Navarro-Millán and colleagues on the use of anakinra in patients with severe coronavirus disease 2019 (COVID-19) with acute respiratory syndrome coronavirus 2 and hyperinflammation (1). The authors tried to identify the clinical phenotype most likely to benefit from treatment with anakinra, in order to maximize utility and prevent exposure to unnecessary risks of immunosuppression. Indeed, administration of anakinra to 11 patients yielded promising results overall, although the lack of a control group and prior treatment with high-dose glucocorticoids in 8 patients limit interpretation of the findings. However, Navarro-Millán et al state that in previous studies of anakinra in COVID-19, severe respiratory failure was not a requisite for treatment initiation. This is incorrect, as a previous cohort study from our group in Milan, Italy, had remarkably similar eligibility criteria for administration of anakinra. Specifically, all patients had hyperinflammation, defined as elevated ferritin and/or C-reactive protein levels, and acute respiratory syndrome requiring noninvasive ventilation (2). The outcome measures were also similar, as was the ultimate aim to avoid mechanical ventilation.

Similarities between these studies help in interpreting another finding from Navarro-Millán and colleagues—elevated serum liver transaminase levels in patients receiving anakinra. Both the study by Navarro-Millán et al and ours included this finding, which led to tapering or discontinuation of anakinra in some patients. However, our study also included a control population of patients who, despite not receiving anakinra, exhibited similar elevations of serum liver enzyme levels (2). This led us to hypothesize that elevations of liver enzyme levels reflect underlying disease severity, rather than treatment toxicity. Elevation of serum liver enzyme levels is uncommon in patients receiving anakinra for approved indications. Conversely, it is a hallmark of both viral infections and macrophage activation syndrome, a condition that shares similarities with the hyperinflammatory response observed in some COVID-19 patients and is commonly treated with high-dose anakinra (3,4). Whether anakinra should be discontinued in patients with COVID-19 and elevated liver enzymes thereby remains debatable. Though perceived as the clinically responsible choice, discontinuation of anakinra in these patients may actually lead to detrimental hyperinflammation, of which elevated liver enzyme levels are merely an accompanying feature.

Dr. Cavalli has received consulting fees, speaking fees, and/or honoraria from Novartis and Pfizer (less than $10,000 each). Dr. Dagna has received consulting fees, speaking fees, and/or honoraria from Novartis and Pfizer (less than $10,000 each).

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Reply

To the Editor:

We appreciate Drs. Cavalli and Dagna's comments regarding our article addressing the potential utility of anakinra for avoiding the need for mechanical ventilation in patients with COVID-19, acute hypoxic respiratory failure, and evidence of cytokine storm syndrome. We thank them for pointing out the similarities between our patients and the patients in their recently reported study of COVID-19 patients who received high-dose intravenous anakinra. Indeed, 25 of 29 patients treated with anakinra in their similar study had severe acute respiratory distress syndrome, which Drs. Cavalli and Dagna defined as a partial pressure of arterial oxygen:fraction of inspired oxygen ratio of ≤100 mm Hg in the setting of bilateral pulmonary infiltrates and a positive end-expiratory pressure of ≥5 cm H_2O (1).

Drs. Cavalli and Dagna discuss the observations of elevated serum liver enzyme levels in some patients receiving anakinra in both studies and suggest that those elevations might not be attributable to anakinra. In their study, 3 of 29 patients who received anakinra developed elevated liver enzyme levels, while 5 of 16 similar patients who did not receive anakinra also had increased enzyme levels. We also noted that the observed elevations of liver enzyme levels could be a consequence of cytokine storm syndrome. We chose to taper anakinra and observed that the liver enzyme levels responded to decreasing the anakinra dose. We agree that additional data will be needed to understand whether anakinra can promote altered liver function in the special clinical circumstances of severe acute respiratory distress syndrome coronavirus 2 infection.

Results from both studies point to the significant need for well-controlled investigations to evaluate the efficacy and safety of anakinra in patients with severe COVID-19 with the goal of gaining control of cytokine storm syndrome and avoiding the need for mechanical ventilation. In addition, our results suggest that the timing of initiation of anakinra should be carefully considered, as the outcomes in our patients who received treatment within 36 hours of the onset of severe respiratory failure were more favorable than those in patients with more prolonged respiratory failure prior to initiation of therapy.

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