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CORRESPONDENCE

"*L'histoire se répète*", one size does not fit all

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We read with interest the systematic review and meta-analysis conducted by Snow and colleagues examining the potential benefit of interleukin 6 (IL-6) blockade with tocilizumab for coronavirus disease 2019 (COVID-19) [1]. The authors concluded that tocilizumab did not provide a significant improvement in overall mortality (24.4% vs. 29%; OR 0.87 [0.74–1.01]) in COVID-19 patients after analyzing 6493 patients from nine randomized controlled trials (RCTs).The authors are to be congratulated with their work. However, we would like to raise several points.

What can we learn from these data, except that conclusions should be drawn cautiously with regard to subgroup analyses? Firstly, looking beyond the dichotomous *p* values of mortality, this meta-analysis seems to be more compatible with benefit than with harm. Secondly, there was a clear association between disease severity and the potential effectiveness of tocilizumab but not with the level of baseline c-reactive protein (CRP) (log odds ratio (OR) vs. baseline CRP beta = 0.005 [− 0.005 to 0.016]; $p = 0.32$). Although this is an intriguing finding, the trial level meta-analysis using pooled data of the baseline CRP is not suitable for identifying the association between outcome and baseline CRP level [2].

This bares the question whether it is to be expected that baseline CRP is capable to discriminate between severe and mild COVID-19 associated acute respiratory distress syndrome (ARDS). Alternatively, additional hyperinflammatory criteria could be used in combination with the inclusion criteria of the largest trials (e.g. organ support, admission to intensive care unit (ICU), oxygen requirement, baseline CRP > 75) to identify patients that potentially will benefit the most. [3] This builds on two assumptions; 1- COVID-19 related ARDS, similar to ARDS of other origins, is a heterogeneous disease with hypo- and hyperinflammatory subphenotypes, and 2- that patients with hyperinflammatory features have the greatest potential of benefit [4].

An hyperinflammatory phenotypes could be identified using a combination of clinical parameters such as systemic inflammatory response syndrome (SIRS) criteria (i.e., tachycardia, tachypnea, fever) and biomarkers such as IL-6, interleukin 18 (IL-18) and ferritin. [5] However, the exact significance of these criteria for initiating tocilizumab in COVID-19 has not yet been clarified. In addition, there are the practical drawbacks of the availability of IL-6 and IL-18 assays in the average hospital where the bulk of patients are treated. Potentially, ferritin with a cut-off point > 1500 ng/l might be the most widely available biomarker that correlates well with the severity of COVID-19 associated ARDS, although its role in initiating anti-IL-6 therapy is still unclear.

Awaiting crystallized selection criteria, we suggest incorporating the aforementioned criteria into the day-to-day decision making to initiate tocilizumab, also during the early course of disease while receiving non-invasive oxygen therapy. On the other hand if the disease has progressed and the clinical characteristics do not fit a hyperinflammatory subphenotype of ARDS, one may consider not starting tocilizumab, despite serious critical illness. We have learned the hard way in the last 5–6 decades that one single approach is not likely to be successful in all ICU patients. Let's look carefully at the individual COVID-19 patient in the ICU and prepare a tailored therapeutic strategy that may, or may not include the use of tocilizumab.

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Declarations

Conflicts of interest
The authors declare that they have no conflict of interest.

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