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## Correspondence

**Answer to Vieira et al. "Cytokine profile as a prognostic tool in coronavirus disease 2019". Joint Bone Spine 2020. Doi:10.1016/j.jbspin.2020.09.006**



## ARTICLE INFO

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Vieira and colleagues support with their data the hypothesis and suggestions written by us at the beginning of the COVID-19 pandemic [1]. Based on the experience of rheumatologists in systemic autoimmune diseases, such as Sjögren's syndrome [2], we stressed the importance of disease stratification as a key step to curing the patients in the best way possible.

Consistent with Vieira's report, we found that using tocilizumab on the basis of the level of systemic inflammation, and IL-6 levels in particular, led to a low rate of death (7/42, 17%), with most of them confined to the group of patients treated in the Intensive Care Unit (6/27, 22%) rather than in the ward (1/15, 7%) [3]. In addition, looking at the level of IL-6 soon after tocilizumab might distinguish survivors from non-survivors [4]. Notably, those patients who subsequently died despite anti-IL-6 receptor treatment showed very much higher levels of IL-6 post-tocilizumab than survivors, with a IL-6 cut-off level of 442.5 pg/ml showing the best discriminating power between the two groups [4]. Therefore, taken together, these observations strongly suggest the need for a cytokine profile of the patient infected by SARS-CoV-2 in order to correctly apply targeting therapies in COVID-19. To further support that, when tocilizumab was used on the basis of the clinical grounds only, the drug failed to reach the endpoint [5]. Overall, based on a recent meta-analysis, tocilizumab is likely to reduce death rates in severe COVID-19, but the rate of infections may be increased. Importantly, the benefit of tocilizumab was greater in subjects not receiving corticosteroid therapy [6].

Moreover, the clinical scenario is becoming increasingly complex since targeted therapies other than tocilizumab have been reported to be potentially effective in COVID-19 [7,8], rendering the discovery of prognostic biomarkers and the patients' profiling an urgent need in COVID-19. In this light, higher baseline levels of IL-6 and IL-8 may predict the worst outcome, and those with baseline high viral load presented significantly higher levels of IL-10, IFN- $\gamma$  and TNF, but not IL-6 as Vieira et al. In our experience, patients undergoing tocilizumab did not show a delayed viral clearance in comparison with patients treated with standard of care [4]. Combination therapy remdesivir plus tocilizumab is under investigation

(ClinicalTrials.gov Identifier: NCT04409262). The effect of other targeted therapies on this outcome should be further explored. The specific properties of the different cytokines in this infectious disease need to be further investigated.

Finally, the greater amount of IL-6 in conjunction with IL-8 highlighted the role of the innate immune response in COVID-19. In fact, while rheumatic patients under TNF inhibitors do not seem at higher risk of COVID-19 [9], psoriatic patients under biologics, mostly IL-17 inhibitors [10], may be more exposed to that risk. Thus, each step of the disease should be more thoroughly profiled and caution should be used when employing selective immunosuppressors in a new disease entity (and this is an infectious disease) with particular attention to uncommon side effects and serious superimposed infections.

## Disclosure of interest

The authors declare that they have no competing interest.

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