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## Letter to the Editor

## Reply



## Respuesta

Dear Editor,

We would like to thank Aomar et al. for their interest in our work, as well as for their kind and valuable considerations. We also wish to extend our gratitude to the journal's editorial committee for giving us the opportunity to respond to the comments made.

In our study, the patient inclusion criteria were defined to match the likelihood of having received tocilizumab at the time of the study. Thus, the chosen criteria were those set by the Spanish Agency for Medicines and Medicinal Products (AEMPS, *Agencia Española de Medicamentos y Productos Sanitarios*) at that time of the pandemic; i.e., interleukin 6 (IL6) levels >40 µL/L, D-dimer levels >1500 µg/L or a sustained increase in these levels, with no mention of C-reactive protein (CRP) levels.<sup>1</sup> This might be the reason why the CRP data within the first 72 h in our cohort were only present in approximately 40% of the patients and with few values falling above 75 mg/dL. On the other hand, at the time of completion of our work, the cited RECOVERY study had not yet been published.<sup>2</sup> Interleukin 6 levels were determining for the inclusion of approximately 93.6% of the patients in our study, there being no differences between both groups in terms of their IL6 or D-dimer levels.<sup>1</sup>

As stated by Aomar et al. in their letter, the RECOVERY study was conducted on patients with COVID-19 pneumonia and CRP levels >75 mg/L, and featured certain peculiarities in its design. In this regard, a recent meta-analysis of randomized clinical trials on the use of interleukin-6 receptor antagonists (IL-6ras), essentially tocilizumab, in patients hospitalized for COVID-19, with 60% of the evaluated patients being sourced from the RECOVERY study, demonstrated the existence of an association between the administration of IL-6ras and a lower 28-day mortality compared to the standard of care.<sup>3</sup>

Notably, this benefit was only found when an IL-6ra was administered concomitantly with glucocorticosteroids. In this subgroup, the number of events (838 and 827 among a total of 2848 and 3468 patients of the control group and that treated with IL-6ras, respectively) reflected an association between the use of IL-6ras and a lower mortality (odds ratio [OR]: 0.78; 95% confidence interval [95% CI]: 0.69–0.88) in comparison with the subjects who did not receive treatment with IL-6ras. However, the underlying data also revealed a greater rate of events among patients treated with glucocorticosteroids, regardless of the use of IL-6ras (1665 events among 6316 treated patients versus 830 events among 3637 patients not treated with glucocorticosteroids), which demonstrates a positive association between the use of glucocorticosteroids and 28-day mortality (OR: 1.21; 95% CI: 1.10–1.33). This is a very surprising finding, as it is a well-known fact that the use of corticosteroids in hospitalized

COVID-19 patients results in lower 28-day mortality rates compared with the standard of care (age-adjusted odds ratio: 0.83 [95% CI: 0–75–0.93]).<sup>4</sup> Moreover, in patients not treated with IL-6ras, the association between treatment with glucocorticosteroids and 28-day mortality was found to be even worse (838 events among 2848 patients treated with glucocorticosteroids versus 293 among 1280 patients not treated with glucocorticosteroids; OR: 1.40; 95% CI: 1.20–1.64).

On the other hand, the effect of glucocorticosteroids in the group of patients treated with IL6ras was found to be neutral (827 events among 3468 patients treated with glucocorticosteroids versus 537 deaths among 2357 patients; OR: 1.06 [95% CI: 0.94–1.02]). Although the effect of IL-6ras seems to be beneficial for patients receiving glucocorticosteroids (reporting odds ratio [ROR]: 0.718;  $p = 0.008$ ), this result is based on the unexpected and unexplainable effect of glucocorticosteroid use, contrary to current evidence and showing very different mortality rates between patients receiving IL-6ras and those not receiving this type of drug.<sup>3</sup>

We agree with Aomar et al. regarding the use of tocilizumab in states of severe hyperinflammation considering the results obtained in both our patient cohort and the cohort studied by Aomar-Millán et al.<sup>1,5</sup> Nevertheless, we believe that a greater research effort is still necessary in view the inconsistencies observed, albeit not highlighted, in the cited meta-analysis.<sup>3</sup>

## Funding

This work was not funded by any institution.

## References

- Cardona-Pascual I, Berlana D, Martínez-Valle F, Campany-Herrero D, Montoro-Ronsano JB. Effect of tocilizumab versus standard of care in adults hospitalized with moderate-severe COVID-19 pneumonia [Article in English, Spanish]. *Med Clin (Engl Ed)*. 2022;158:301–7. <http://dx.doi.org/10.1016/j.medcle.2021.03.036>.
- The RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. *Lancet*. 2021;397:1637–45. [http://dx.doi.org/10.1056/S0140-6736\(21\)00676-0](http://dx.doi.org/10.1056/S0140-6736(21)00676-0).
- WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA*. 2021;326:499–518. <http://dx.doi.org/10.1001/jama.2021.11330>.
- The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384:693–704. <http://dx.doi.org/10.1056/NEJMoa2021436>.
- Aomar-Millán IF, Salvatierra J, Torres-Parejo Ú, Nuñez-Nuñez M, Hernández-Quero J, Anguita-Santos F. Glucocorticoids alone versus tocilizumab alone versus tocilizumab alone or glucocorticoids plus tocilizumab in patients with severe SARS-CoV-2 pneumonia and mild inflammation [Article in English, Spanish]. *Med Clin (Barc)*. 2021;156:602–5. <http://dx.doi.org/10.1016/j.medcli.2021.01.006>.

David Berlana\*, Ignacio Cardona-Pascual,  
J. Bruno Montoro-Ronsano

*Servicio de Farmacia, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain*

\* Corresponding author.

E-mail address: [david.berlana@vallhebron.cat](mailto:david.berlana@vallhebron.cat) (D. Berlana).

DOI of original article: <https://doi.org/10.1016/j.medcle.2022.04.017>