Review of: "Tocilizumab plus corticosteroids in elderly patients hospitalized with COVID -19 pneumonia: A retrospective cohort study"

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Potential competing interests: No potential competing interests to declare.

This observational cohort study was conducted to determine whether adding tocilizumab to corticosteroids decreases the incidence of mechanical ventilation in older patients with COVID pneumonia compared to use of corticosteroids alone. Secondary objectives were to assess the mortality and improvements in the respiratory status.

The study was carried out in a community hospital; patients aged 65 and older with COVID pneumonia. Appropriate exclusion criteria were applied.

Outcomes were incidence of mechanical ventilation, respiratory support reduction, and mortality.

Exposure was corticosteroid or corticosteroid plus tocilizumab.

The results presented in this paper estimated a higher risk of being intubated among users of steroid + tocilizumab treatment compared with those on steroid treatment alone. There was no indication of respiratory improvement and risk of mortality was higher in the treatment group (both) vs comparator (steroid alone) though the effect measure was not provided.

Without going into details of the methods or analysis of the study, there is one overwhelming problem that renders the results uninterpretable. While attempts were made to address differences in the 2 treatment groups, confounding by indication, one of the biggest challenges to validity in observational drug safety studies, is still a major concern. That is, the investigators do not acknowledge that, despite looking at baseline characteristics, people who were treated with both a corticosteroid and tocilizumab (treated) were likely not the same as people who received only a corticosteroid (comparator). The patient characteristics provided in table 1 support the concern that the treated group was sicker at baseline, thus, the poorer outcomes in this group could be attributed to their underlying morbidity. More patients in the treatment group were on higher levels of respiratory support (45% vs. 18% on high flow nasal cannula/nonrebreather mask/Venturi mask and 26% vs 20% were on BIPAP/CPAPA…). This large difference in baseline pulmonary function could explain the study results. The investigators attributed the poorer outcomes to the treatment, not to the underlying health of the patients in each group. The possibility that treatment choice (selection bias) could explain the findings rather than being causally associated was not adequately stressed. One suggestion is that the investigators could stratify the

results according to baseline pulmonary support to assess treatment differences by pulmonary status. It is important for the reader to recognize that this is not a randomized trial, meaning that the patients included in the study received the treatment chosen by the doctor. It is likely that doctors chose the combined corticosteroid and tocilizumab treatment based on the patient's condition.

The authors' conclusion is not supported by the data as mentioned above given the likely difference in the study treatment groups. Conclusion: "There was no difference in the incidence of mechanical ventilation with tocilizumab and corticosteroid combination as compared to corticosteroid alone, but it was associated with a clinically-important higher in-hospital mortality, similar effects on patients' respiratory status, and more cases of hepatic injury and bacteremia in older patients." It is possible that the addition of tocilizumab does not improve patient treatment but this study does not add to the current knowledge on this topic.

Here are some small additional concerns about the paper.

On page 8, under secondary outcome results the authors provide this result: "….deceased in the comparator group (OR: X; 95% CI: X to X; p = X)." The actual results need to be provided, not "x's".

There is no indication in the text or the tables of what if any covariates were adjusted in the analyses. There were covariates that were associated with the 2 treatment groups yet there is no indication that these were adjusted in the analysis in any way. This limitation goes back to the concern about the presence of confounding by indication. The authors need to assess the effects of the patient differences carefully before coming to any conclusion about the causal effects of tocilizumab treatment.

Regarding the analysis of adverse effects, it would be helpful to know about comorbidities related to liver disease at baseline. Were there differences in the 2 treatment groups at baseline? This should be added to Table 1. There is no information provided to interpret the difference in hepatic injury between the 2 treatment groups.

Regarding the analysis of mortality (I think the authors say that 57 and 30 patients died ("patients deceased"). Again, their baseline pulmonary function could explain this difference.