Rapid Reviews COVID-19

Review 1: "Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report"

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Published on: Mar 01, 2021

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RR:C19 Evidence Scale rating by reviewer:

- **Strong.** The main study claims are very well-justified by the data and analytic methods used. There is little room for doubt that the study produced has very similar results and conclusions as compared with the hypothetical ideal study. The study's main claims should be considered conclusive and actionable without reservation.

Review:

This REM-CAP trial was a multi-center randomized clinical trial (RCTs) that evaluated IL-6 receptor inhibitor (IL-6ri) (Tocilizumab and Sarilumab) in COVID-19 disease. Previously, there were multiple small observational studies that had implied IL-6ri treatment decreased COVID-19 morbidity and mortality, but these results were not confirmed with subsequent RCTs. The prior RCTs were comprised of patients at diverse stages of the disease and a smaller number of individuals as compared to the REM-CAP study. In general, these previous RCTs examined IL-6ri in a specific group of individuals that were at various stages in their COVID-19 disease. COVID-19 has generally been framed as comprising a virologic followed by an immunologic inflammatory phase. The inflammation has been presumed to primarily lead to lung damage and subsequent COVID-19 morbidity and mortality. REM-CAP examined IL-6ri in COVID-19 patients that were transferred to an intensive care unit within the past 24 hours, presumably comprising the patients entering a lung-damaging phase. All enrolled patients were on local standard care of treatment prior to randomization. Specifically, the majority of the patients in the REM-CAP trial were already being treated with Dexamethasone, which is different from all previous trials. The study randomly assigned 403 patients to IL-6ri and 402 to the standard of care (SOC). The trial used a Bayesian statistical model with pre-defined triggers to declare superiority, efficacy, equivalence, or futility. Furthermore, the adaptive phase design and Bayesian analysis allowed the investigators to conduct the trial without a pre-specified number of required individuals. Relative to the standard of care, active treatment was associated with a greater number of organ support-free days. Hospital mortality was 28.0% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control. All secondary outcomes and analyses supported the efficacy of these IL-6 receptor antagonists. These findings were statistically justified based on Bayesian statistics.

The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision. Indeed, multiple treatment guidelines have stated that IL-6ri therapy should now be considered for treatment in COVID-19 patients, although this has not been the case in the United States. These guidelines are likely to be modified further based on these and RECOVERY trial data. Based on these results, IL-6ri treatment may have shown a benefit here because of the timing. IL-6ri administration. As compared to previous trials, IL-6ri was administered within 24 hours of deterioration (ICU admission) rather than based on relatively longer standing oxygen status and plasma inflammatory markers.

In this study, much higher COVID-19 mortality was observed in both arms as compared to published experience and previous RCTs. It remains uncertain if the benefit observed with IL-6ri may be specifically applicable to individuals at very high risk of a poor COVID-19 outcome.

The trial evidence is very strong and actionable without reservation because it is based on the gold standard for evidence-based medicine, primarily an RCT.

I would accept the manuscript without revision.