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Interleukin-6 blockade with tocilizumab in COVID-19: Does it live up to its hype?

A recent systematic review by Cortegiani et al.[1] reviewed the evidence and appraised the quality of evidence concerning the use of tocilizumab in patients with coronavirus disease 2019 (COVID-19). Despite a thorough appraisal of a large number of clinical studies (n = 28) on tocilizumab in patients with COVID-19, Cortegiani et al.[1] concluded that there is still insufficient evidence on its clinical efficacy in patients with COVID-19 because these studies are associated with a high risk of bias and poor quality. We would like to complement the discussion on the evidence of tocilizumab use in patients with COVID-19.

Interleukin (IL)-6 blocking agents such as tocilizumab have been touted as the potential treatment for COVID-19 since the recognition of the cytokine storm associated with a severe course of COVID-19, which involves increased levels of several cytokines where one of them is IL-6. However, a more pressing question is ''Do increased concentrations of an IL-6 imply that its neutralisation will be effective in COVID-19?'' While a recent observational study[2], not included in the systematic review, demonstrated mortality benefits associated with the use of COVID-19, the two recent randomized controlled trials[3,4] did not replicate the findings. The randomized, double-blinded, placebo-controlled COVACTA trial[3] among hospitalized patients with COVID-19 reported no difference in 28-day mortality between the tocilizumab arm and placebo arm (19.7% and 19.4%, respectively). Furthermore, based on the results released on September 18, 2020, from the randomized, double-blind, placebo-controlled EMPACTA trial[4], there was no statistical difference in 28-day mortality between patients who received tocilizumab and patients who received a placebo (10.4% and 8.6%, respectively).

The findings from randomized controlled trials have proved that the use of tocilizumab in COVID-19 did not live up to the hype, where the increased concentration of IL-6 does not imply that its neutralization will be effective in COVID-19. There is a possibility that the wrong cytokine was targeted to dampen the cytokine storm in COVID-19. A recent prospective study by Blot et al.[5] compared the concentrations of IL-6 between 27 patients with COVID-19 pneumonia and 36 patients with non-COVID-19 pneumonia. It was reported that the plasma concentrations of IL-6 were significantly lower in the patients with COVID-19 pneumonia compared to the patients with pneumonia other than COVID-19 (121.0 pg/mL versus 460.4 pg/mL).

The findings of this prospective study, coupled with the findings from two randomized controlled trials that failed to detect mortality benefits with tocilizumab, suggest that IL-6 may not be the cytokine that drives the progression of COVID-19. The use of tocilizumab is not harmless since it may predispose patients to the development of secondary infections. We suggest a shift in focus and to target other mediators of hyperinflammatory state in patients with COVID-19.

Conflicts of interest

The authors have no conflicts of interest.

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Rationale and evidence on the use of tocilizumab in COVID-19: A systematic review. Authors' reply

Dear Editor,

We read with interest the Letter from Siang Kow et al.[1] commenting on our systematic review[2] and their discussion of the preliminary evidence from recent randomized controlled trials (RCTs) on the efficacy and safety of tocilizumab for COVID-19. We concur with the authors that it may indeed be time to divert some of our attention from IL-6 to other mediators of inflammation in COVID-19 patients. In fact, previous pharmacological attempts to modulate the inflammatory response in patients with ARDS and sepsis have repeatedly proven unsuccessful. It is therefore reasonable to also question whether suppressing the pathophysiological inflammatory response, or blocking a single mediator for that matter, will be beneficial for patients with COVID-19.

The authors commented on the absence of significant difference in mortality between patients who received tocilizumab (Actemra/RoActemra) or placebo in the industry funded COVACTA (NCT04320615 - https://www.roche.com/dam/jcr:6d8de90d-2e31-43c8-b4e1-0a24a2675015/en/29072020-mr-covacta.pdf) and EMPACTA (NCT04372186 - https://www.roche.com/media/releases/med-cor-2020-09-18.htm) trials.

The results of these trials confirm that findings from non-randomized trials should be interpreted with caution and that such caution is warranted particularly during public health emergencies when large numbers of patients may subsequently receive redundant treatments. As discussed by the authors in the context of tocilizumab and exemplified also by the hydroxychloroquine landslide,[3] experimental drugs are not always harmless, particularly when indiscriminately used. Patient safety should always be prioritized, which is why experimental drugs must be administered within the framework of registered RCTs that are accompanied by appropriate monitoring and regulation.

Research methodology may have also contributed to the negative findings of the above-mentioned RCTs. One example of a potential determinant of outcome in relation to treatment is the timing of administration in respect to the clinical phase of the disease.[4] Another is the treatment dose. Case mix may also have diluted the results; there may be sub-populations of COVID-19 patients who do actually benefit from receiving tocilizumab. Hopefully the full reports of the COVACTA and EMBACTA trials will shed some light on these questions and more. These analyses combined with additional data from the interventional tocilizumab arm of the RECOVERY trial (www.recoverytrial.net) may yet change our perspective on this drug. To summarize, although oft repeated, the following rhetoric is simply the truth: more (high quality) research is urgently needed.

Authors' contribution

AC, MI, SE conceived the content, drafted the manuscript and approved the final version for publication.

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