EDITORIAL

Tocilizumab in COVID-19: Is the Temptation Worthwhile?

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The mysterious respiratory illness, which has shaken the entire world, has still not found its magical cure. The speed of the research done for COVID-19 has crossed all boundaries in the last one year, and still, we do not know the efficacy of various therapies like antivirals (remdesivir) or interleukin 6 (IL6) receptor antagonist (tocilizumab) or convalescent plasma.

The cytokine release syndrome is a life-threatening systemic response, which can lead to multiorgan failure, and it is considered to play a pivotal role in the pathogenesis of COVID-19-related acute respiratory distress syndrome (ARDS). The presence of increased IL6 levels in COVID-19 has been associated with high viral load, increased disease severity, and high mortality.[1] Tocilizumab (TCZ), an FDA-approved IL6 receptor monoclonal antibody, showed promising results against COVID-19 in certain observational studies.[2–4] The biggest observational study by Gupta et al.[5] is probably the only study showing mortality benefit by the use of tocilizumab in severe COVID patients. Few other retrospective studies by Toniati et al.[6] and Guaraldi et al.[2] showed rapid improvement with the use of tocilizumab in terms of need for mechanical ventilation and mortality benefit. But the efficacy of any drug cannot be established without looking into randomized trials.

The RCT-TCZ-COVID-19 trial by Salvarani et al.[7] and CORIMUNO-TOCI-1 trial by Hermine et al.[8] did not find any statistically significant difference in 28-day mortality in tocilizumab vs the placebo group (3.3 vs 1.6%; 11.1 vs 11.9%). In addition to these two trials, the preliminary results of COVACTA[9] and EMPACTA,[10] which are double-blinded multicenter randomized controlled trials, have been published. The COVACTA trial did not show any 28-day mortality benefit (19.7 vs 19.4%) as most of the patients enrolled were of higher severity. The EMPACTA trial showed that the patients with moderate to severe disease but not on mechanical ventilation are the ones who benefit most by tocilizumab, although once on mechanical ventilation, there is no difference in 28-day mortality (10.4 vs 8.6%). The BACC Bay Tocilizumab Trial,[11] however, did not show any benefit of tocilizumab in preventing intubation or death in patients suffering from moderate disease severity [hazard ratio 0.83 (95% CI, 0.38–1.81; $p = 0.64$)]. These all trials leave us with no solid proof of evidence and with a guesswork of pick and choose the patients who will benefit from IL6 blockade. It also makes us think that patients who are on mechanical ventilation are the most sicker lot, and hence, the probability of them dying is also high.

In this month's issue of *Indian Journal of Critical Care Medicine*, Rankawat et al.[12] presented a retrospective data analysis of 30 patients with severe grade of COVID-19 infection who received tocilizumab infusion. Before administering the drug, the mean PF ratio (PaO_2/FiO_2) was 205.41 and 89.65% of patients had SpO_2 less than 90% with a mean FiO_2 requirement of 59.93%. Only one patient was on mechanical ventilation, and the rest were on either oxygen by mask or noninvasive ventilation. The mean IL6 was 206.56 pg/mL. Post-TCZ infusion, they found dramatic improvement in terms of PF ratio (p <0.001), oxygen requirement (p <0.001), and fall in IL6 levels (p <0.001). They could discharge 28 patients with an average hospital stay of 12.25 days. The chest radiology also showed clearing of ground glass densities. The results look fascinating, but there are certain limitations we need to consider. First, it is a single-center study, so we cannot rule out bias. Secondly, it is a small subset observational study. Thirdly, there is no control arm during the same study period, so the comparison with placebo or no drug application is not there.

The abovementioned study has been carried out on patients who are not on invasive mechanical ventilation and hence has shown promising results. They almost corroborate with the preliminary findings of the EMPACTA trial, but one should wait for the final results and subgroup analysis if any. The authors did not mention the timing of administration of TCZ as timing is crucial in terms of repeating the second dose. They also did not administer the second dose in patients who were slow responders or nonresponders, although there is no clear consensus on the same. In the study, roughly 21% of patients were still on oxygen therapy after a week of TCZ and whether they should be considered as nonresponders or slow responders is debatable. We are still not sure about the efficacy of tocilizumab in patients who are on mechanical ventilation with severe COVID-19 disease. The authors also did not comment on the incidence of secondary infections, if any, as it has been found that tocilizumab administration increases the likelihood of secondary bacterial and fungal infections, especially in diabetic individuals.

As the jury is still out and with no clear-cut recommendations for use of tocilizumab, the clinical judgment should be taken with caution, and till the time the final results of EMPACTA are available, TCZ use should be limited to patients with moderate to severe disease. Patients on mechanical ventilation may not be suitable candidates for tocilizumab as the studies have not shown any promising results.

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