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Response to "Tocilizumab therapy and COVID-19"

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Letter to the Editor

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To the Editor:

Thank you for your interest [1] in our experience [2] using tocilizumab (TCZ) in critically ill patients with coronavirus 2019 (COVID-19). As you rightly pointed out, optimum timing of the drug's administration is critical for the mortality benefit that may come from use of the IL-6 antagonists (IL-6a). It is worth noting that in the REMAP-CAP trial [3] which reported mortality benefit from IL-6a, patients were enrolled and randomized to receive the agent within 24 h of ICU admission and at a median of 1.4 days (IQR, 0.8–2.8) of hospital admission. Patients enrolled in the RECOVERY trial received TCZ within a median of two days from hospitalization [4]. Even with this timely administration, the benefit of reduced progression to invasive mechanical ventilation (IMV), death, and cardiovascular support was greatest amongst the ones who were on high flow nasal canula (HFNC) and noninvasive ventilation (NIV). In a recent prospective meta-analysis [5] based on 10,930 patients hospitalized for COVID-19 from 27 randomized clinical trials, administration of IL-6a was associated with lower all-cause mortality 28 days after randomization. The association of IL-6a with lower 28-day all-cause mortality was more marked among patients who were not on IMV at randomization. Once again, the benefits of IL-6 receptor blockers were most evident among patients who received respiratory support with oxygen by nasal cannula, face mask, HFNC (OR for death, 0.81 [95% CI 0.67–0.98]), or NIV (OR 0.83 [95% CI 0.72–0.96]) vs. those who required IMV (OR 0.95 [95% CI 0.78–1.16]). There was no clear benefit associated with IL-6 blockade for reducing 90-day mortality or the duration of IMV among patients who were already on a IMV at the time of randomization [5, 6]. Additionally, benefit was more marked when patients were already on corticosteroids at the time of randomization for TCZ [3–5].

Our TCZ experience [2] was from early in the pandemic (March–May 2020) when the drug was non-formulary, in short supply, and of unproven benefit. Its use was restricted per system guidelines for critically ill patients. All of our patients (100%) received corticosteroids. Our data shows the real-world experience in predominantly mechanically ventilated patients (87%) who received the medication at a mean of 12.6 days from illness onset and at day 6 after admission. TCZ use in our hospital system is now based on the NIH [7] and IDSA guidelines [8]. It is administered (at 8 mg per kg of actual body weight with a maximum dose of 800 mg IV) early after admission to patients who have rapidly escalating O_2 requirements, elevated CRP, other markers of inflammation, or soon after admission in patients who require HFNC or ventilatory support in absence of active bacterial infection. Our experience [2] highlights that TCZ offered no survival advantage at day 30 in our cohort when it was used late in mechanically ventilated patients with acute respiratory distress syndrome (ARDS) from COVID-19.

We outlined in the limitations section that 90% of the patients who received TCZ in our study [2] had severe disease with respiratory failure requiring IMV before TCZ was given; therefore, we could not assess the potential benefit of TCZ in preventing disease progression in patients with less severe disease. More studies are needed to show benefit, if any, from TCZ use in mechanically ventilated patients with COVID-19 ARDS.

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