Impact of Timing of Tocilizumab Use in Hospitalized Patients With SARS-CoV-2 Infection

To the Editor,

We appreciate the comments brought forth by Mungmunpuntipantip et al[1] as these will allow us to clarify and shed more light on the finer points of our paper.[2] We agree that with retrospective studies controlling for confounding factors can be difficult, and hence, we used propensity score matching to match tocilizumab and non-tocilizumab groups to minimize selection bias. We don't believe that ferritin levels are an important source of confounding in our paper since both groups were matched for laboratory markers including ferritin levels. Also, usually ferritin levels in metabolic syndrome are much lower than the levels seen in COVID pneumonia. In a 2015 study of 50 subjects with metabolic syndrome, ferritin levels in the range of 187.97 ± 35.95 μg/L were seen compared with > 400 μg/L in subjects with severe COVID pneumonia.[3,4]

In our study, a higher percentage of people in tocilizumab group received methylprednisolone when compared with non-tocilizumab group even after propensity matching (80% vs 65%, $P < .001$).[2] Mungmunpuntipantip et al[1] brought up the point that this discrepancy in steroid therapy can increase the favorable outcome rate in the tocilizumab group. However, when selecting for patients at the nasal cannula level in the tocilizumab and non-tocilizumab groups, the number of subjects receiving methylprednisolone was not statistically significantly different (56% vs 55.3%, $P = .89$); and hence, it is unlikely that the mortality difference of 11.6% (22.0% in non-tocilizumab group vs 10.4% in the tocilizumab group at nasal cannula stage) was due to steroid use.

In our study we observed a significant decrease in progression to mechanical ventilation when tocilizumab was given at the nasal cannula stage when compared to the non-tocilizumab group (6.3% vs 18.7%, $P < .001$). This is in line with the study quoted by Mungmunpuntipantip et al.[5]

In the above-referenced study by Milic et al,[5] 32.3% of subjects on room air or oxygen therapy progressed to noninvasive ventilation (NIV)/invasive ventilation after tocilizumab compared to 40.1% progression in the non-tocilizumab group. Of note, their study also showed a decreased risk of transition from the NIV/invasive ventilation state to death (15.0% vs 55.6%; hazard ratio 0.4, 95% CI 0.2–0.9) in the tocilizumab group.[5] This was not seen in our study, and hence, we recommended early use of tocilizumab when a patient is at the nasal cannula stage.

We agree with Mungmunpuntipantip et al[1] in that dosing of tocilizumab might affect outcomes. The recommended dose for tocilizumab is 8 mg/kg or 800 mg, and this is considered to be the upper limit for all approved indications including giant cell arteritis, rheumatoid arthritis, juvenile idiopathic arthritis, and cytokine release syndrome (Actemra package insert). Considering that patients with COVID-19 pneumonia are prone to secondary bacterial and fungal infections, we balanced tocilizumab's immunosuppressive properties with its anti-inflammatory properties and chose to keep 400 mg as a standard dose with possibility of additional 400 mg if no improvement was noted in a subject's inflammatory markers.

The timeline of COVID-19 progression in individual patients can certainly vary; however, most COVID-19 patients have been shown to follow a typical pattern of disease progression. Marik et al[6] have highlighted 5 stages of COVID disease progression. Most patients will likely experience disease resolution by phase 2 (viral symptom phase). However, some patients will progress through stage 3 (early inflammatory phase) to stage 5 (multisystem inflammatory phase). It is difficult to get an exact estimate of symptom onset from a retrospective chart review; however, presence of lymphopenia, persistent fever with elevated C-reactive protein, lactate dehydrogenase, and ferritin appear to be consistent markers of the early inflammatory phase that we believe to be an appropriate time for tocilizumab administration.

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