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Tocilizumab in Coronavirus Disease 2019: Give It Time! Reply

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Reply to Richier et al

TO THE EDITOR—We thank Richier and colleagues for their letter [1] regarding our paper and we appreciate the opportunity to respond [2].

Richier et al [1] provide a nuanced interpretation of the correspondence of Huang et al [3], who reported meta-analyses on 5 randomized controlled trials (RCTs). Based on their meta-analyses, Huang et al [3] concluded that tocilizumab does not provide a beneficial effect on mortality and that there was no observed difference in serious adverse events. We agree with Richier et al [1] that judgment as to whether or not tocilizumab may be of benefit to patients with coronavirus disease 2019

(COVID-19) should be given more time and that results from ongoing RCTs are needed.

Recently, the preliminary report from the REMAP-CAP RCT has been published showing that tocilizumab (and sarilumab) improves outcome including survival in critically ill patients with COVID-19 who receive organ support in the intensive care unit (ICU) [4]. The mortality was 28.0% for patients in the tocilizumab group and 35.8% for patients in the control group, suggesting a clear survival benefit for patients treated with tocilizumab [4]. The mortality of 35.8% in the control group was notably higher than the pooled mortality of 11% for the control group in the meta-analyses on RCTs of Huang et al [3]. As a matter of fact, the mortality of 35.8% in the control group of the REMAP-CAP RCT is almost similar to the pooled mortality of 31% for the control of the observational studies [2], and the benefit in survival for patients treated with tocilizumab is also very similar (risk difference of 7.8% for the REMAP-CAP study compared with 9.4% for observational studies). The same applies for the observational study of Gupta et al [5], which is a study of 3924 critically ill ICU patients either receiving tocilizumab or not: the mortality in the control group was 40.6% compared with the mortality in the tocilizumab-treated group of 28.9%. These results suggest an association between severity of COVID-19 (ie, mortality risk in the control group) and efficacy of tocilizumab in reducing the risk of mortality. This observation that patients with a higher risk of mortality could benefit from immunomodulatory treatment is in line with the results from the RECOVERY trial on dexamethasone, which showed patients receiving respiratory support had a lower mortality when treated with dexamethasone compared with controls, but not among patients receiving no respiratory support [6]. Similarly, the administration of systemic corticosteroids is associated with a lower all-cause mortality among critically ill

patients with COVID-19, as shown in a meta-analysis from the World Health Organization Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group [7].

Giving tocilizumab time to prove itself as a treatment for COVID-19, as Richier et al [1] suggest, is warranted and this would also allow identification of patients who could benefit most.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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