Outcome heterogeneity in COVID-19 patients receiving tocilizumab

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Dear Editor:

In a recent meta-analysis published in *Clinical Infectious Diseases*, Malgie *et al.* [1] analyzed 10 observational studies encompassing 1358 coronavirus disease-2019 (COVID-19) patients and revealed that a 12% lower mortality rate was observed among patients receiving tocilizumab treatment compared with untreated controls, and the number needed to treat to save a life may be as low as 11. Paradoxically, Tleyjeh *et al.*[2] conducted a meta-analysis of 24 COVID-19 studies and found that tocilizumab reduced the risk of mechanical ventilation in hospitalized patients with COVID-19, with no definitive evidence of a reduction in short-term mortality or an increased risk of infection. An editorial comment by Moehring *et al*. [3] showed that illness severity and immunotherapy programmes accounted for the outcome heterogeneity after tocilizumab treatment. In addition, the other 2 items should also be considered.

Interleukin (IL)-6 stimulates desirable antibody production by immune cells that express membranous IL-6 receptors, but also initiates series of undesirable proinflammatory processes by cells that lack IL-6 receptors. IL-6 trans-signaling to cells that lack IL-6 receptors requires dimerization of shed soluble IL-6 receptors with another membrane protein, glycoprotein 130 encoded by IL6ST [4]. Two variants of IL6ST, p.Ile454Thr (rs2228046) and p.Gly148Arg (rs2228044), have been documented as the possible explanations for the variable efficacy of tocilizumab. According to data from UK Biobank, the sorting intolerant from tolerant scores of p.Ile454Thr (rs2228046) and p.Gly148Arg (rs2228044) are 0.004 and 0.01 respectively, and associated with deleterious outcomes of COVID-19. The higher frequencies of risk alleles in both loci may contribute to a higher mortality from COVID-19 in African (rs2228046: 42%, rs2228044: 60%), compared with European (rs2228046: 0.08%, rs2228044: 11%) [5].

After undergoing almost 2-year prevalence worldwide, multiple SARS-CoV-2 variants have been characterized. B.1.617.2, also named as Delta variant, is a representative of the highly pathogenic SARS-CoV-2 variants and mainly

causes the second wave of extensive COVID-19 [6]. Wall *et al*. [7] carried out an initial analysis of the Legacy study to track serological responses to vaccination and identified a reduction of 5.8-fold in neutralising activity against B.1.617.2 relative to wild-type. In addition, a retrospective study from Singapore also indicated that patients infected with B.1.617.2 were more susceptible to hypoxia, intensive care unit admission, or even death than those who had wild-type SARS-CoV-2 infection (adjusted odds ratio for composite outcomes: 4.9) [8]. Despite limited direct evidence on the efficacy of tocilizumab among COVID-19 patients with diverse variants, the current knowledge of virology demonstrates that the therapeutic response to tocilizumab may be distinctive in patients infected with B.1.617.2.

In summary, a significant heterogeneity for the composite outcomes exists in available studies on COVID-19 patients receiving tocilizumab treatment, which is mainly associated with 4 influential factors including but not limited to, illness severity, immunotherapy programmes, IL6ST polymorphism and SARS-CoV-2 variants.

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Compliance with ethical standards

Competing interests The authors declare no conflict of interest.

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