CORRESPONDENCE

Severe COVID-19 and interleukin-6 receptor antagonist tocilizumab: Some notes of concern

To the Editors:

We read with great interest the article by McCarthy *et al.*,[1] regarding the favourable use of tocilizumab in a series of patients presenting with cytokine storm related to coronavirus disease 2019 (COVID-19) infection. The promising role of tocilizumab has been highlighted in recent reports of critically ill patients with COVID-19 pneumonia, showing encouraging results.[2] However, data remain conflicting[3] and anti-inflammatory intervention does not go without critical thought or cost.[4]

One has to bear into mind the increased risk of bacterial superinfections, following viral pneumonia in these patients. Reducing short-term mortality from cytokine release syndrome may come at the expense of long-term fatality rate, due to secondary healthcare or ventilator-associated bacterial or fungal infections, especially in critically ill patients with increased length of hospitalization in intensive care units (ICU). In view of long-term immunosuppression, need for prophylaxis against latent tuberculosis, herpes complex or hepatitis B virus re-activation before administration is still open to discussion. Compromised mucosal integrity in these patients due to hypoperfusion could further promote bacterial translocation and lead to fatal sepsis or bowel perforation. In this context, perhaps early rather than late administration in COVID-19 ward patients could be of certain value, before the need of intensive care and at the very beginning of inflammatory cascade, based on specific diagnostic criteria that need to be clearly established.

The best dosing scheme is still to be defined. Although one can argue that a single dose of tocilizumab has negligible long-term impact on immune responses, the exact number of doses and determination of specific criteria for need of more than one dose remains to be clarified. Current protocols recommend administration of 5–8 mg/kg followed by an extra dose 12–24 h later depending on clinical response. What the adequate clinical response would be, given the cost and risk of adverse events of such regimen needs to be strictly defined. These would be clinical, laboratory or imaging? And if so, at what time following initial administration would re-assessment be wise to be performed? Experience with rheumatoid arthritis patients dictates at least 2 weeks of watchful wait regarding clinical response, while even in the series of COVID-19 critically ill patients that tocilizumab was eventually used, no data on interleukin (IL)-6 levels have in the end been recorded.

Lastly, pharmacoeconomically speaking, increased cost cannot be ignored. In the absence of another efficient therapeutic or preventive regimen, use seems justifiable. However, in view of a second epidemic wave and a healthcare system facing mass number of cases, stringent budgets and allocation of financial resources to alternative equally necessary measures (e.g. ventilator machines) and long-term administration of such regimen to a vast amount of patients will not be viable.

All that said, we believe that at this point of the pandemic use of tocilizumab is promising and in certain cases necessary to increase chances of better outcomes, in failure or absence of other means. However, further larger clinical trials are needed to justify and clearly define its use, as wide administration will not be sustainable.

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Reply

From the Authors:

We thank Dr Akinosoglou and Dr Gogos for their valuable comments regarding our recent report on real-world experience in the use of tocilizumab for treatment of coronavirus disease 2019 (COVID-19) with hyperinflammatory state.[1] As they state, data on the potential benefit of treatment with interleukin-6 receptor antagonists (IL-6RA) in COVID-19 remains inconsistent and they highlight potential concerns for adverse outcomes arising from blockade of IL-6 receptor in those who are critically ill. However, observational studies demonstrate favourable outcomes regarding mortality and risk of proceeding to endotracheal intubation when IL-6RA are used in a pre-critical (pre-intensive care unit (ICU)) setting, such as that described in our report, before the onset of severe respiratory failure.[2] Apart from optimal timing of drug administration, there also remains uncertainty regarding the optimal dosing of tocilizumab in this clinical setting. It has been suggested that some individuals might need higher or repeated doses of tocilizumab, due to persistently high levels of IL-6 post-treatment, which have been associated with worse clinical outcomes in some reports.[3]

While the potential risk of bacterial infections represents a concern, a recently published rapid review and meta-analysis including 28 studies showed that bacterial co-infections and superinfections were reported in only 3.5% and 15.5% of patients with COVID-19, respectively.[4] However, more than 70% of patients were treated with antibiotics, mostly empirically, which raises the concern that patients with COVID-19 might receive unnecessary antibiotic treatment. On the other hand, the risk of bacterial infection may be higher in the ICU setting, where more frequent use of vascular and other indwelling devices represent a risk for bloodstream infections (BSI), which are also often reported in patients with COVID-19.[5] Moreover, the use of anti-inflammatory agents in the ICU setting, including tocilizumab, was associated with a higher risk of developing BSI, especially when used in combination with methylprednisolone. Considering the lack of convincing evidence on the clinical improvement of critically ill patients treated with IL-6RA, the risks might outweigh the benefits in the critical setting.[2]

Hence, optimal dosing and timing of such agents is essential and likely the administration in the pre-ICU setting, prior to the establishment of end organ damage or acute respiratory distress syndrome (ARDS), may be of most benefit. To address these questions, our group has designed a phase 2, open-label, two-stage, multi-centre, randomized trial comparing different doses of single-dose administration of tocilizumab in adults with severe, non-critical, COVID-19 with evidence of hyperinflammatory state.[6] This study is limited to patients in a pre-ICU setting, with specific exclusion criteria (such as history of immunosuppression, active malignancies, diverticulitis or intestinal perforation). In the first stage,
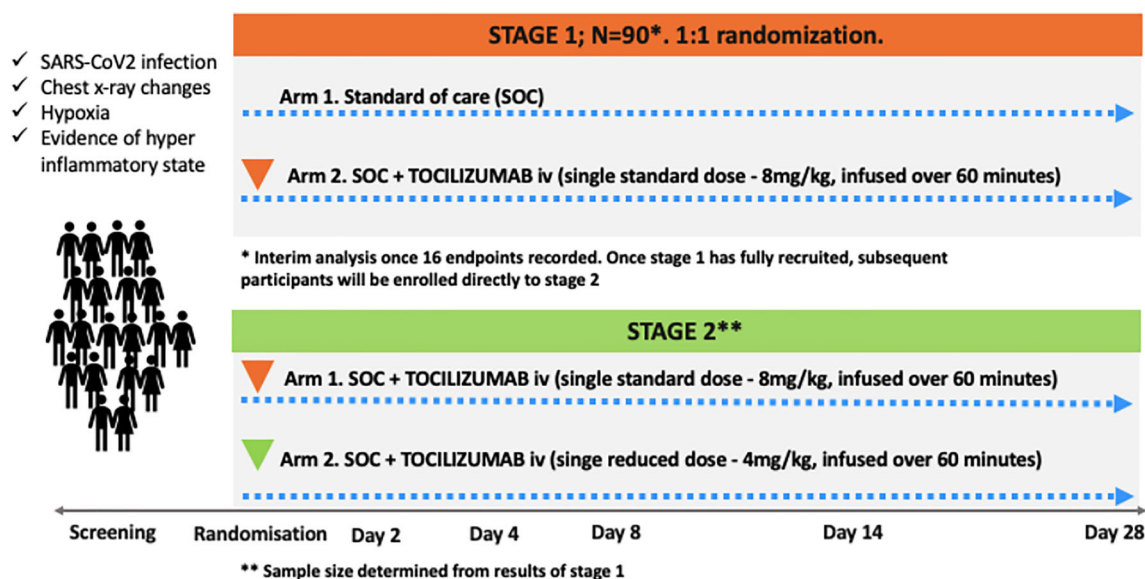

Figure 1 Clinical trial plan. Brief description of patient population (top left). Description of the two stages of the clinical trial (stage 1 and stage 2), with definition of the two study arms for each stage.

standard of care (SOC) will be compared to SOC plus a single infusion of tocilizumab (8 mg/kg). (Fig. 1). On the basis of the findings from stage 1, the study will progress to stage 2, where patients will be randomized to a single dose of either standard dose (8 mg/kg) or a lower dose (4 mg/kg) of tocilizumab plus SOC. This and other ongoing trials on the use of IL-6RA in patients with COVID-19 will hopefully produce the much needed, high-quality evidence on the efficacy and safety of treatment with immune modulatory agents in patients with severe COVID-19.

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