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LETTER TO THE EDITOR

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Tocilizumab's efficacy in patients with Coronavirus Disease 2019 (COVID-19) is determined by the presence of cytokine storm

Dear Editor,

We read with great interest the research article written by Borku Uysal et al[1] which is in accordance with the so far accumulating knowledge that tocilizumab is an effective treatment for coronavirus disease 2019 (COVID-19) cytokine storm syndrome (CSS).[2-6] On the other hand, preliminary results from the Smatteo COVID-19 registry (SMACORE) study are contradictory.[7] In this published article there was no difference between the control and the tocilizumab treatment groups in mortality and intensive care unit (ICU) hospitalization. This leads us to two hypotheses: one that tocilizumab is not effective in patients with COVID-19 as evidence from a clinical trial is stronger than observational studies or that tocilizumab is indeed effective and there are certain reasons that the clinical trial has failed to prove the primary hypothesis.

First of all in our opinion SMACORE is grossly underpowered to answer the question of death and ICU admission. A rough estimation of statistical power indicates that 250 patients are needed in each arm to show 20% reduction in deaths with p 0.05 (statistical power 80%).[8]

Our limited experience on tocilizumab suggests that in the setting of acute respiratory failure where the patient has fever, bilateral infiltrates on chest x-ray, raised C-reactive protein (CRP) (above 100 mg/dL), raised interleukin-6 (IL-6) (≥80 pg/mL) and significant hypoxemia (Po_2: FiO_2 [PFO] ratio <150) tocilizumab is indeed effective in putting breaks on the disease and potentially avoiding further deterioration, leading to intubation, prolonged mechanical ventilation, and potentially death. The above is also in accordance with the findings from the Brescia study, that early treatment with tocilizumab improves outcome in patients with well-established CSS.[4]

In the SMACORE study inclusion criteria are significantly different. First of all, the mortality and ICU rate of admission of the patients in the trial was lower than the one noted in the observational studies, but comparable to the mortality and ICU admission rate of all hospitalized patients in the New York City area suggesting that the population pool of the study was all hospitalized patients rather than the sicker ones that the other studies probably included.[9] This is also deduced from the median PFO ratio which was rather high for the tocilizumab group of patients (224.8) which suggests that patients that received tocilizumab in this study did not have the severity of hypoxemia used in most studies.

If the conclusions of this preliminary analysis are confirmed by the final results of SMACORE study, then this might suggest that not all hospitalized patients benefit from tocilizumab (as it happens in all treatments), as around 80% of these patients will improve with standard care treatment anyway. Recent data show that severe COVID-19 disease is driven by a complex immune dysregulation that involves the production of inflammatory cytokines (such as IL-6) as well as immune-dysregulation through IL-6 driven human leukocyte antigen D related (HLA-DR) decreased expression.[10,11] Immune dysregulation through an IL-6 driven mechanism appears to be more frequent than the macrophage activation syndrome in patients with severe COVID-19 disease. This immune dysregulation, that is generally referred to as COVID-19 associated CSS, appears to be present in almost all patients with acute respiratory failure.[11] The tocilizumab hypothesis of treatment is that it blocks this immune dysregulation-hyperinflammatory reaction that COVID-19 causes in patients mainly through restoration of the HLA-DR expression.[11] Hyperinflammation syndrome is clinically well defined and associated with the combined presence of high fever, raised CRP, hyperferritinemia, hypertriglyceridemia, low platelets, and raised IL-6 levels and all these criteria need to be taken into account, as well as hypoxemia, when tocilizumab treatment is considered in patients with COVID-19.[12] In our opinion the use of tocilizumab must be restricted to patients with evidence of CSS, and clinical trials should be designed with a clear clinical definition of cytokine storm. Since tocilizumab is not an antiviral drug and not all patients have CSS, it is expected that not all patients will benefit from such treatment and this is the major reason that this clinical trial fails to show the benefits of tocilizumab treatment demonstrated by other observational studies. Aside from this, COVID-19 is a complex disease and thromboembolic complications are also a major contributor to mortality. Tocilizumab controls cytokine storm but may not have a strong effect on coagulopathy. Thus, a combination of efficient anticoagulation treatment (eg, treatment dose low molecular weight heparin) and Tocilizumab may be more effective than Tocilizumab alone in reducing mortality and this should be investigated in future studies.

In conclusion, tocilizumab is rather safe[4] and possibly effective, if administered early, in patients with confirmed CSS, bilateral lung infiltrates, and severe hypoxemia, in preventing the use of invasive ventilation. To evaluate its efficacy on mortality, there is a need for larger randomized studies with significant statistical power and well defined inclusion criteria (definition of CSS, other medication etc).

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