

# Tocilizumab as a promising agent against COVID-19: Issues and challenges

Dear Editor,

In December 2019, novel coronavirus (SARS-CoV-2) pneumonia started to spread in the entire world and is causing growing concerns in the medical community as the virus continues to spread globally. Up to September 22, 2020, 31,485,162 cases were diagnosed as SARS-CoV-2 positive and 969,298 cases died. In the absence of effective treatment for COVID-19, there is an urgent need to identify alternative therapies to control this pandemic. Several agents such as chloroquine, hydroxychloroquine, antivirals, intravenous immunoglobulins, interferons, and immune modulators are now under investigation,<sup>[1]</sup> among which tocilizumab has emerged as a promising medication for COVID-19. Here, we conducted a quick review of tocilizumab in treating COVID-19.

Tocilizumab is a recombinant humanized monoclonal antibody of the immunoglobulin G1k subclass developed against both soluble and membrane-bound interleukin-6 (IL-6) receptors. Tocilizumab was first approved in 2005 as an orphan drug in Japan for the treatment of Castleman disease. It has also been considered for other diseases such as Crohn's disease, systemic lupus erythematosus, Takayasu arteritis, giant cell arteritis, cytokine release syndrome, and polymyalgia rheumatica.<sup>[2]</sup>

In some COVID-19 cases, especially those with impaired immune functions, the occurrence of an uncontrolled immune response triggers an overproduction of immune cells and their signaling molecules, causing cytokine release syndrome. IL-6 plays an essential role in the pathways of cytokine release syndrome, whereas tocilizumab, approved by the FDA for the treatment of cytokine release syndrome, can interfere with these pathways. It has been demonstrated that cytokine storms occur in severe acute respiratory syndrome, leading to the release of pro-inflammatory cytokines including IL-6, tumor necrosis factor- $\alpha$ , and IL-12. In Middle East respiratory syndrome, the levels of IL-6, IL-1 $\beta$ , and IL-8 also increase significantly. Hence, tocilizumab may be considered a promising option to stop cytokine storms in COVID-19.

However, there are some important considerations independent of tocilizumab and COVID-19. First, it is necessary to measure IL-6, IL-8, and INF-1b levels before tocilizumab administration, which can characterize the involvement of IL-6 in cytokine storms. If the level of IL-6 is within the normal range, it can be concluded that IL-6 does not play an essential role. However, if the level of IL-6 is higher than the upper limit of the normal range, it is reasonable to consider tocilizumab administration.<sup>[3]</sup> However, there is not any defined cut point for IL-6 level in this situation. Although tocilizumab is a promising agent against COVID-19, it is not appropriate for patients with active or latent tuberculosis or bacterial and fungal infections. Tuberculosis is an important public health concern in several countries, and the use of some monoclonal antibodies has exacerbated the issue, especially in immunosuppressed patients. It seems that QuantiFERON test is a reasonable method to check tuberculosis in this situation. In case of tuberculosis activation, it is necessary to initiate the antituberculosis regimen promptly, and tocilizumab should be discontinued. Tocilizumab may not be suitable in patients with multi-organ failures due to its unpredictable pharmacokinetics and safety. Since tocilizumab is associated with gastrointestinal perforation, it is reasonable to exclude patients with gastrointestinal disorders from receiving this medication. Other adverse effects such as hepatotoxicity and hypersensitivity have been previously observed with tocilizumab therapy, and close monitoring is necessary during its administration.<sup>[4]</sup> The reports of early trials on tocilizumab were promising. In these studies, tocilizumab was administered as the fixed-dose regimen (400 mg) or the weight-based regimen (8 mg/kg). Both intravenous and subcutaneous routes were effective. The safety results also showed that this agent contributed to the increased rate of superinfection.<sup>[5]</sup> Tocilizumab is a promising agent in the COVID-19 treatment based on recent studies, but the exact criteria for patient selection should be evaluated with caution, and it is necessary to monitor any probable adverse drug reactions. All of these drugs are currently under investigations until the results are reported in future large-scale studies.

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## Conflicts of interest

There are no conflicts of interest.

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