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Commentary

Tocilizumab is recommended for the treatment of severe COVID-19

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We read with great interest the prospective cohort study by Mar Masiá and colleagues published in this article of *EBioMedicine*. They suggested that tocilizumab treatment of patients with severe coronavirus disease 2019 (COVID-19) does not impair the specific antibody response against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1].

A comparative analysis based on results from enzyme-linked immunosorbent assays, serum levels of antibodies against the SARS-CoV-2 internal nucleocapsid (N) protein (N-IgG) and surface S1 domain of the spike protein (S-IgG) was performed in 138 patients with COVID-19, and the 76 patients treated with tocilizumab showed no lower viral specific antibody response than those who had undergone other treatments. This finding suggests that use of tocilizumab to block interleukin 6 (IL-6) signaling in COVID-19 patients may be safer than expected.

IL-6 is produced to stimulate the acute-phase response to deal with various infections and tissue injuries. Upon infection with SARS-CoV-2, pathogenic T cells are activated rapidly to produce proinflammatory cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-6. GM-CSF activates cluster of differentiation (CD)$14^{+}CD16^{+}$ inflammatory monocytes to produce a severe excess of IL-6 and other proinflammatory factors. These actions form an 'inflammatory storm' (IS), which leads to severe lung inflammation and multiorgan failure [2]. In severe inflammation, IL-6 contributes to coagulation activation and promotes the maturation of platelet-producing megakaryocytes, and hypercoagulability further aggravates the patient's condition [3]. These findings led to the concept of targeting IL-6 or GM-CSF to alleviate the IS in COVID-19 patients.

Tocilizumab is a monoclonal antibody that blocks IL-6 receptors effectively. It was first approved for treatment of rheumatoid arthritis. Due to its excellent ability to block IL-6 signaling, it has been approved recently to alleviate the acute 'cytokine release syndrome' in cancer patients after chimeric antigen receptor-T cell therapy. Based on the primary safety of these applications, tocilizumab became the first monoclonal drug used to treat severe COVID-19 [4]. About 60 clinical trials of tocilizumab for COVID-19 treatment are registered in the International Clinical Registration Center. Although most of them have not ended, the role of tocilizumab in helping COVID-19 patients reduce their stay in hospital and improve clinical outcomes has been recognised gradually [1,4,5]. New safety signals have not been reported in tocilizumab treatment of COVID-19 patients in these reports.

However, IL-6 was used as a factor that induces immunoglobulin production in B lymphoblastoid cells when it was cloned. Subsequent studies demonstrated that IL-6 can promote the proliferation and differentiation of B cells directly and secrete antibodies [6], as well as increase expression of BCL6 in the presence of IL-21 and T-cell receptor stimulation to promote the differentiation of lymphoid $CD4^{+}$ T follicular helper (Tfh) cells, thereby indirectly promoting the affinity maturation and subtype transformation of antibodies [7]. IL-6 overexpression can lead to an increased number of plasma cells and even hypergammaglobulinaemia, and IL-6 deficiency can lead to defects in immunoglobulin production after antigen treatment [8]. IL-6 plays an important part in antibody production, and antibodies are the body's most direct and effective immune weapon against viruses. Therefore, whether IL-6 blockade by tocilizumab will affect the antiviral immune response of COVID-19 patients (especially the formation of antiviral antibodies) has become an important concern for targeted IL-6 immunotherapy in COVID-19 patients. The cohort-study data provided by Mar Masiá and colleagues alleviated this concern to a certain extent. The tocilizumab-treatment group did not show a reduction in the concentration of antiviral antibodies in the middle and end of treatment [1]. Indeed, the antibody content of N-IgG and S-IgG in serum was higher than that in the non-tocilizumab group [1]. The increase in the level of antiviral antibodies may have been related to blockade of the excessive IL-6 signal, alleviation of the IS, and lifting its restriction on Tfh-cell differentiation and germinal-center formation [9]. In addition, drugs that block IL-6 signaling also include anti-IL-6 antibodies (siltuximab) and Janus kinase1/2 inhibitors (ruxolittinib), so we call for increased evaluation of the impact of antiviral antibodies in the clinical trials that have been carried out.

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There are millions of confirmed COVID-19 cases worldwide. We lack efficacious drugs to treat severe COVID-19. Tocilizumab could relieve the IS of COVID-19 patients to buy time for antiviral treatment and recovery of the immune system [2,4,5,10]. The best time for tocilizumab treatment for COVID-19 is during bilateral multilobe infiltration in the lungs, which is also the peak period of the IS. There is no need for excessive treatment in the mild disease stage, but it is also difficult to treat older cases and patients with advanced disease. The safety conclusions provided by Mar Masiá and colleagues provide confidence in the development of a larger multicentre randomised controlled clinical study of tocilizumab in COVID-19 treatment. They also lay the foundation for the development of earlier and higher-dose tocilizumab treatment for severe COVID-19.

Contributors

Y.G.Z. searched and summarised the literature and wrote the commentary. H.M.W. conceptualised and wrote the commentary.

Declaration of Interests

H.M.W. and Y.G.Z. are inventors on patent application (CN202010103449.6) submitted by the University of Science and Technology of China that covers the new use of anti-IL-6R antibody for COVID-19.

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