

Letter to the Editor

Cytokine-Targeted Therapy in Severely ill COVID-19 Patients: Options and Cautions

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Dear Editor,

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the symptoms including fever, dry cough and shortness of breath.^[1, 2] Most COVID-19 patients will develop mild to moderate symptoms, while some infected people may face to hyper-inflammation induced by massive cytokines/chemokines production, called as cytokine storm, which may lead to fatal pneumonia and acute respiratory distress syndrome.^[1, 2] Although, there is no specific antiviral therapy for COVID-19, understanding of cytokine storm mechanism in this disease can help to speculate possible therapeutic interventions.^[3] Current reports have presented different cytokine profiles in patients with severe COVID-19.^[1, 4–9] For example, the higher levels of interleukin (IL)-2, IL-7, IL-10, tumor necrosis factor (TNF), granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10; CXCL10), MCP-1 (CCL2) and MIP-1A (CCL3), but not IL-6, have been first shown in intensive care unit (ICU) patients compared to non-ICU patients.^[1] Subsequent studies revealed the contribution of other cytokines, including IL-1 β , IL-1ra, IL-2R, IL-6, IL-8 (CXCL8), IL-17, interferon (IFN)- γ and GM-CSF (granulocyte-macrophage colony-stimulating factor), during severe COVID-19 infections.^[4, 5, 8, 9] Figure 1 displays the protein-protein interaction between these cytokines/chemokines. In most existing reports, the elevated levels of several cytokines/

chemokine (ie., IL-6, IL-10, IFN- γ , TNF and IP-10), have been greater emphasized in severely ill (ICU) COVID-19 patients than mild to moderate (non-ICU) group.^[1, 4–7] Involvement of the T helper 2 cytokine IL-10, that suppresses inflammation, is a prominent feature of all reports, and an imbalance and/or exhaustion of T cells may be also involved.^[1, 10] Several approaches, including global targeting of the inflammation or neutralizing a single key inflammatory mediator, are being employed to cope with cytokine storm in COVID-19. Among key cytokines, IL-6 has attracted high

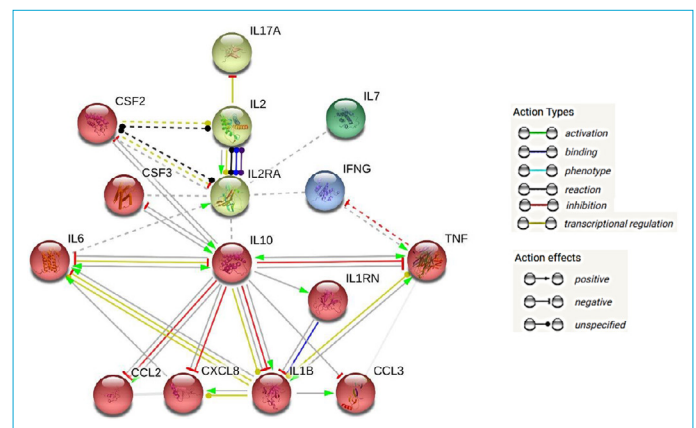


Figure 1. The interaction among common cytokine storm mediators in COVID-19. The protein-protein PPI was obtained from STRING (<https://string-db.org/cgi/network.pl>) database after uploading the common genes list reported in the text.

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levels of interest and antibodies that block the IL-6 receptor (tocilizumab and sarilumab) are currently under phase 2/3 clinical trials for the potential treatment of COVID-19.^[2] Targeting IFN- γ is another promising approach, which has been highlighted by launching a clinical trial for JAK-STAT inhibitor (ruxolitinib) for controlling COVID-19 severity.^[11] TNF acts upstream of IL-6 and anti-TNF therapies previously revealed protective effects in lethal SARS-CoV infection.^[12] Several TNF-blocking antibodies (eg., adalimumab, etanercept, and golimumab) are successfully used to treat inflammatory diseases, and these therapies have been urgently recommended for the hospitalized COVID-19 patients.^[13] IL-10 is likely upregulated to counter overwhelming infection during SARS-CoV-2 infection, but it may be also involved in the infiltration of inflammatory cells and lung fibrosis.^[14] IL-10 blocking, alone or in combination with programmed cell death protein 1 (PD-1), is promising for reinvigorating exhausted T cells and may control COVID-19 pathogenesis.^[10] Despite the benefits, there are still disadvantages, such as the development of chronic inflammatory disorders, thus more experimental studies should be done to clarify whether overactivation or ablation of IL-10 could be helpful for severe COVID-19. In some countries, including Iran and Turkey, tocilizumab is a recommended therapeutic strategy for ICU patients with severe COVID-19.^[15] However, it should be noted that the elevated IL-6 levels, in common with other cytokines such as TNF, have no specific pattern in all severe COVID-19 patients, so that their levels were not associated with the disease severity in some patients.^[1, 4, 5] Therefore, as patients with severe COVID-19 represent the differential cytokine patterns, more care should be taken before immunosuppressive therapy by cytokine blockers in COVID-19. This is important that the doctors evaluate a cytokine panel, at least including IL-6, IFN- γ , and TNF- α , to precisely identify the needs of each patient before administration of selective immunosuppressive therapy. Obviously, a combination of immunosuppressive therapy with antiviral therapies that diminish virus titer should be also into account.

Disclosures

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