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The Controversies Surrounding Tocilizumab Administration Following Pathogen-Associated Molecular Pattern (PAMP) Induced by COVID-19

Shayesteh Gheibi*, Farhad Najmeddin*, Bita Shahrami*, Kourosh Sadeghi*, Mojtaba Mojtahedzadeh*

*Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

A new corona virus disease (COVID-19) has affected more than 17 million people worldwide so far, and has become a global pandemic. Since there is no definitive cure for this life threatening disease, many clinical studies are in progress in this regard. Pathogen-associated molecular patterns (PAMP) prompting by coronavirus seems to generate cellular, structural, and functional derangements induced by immune dysregulation as well as many biological abnormalities including cytokine storm. The role of IL-6 in viral pneumonia and also its inhibition impact on the prevention of organ damage are still unknown.IL-6 seems to behave as a double blade evil cytokine, by playing a valuable role in cell to cell natural physiological communication. Tocilizumab, as an inhibitor of interleukin (IL)-6, may interrupt the paracrine system while causing dissemination of bacterial, fungal, and other viral infections, especially COVID-19, who are at a high-risk for development of sepsis and life-threatening superinfection.

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Background

Coronavirus is a single-stranded RNA virus that was firstly recognized in December 2019 in Wuhan, China, and then caused a widespread pandemic around the world. Accordingly, its common symptoms include fever, cough, fatigue, shortness of breath, and loss of smell and taste. Moreover, in severe cases, new coronavirus disease (COVID-19) can be complicated by acute respiratory distress syndrome (ARDS), sepsis, septic shock, and multi-organ failure (MOF) with a high mortality rate (1). In the era of COVID-19, as a physiological disaster, there were many identifiable pulmonary and extra pulmonary organ dysfunctions. Pathogen-associated molecular patterns (PAMP) prompting by coronavirus seems to generate cellular, structural, and functional derangements induced by immune dysregulation and many biological abnormalities including cytokine storm. Theoretically, although suppression of the immune system and inhibition of cytokines self-generation may also sound logical, they may cause serious cell to cell communication abnormalities and many long term morbidity concerns. Tocilizumab, as an inhibitor of interleukin (IL)-6, has received much attention in reducing this inflammatory storm.

IL-6 in COVID-19

In an infectious lung, bronchoalveolar lavage fluid (BALF) may contain extracellular vesicles (predominantly alveolar macrophage-derived) that overexpress the toll-like receptor-6 (TLR6) on macrophages, and then both of IL-1β and tumor necrosis factor-alpha (TNF-α) dropped by alveolar macrophages. Early in ARDS, the elevated concentration of leukocytes extracellular vesicles in BALF and plasma was related to the increased survival and ventilator-free days. Also, attachment of the neutrophil-derived extracellular vesicles (EVs) to Mer tyrosine kinase (MerTK) receptors on macrophages

*Corresponding Author: Dr Mojtaba Mojtahedzadeh
Address: Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Enqelab Square, Tehran, Iran. Tel:+982166954709/ Fax:+982188322029.
Email: mojtahed@sina.tums.ac.ir

increases the sprinkle of the pro-repair factor transforming growth factor-beta (TGF-β). On the other hand, a sprinkle of some pro-inflammatory cytokines such as TNF-α and IL-8 may decrease. Therefore, EVs have an anti-inflammatory impression on macrophages. Moreover, EVs containing microRNA-223 (miR-223) suppressed poly-polymerase-1 leading to an anti-inflammatory effect on alveolar epithelial cells. Furthermore, surfactant protein-D (SP-D) is a key to lung epithelial injury related to ARDS. Soluble receptor for the advanced glycation end products (SRAGE), which is the extracellular domain of a multi-ligand receptor expressed on alveolar type 1 cells, as well as angiopoietin-2 (Ang-2) as a molecule leading to the impairment of lung endothelial barrier function are the other biomarkers of ARDS (2).

IL-6 is a polytrophic cytokine with many properties, including immunosuppressive and inflammatory responses (e.g., interaction with neutrophils in the synovium), bone metabolism, and hematopoiesis. Moreover, it is a monomeric protein that binds to both soluble and transmembrane IL-6 receptors. Accordingly, soluble receptor (sIL-6R) is present in many body fluids inclusive of synovial and serum fluids, while transmembrane IL-6 receptor (mIL-6R) is only expressed in a limited number of cell types including liver cells, monocytes, macrophages, and some lymphocytes. When the mIL-6R is stimulated by IL-6, the short intracytoplasmic segment of the mIL-6R receptor binds to glycoprotein (gp) 130, which stimulates receptor dimerization and intracellular signal transmission. Similarly, when IL-6 connected to the soluble receptor, the sIL-6R is assembled on the cell membrane with gp130 to transmit the signals inside the cells. IL-6 receptor (IL-6R) signaling activates the Janus kinase (JAK), so it consequently activates the JAK/signal transducer and transcription activator pathways. Correspondingly, these two pathways play important roles in controlling the immune response and the acute-phase reactant, the target of these pathways is C-reactive protein (CRP). In addition, IL-6 plays a pathological role in inflammatory immune diseases and may be involved in the absorption of neutrophils into the peripheral blood, modulation of the neutrophils apoptosis, and the neutrophil cell infiltration (3).

IL-6 can also play a role as a multifunctional cytokine with several pro- and anti-inflammatory properties. In animal studies with acute pancreatitis, IL-6 is rapidly synthesized, which plays a protective role in the host defense. Also, disruption of the continuous synthesis of IL-6 during this inflammatory process causes fatal complications that consequently lead to the onset and development of severe acute pancreatitis (SAP). Although surfactant protein A (SP-A) and SP-D have significantly degraded in the SAP group within 24 hours, they have improved in the SAP-tocilizumab group. IL-6, IL-10, and IL-1β were down-regulated in SAP rats after the treatment with Tocilizumab at a dose of 2 mg/kg (4).

Hepatocyte regeneration could also be considered as another anti-inflammatory example of IL-6. However, it may reduce the productions of fibronectin, albumin, and transferring. Finally, the acute cellular response following an injury to the heart may cause the synthesis of IL-6 and IL-6-related cytokines that defend cardiac myocytes against oxidative stress and apoptosis (5).

Cytokine release syndrome (CRS) is known as a significant clinical complication of COVID-19, which can cause systemic inflammation due to infection. In this situation, the activations of monocytes, macrophages, and dendritic cells result in the secretion of the IL-6 as well as other cytokines. In this regard, features of CRS include fever, fatigue, headache, encephalopathy, hypotension, tachycardia, coagulopathy, nausea, capillary leakage, and MOF like ARDS (6).

In adults, some conditions like viral infection can lead to secondary hemophagocytic lymphohistiocytosis (sHLH), characterized by the activation and proliferation of lymphocytes with inflammatory cytokine release. This phenomenon results in sepsis-like syndrome and multiple organ disease. Also, pulmonary involvement (including ARDS) occurs in approximately 50% of patients. The cytokine-like profile of sHLH is associated with the severity of COVID-19 disease, which is characterized by increase in IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α. However, there is not sufficient evidence to support the key role of IL-6. The role of IL-6 in viral pneumonia as well as its inhibition impact on the prevention of further damages is still unknown. Delays may even occur due to the effects of IL-6 on wound healing process. The history of using other immunosuppressants in various sepsis and ARDS models has never been successful, which indicate that the complexity of these problems and the suppression of an important cytokine in this situation may lead to dysregulation of the immune system and the increased morbidity and mortality (7).

Tocilizumab efficacy and safety in COVID-19

Tocilizumab (Actemra®) is a drug prescribed for rheumatoid arthritis, giant cell arteritis, and CRS syndrom since the past. Moreover, it may bind to both sIL-6R and mIL-6R, as an IL-6 inhibitor, leading to the inhibition of IL-6 signaling through both receptors; however, it does not block signaling from other IL-6 family cytokines. It also blocks IL-6 performance without increasing the half-life of IL-6, and besides, it may cause neutropenia (8). Although the mechanism of neutropenia is still unknown, the margination effect may be the cause, rather than the

myelosuppression (6).

The recommended dose of this medication in CRS has been proposed as 8 or 12 mg/kg based on body weight (less or more than 30 kg). Tocilizumab can be prescribed alone or in combination with corticosteroids in this situation. If no clinical improvement occurs in CRS symptoms after the first dose, a maximum of three additional doses of Tocilizumab may be prescribed. The interval between successive doses should be at least 8 hours. Also, prescribing doses greater than 800 mg per injection is not recommended in CRS patients. The maximum concentration of Tocilizumab was observed after the first dose in patients with CRS that was 41% lower than in patients with other inflammatory diseases, which indicate a faster clearance of this drug following CRS (6). Tocilizumab is contraindicated for patients with the human immunodeficiency viruses (HIV), positive nucleus antibodies for hepatitis B, previous hepatitis C infection, and symptomatic Epstein-Barr virus (EBV) infection, because reactivation of the virus (eg, hepatitis B) has been reported. Initiation of Tocilizumab is not recommended under some following conditions: absolute neutrophil counts (ANC) less than 2000 per mm3, platelet counts less than 50000 cells/mm3, dyslipidemia, severe renal impairment, the demyelinating disorder, elevated liver enzymes, and patients with high risk of gastrointestinal perforation. The risk of infections was higher in the dose of 8 mg/kg compared with 4 mg/kg. Moreover, the most common serious infections were skin (cellulite) and lung (pneumonia) (9).

Conclusion

Tocilizumab is an effective and widely used disease-modifying drug for inflammatory and connective tissue diseases, with a good tolerance and safety profile, but rare toxic events. Nonetheless, after a decade of usage and numerous treated patients, it appears that Tocilizumab may induce a rare, but wide panel of potentially serious and lethal toxicities. Notably, infusion-related reaction, tumor lysis syndrome, digestive perforation, lung toxicity, and even severe cytokines release may increase morbidity and mortality rates following Tocilizumab administration in critically ill patients with COVID-19. Severe late-onset toxicities such as pneumocystis, pneumonia, viral reactivation, bacterial infections, late-onset neutropenia, hypogammaglobulinemia, and even organizing pneumonia may occur immediately, shortly, or in long term after the treatment by Tocilizumab. As understanding in the field of critically ill patients with COVID-19 related immune anergy and apoptosis grow, the gap between dream and reality of Tocilizumab will be further narrow. Although this medication has been used for some severely or critically ill COVID-19 individualized patients, none of these reports were controlled studies and no survival analysis has been presented. In a systematic review, they found that none of the studies were the randomized, controlled trials. Furthermore, the total number of the patients included in this review was small and may not be extensible to the whole population of patients (10).

In summary, IL-6 due to its anti-inflammatory and pro-inflammatory effects, if completely inhibited by Tocilizumab, besides having positive effects, can cause some side effects that may be harmful to patients with COVID-19. Finally, the physician should also consider the safety and efficacy of this medication and make a decision on prescribing Tocilizumab.

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