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REVIEW

Therapeutic targeting of interleukin-6 for the treatment of COVID-19

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ABSTRACT. Coronavirus disease 19 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in China and has spread worldwide with a significant rate of infection. Considering the elevated levels of proinflammatory cytokines in COVID-19, it is suggested that cytokine storms play a critical role in its pathogenesis, including acute respiratory distress syndrome (ARDS). However, there is no specific drug for preventing the cytokine release syndrome (CRS) caused by COVID-19. Indeed, interleukin 6 (IL-6) has been highlighted for its many biological functions, such as immune regulation, inflammatory response, and metabolism. Therapeutic blockade of the IL-6 signaling pathway is expected to reduce the excessive immune reponse observed in COVID-19. Currently, the IL-6 receptor antagonists tocilizumab and sarilumab, have been adopted for preventing CRS during the progression of COVID-19, and remarkable beneficial effects were observed by using these humanized monoclonal antibodies. Based on the pathogenesis of COVID-19, we reviewed the biological mechanism of IL-6 blockade in the treatment of SARS-CoV-2 infection and evaluated its clinical applications.

Key words: COVID-19, cytokine storm, interleukin-6, monoclonal antibody

Abbreviations

COVID-19	Coronavirus disease-2019
ARDS	acute respiratory distress syndrome
CRS	cytokine release syndrome
IL-6	interleukin 6
CAR-T:	chimeric antigen receptor T-cell immunotherapy
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
IFN-γ	interferon gamma
TNF-α	tumor necrosis factor alpha
PAMPs	pathogen-associated molecular patterns
DAMPS	damage-associated molecular patterns
RA	rheumatoid arthritis
GCA	giant cell arteritis
GM-CSF	granulocyte-macrophage colony-stimulating factor
IBV	infectious bronchitis virus
MERS-CoV	Middle East respiratory syndrome coronavirus
TCZ	tocilizumab
JIA	juvenile idiopathic arthritis
TAK	Takayasu arteritis
GCA	giant cell arteritis
PMR	polymyalgia rheumatica
SSc	systemic sclerosis
SLE	systemic lupus erythematosus
GVHD	graft-versus-host disease
FDA	Food and Drug Administration
CRP	C-reactive protein

INTRODUCTION

Coronavirus disease-2019 (COVID-19) caused by a novel β-coronavirus is a highly infectious disease [1]. In December 2019, the epidemic first broke out in Wuhan, China. As of May 24, 2020, approximately 5,200,000 cumulative cases have been confirmed, with more than 330,000 deaths globally, causing a severe public health burden [2, 3]. COVID-19 causes three stages of clinical manifestations, ranging from mild or moderate to severe [4]. Serious lung inflammation and ARDS occur in severe cases, suggesting that cytokine storms may play an important role in the pathological process of COVID-19 [5]. The main causes of death due to COVID-19 are respiratory failure and multiple organ failure [6]. A cytokine storm is a systemic inflammatory response that denotes excessive activation of the immune system, releasing uncontrolled and overwhelming proinflammatory mediators and finally aggravating many pathological processes [7].
Accumulating evidence shows that some patients, especially severe patients, have an elevated cytokine profile and impaired immune system [8, 9]. Moreover, lung injury caused by coronavirus infection exaggerates the production of proinflammatory cytokines;

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thus, an excessive inflammatory response in the context of cytokine release syndrome can cause severe disease and worsen prognosis [10]. In patients with CRS in the context of COVID-19, the increase in plasma levels of IL-6 compared to those at baseline results in poor survival [11-13]. IL-6 is one of the core cytokines participating in the process of pulmonary fibrosis after respiratory infection [14, 15]. Therefore, the treatment of CRS is a significant task to cure critical patients with viral infection. To date, there are still no specific antiviral therapeutic agents for COVID-19. Tocilizumab has been recommended as an immunotherapy drug for severe patients in the "Diagnosis and Treatment Plan of Novel Coronavirus Pneumonia (seventh trial edition)" in China [16]. Therefore, IL-6 inhibitors are being considered immunotherapy drugs for treating cytokine storms caused by COVID-19. This paper reviews the latest research advances of anti-IL-6 antibodies in coronavirus infection to obtain a better understanding of potential therapeutic use of IL-6 inhibitors in the modulation of COVID-19.

IMMUNE OVERACTIVATION PHENOMENON PRODUCED BY COVID-19

The pathogenesis of COVID-19 is largely due to disruption of immune and inflammatory processes, and the mechanisms have not been explored clearly [9, 12]. According to the disease progression, in the advanced period of COVID-19, the most common symptoms include serious pneumonia, ARDS, tissue injury, and multiorgan failure, particularly in elderly individuals or patients with comorbidities [10, 17]. These complications caused by cytokine storms are the main causes of aggravation and even death [18]. Clinically, cytokine storms can be triggered by viral infections or certain drugs, and they commonly present with a series of symptoms, such as high inflammatory parameters, overactivation of inflammatory responses, and multiple organ failure [19]. Inflammation is the first line of defence against external stimuli in general [20]. Therefore, due to the level of activated lymphocytes, macrophages, or myelocytes, uncontrolled release of cytokines eventually leads to systemic inflammation. Recently, CRS has been one of the most severe and frequent adverse effects of chimeric antigen receptor (CAR) T-cell therapies [21].

In the progression of the cytokine storm in COVID-19, after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the host can induce effective antiviral responses consisting of innate and adaptive immunity [22]. In general, to control viral replication and spread, the initial release of proinflammatory cytokines, interferon gamma (IFN-γ), or tumor necrosis factor alpha (TNF-α) is activated or induced by effector cells, and a series of proinflammatory cytokines, chemokines, and immune cells are produced [23]. Moreover, the tissue injury caused by the virus can recruit proinflammatory macrophages and granulocytes [24]. Macrophages play an important role in CRS pathophysiology, contributing to excessive amounts of additional cytokines, such as IL-1β, IL-6, and TNF-α [25]. Data observed in coronavirus infections have shown that pneumonia is the most common complication and that severe patients may be characterized by a cytokine storm finally progressing to ARDS [26]. According to the latest clinical features of patients with novel coronavirus, 12 (29%) of 41 patients had complications, including ARDS [8]. Additional significant clinical evidence is that the severity of COVID-19 is related to the levels of inflammation. In SARS-CoV-2-infected patients, the disease exhibits different levels of cytokines and chemokines from mild to severe [27, 28]. A striking feature of ICU patients is respiratory failure contributing to ARDS soon after elevation of various inflammatory markers [29]. Several recent case reviews have shown that the plasma level of IL-6 in severe patients is higher than that in mild or nonsevere patients [30-32]. Moreover, IL-6 levels are apparently increased in patients with ARDS who have a large area of lung injury ($\geq$50%) compared with those in normal controls [33].

THE ROLE OF IL-6 IN CYTOKINE STORMS

IL-6 appears to be a pleiotropic cytokine that is widely involved in immune regulation and inflammation development. In response to infections or tissue injury, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are recognized [34]. IL-6 can be transiently produced by immune cells, macrophages, mesenchymal cells, endothelial cells, and fibroblasts. After targeting its specific receptors, IL-6 cis-signaling or trans-signaling regulates a cascade of signaling events, including the PI3K-AKT signal, JAK-STAT3, and Pas-MAP kinase activation pathways, and then promotes the transcription of several downstream genes related to cellular signaling processes [35, 36]. Especially at the pulmonary level, the proliferation of innate and adaptive immune cells is strongly influenced by this cytokine [37]. IL-6 participates in the immune response by inducing the differentiation of B lymphocytes to produce antibodies and is also involved in the proliferation and differentiation of T lymphocytes [38]. Dysregulation of IL-6 participates in the pathogenesis of multiple immune diseases, such as rheumatoid arthritis (RA), Castleman disease, CRS, giant cell arteritis (GCA), and Takayasu arteritis (TAK) [39]. Considering that trans-signaling drives inflammation generally, IL-6 may impact COVID-19 immunity [40].

Experimental evidence suggests that in the latent state of virus infection, increased IL-6 levels may have adverse effects on the cellular immune system, thus affecting viral clearance and causing host injury [41]. New research also showed that after SARS-CoV-2 infection, inflammatory CD14 + CD16+ monocytes were induced under the cytokine environment, and then IL-6 was highly expressed and inflammation accelerated, which is part of the cause of devastating acute respiratory distress syndrome [42]. Additionally, at 2 weeks after disease onset, the levels of IL-6 were increased in patients with COVID-19, with 2.9-fold higher levels in severe patients than in noncomplicated patients [43]. The risk of death is associated with surging IL-6 levels, and IL-6 has been a potential prognostic biomarker for the course of COVID-19.

Indeed, it has been proven that CD4+ T lymphocytes are activated rapidly and differentiate into pathogenic Th1 cells, further inducing monocyte activation with high expression of IL-6 by producing granulocyte-macrophage colony-stimulating factor (GM-CSF) and other proinflammatory cytokines [44]. Furthermore, IL-6 is considered a central mediator of toxicity in CRS and an inflammatory trigger [45]. IL-6 mediates physiological function most notably by controlling the acute phase response when acute inflammation occurs, and acute phase response proteins are induced mainly by IL-6 [39]. In previous studies, IL-6 $^{-/-}$ mice represented a compromised acute phase response dependent on classic IL-6 signaling [46, 47]. In the murine SARS model, a high level of IL-6 was closely connected with virus replication and disease severity, revealing the significant role of this cytokine in lung pathogenicity [48, 49]. Another report suggested that IL-6 is a key epithelial cytokine induced by SARS-CoV that could inhibit the T cell-priming ability of dendritic cells [50]. In coronavirus infectious bronchitis virus (IBV), the induction of two proinflammatory cytokines, IL-6 and IL-8, is regulated at the transcriptional level [51]. In addition, the study of Middle East respiratory syndrome coronavirus (MERS-CoV) clarified the overwhelming immune response resulting from dysregulation of the cytokine network and resulting in the overexpression of inflammatory cytokines [52].

IL-6 INHIBITORS: FROM THE PAST TO THE PRESENT

Drug species targeting IL-6 cytokine family members are divided into the following types: monoclonal antibodies acting directly on cytokines or cytokine receptors, recombinant cytokine regimes and small molecule therapies interfering with the cytokine receptor pathway through gp130 and JAK–STAT signalling [38]. The strategy of IL-6 inhibition began with the development of tocilizumab (TCZ). In the late 1980s, the anti-IL-6R antibody (chemical name: tocilizumab) was developed as the first biologic drug blocking IL-6 binding to membrane-bound IL-6R and sIL-6R [53]. Tocilizumab is currently approved for the treatment of RA and juvenile idiopathic arthritis (JIA) in more than 100 countries around the world. In fact, this anti-IL-6R antibody has been approved not only for Castleman's disease and TAK in Japan but also for giant cell arteritis (GCA) and CAR-T cell-induced CRS in the European Union and the United States [54]. At present, the efficacy of acute and chronic inflammatory diseases, such as polymyalgia rheumatica (PMR) and systemic sclerosis(SSc), has also been proven effective in phase II or phase III clinical trials. Diseases with substantial case reports, such as systemic lupus erythematosus (SLE) and graft-versus-host disease (GVHD), show that TCZ efficacy is credible [55]. Another human anti-IL-6R mAb, sarilumab, inhibits activation of the IL-6 classic and trans-signalling pathways, and it has a higher affinity than tocilizumab [56, 57]. In May 2017, sarilumab received its Food and Drug Administration (FDA) approval for treating RA. Monoclonal antibodies against IL-6 or IL-6 receptor have become significant immunotherapies alone or combined with conventional chemotherapy [56].

Based on past facts, we propose the possibility of using these drugs to treat severe respiratory tract infections caused by viruses. On the one hand, from the aspect of the mechanism of IL-6 during viral infections, IL-6 can induce immune overactivation phenomenon and mediate viral replication in experimental models [58, 59]. On the other hand, from the perspective of clinical features, there are surging plasma levels of IL-6 in severe COVID-19, also the symptom of inflammatory changes similar to CRS under an abnormal innate immune response stimulated by IL-6 [60]. At present, hyperinflammation may be the key to virus control in the case of an ineffective type 1 interferon response [61]. The immunology-informed approach may be an alternative strategy to control pathological inflammation in COVID-19 patients [62]. A few IL-6 inhibitors are already being used to treat patients with severe COVID-19 to suppress inflammatory responses. The efficacy of tocilizumab in COVID-19 has been evaluated in a number of clinical trials to test the effectiveness of this approach based on blocking IL-6 in host defence. Anti-IL-6RAb initially induces a momentary increase in the plasma level of IL-6, but its continuous administration subsequently leads to a tendency for IL-6 levels to decrease and improves the clinical conditions [63].

A single dose of tocilizumab by intravenous injection of 400 mg was administered to 21 infected patients with severe respiratory syndrome in China; after a few days, 90% of patients recovered, and lung opacities disappeared [64]. A second study from France analyzed 30 selected patients (23% in the ICU) regarding IL-6 blockade with tocilizumab (*figure 1*). IL-6 blockade curbed the cytokine storm, decreasing the risk of ICU admission and mechanical ventilation [65]. A third report revealed two patients with myeloma diagnosed as COVID-19 who developed CRS-like syndrome and respiratory failure. Patients successfully responded to biotherapy with tocilizumab. The authors concurrently proposed that early application of IL-6 blockade therapy can prevent the progression of critical illness and invasive ventilation [66]. In a fourth study, 21 COVID-19-infected patients who developed pneumonia or ARDS all received intravenous siltuximab at a median dose of 900 mg (between 700 and 1,200 mg) and were followed for a median of eight days. In 16 patients, serum C-reactive protein (CRP) levels were reduced, according to available data, following treatment. Clinical improvement was observed in 7 (33%) patients, and 9 (43%) patients were stable [67]. Finally, there is a case report of tocilizumab for respiratory failure related to COVID-19. Patients had a rapid favorable outcome after two infusions of tocilizumab [68]. These clinical trials reveal that IL-6 inhibition could reduce the risk of COVID-19 progression by alleviating the cytokine storm in the lungs. In addition, a phase II trial of the therapeutic effect of IL-6 inhibitors is ongoing in Italy, and a phase III trial was approved by the FDA in March 2020 [69].

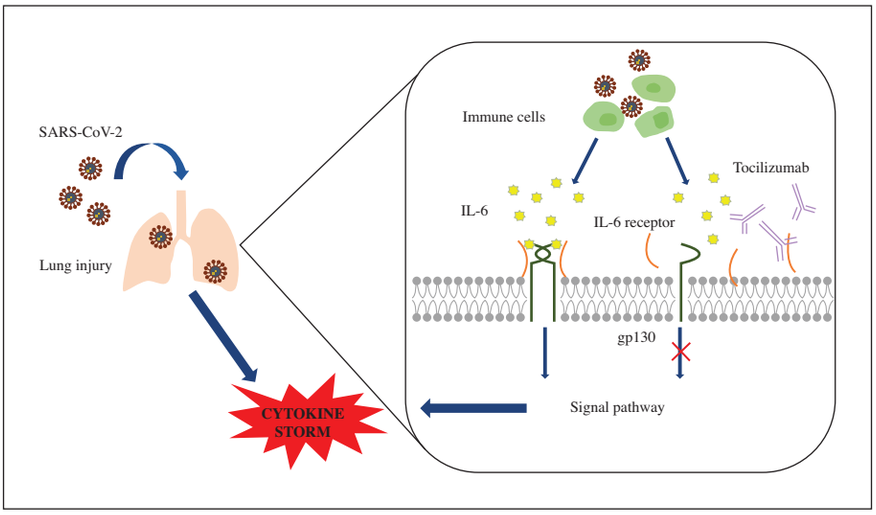

Figure 1
The potential mechanism of IL-6 blockade therapy using tocilizumab in the treatment of cytokine storm-induced SARS-CoV-2.

CONCLUSIVE REMARKS

Recent reports have confirmed that based on the mechanism of disease progression, cytokine storms play a significant role in the progression of COVID-19, and IL-6 is at the core of cytokine storms. According to the mechanism of their immune response targeting the host, they seem to have potential benefits, with anti-IL-6 activity, to interfere with COVID-19 infection. Tocilizumab and sarilumab are human monoclonal antibodies against the IL-6 receptor and are currently being considered for treating autoimmune and inflammatory diseases in many countries. The applications are being extended to, most recently, COVID-19 pneumonia that has developed into CRS. Considering the clinical characteristics of COVID-19, we recommend that clinicians closely monitor the level of IL-6 as a marker for potential progression to critical illness [70].
Although in the preliminary study, inhibition of IL-6 appears to be efficacious and safe, considering that IL-6 antagonists increase the risk of serious infection, the dose and time of the injection have to be further determined. Note also due to the risk of transient or sustained neutropenia and other opportunistic infections after IL-6 blockade [71], such conclusions must await additional clinical studies. In conclusion, cautious must be taken to monitor patients for potential side effects. Therefore, we still need to collect additional case observations and further in-depth research data on treatment options that improve survival.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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