



Cytokine Storm, Corticosteroids and Interleukin-6 Receptor Antibodies in Context of Antiinflammatory Treatment in COVID-19

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Authors' contributions

This work was carried out in collaboration among all authors. Author OK designed the study, wrote the protocol, performed the critical analysis of the literature and wrote the first draft of the manuscript. Authors GA, BO and EY managed the analyses of the study. Authors EE, SY and MH managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i2530824

Editor(s):

(1) Dr. Mohamed Salem Nasr Allah, Weill Cornell Medical College, Qatar.

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Complete Peer review History: <http://www.sdiarticle4.com/review-history/61497>

Review Article

Received 12 September 2020

Accepted 30 September 2020

Published 26 October 2020

ABSTRACT

It is well established that cytokine storm is associated with more severe clinical course of COVID-19. Many clinical findings of COVID-19 and other severe viral infections (e.g. fever, muscle pain,

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respiratory distress, cough), are directly attributed to cytokine storm. For example, IL-6 and IL-10 can be used as predictors for expedient diagnosis of patients with higher risk of deterioration. Hyper-inflammatory status in patients with severe COVID-19 is to be mitigated to alleviate signs and symptoms in cytokine storm. In case of deterioration of oxygenation and rapid progression of imaging (CT) findings, glucocorticoids can be used for a short time (3-5 days) for patients in whom overactivation of the body's inflammatory response is suspected. On the other hand, interleukin-6 receptor antibodies tocilizumab, sarilumab, siltuximab can be used as immunomodulators, to suppress inflammation and to alleviate fever and other manifestations of immune response. Their beneficial efficacy is especially remarkable during the cytokine storm period. It should be kept in mind that the agents to be used in the management of any given patient should be tailored for each situation.

Keywords: Cytokine storm; corticosteroids; interleukin-6 receptor antibodies; tocilizumab, antiinflammatory treatment; COVID-19.

1. INTRODUCTION

1.1 Cytokine Storm

Coronavirus disease 2019 (COVID-19) has emerged in China and since December 2019, it spreaded thorough the world, afflicting nearly 30 millions of people in regard to official announcements. The pathogenesis of the disease precipitated by the "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) is yet to be enlightened further. Inflammatory process along with the damage of the host's immune system plays a pivotal role in all pathophysiological mechanisms and complications in the clinical course of those with COVID-19.

The exuberant activation of immune systems is critical in protecting against infectious agents; and accompanied by inflammatory mediator release. High inflammatory cytokines levels have been strongly correlated with grave outcomes in viral infections. Furthermore, massive inflammatory cell infiltration and remarkable pro-inflammatory cytokine responses induced by SARS-CoV and MERS-CoV infection played a crucial role in deterioration of the patients [1,2].

Findings from recent researches pointed out that elevated levels of cytokine storm is associated with more severe clinical course of COVID-19. Given the high levels of cytokines induced by the virus, treatment to reduce inflammation-related lung damage is critical. Of note, IL-6 and IL-10 are serum cytokines that can be used as disease severity predictors in patients with COVID-19. Han et al. demonstrated that COVID-19 patients have higher serum level of cytokines (TNF- α , IFN- γ , IL-2, IL-4, IL-6 and IL-10) and CRP than control individuals [3]. Within COVID-

19 patients, serum IL-6 and IL-10 levels are significantly higher in critical group than in moderate and severe group. The levels of IL-10 is positively correlated with CRP amount ($r = 0.41$, $P < 0.01$). Using univariate logistic regression analysis, IL-6 and IL-10 are found to be predictive of disease severity and receiver operating curve analysis could further confirm this result (AUC = 0.841, 0.822 respectively). These findings indicated higher levels of cytokine storm is associated with more severe disease development. Among them, IL-6 and IL-10 can be used as predictors for fast diagnosis of patients with higher risk of disease deterioration. Given the high levels of cytokines induced by SARSCoV-2, treatment to reduce inflammation-related lung damage appears to be critical.

Studies showed that male patients exhibit higher serum levels of markers of cytokine storm (soluble IL-2R, IL-6, ferritin, procalcitonin, LDH, and hsCRP) when compared to female patients [4]. Accordingly, IL-6 > 50 pg/mL and LDH > 400 U/L on admission were independently associated with disease severity in patients with COVID-19. The severe cases showed the similar response patterns when compared to those with moderate courses. The longitudinal assays showed the levels of pro-inflammatory cytokines, LDH, hsCRP, and hsCRP/L gradually declined within 10 days post admission in moderate, severe cases or those who survived. The authors concluded that exuberant inflammatory responses within 24 h of admission in patients with COVID-19 may correlate with disease severity. SARS-CoV-2 infection appears to elicit a sex-based differential immune response. IL-6 and LDH were independent predictive parameters for assessing the severity of COVID-19. An early decline of these inflammation

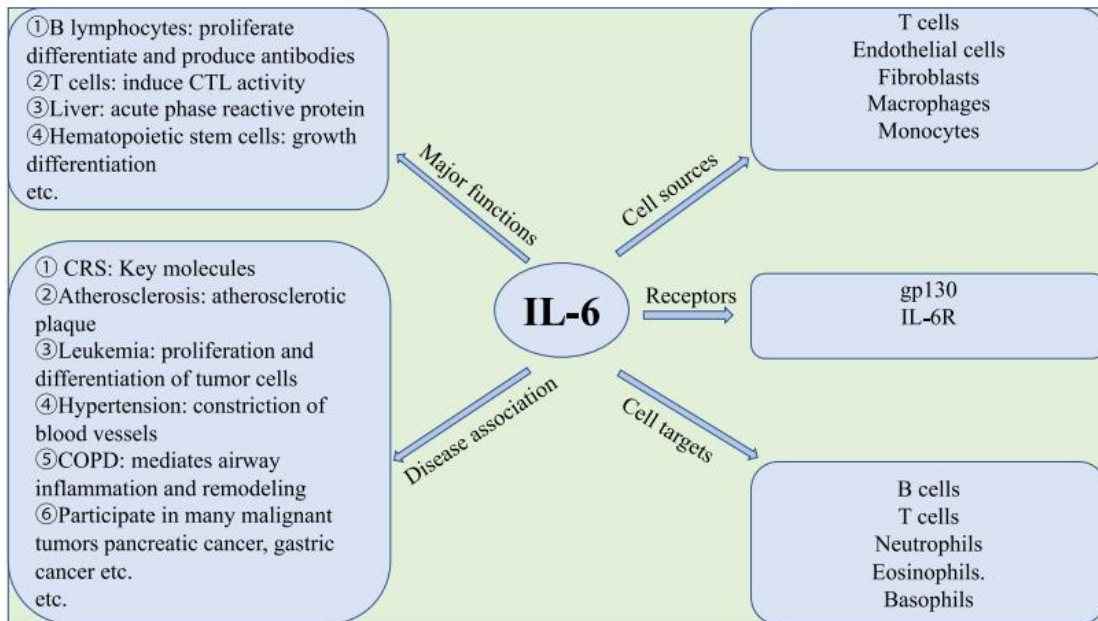


Fig. 1. Role of interleukin-6 (IL-6) in inflammatory process, including COVID-19. CTL, cytotoxic T lymphocyte; CRS, cytokine release syndrome; COPD, chronic obstructive pulmonary disease; GP130, glycoprotein 130; IL-6R, interleukin-6 receptor (Adapted from Zhang et al, 2020)

markers may be associated with better outcomes.

1.2 Role of Interleukins in Covid 19, and Mechanism of Action of Anti-IL-6 Receptor Antibodies

Cytokine release syndrome has a pivotal role in the pathophysiology of COVID-19, as well as in many infectious processes. SARS-CoV-2 infects alveolar epithelial cells [mainly alveolar epithelial type 2 (AEC2) cells] through the angiotensin-converting enzyme 2 (ACE2) receptor. Destruction of epithelial cells and the increase of cell permeability lead to release of the virus. SARS-CoV-2 activates the innate immune system; macrophages and other immune cells not only capture the virus but also release a large number of cytokines and chemokines, including interleukin-6 (IL-6). Adaptive immunity is also activated by antigen-presenting cells (mainly dendritic cells). T- and B-cells not only play an antiviral role but also directly or indirectly promote the secretion of inflammatory cytokines. In addition, under the stimulation of inflammatory factors, a large number of inflammatory exudates and erythrocytes enter the alveoli, resulting in dyspnoea and respiratory failure [5].

2. CORTICOSTEROIDS

So far, no definitive conclusions have been found regarding the effects of immunosuppressants in severe influenza virus infections and thus, their therapeutic use is controversial [6]. Corticosteroids (CST), which are known as an option for immunomodulatory treatment in the treatment of SARS-CoV, affect the whole body and have a very strong effect and have anti-inflammatory and immunosuppressive effects, provide early recovery of fever and less harmful radiographic leaks [7]. The use of CST to treat influenza virus has been associated with a higher risk of superinfection, long-term viral replication, and an increased risk of death [8]. On the other hand, it has been reported that CST treatment for MERS-CoV infections was not significantly associated with mortality, but a delay in MERS-CoV RNA clearance was observed [9]. Moreover, patients who received CST were more likely to receive invasive ventilation ([93.4%] vs. [76.6%]; $P < 0.0001$) and had higher 90-day crude mortality ([74.2%] vs. [57.6%]; $P = 0.002$).

Zha et al. studied on the efficacy of CST treatment of patients with COVID-19 and reported that they have found no association

between therapy and outcomes in patients without acute respiratory distress syndrome [10].

Management options of fever and inflammatory manifestations attributed to COVID-19 are not so straightforward. There are many choices to alleviate pain, fever and other complaints related to the hyperinflammatory state in these patients. Agents recommended to support a non-hospitalized patient with a confirmed or suspected COVID infection is summarized in Table 1.

It is recommended that the dose not exceed the equivalent of 1-2 mg / kg / day methylprednisolone [14,15]. It has been reported that a larger glucocorticoid dose will delay the elimination of CoV due to immunosuppressive effects [16]. Care should be taken when using glucocorticoids, as they can suppress the body's immune system and slow the clearance of the virus [17]. Low-dose CST have been used to treat those with severe COVID-19 infection for possible benefit by attenuating inflammatory lung damage, as cytokine storm was observed. However, CST did not reduce mortality in SARS-

CoV and MERS-CoV infections according to the WHO guideline [9, 18]. In the guidelines, it has been reported that systemic CST are not routinely recommended and should not be given as an adjunctive therapy in the treatment of COVID-19 [18,19].

In the review published in JAMA in July 2020, it was stated that new information and evidence revealed that dexamethasone reduced mortality, but the beneficial effect was limited to those who need supplementary oxygen and / or MV and severe patients with a protracted clinical course [20]. In the randomized Evaluation of COVID-19 Therapy (RECOVERY) study, 2104 patients were randomized to receive 6 mg dexamethasone + other treatments for 10 days, and 4321 patients to receive only other treatments without steroids [21]. 28-day mortality is lower in the dexamethasone group. (21.6% vs 24.6%; age adjusted rate ratio, 0.83 [95% CI, 0.74-0.92]; P <.001). In a smaller retrospective cohort study reported from Wuhan, a lower mortality rate was observed among 201 patients who received methylprednisolone (hazard ratio, 0.38 [95% CI, 0.20-0.72]) [12].

Table 1. Treatments recommended to support a non-hospitalized patient with a confirmed or suspected COVID infection

Intervention	Description
Fever	Having plenty of fluids and a warm shower at intervals of several hours will be most effective means to alleviate fever. Also ventilate the house / environment, dress thin or not at all, keep the ambient temperature low (18-22C).
Antipyretic-pain medications:	Paracetamol can be the first choice. Caution should be taken since the NSAID group profens (ibuprofen / ketoprofen / dexketoprofen / flurbiprofen) are active antipyretic and NSAID agents, as they can disguise / increase the signs and symptoms of COVID-19 infection [11]. However, this opinion was not supported on the basis of evidence and does not appear to be a real threat in the management.
Tocilizumab (anti-interleukin-6 receptor antibody)	The agent can be used as an immunomodulator, to suppress inflammation and to alleviate fever. Its beneficial efficacy is remarkable during the cytokine storm period.
Corticosteroids	Methylprednisolone is useful in patients with ARDS with its anti-inflammatory effects, it may be effective on inflammatory muscle pain. It is recommended only in the treatment of ARDS [12]. Mostly not recommended if there are not any other indications.
Vitamin supplements	The beneficial efficacy of vitamins C and D have not been proven yet in routine treatment. Thus it appears to be useful only in people with deficiency, malnutrition and debility. Notably, there are contradicting opinions about use of vitamin D in patients with infection. In Ireland, Laird et al. reported that optimising vitamin D status to recommendations by national and international public health agencies will certainly have benefits for bone health and potential benefits for Covid-19 [13]. There is a strong plausible biological hypothesis and evolving epidemiological data supporting a role for vitamin D in Covid-19.

Although it has been reported that treatment with methylprednisolone may be beneficial for patients with ARDS following COVID-19, the effect of CST in such patients is still to be elucidated [12].

On 2 September 2020, WHO published a guide for physicians on the use of CST in patients with COVID-19 [22]. These most recent guidelines advocated use of systemic CST for the treatment of patients with severe and critical COVID-19, while the agents are not recommended for those with non-severe COVID-19, as the treatment was not associated with any benefits.

This issue was also evaluated thoroughly by Lamontagne et al. A living WHO guideline in September 2020, who made a strong recommendation for use of CST in severe and critical COVID-19 because there is a lower risk of death among people treated with systemic CST (moderate certainty evidence) [23]. The panel collected data from eight randomised trials (7184 participants) and found that systemic CST probably reduce 28 day mortality in patients with critical covid-19 (moderate certainty evidence; 87 fewer deaths per 1000 patients (95% CI; 124 fewer to 41 fewer)), and also in those with severe disease (moderate certainty evidence; 67 fewer deaths per 1000 patients (100 fewer to 27 fewer). They have also advocated that all or almost all fully informed patients with severe and critical COVID-19 would choose this treatment. In contrast, the panel concluded that patients with non-severe COVID-19 would decline this treatment because they would be unlikely to benefit and may be harmed.

3. TOCILIZUMAB

Tocilizumab (TCZ) is an anti-IL-6 receptor monoclonal antibody, widely used in the treatment of autoimmune diseases and has been approved by the FDA to reduce cytokine release due to CD19-specific chimeric antigen receptor T cell therapy in acute lymphoblastic leukemia [24]. (Fig. 2). In COVID-19, it is used as an IL-6 inhibitor at high serum IL-6 levels in patients with bilateral diffuse pulmonary infiltrations or in severe and critical groups with cytokine storm. Hypercytokinemia provokes the hyperinflammatory state which paves the way to alveolar epithelial injury and damage to vascular endothelial cells, as well as to lung infiltration sustained by neutrophils and macrophages. Therefore, the anti-IL-6-receptor monoclonal antibodies have been advocated as one of the most promising pharmacologic treatments [25].

TCZ treatment was administered in 21 patients who were diagnosed with severe or critical COVID-19. As a result of the study, it was reported that TCZ effectively improves clinical symptoms and suppresses the deterioration of patients with COVID-19 [26]. In another study, TCZ was used in 15 patient with COVID-19 whose mean IL-6 level was 111.05 pg / mL (range 5-15 pg / mL). 47% of them were critical, 40% severe and 13% moderate. After the treatment, a decrease in IL-6 level was observed in 11 patients, along with clinical improvement. However, a steady increase in IL-6 level was observed in four critically ill patients in whom treatment was not successful [27].

In another study, 100 patients with COVID-19 pneumonia and ARDS requiring ventilatory support were given IV TCZ in addition to the conventional treatment, empirically considering that they had high IL-6 levels [28]. 24-72 hours after TCZ administration, 58 patients (58%) showed a rapid clinical and respiratory improvement. 37 (37%) were stabilized clinically, 5 (5%) deteriorated and 4 of these died. In the largest registry study conducted to date, 544 patients with severe COVID-19 pneumonia were retrospectively examined, and IV or SC treatment with TCZ was found to be associated with reduced risk of mechanical ventilation and death (adjusted hazard ratio 0.61, 95% CI 0.40–0.92; $p = 0.020$) [29].

The initial dose of TCZ is 4 to 8 mg / kg. The recommended starting dose is 400 mg, diluted to 100 ml with 0.9% normal saline and given as IV infusion in 1 hour. Patients who do not show a significant improvement after the first dose, the same dose is repeated a second time after 12 hours. The maximum single dose should not exceed 800 mg. Attention should be paid to allergic reactions. TCZ is not used in patients with active infections such as tuberculosis [16].

In an academic medical center, Meleveedu et al. described outcomes in severely ill patients with cytokine release syndrome (CRS) due to COVID-19 following treatment with anti-IL-6/IL-6-Receptor (anti-IL-6/IL-6-R) therapy, including tocilizumab or siltuximab [30]. They have reported that clinical responses to anti-IL-6/IL-6-R therapy were accompanied by significant decreases in temperature, oxygen requirement, CRP, IL-6, and IL-10 levels. There are numerous well-designed research projects ongoing on tocilizumab and sarilumab such as COVACTA and SARCOVID, respectively [31,32].

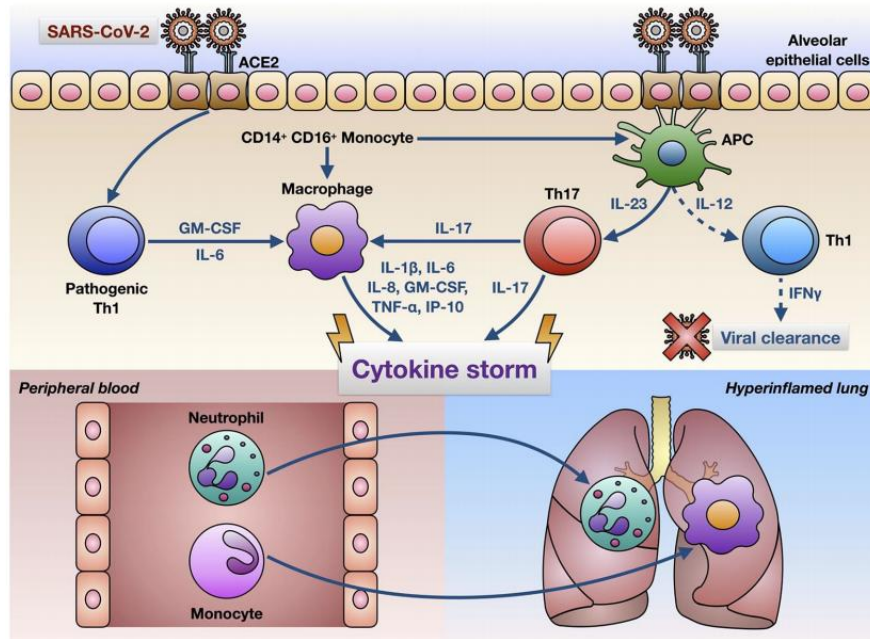


Fig. 2. Mechanisms of effect attributed to anti-IL-6 receptor antibodies tocilizumab and siltuximab at the cellular chemistry level. The figure depicts that cytokines and their receptors, as well as cytokine-dependent intracellular signalling pathways are targeted by the anti-IL-6-receptor monoclonal antibodies (Adapted from [25].)

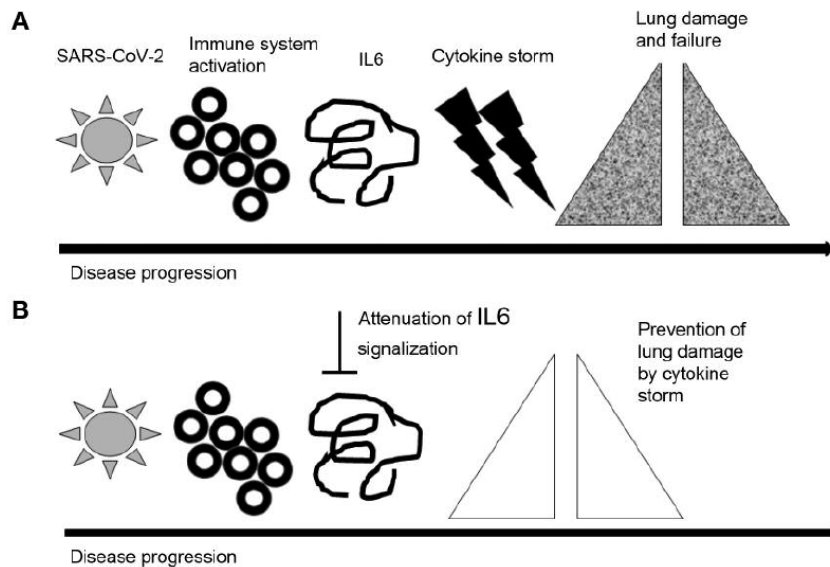


Fig. 3. The role of interleukin-6 (IL6) in a cytokine storm (Adapted from Smetana, 2020). A: Infection by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) activates the immune system, which can produce an boosted amount of IL6 than is necessary. The abundant production of IL6 is important for the initiation of a cytokine storm that is subsequently responsible for lung damage and failure. B: Attenuation of IL6 signaling by suppression of its production (chloroquine and the like) or by targeting of its receptor complex (tocilizumab) has an inhibitory effect on the cytokine storm and protects the lungs from damage

4. CONCLUSION

Many clinical findings of COVID-19 and other severe viral infections (e.g. fever, muscle pain, respiratory distress, cough), are directly attributed to cytokine storm. Hyper-inflammatory status in patients with severe COVID-19 is to be mitigated to alleviate signs and symptoms in cytokine storm. Treatment of the cytokine storm has been a vital part of saving critical patients with COVID-19. Interleukin-6 (IL-6) plays a critical role in cytokine release syndrome. In case of deterioration of oxygenation and rapid progression of imaging (CT) findings, CST-glucocorticoids can be used for a short time for patients with overactivation of the body's inflammatory response. Administration of adjusted doses of CST could inhibit IL-6 production and other cytokines effectively. Moreover, proper use of in patients with COVID-19 do not delay virus clearance. In recent data from evidence-based analyses of clinical trials of critically ill patients with COVID-19, administration of systemic CST was associated with lower 28-day all-cause mortality.

On the other hand, interleukin-6 receptor antibodies tocilizumab, sarilumab, siltuximab can be used as immunomodulators, to suppress inflammation and to alleviate manifestations of immune response. These agents can effectively block the IL-6 signal transduction pathway and therefore, is a promising cure for patients with severe COVID-19. Their efficacy is more prominent during the cytokine storm period. It should be kept in mind that the agents to be used in the management of any given patient should be tailored for each situation.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/61497>