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Relationship between cytokine storm and SARS-CoV-2 infection's worsening

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an infectious disease that causes severe coronavirus disease 2019 (COVID-19) and its complications, this appears to be related to an increase in the release of pro-inflammatory cytokines, described as "the cytokine storm." SARS-CoV-2 by binding to its receptor angiotensin converting enzyme 2 triggers an imbalance in the renin angiotensin aldosterone system, inducing an increase in angiotensin (Ang) 2 and a decrease in Ang 1-7 levels. The cytokine storm is the major cause of respiratory distress syndrome from which suffers patients with severe forms of COVID-19 as well as multi organ failure (lung, heart, kidney, liver, and brain). To resist this cytokine storm, interleukin-1 and 6 inhibitors, tumor necrosis factor inhibitors, interferon inhibitors, and steroid immunomodulators have been used. This review article summarizes COVID-19 patients, disease manifestations, cytokine storm characteristics, general clinical signs symptoms, and targeting the cytokine storm with cytokine inhibitors.

Keywords

SARS-CoV-2. COVID-19. Cytokine storm. Inhibitors.

Introduction

A viral outbreak caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered in Wuhan, China, in December 2019. This disease, known as coronavirus disease 2019 (COVID-19), spread over the world in a matter of months, generating a global health emergency[1]. SARS-CoV-2 is a member of the Beta-coronavirus genus, which contains SARS-CoV and MERS-CoV, which first surfaced in 2002 and 2012. SARS-CoV-2 has a sequence that is 79% identical to SARS-CoV and 50% similar to MERS-CoV[2]. It s a 29.9 kb positive single-stranded RNA virus. A big replicase gene encoded by 2/3 of the genome is translated into two polyproteins, which are then cleaved into 16 non-structural proteins. Spike proteins (S), Hemagglutinin-Esterase proteins (HE), membrane proteins (M), envelope proteins (E), and capsid proteins (N) are all structural proteins encoded by the rest of the genome[3]. SARS-CoV-2 interacts with the angiotensin converting enzyme 2 (ACE2) enzyme. ACE2 is found in alveolar epithelial cells, the nasopharyngeal and oral mucosa, as well as endothelial and vascular smooth muscle cells, the brain, the intestines, and the liver[1]. In COVID-19 patients, elevated blood levels of the follow-

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ing cytokines and chemokines were found: interleukin (IL)-1, IL-1RA, IL-7, IL-8, IL-9, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ, IFN-induced protein 10 (IP-10), and monocyte chemoattractant protein-1 (MCP-1). In extreme cases of SARS-CoV-2 infection, this cytokine storm generates a furious immunological response that appears to be the cause of acute respiratory distress syndrome (ARDS), as well as multiorgan failure and death[4].

The cytokine storm

SARS-CoV-2, like any virus, stimulates our immune system, which is responsible for protecting our bodies from infectious pathogens. A proper immune response eliminates the infection; however, a disruption in this system might cause an excessive reaction, as seen in our instance with the cytokine storm[5]. Innate immunity cells (monocytes, dendritic cells, macrophages, and NK cells), adaptative immunity cells (T cells and B cells), and some non-immune cells (endothelial cells, epidermal cells, and fibroblasts) manufacture and secrete cytokines, which are tiny proteins having biological activities[6,7]. Significant alterations in pro- inflammatory and anti-inflammatory mediators such as IL1-, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, and IL-13, IL-17, IL-33, G-CSF, GM-CSF, IFN-γ, INF-α, IP-10, MCP-1, and TNF-α are seen in COVID-19 patients cytokines and chemokines profiles[8,9]. A metabolic disorder, tumors, primary immunoglobulin deficiency, autoimmune conditions, and immunosuppressive therapy all cause a cytokine storm[10]. The most common clinical manifestations accompanied by cytokine storm, which also include high fever, inflammation with redness and swelling, severe fatigue, and nausea[7,11]. SARS-CoV-2 infection sends out an early alarm signal, which is recognized by the many types of Pattern Recognition Receptors (PRRs) expressed by innate immune cells, particularly monocyte-derived macrophages[12]. Toll-like receptors (TLRs)-3, 7, 8, RIG-1, and MDA-5, which detect viral RNA, and TLR-2, TLR-4, which recognize viral surface proteins, are among these PRRs. Transcription factors (AP-1, IRF-1, IRF7, and NF-KB) are activated as a result of this recognition[3]. This leads to the production of genes that code for pro-inflammatory cytokines (TNF-IL-1, IL-6), chemokines, and adhesion molecules, which attract other immune cells to the infection site[6]. The nod-like receptors (NLRP1, NLRP3, NLRP7, and NLRC4) in the cytosol are another type of PRR that plays a significant role in virus recognition. They trigger the production of cytoplasmic multiprotein complexes called inflammasome after they bind to damage-associated molecular patterns. Procaspase-1 is converted to active caspase-1 by the latter. Caspase-1 is a protein that converts pro-IL-1 to IL-1[13].

The SARS-CoV-2 virus binds to the ACE2 receptor, which seems involved in the RAAS[3]. The RAAS is essential for infection control, blood pressure control, vascular tone, and renal hemodynamics[14]. The enzyme renin cleaves angiotensinogen to angiotensin (Ang) 1, which is subsequently transformed to Ang 2 with the help of ACE in a cascade of enzymatic activity. ACE2 converts Ang 2 to Ang 1-7 in normal circumstances[15]. Because SARS-CoV-2 has taken over ACE2, it will be unable to convert Ang 2 to Ang 1-7, causing an increase in Ang 2 and a drop in Ang 1-7 levels. Ang 2 subsequently binds to the Ang 2 type 1 receptor, which activates the transcription factor (NF-κB) by phosphorylating the p65 subunit, causing IL-1B, IL-6, IL-10, and TNF- to be secreted. Ang 2 also modulates the MAPK pathway (ERK1/2, JNK, and p38 MAPK), thus stimulating the release of other pro-inflammatory cytokines (IL-1, IL-10, IL-12, and TNF-α). Ang 1-7 inhibits the expression of p38 MAPK, NF-KB, ICAM-1, VCAM-1, and MCP-1 by binding to the Masr receptor (Fig. 1). Th2 suppresses the inflammatory response by producing anti-inflammatory cytokines (IL-4, IL-5, IL-9, and IL-13)[16]. ERK 1/2 pathway activity stimulates T helper cells differentiation into Th2 through IL-10 production is also regulated by Ang 1-7, and Th2 attenuates the inflammatory response by producing anti-inflammatory cytokines (IL-4, IL-5, IL-9, and IL-13)[16].

Des-Arg9-bradykinin (DABK) is another factor that accelerates the inflammatory process. ACE2 is known to cleave DABK into an active peptide, DABK can bind to the DABK-BK1 receptor and promote neutrophil infiltration, lung inflammation, and the production of pro-inflammatory cytokines such as IL-1 and TNF-α[17,18]. TGF-β levels were also found to be elevated in patients with severe types of COVID-19, according to other investigations. TGF-β promotes the transformation of Th into Th 17. IL-17, GM-CSF IL-21, and IL-22 are all secreted by Th 17. C5 levels were also found to be high in these patients. C5 is one of the most significant complement system components, as it is involved in several pro-inflammatory cytokines secretion[16]. C3a and C5a anaphylatoxins activate neutrophils, basophils, eosinophils, monocytes/macrophages, T cells, and B cells after C3 and C5 cleavage with C3 and C5 convertase. In response to C3a and C5a, neutrophils and macrophages produce pro-inflammatory cytokines

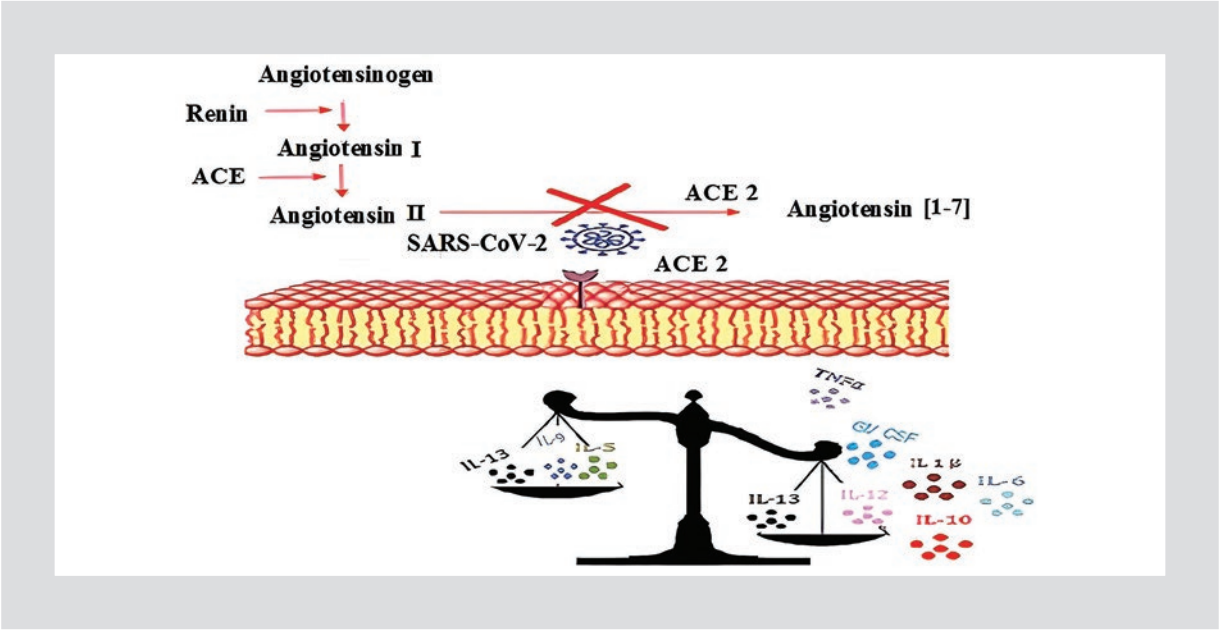

Figure 1. *Dysregulation of the immune system after SARS-CoV-2 infection.*

such as IL-1, IL-6, and TNF-α[19]. Furthermore, numerous studies have revealed that the C5a fragment has a prothrombotic effect[20]. Lung inflammation can be reduced by inhibiting C3 and C5[21].

The cytokine storm is characterized by an overactive immune system and excessive cytokine release. Changes in the lungs accompany the cytokine storm, resulting in ARDS and organ failure. Inflammation of the alveolar-capillary membrane causes pulmonary permeability and significant protein-rich fluid exudation into the airspaces, leading to respiratory failure. The most common cause of death is ARDS[22].

Consequences of the cytokine storm on organs

Lungs

Several studies have attempted to establish a link between cytokine levels, organs, and the severity of COVID-19 (Fig. 2). They used computed tomography (CT) severity score and PaO_2/FiO_2 to determine the degree of lung damage because the lung is the most damaged organ. Patients with severe forms of COVID-19 had a higher CT severity score and a lower PaO_2/FiO_2, and are more likely to have severe pneumonia, according to the findings. They also found that these individuals had greater levels of IL-2R, IL-6, and TNF-α than those who did not get pneumonia[23]. Another study in Wuhan found an increase in IL-1, G-CSF, IFN-, MCP-1, MIP-1, and TNF-α in 41 patients with COVID-19 who were hospitalized in intensive care units[24].

The cytokine storm, or the excessive release of cytokines, appears to be the primary cause of SARS-CoV-2-induced lung injury[25]. This cytokine storm is characterized by intra-alveolar fibrin buildup, which increases the synthesis of both pro-fibrotic growth factors and pro-fibrotic cytokine transcripts, as well as a decrease in pulmonary surfactant, which leads to collapse. An intra-alveolar area with high fibrin and low surfactant provides an excellent environment for fibroblast adhesion, development, and collagen deposition, leading to pulmonary fibrosis. In addition, fibrin breakdown products increase vascular permeability, increase migration and proliferation of inflammatory cells, and boost neutrophil recruitment to the lungs. Hypercoagulation and disseminated intravascular coagulation are also linked to increased release of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1.), which can lead to changed clinical conditions outcomes[24].

ARDS is the most common symptom of a cytokine storm[4]; however, other symptoms such as sneezing, sore throat, hemopotysis, and rising fever are also common[10].

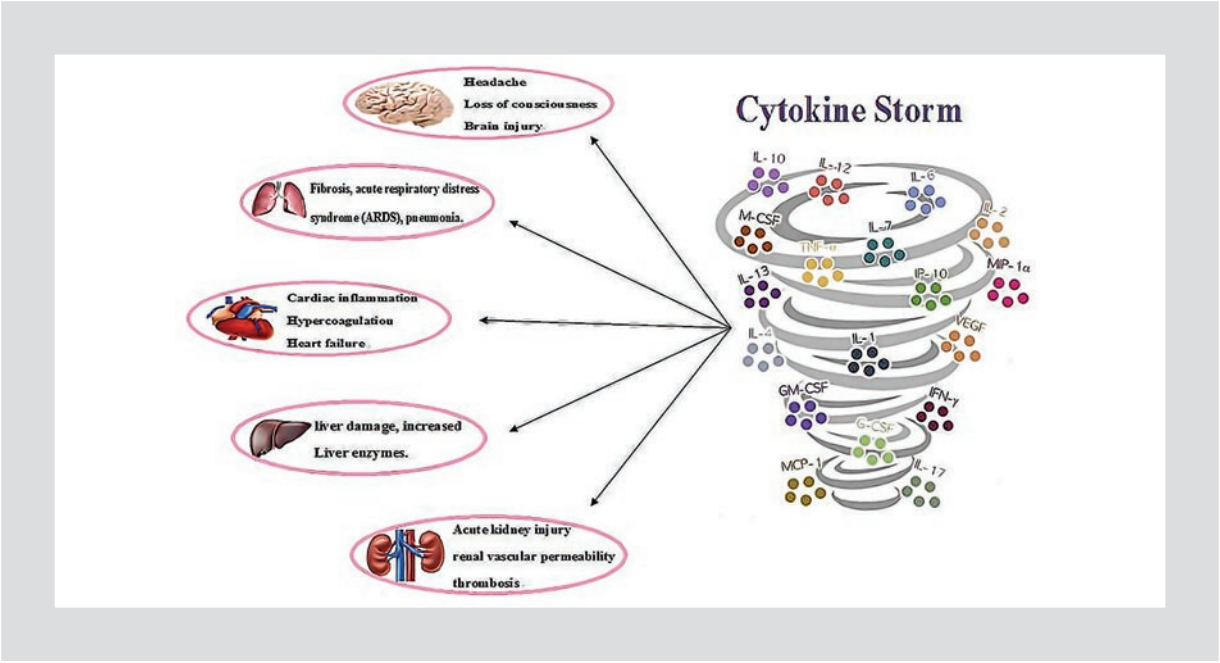

Figure 2. *Consequences of the cytokine storm on organs.*

Heart

Heart failure (HF) is frequently associated with elevated cytokine levels[26]. A retrospective analysis of 799 patients with moderate to severe COVID-19, 131 of whom died, found that HF occurred in 49% of these patients[27].

These cardiac complications can occur in both people with and without heart issues who have recently been infected with COVID-19[28]. ACE2 has anti-inflammatory, anti-fibrotic, antioxidant, and vasodilatory properties when expressed in the heart.

SARS-CoV-2 binding to ACE2 reduces Ang 1-7 production, decreasing the ACE2/Ang 1-7/Mas receptor axis' cardiac protection. ADAM-17 phosphorylation is enhanced by increased Ang 2 levels. TNF-α production is increased by ADAM-17, which worsens systemic inflammation. Ang 2 also increases the expression of significant neutrophil chemoattractants like IL-6, which boosts lymphocyte activation and proliferation directly, resulting in chronic inflammation and a cytokine storm. In cardiac endothelial cells, the expression of adhesion molecules caused by pro-inflammatory cytokines such as IL-1 controls immune cell adherence and migration, increasing inflammation, while defective endothelial cells induce oxidative stress. When exposed to oxidative stress, cardiac endothelial cells increase the synthesis of plasminogen activator inhibitor-1, which inhibits fibrinolysis (PAI-1). Microvascular thrombi that persist due to fibrinolysis inhibition accelerate HF progression[27].

Younger COVID-19 patients have a higher risk of hypercoagulability and arterial and venous thrombosis; also, an increase in D-dimer level and prothrombin time predicts thrombotic complications in COVID-19 patients[29,30]. Coagulopathy markers related to cytokine storm are correlated to the severity of COVID-19 clinical manifestations[10], and anticoagulation treatments have been suggested to prevent and correct coagulopathy[31].

Heart palpitations, cardiac inflammation, chest tightness, and heart attacks are all symptoms of cytokine storm[10].

Kidney

According to a study conducted by clinicians at the Feinstein Institutes for Medical Research, more than a third of COVID-19 patients have acute kidney injury (AKI)[32].

Cytokines interact with renal cells to produce tubular and endothelial dysfunction in COVID-19, the cytokine storm that causes AKI[33]. TNF-α, for example, causes tubular cell death by attaching to its receptor[34]. Renal endothelial cells release chemokines and cytokines in response to IL-6, which increases renal vascular permeability. Capillary permeability and thrombosis can

also be induced by pro-inflammatory cytokines, leading to disseminated intravascular coagulation. Cytokines can generate erythrophagocytosis and anemia in macrophages, which can lead to multi visceral failure in the kidney. This cytokine storm causes hemophagocytosis, which causes renal failure[33].

In COVID-19 patients with cytokine storm, kidney impairment causes a significant decrease in blood pressure, oliguria, hematuria, and proteinuria[10].

Liver

In addition, patients with COVID-19 pneumonia have liver damage. This interaction appears to be linked to a cytokine storm and an acute inflammatory response[35]. These patients show high levels of C-reactive protein (CRP), D dimer, ferritin, and IL-6. CRP release is dependent on IL-6[36]. This hepatic injury could be related to the cytokine storm, but it could also be linked to the virus's significant impact on hepatocytes or the biliary epithelium throug ACE2 expression. In the context of hepatocyte injury, an increase in liver enzymes (AST and ALT) occurs (abnormal liver function). More than 30% of patients with increased AST and ALAT levels have extended hospitalization, according to previous research[37]. The most common cause of liver damage is elevated liver dysfunction marker AST[10].

Brain

Headaches, loss of consciousness, seizures, brain inflammation, confusion, stroke, anosmia, and skeletal muscle injury were among the signs of COVID-19 infection[10,38]. Brain scans with magnetic resonance imaging and CT have also revealed acute brain pathology and brain injury associated with hemorrhage probably due to inflammation in other COVID-19 patients[39].

Many studies provided a correlation between these neurological diseases and cytokine hypersecretion. Brain peripheral inflammation can cause endothelial activation and disruption of the blood-brain barrier (BBB), leading to microglia, and astrocyte activation. This generates a neuroinflammatory response in the CNS that enhances cytokines generation. Oxidative stress and immune cell flux both contribute to BBB disruption. Mild abnormalities with noticeable inflammation due to diffuse astrocyte, microglia activation, and lymphocyte infiltration were found in COVID-19 patients, comparable to those seen in individuals with sepsis. Preclinical models have shown that the frontal lobes are the most reactive to cytokine-induced inflammation through NF-κB, which could explain why frontal dysfunction is so common[40].

Targeting the cytokine storm

IL-1 inhibitors

IL-1 is involved in the recruitment of immune cells as well as the generation of other pro-inflammatory cytokines[41]. While inhibiting IL-1 reduces the production of inflammatory factors such TNF-α, IL-6, and G-CSF, it could be an effective treatment for COVID-19 patients[42]. Anakinra is a human IL-1 inhibitor that has been modified[41]. Anakinra has been linked to a considerable improvement in individuals with severe sepsis in previous research[43]. Another prospective cohort trial of patients with severe COVID-19 showed that Anakinra reduced the need for mechanical ventilation while also lowering mortality without causing serious side effects[41]. Canakinumab, a monoclonal antibody that binds to the human IL-1 receptor specifically, has also demonstrated effectiveness.

IL-6 inhibitors

Vascular permeability, tissue hypoxia, hypotension, and myocardial dysfunction, as well as multi-organ failure and intravascular coagulation, are all due to excessive IL-6 secretion[41]. IL-6 levels are associated with the ARDS severity[43]. Studies have also revealed that IL-6 release lasts longer than other cytokines during a cytokine storm, suggesting that inhibiting IL-6 or its receptor IL-6R could be a potential therapeutic strategy during SARS-CoV-2 infection. Tocilizumab is a monoclonal antibody that suppresses IL-6R signaling by blocking IL-6 binding to its receptor. Tocilizumab has also been shown to reduce excessive production of IFN-γ, IL-10, and IL-2 cytokines.

Retrospective Chinese investigations confirm tocilizumab's beneficial effects in COVID-19 patients with the severe or critical disease[41]. Tocilizumab, on the other hand, proved ineffective in preventing intubation or death in hospitalized patients with significant COVID-19[44].

TNF-α inhibitors

TNF-α activates NF-κB, which then translocates to the nucleus and upregulates transcription of numerous genes, when it binds to its receptor. Increased

TNF-α secretion causes a cytokine storm, which causes cell death, whereas appropriate TNF-α levels are essential for tissue regeneration after acute injury[42]. TNF-α mediated acute lung injury was demonstrated to be decreased when a TNF-α targeting aptamer was used. This finding suggests a potential treatment strategy for treating the cytokine storm that occurs after SARS-CoV-2 infection and lung damage[43].

Inhibitors of INF

Sifalimumab is an IFN-α receptor inhibitor and human monoclonal antibody. Sifalimumab is currently being tested in clinical trials to combat autoimmune illnesses[43]. Emapalumab, an IFN-γ directed antibody, has been clinically approved for the treatment of pediatric and adult patients with primary hemophagocytic lymphohistiocytosis who are resistant, relapsed, or progressing illness, or who are incompatible with conventional therapy[42].

Steroid treatment

Corticosteroids are among the immunomodulators that have been used to treat COVID-19 cytokine storm[45]. The use of methylprednisolone early in the course of a disease can help to relieve symptoms and prevent disease progression[46]. In the first therapy of cytokine storm and COVID-19 patients, modest and intermediate doses may reduce inflammation[47]. In patients with invasive mechanical ventilation or oxygen alone, dexamethasone therapy reduces 28-day mortality[48]. Furthermore, Anakinra therapy reduces the severity of COVID-19, as well as the clinical progression scale and organ failure[49].

Conclusions

SARS-CoV-2-induced hyperinflammation, which results in a cytokine storm, continues to be the major cause of COVID-19 severe forms. ARDS and other organ failure are common in people with this disease: Liver, heart, brain.

Anakinra, tocilizumab, and other cytokine inhibitors have been used to target the cytokine storm with promising effects. Treatment should, however, preferably, try to boost the antiviral response, reduce the inflammatory response, and maintain a pro- and anti-inflammatory cytokine levels balance.

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