

Review Article

Cytokine storm in SARS-CoV-2 infection and the potential treatments

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Abstract

Cytokine storm is one of main features during respiratory distress caused by COVID-19 infection. Acute Respiratory Distress Syndrome (ARDS) is directly linked with elevated number of COVID-19 mortality cases. Extreme amounts of pro-inflammatory cells are found in the lung of dead patients, mainly macrophages and IL-17 cells. A high level of IL-6 was found in the plasma COVID-19 patients and indicated the severity of diseases. Some other chemokines, such as CXCL10, IL6, CCL2, CXCL1, and CXCL5, were upregulated as well as in COVID-19 patients and regulate the disease. In this review, we discuss the feature of cytokine storms and the current treatments used. We found that IL-6 has a significant role in exacerbated patients' condition, and the suppression of this cytokine most likely benefits the patient. Another treatment with various targets has been proposed and proven as effective as well. Some of them are corticosteroids, anakinra, plasmapheresis, and interferons.

Keywords: Coronaviruses, SARS-CoV-2, pandemic, cytokine storm, hypercytokinemia

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). World Health Organization (WHO) announced this disease as a Public Health Emergency of International Concern on March 11, 2020 (Cucinotta and Vanelli, 2020). SARS-CoV-2 mainly attacks the respiratory system with early manifestations such as fever and cough, then aggravates with pulmonary involvement and dyspnea (Dhama et al., 2020; Harapan et al., 2020; Machhi et al., 2020; Shi et al., 2020; Zhang et al., 2020a). The virus could affect the digestive (Tian et al., 2020), nervous (Wu et al., 2020b), cardiovascular (Dhakal et al., 2020; Rojulpote et al., 2020), renal (Adapa et al., 2020), and integument system (Catalá Gonzalo and Galván Casas, 2020). SARS-CoV2 has a higher fatality rate and reproduction number (Ro) than influenza viruses (Faust and del Rio, 2020; Piroth et al., 2020; Viceconte and Petrosillo, 2020). The fatality rate of this infection is between 2-2.5% as declared by WHO (Viceconte and Petrosillo, 2020), although the number varies among countries (Giangreco, 2020). Many factors influence this variance, including inadequate health facilities and screening scope (Giangreco, 2020).

SARS-CoV-2 showed large variety in clinical manifestation from asymptomatic to severe illness. Some COVID-19 cases present with pneumonia that could develop into ARDS, a significant cause of death in patients (Castagnoli et al., 2020; Du et al., 2020; Fung et al., 2020; Giamarellos-Bourboulis et al., 2020). Some studies indicate ARDS is mainly caused by cytokine syndrome or hypercytokinemia (Channappanavar and Perlman, 2017; Lipworth et al., 2020; Zhang et al., 2020b). Cytokine storm is lethal exaggerated systemic inflammatory syndromes involving

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raised circulating cytokine levels and immune-cell hyperactivation. The conditions can be activated by various factors such as treatments, pathogens, malignancy, autoimmune conditions, and monogenic syndromes (Fajgenbaum and June, 2020; Teijaro, 2017; Tisoncik et al., 2012). Controlling cytokine storms in COVID-19 patients can lower both mortality and morbidity (Chau et al., 2020; Lipworth et al., 2020; Tang et al., 2020a; Zhang et al., 2020b).

In this review, we discuss the current evidences, treatment of cytokine storm, and its role in severity and mortality in COVID-19 patients.

COVID-19: Pathophysiology

The first case of COVID-19 was testified in Wuhan due to the wet market and exotic animal exploitation in December 2019. Until this article written, no explicit confirmation regarding bat as the animal source of COVID-19 has been published (Chiappelli et al., 2020; Guo et al., 2020; Tetro, 2020; Zhang et al., 2020b). At the early of May 2022, COVID-19 has spreaded and infected approximately 514 million people around the globe, placing this disease as the largest pandemic after the 1918 flu pandemic (Esposito et al., 2020; Villapol, 2020; World Health Organization, 2021, 2022b). The symptoms of the disease itself are dissimilar among patients (Butt et al., 2020; Mackett and Keevil, 2020; Tay and Harwood, 2020), depending on the immune response and various factors (Su et al., 2020). Most patients reported dry cough, fatigue, myalgia, dyspnea, anosmia, and fever as the primary symptoms. Some reported the additional symptoms like headache, dizziness, nausea, abdominal pain, diarrhea and vomiting, while others develop more complex symptoms (Chakraborty et al., 2020; Chiappelli et al., 2020; Klopfenstein et al., 2020).

The manifestations become more distinct after an incubation period of about 0-24 days, with most patients becoming symptomatic in 5.1 days (Lauer et al., 2020). Initially, the symptoms are close to classical flu-like diseases, including mild to high fever, dry cough, exhausted feeling (fatigue), muscle pain (myalgia), and, less frequently, headache and abdominal pain followed by diarrhea (Chen et al., 2020a). The infection progression could affect the lower respiratory tract. At this time, other symptoms may appear: dyspnea, rapid respiratory rate, reduced oxygen saturation; worsened into respiratory failure, multiorgan dysfunction, septic shock, then lead to death (Chen et al., 2020a; Licciardi et al., 2020; Singhal, 2020).

Infections in digestive and nervous system have diverse symptoms. In the digestive tract, viral infections manifest as stomachache, anorexia, nausea, vomitus, to gastrointestinal bleeding. Unfortunately, the patients who present with GI symptoms usually have delayed diagnosis (Mao et al., 2020; Tian et al., 2020). However, the nervous system involvement in COVID-19 is just explained in fewer studies. Several findings showed some COVID-19 cases with neurological manifestations such as dizziness, lack of attention, unorganized movement and altered mental status (Butt et al., 2020; Helms et al., 2020; Wu et al., 2020b).

As the fatality rate elevates from the first predicted value, COVID-19 has been announced as a more fatal and transmissible disease than ordinary seasonal flu (Faust and del Rio, 2020). COVID-19 has semblances with other pandemic coronavirus, like SARS-CoV-1 and MERS (Lu et al., 2020). In reverse, COVID-19 is less fatal than these two (Abdelghany et al., 2020; Petrosillo et al., 2020). Even though this virus shares 75-80% genome resemblance with SARS-CoV-1, it has some distinct features like molecular properties, transmission, clinical course and manifestations (Chen et al., 2020a; Fani et al., 2020).

The virus can infect any age group. However, the infection becomes more vicious in adults with comorbid and elderly above 60 years old in comparison with young age group (Liu et al., 2020b). For instance, in the young age group under 60 years old, the fatality solely reaches 4% in Italy (Signorelli and Odone, 2020), making it less hostile for young people and children. In contrast, the disease appears to be more potent in transmission than other coronaviruses. It can be transmitted from asymptomatic patients to healthy people, unlike SARS-CoV-1, which only can be transmitted when the patients show severe symptoms such as high fever and dyspnea. These facts led to the more complicated COVID-19 containment strategies than the previous coronavirus pandemics (Ge et al., 2020).

Since 2021, WHO has classified mutation of COVID-19 into five Variant of Concern (VOCs) including Alpha, Beta, Gamma, Delta, and Omicron (World Health Organization, 2022a). Omicron has been put in strict monitoring from the beginning of 2022, followed by its spread among the population. However, Omicron has not shown severe symptoms as the previous variants (Ding et al., 2022).

Cytokine Storm in COVID-19

One of the significant terrifying effects of COVID-19 is respiratory distress followed by mechanical ventilation (MV) use. The mortality of ICU patients reached 65% due to respiratory failure (Chen et al., 2020a). Furthermore, cytokine storm, as one of the foremost hallmarks of ARDS, mimics the immunopathogenic attributes in SARS and MERS (Huang et al., 2020; Nile et al., 2020). Cytokine storm or hypercytokinemia is the foremost cause of death in COVID-19 patients (Chau et al., 2020; Liu et al., 2020a). The cytokine storm is triggered when there is an imbalance of type 1 and type 2 T helper (Th) cell responses (Rizzo et al., 2020), leading to excessive cytokine release (Henderson et al., 2020). Cytokine storm is typically initiated by macrophages, dendritic cells, T cells and natural killer (NK) and responding to pathogen-associated molecular patterns (PAMP) (Zhou et al., 2020a).

The release of chemokines and inflammatory cytokines

There are several studies showing that COVID-19 triggers the release of several chemokines and inflammatory cytokines. Some are more common than others, such as monocyte chemoattractant protein-1 (MCP-1), interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) (Liu et al., 2020a). Other recognized chemokines and cytokines are IL-2, IL-7, IL-10, G-CSF, MCP-1, CXCL10, CCL3, TNF- α , IP-10 and MIP-1a. These cytokines were found at high level in critically ill ICU patients than non-ICU patients (Chen et al., 2020c; Del Valle et al., 2020; Du et al., 2020; Licciardi et al., 2020; Otsuka and Seino, 2020; Ruan et al., 2020; Zhou et al., 2020a).

SARS-CoV-1 aggressively invades airway and alveolar epithelial cells but is less potent in infecting hematopoietic cells such as monocyte-macrophages, dendritic cells (DCs), and other cells. However, infection of SARS-CoV-2 to DCs leads to some major events: decrease in the production of IFN- $\alpha\beta$ followed by modest up-regulation of pro-inflammatory cytokines IL-6 and TNF. The considerable elevation of inflammatory chemokines was also shown (Coperchini et al., 2020). Likewise, high level of IFN γ and other pro-inflammatory cytokines were shown as the consequence of infected macrophages (Blanco-Melo et al., 2020; Park and Iwasaki, 2020). Hyperinflammation in COVID-19 seems unidentical with Macrophage Activation Syndromes (MAS), while the clinical and laboratory features mimic MAS with significant differences (Henderson et al., 2020; Otsuka and Seino, 2020).

One of the main features of macrophages activation in the alveoli of COVID-19 patients with ARDS is the role of the NLRP3 inflammasome. This protein complex has the major role in caspase-1 activation and pro-inflammatory cytokines release.

The innate immune response during infection and tissue damage was related to the activation of this molecular platform (Kelley et al., 2019). Four classes of inflammasomes have been found during inflammatory processes: NLRP1, NLRP3, NLRC4, and AIM-2 (Sharma and Kanneganti, 2016). Among them, the study of NLRP3 was the most prominent. This complex of protein contributes by detecting the potential danger, either endogenous (DAMPs) or exogenous (PAMPs) signals that stimulate several intracellular signaling pathways, mainly through toll-like receptors (TLRs). Inflammasomes target the process and activation of caspase-1, which directly relates to the maturation of pro-IL-1 β and pro-IL-18 (Favero et al., 2017; Franchi et al., 2012; Muñoz-Jiménez et al., 2021).

After being infected, the epithelial cells of airway track produce massive amounts of CCL2, CCL5, CCL3, and CXCL10. However, IFN- γ production was decreased at the initial phase of infection but increased along with the deterioration of the patient's condition (Channappanavar and Perlman, 2017). In contrast, IFN- γ may set up cytokine storm in SARS patients; in COVID-19, the case looks different (Liu et al., 2020a). The decline of type I IFN links with the structure of the virus. NSP1, the viral nonstructural protein 1, curbs the phosphorylation of STAT1, hence inhibiting the secretion of IFNs (Jauregui et al., 2013; Narayanan et al., 2008; Wathelet et al., 2007). Other immune cells such as NK cells and transcription factors such as NF- κ B may be involved as regulator of cytokine release (Zhou et al., 2020a).

Additionally, the elevated level of pro-inflammatory chemokines seems to depict COVID-19 infection (Coperchini et al., 2020). Besides the ones already mentioned before, only five chemokines (CXCL10, IL6, CCL2, CXCL1, CXCL5) were upregulated in SARS-CoV-2 infection (Chu et al., 2020). The concentrations of CCL2 and CXCL10 were remarkably elevated in the critical patients in ICU care (Coperchini et al., 2020).

A study confirmed that following SARS-CoV-2 infection, CD4⁺ T-cells hastily activate pathogenic T helper (Th) 1 cell and produce cytokines, including GM-CSF. These cytokines invoke inflammatory CD14⁺CD16⁺ monocytes followed by the high raise of IL-6 level and hasten the inflammation process. These T cells and monocytes circulated in the pulmonary system, where the monocytes differentiate into macrophages and become one of the cytokine storm triggers (Zhou et al., 2020a).

Nevertheless, the level of CD4⁺ and CD8⁺ T cells remained low until convalescence. CD8⁺ T cells have been known for their crucial role in facilitating viral clearance after several acute infections such as in human metapneumovirus infections and others (Wang et al., 2020a). SARS-CoV-2 patients likewise show lower levels of T lymphocytes followed by declines in both helper and regulatory T cells. The decrease in regulatory T cells is especially noteworthy agreed to their significant role in homeostasis of immunity and immoderate inflammation following prevention of infection (Akhmerov and Marbán, 2020).

The after effect of cytokine storm at the cell level includes endothelial cell apoptosis following ruptured vascular, error in T cell responses, the alteration of tissue homeostasis, and accumulation of activated macrophages, resulting in acute lung injury and ARDS (Tang et al., 2020b). Cytokine storm was predicted after death based on necrosis and tissue destruction. Some associated symptoms linked to cytokine storm are extensive pulmonary edema, bilateral alveolus damage indicating ARDS, and sign of acute bronchopneumonia (Xu et al., 2020b). Other cytokine storm remarks include continuous fever, hepatomegaly followed by liver impairment, vascular disruption, splenomegaly, indigestion, skin rash, and neurological disorder (Zhou et al., 2020a).

Major role of IL-6

IL-6 has a crucial role in the cytokine storm among all cytokines involved (Akhmerov and Marbán, 2020; Chu et al., 2020; Liu et al., 2020a; Tang et al., 2020c; Wang et al., 2020a). IL-6 roles in acute-phase reaction and promotes the induction of several proteins, such as CRP, ferritin, hepcidin, and others (Chen et al., 2020b). While IL-6 was often discussed as a pro-inflammatory cytokine, numerous findings have found its protective properties. Numerous studies have linked the inflammatory suppression of IL-6 to the respiratory organs, especially the lungs (Voiriot et al., 2017).

Some initial studies have demonstrated the benefits of IL-6, such as its protective effect in murine viral infection (Percopo et al., 2019), protection of the lung during influenza infection (Yang et al., 2017), and contribution to the resolution process of SARS-Cov-1 (Magro, 2020). In a study, the lung damage in IL-6 knockout (KO) mice treated with exogenous recombinant IL-6 was slighter compared to KO mice without recombinant IL-6. The results suggested that IL-6 improved the survival of lung epithelial cells and stimulated macrophage migration. Equally, the raising IL-6 during coinfection was the most projecting of all cytokines measured. In conclusion, this information highlighted the benefit of IL-6 to the immune system against infection. The finding proposed that blocking IL-6 action might not beneficial but on the other hand, it weakened host defense during lung infections (Du et al., 2021).

Otherwise, the high level of IL-6 correlates with high mortality and disease severity in COVID-19 patients (Day et al., 2009; Liu et al., 2020a; Magro, 2020; Nagata et al., 2008). It has been demonstrated that the level of IL-6 was sustained in many COVID-19 cases. It has been found that the level of IL-6 can reach 2.9-fold higher in severe cases than in mild to moderate cases (Chen et al., 2020b; Diao et al., 2020; Liu et al., 2020c). One study demonstrated IL-6 levels were >100pg/mL in the critical patients, which was defined as the emergence of an inflammatory storm. In mild patients, IL-6 was lower than 100 pg/mL (Gong et al., 2020).

IL-6 triggers its downstream Janus kinase (JAK) signal. It started when the IL-6 soluble form (trans-signaling) or transmembrane (cis signaling) binds to the IL-6 receptor (IL-6R), the complex joining the membrane bound gp130 (Johnson et al., 2018). Elevation of IL-6 signaling leads to innumerable effects that may cause organ injury. For example, the elevation of IL-6 followed by naive T cells maturation into effector T cells. These events induce the occurrence of vascular endothelial growth factor (VEGF) in epithelial cells, expanding vessel permeability and attenuating myocardium vasoconstriction (Liu et al., 2020a). Plus, IL-6 contributes in T helper 17 (Th17) cells development. The massive amount IL-6 may affect the elevation of activated Th17 cells during COVID-19 infection (Gong et al., 2020; Liu et al., 2020a).

Th17 cells generate IL-17A, IL-21, IL-17F, IL-6, IL-22, and TNF- α , which are correlated with crosstalk between tissues and the immune system (Kimura and Kishimoto, 2010). Th17 and their effector cytokines have been known for their protective and pathological role during inflammation. IL-17 induces cytokine G-CSF, three inflammatory cytokines (IL-1 β , IL-6, TNF α), and several chemokines (KC, IP10, IL-8, MIP2A, and MIP3A (Waite and Skokos, 2012). All these chemokines attract more immune infiltrates to the infected area. Therefore, it shows that a strong response of Th17 cells is associated with tissue damage and pulmonary edema (Ouyang et al., 2008).

However, the exact cause of the cytokine storm in COVID-19 remains unclear. It is still confusing whether the cytokine storm is the main result from a persistent viral infection on immune cells and other cells involved or the effect of hyperreactivity of innate and adaptive immune reaction post-viral infection (Otsuka and Seino, 2020;

Soy et al., 2020). So far, studies have partly discovered that the fatality of coronavirus and other pneumonia-related viruses is associated with the aggregation of immune response linked to severe lung injury. Hence, interfering with the inflammation process initiated by COVID-19 might reduce mortality among severe and critical COVID-19 patients (Otsuka and Seino, 2020).

Treatment Approaches

When facing SARS and MERS, corticosteroid therapy has an insignificant impact and can inhibit viral clearance (Yang et al., 2020; Zhang et al., 2020b). Earlier, the effect looked promising in COVID-19 patients. Some hospitals in Hubei province, China, found that treatment with systemic corticosteroids on COVID-19 infection significantly revealed less acute pulmonary injury in radiology examinations (Zhou et al., 2020a). Similar to the previous study, COVID-19 patients with ARDS improved after methylprednisolone treatment (Wu et al., 2020a). It showed improved symptoms after corticosteroid treatment for severe patients compared with those who did not (Wang et al., 2020b).

Even though the benefit of corticosteroids to treat cytokine storm in SARS, MERS and influenza is limited; instead of leading to fatal and extension of the infection (Wang et al., 2020b; Yang et al., 2020), corticosteroid therapy showed promising result in severe COVID-19 patients (Yang et al., 2020; Zhou et al., 2020b). Some studies reported that the use of corticosteroid has improved the oxygenation of COVID-19 sufferers, reducing the length of hospitalization and intensive care (Wang et al., 2020b; Zhou et al., 2020b). At the molecular level, corticosteroid administration seemed like decreasing the level of C-Reactive Protein and IL-6 (Wang et al., 2020b). The decline of other inflammatory cytokines were shown following corticosteroid administration (Kolilekas et al.). However, many studies still doubt the benefit of corticosteroids for long-term administration and are cautious about the adverse effect and the potential of delayed viral clearance (Spagnuolo et al., 2020). As reported in SARS patients treated with corticosteroid, more than half of them suffer from pain and bone marrow abnormalities (Griffith et al., 2005). However, short-term and low-dose corticosteroid administration before ARDS occurs is adequate for better prognosis in severe COVID-19 patients (De Backer et al., 2020; Villar et al., 2020).

Other medications target specific sites of inflammation. Anakinra, which targets IL-1 β , and IL-6 inhibitors such as Tocilizumab, Siltuximab, and Sarilumab have been used in critical patients (Xu et al., 2020a). Among others, Tocilizumab demonstrated high effectiveness in treating severe COVID-19. For other IL-6 inhibitors, their effectiveness were proven unsatisfactory (Khan et al., 2000).

Tissue macrophage produces IL-1 β aggressively, triggering hyperproduction and leading to secondary hemophagocytic lymphohistiocytosis (sHLH). Then it was followed by pancytopenia, kidney damage, hypercoagulation, and maladjusted hepatobiliary. When sepsis occurs, sHLH leads to early mortality. Administration of anakinra on patients with sHLH symptoms showed lower mortality by 30% (Dimopoulos et al., 2020; Monteagudo et al., 2020) and dropped the mortality rate after 21 days of treatment (Cavalli et al., 2020).

Interferons (IFNs) have systematically improved pulmonary function and reduced mortality in SARS and MERS (Stockman et al., 2006) yet in COVID-19. The benefit of IFN-I in SARS and MERS was not proven in severe patients with comorbid. Also, viral titer decreases in the early course of the disease but not in the latter (Al-Tawfiq et al., 2014). However, it has been found that some subtypes of IFN-1 are more potent than others. IFN β 1a or IFN β 1b was the most effective IFN-I subtype in treating SARS-CoV, concluding the role of IFN β 1b in combating coronavirus

infection yet COVID-19 (Hensley et al., 2004). Another study proved the role of IFN in activating cellular immunity by activating macrophages, NK cells and cytotoxic T lymphocytes (Shen and Yang, 2020). A randomized open-label phase 2 trial combined IFN β 1b and anti-viral for treating mild to moderate patients. The result showed that IFNs improve antiviral effectiveness compared to the use of antiviral alone (Hung et al., 2020).

Other immunotherapies including continuous renal replacement therapy (CRRT) and plasmapheresis still lack of beneficial evidences. Specific equipment or documented value is still needed, even though permission to use these methods is solely given to treat patients with septic shock or acute kidney injury (Katagiri et al., 2021). The use of a monoclonal antibody was tried before for critical patients. The report showed that the result was encouraging (Gong et al., 2020). Another promising approach is using small molecules to block several pathways, including the Notch pathway and others (Rizzo et al., 2020). Yet, stem cell-based approaches were already proposed to protect patients' lungs during acute respiratory distress (Basiri et al., 2021).

Conclusions

Within other major events in patients infected with COVID-19, the presence of ARDS induced by cytokine storm was proven as the main cause of mortality in most cases. Several cytokines and chemokins have major role in conducting the cytokine storm. The discovery of several effective drugs and immunotherapy reduces mortality and improves clinical outcomes in severe COVID-19 patients. Still, better approaches to prevent the incidence of cytokine storm and cure the patients must still be investigated.

Authors' contributions

Conceptualization: AO, ZH, and TMZ; Data curation: AO, ZH, and TMZ; Investigation: AO; Project administration: ZH; Resources: TMZ; Supervision: ZH and TMZ; Validation: ZH; Writing-original draft preparation: AO; Writing-review and editing: AO, ZH, and TMZ.

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Conflict of interest

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