REVIEW ARTICLE

Inhibition of IL-1/IL-6 Pathway Reduces Mortality in Patients with SARS-CoV-2

Elham Keshtzar[1], PhD;
Marzieh Rashedinia[2,3], PhD

Abstract

Background: Novel 2019 Coronavirus (covid-19) or SARS-CoV-2 disease is spreading quickly throughout the globe and threatening public health. Severe acute respiratory syndrome SARS-CoV-2 may precipitate "cytokine" storm, immune system dysregulation, and hyper-coagulation that are responsible for several organ failure, morbidity, and mortality. The severity of infection symptoms is extremely variable from mild symptoms to acute respiratory distress syndrome. Overproduction of inflammatory cytokines and interplay between the immune system response and dysregulation of coagulation system are hypothesized to play a critical role in the pathological mechanism of seriously ill patients with covid-19 infection via the IL-1/IL-6 central pathway.

Methods: The role of SARS-CoV-2 virus in covid-19 disease through cytokine storm and coagulopathy has been discussed in the present brief review. The electronic databases Pubmed, Google Scholar, and SCOPUS were searched to retrieve related English-language articles published between the years 2019 and 2021.

Results: The interplay between immune system responses and coagulation pathway was observed in pathological condition of coronavirus patients, leading to abnormal condition of clot formation and increasing incidence of strokes. Indeed, in non-survivor patients, the levels of IL-6, IL-1, and D-dimer were higher than survivor coronavirus patients.

Conclusion: Severe SARS-CoV-2 patients with higher level of IL-1/IL-6 and coagulation abnormality confirm this hypothesis that anticytokine drugs are effective for managing cytokine storm, preventing the risk of strokes, and reducing hospitalization and mortality in covid-19 patients.

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[1]Department of Toxicology and Pharmacology, Faculty of Pharmacy, Shiraz University of Medical Science, Shiraz, Iran
[2]Food and Supplements Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Medicinal Plants Processing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Marzieh Rashedinia, PhD;
Food and Supplements Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
Tel: +98 9178842860
Fax: +98 71 32424126
Email: rashedinia@sums.ac.ir
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Introduction

New coronavirus disease 2019 (covid-19) is a contagious and infectious disease that spreads rapidly throughout the globe and threatens the public health.[1,2] SARS-CoV-2 infection is associated with remarkable mortality rate, particularly in older adults and people of any age who are at higher risk for severe illness and serious underlying medical conditions such as Diabetes, Cardiovascular diseases, Asthma, Hypertension, immune system deficiencies, COPD, and Cancer.[3,4] Common symptoms of covid-19 are fever, dry cough, fatigue, shortness of breath, loss of smell and taste, and acute respiratory distress syndrome (ARDS).[5] According to the reports of the WHO, on December 20, 2021, over 273,900,334 million cases have been confirmed worldwide, with 5,381,812 death.[6] The pathophysiology of covid-19-induced ARDS has similarities with pneumonia caused

by other bacteria or viruses.[7]

Based on current studies, patients with severe covid-19 infection start with cytokine storm after a few days of hospitalization.[8] According to previous studies, higher levels of pro-inflammatory and cytokines in the lungs observed in severe influenza such as H1N1 and H5N1 are associated with increase in the mortality rate in healthy young people. Over-induction of interleukins such as IL6, IL-1β, IL 8, tumor necrosis factor-α (TNF-α), and monocyte chemotactic protein-1 (MCP-1) has been observed in H1N1 and H5N1 influenza.[9]

Also, acute SARS-CoV-2 infection is correlated with high concentrations of an inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-8, and interferon (IFN)-γ.[10] It is confirmed that cytokine storm plays a key role in activation of coagulation pathway. In addition, systemic inflammatory disorder affects the platelet and RBCs. It seems that cytokines change the clot formation and induction of platelet activity since platelets have receptors for IL-6, IL-8, and IL-1β. Also, IL-6 has receptors on RBC.[11]

It is reported that covid-19 patients with severe pneumonia exhibited an imbalance between coagulant and anticoagulant parameters. Moreover, infection affects the immune system response and lead to activation of coagulation pathways and over-production of pro-inflammatory cytokines.[7]

In this review, we summarize the relationship between inflammation and coagulation disorder in covid-19 and discuss the possible therapeutic benefits of anti-inflammatory agents on acute and recovery phase of the illness and their implications for potential COVID-19 treatments.

Methods

The role of SARS-CoV-2 virus in covid-19 disease through cytokine storm and coagulopathy is reviewed based on literature survey through electronic databases such as Scopus, PubMed, Google Scholar, and MEDLINE to identify the related English-language articles published from 2019 to 2021. The keywords used were 'covid-19', 'coagulation', 'interleukin-1', 'interleukin-6', 'SARS-CoV-2', 'D-dimer', 'stroke', 'cytokine storm', 'anakinra' and 'tocilizumab' in combination with MeSH terms: "coronavirus" [MeSH Terms] OR"coronavirus" [All Fields] AND "covid-19" [All Fields] OR "covid-2019" [All Fields] OR "severe acute respiratory syndrome coronavirus 2".

Results

Severe Covid-19 Infection Is Associated with Coagulation Disorder

According to previous studies, functional abnormality occurs in the coagulation system of patients with acute covid-19 disease, which can enhance the risk of venous thromboembolism (VTE). The findings of Chinese studies indicated that high levels of D-dimer (>1μg/ml) in patients with covid-19 were significantly correlated with hospitalization and death (OR 18.4 95% CI 2.6–128.6, P=0.003).[12, 13]

D-dimer is a biomarker of fibrin degradation product which is routinely assayed in clinical laboratory for VTE diagnosis and pulmonary embolism.[14] Considerably, in covid-19 patients with acute infection, high levels of D-dimer play a dominant role in requiring hospitalization. Analysis of 1099 confirmed covid-19 patients in China hospitals showed higher levels of D-dimer in non-survivors (>2 μg/mL) than survivors (>0.5 μg/mL) among covid-19 patients.[15]

Zhang and colleagues analyzed 191 covid-19 patients and found that higher D-dimer (>1.0 μg/mL) (P=0.0033) was correlated with severity and mortality among covid-19 patients. In addition, they found a strong link between D-dimer levels of 2.0 μg/mL or more and mortality in covid-19 patients.[16]

Previous studies revealed that approximately 90% of hospitalized patients with pneumonia had enhanced activity of coagulation factors, particularly a noticeable increasing D-dimer levels.[17] The retrospective comparison of D-dimer levels in survivors and non-survivor covid-19 patients indicated that approximately 71.4% of the mortality had clinical criteria of disseminated intravascular coagulation (DIC).[12]

Relationship between Cytokine Storm and Coagulation System

The activation of both inflammatory and coagulation systems does not happen simultaneously, but evidence indicated a crosslink between these two systems.[7] During damage by a microorganism, the immune cells activity initiates and several inflammatory cytokines are produced; these cytokines lead to activated coagulation pathway.

In this process, inflammatory factors and coagulation affect each other.[9] It means that inflammation leads to activation of coagulation pathway through reduced production or impaired functional anticoagulants agents such as anti-thrombin III, tissue factor-mediated thrombin generation, and the protein C system. Thrombin also affects the inflammatory system by inducing IL-6 and IL-8 in the endothelial cells.[7]

The effect of acute infections on coagulation and fibrinolytic systems can lead to ischemic events. This event may occur in covid-19 infection as well.[18]

High levels of IL-6 and IL-8 have been related to SARS CoV-1 and SARS-CoV-2, and higher levels of these cytokines are also linked to the mortality rate.[18] Moreover, the results of clinical studies showed

that there was a clear link between inflammatory factors and progress of thrombo-vascular disease in several clinical studies; SARS-CoV-2 patients had significantly elevated D-dimer levels and prolonged PT/PTT.[18] Pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, TNF-α, MCP-1, IFN-γ, HGF, and other cytokines are important mediators of inflammation system that stimulate the coagulation dysfunction. For instance, IL-1 leads to anticoagulant proteins impairment, particularly protein C inactivation.[11]

In a healthy person, initiation of protein C activity is a key role in anti-coagulant pathway. Moreover, IL-6 affects the coagulation pathway by up-regulation of the tissue factor and also TNF-α due to anticoagulation factors regulation.[11, 19] Considerable evidence has shown that higher levels of pro-inflammatory cytokines are more closely related to acute infectious covid-19 patients and critical condition of disease.[20]

It is noteworthy that among inflammatory cytokines, IL-1 and IL-6 were elevated in the plasma of patients with severe covid-19 infection, particularly in those admitted to the ICU. In contrast, the level of TNF-α was low in patients with SARS-CoV-2 infection, with no significant difference between both ICU and non- ICU patients with covid-19.[21] Based on the reports of 452 patients with confirmed covid-19 infection, the higher level of IL-6 was more distinguished by more severe infection.[22] Elevation of IL-6 levels was also found in survivor patients with coronavirus than in those who did not survive.[4]

It is interesting to mention that activation of IL-1β during covid-19 infection induced the activity of IL-6 and TNF-α.[23, 24] In a clinical trial, administration of multiple drugs with anti-inflammatory properties in patients with coronavirus such as tocilizumab, isarilumab, siltuximab, and anakinra has been shown to have a protective effect against coronavirus infection.[25] It seems that IL1/IL6 axis in cytokine storm is plays a central role in severe complications of covid-19 patients.

Discussion

COVID-19 Infection and Stroke Incidence

Based on previous studies, respiratory tract infection is related to incidence of stroke , mainly ischemic stroke.[26] Cytokine storm or over-reaction of inflammatory system plays a key role in the progress of severe disease with coagulopathy disorder, thrombosis, and multi-organ failure. Immune response against viral infection is a normal mechanism, but in some patients an immune response extremely develops and causes damage to several host tissues.[27]

High levels of IL-1, IL-6, TNF-α, and chemokines are indexes of immune response hyperactivity.[28] After coronavirus infection, the activated monocyte-derived macrophages (MDM) can release large amounts of pro-inflammatory cytokines such as interleukins and TNF-α.[29, 30] In response to cytokines inflammation, specially IL-6, platelet tissue factor is released from the MDM and endothelial cells.[22, 31] Tissue factor affects the coagulopathy and stimulates the external coagulation pathway due to fibrin degradation product (D-dimer) and blood clotting pathway activity.[29]

It is interesting to mention that the level of IL-6 is related to stroke and is an indicator for predicting the risk of stroke.[32] It is possible that hyperactivity of the inflammatory system participates in development of two important risk factors of stroke, i.e. atrial fibrillation and atherosclerosis.[33] It is believed that the intensive immune reaction to viral infections which lead to local release of TNF-α and IL-1β from macrophages and release of reactive oxygen species and myeloperoxidases from neutrophils contribute to the pathogenesis of atrial fibrillation.[26]

This inflammatory response leads to thrombosis via different mechanisms, involving endothelium damage, coagulopathy initiation through the tissue factor VIIa, platelets activity, anticoagulant pathways dysregulation, and fibrinolysis disorder.[34] It seems that patients with coronavirus-associated stroke have a poor clinical prognosis with a high rate of mortality.[28]

According to the results of previous retrospective cohort study, the prevalence of stroke is 7-8 times higher in hospitalized coronavirus patients compared with those hospitalized by influenza infection, supporting the risk of SARS-CoV-2 in hyper-coagulant condition.[26] In addition, recent pathological finding revealed that patients with covid-19 were at higher risk of thromboembolic disorders.[35]

Covid-19 infection has been demonstrated cytokine storm, which may be one of the factors through which SARS-CoV-2 causes acute cerebrovascular disease.[36] On the other hand, patients with severe covid-19 infection often show high levels of D-dimer and reduction of platelet levels, which may indicate that these patients are at risk of acute cerebrovascular diseases. In addition, patients with acute coronavirus infection often suffer from hypoxia that leads to damage to the nervous system.[36, 37]

The results of a study showed that patients with confirmed coronavirus PCR test who were younger than 50 years old had large vessel ischemic stroke.[38] Mao and colleagues investigated 214 coronavirus patients including 126 patients with non-severe infection and 88 patients with severe infection; their result showed that in severe patients high level of D-dimer and coagulopathy activity increased the risk of cerebrovascular diseases, specially ischemic stroke (5.7%).[39] Another study on six covid-19 patients showed dramatically increased level of D-dimer and ischemic stroke.[40]

A previous retrospective study assessed 219 confirmed coronavirus patients from Wuhan, China; the results showed that 10 patients (4.6 %) had a severe ischemic stroke, and one (0.5%) had a cerebral hemorrhage. The average period for initiating the stroke symptoms in coronavirus patients was 10 days.[22]

Therapeutic Benefits of Interleukin 1 Inhibitors in Covid-19

Interleukin 1β is unregulated in cardiovascular disease, infection, autoimmune disorder, and chronic diseases such as type 2 diabetes and atherosclerosis. IL-1 induces changes in several metabolic and hematological factors.[41] Based on the results of animal studies, treatment with IL-1 leads to rapid reduction of systemic blood pressure, vascular resistance depletion, heart rate enhancement, and leukocyte accumulations.[42]

Over-production of IL-1 causes endothelial dysfunction, which may be related to pathogen infection. Endothelial dysfunction, as a results of cytokines and arachidonic acid products, causes macrophage hyperactivity and increases the protein permeability in different pathological conditions, such as SARS-CoV-2 viral infections, which evoke covid-19 disease.[41]

Anakinra

Anakinra is a 17 kD recombinant soluble receptor antagonist of IL-1 which suppresses the pro-inflammatory cytokines and is used in autoimmune disorders with a good safety profile.[20] A previous study indicated that Anakinra had several positive effects in acute infection, but only in patients with multiple organ failure, in which the inflammation pathway is also complicated.[1] Also, beneficial effects of Anakinra were reported in pediatric patients with macrophage activation syndrome, including cases provoked by viral infection.[1]

IL-1 has a key role in cytokine storms that stimulate cytokines such as IL-6 which is well known. Recent data have demonstrated that Anakinra is mostly effective in treatment of inflammatory cytokine storm and has been used in patients with H1N1 and Ebola viral infection.[43] In a cohort study of Covid-19 from March 24 to April 6, 2020, 52 patients were treated with subcutaneous Anakinra (100 mg twice daily); also, there were 44 patients in the control group who received standard and supportive care. 13 patients (25%) in the Anakinra group who required invasive mechanical ventilation and 32 (73%) patients in the control group died.[1]

High dose of Anakinra (IV 100 mg every 8 hours) was examined in a few severe covid-19 patient population (5 patients) who exhibited dyspenea, systemic inflammation, elevated D-dimer, and reduced ferritin and platelets. After Anakinra therapy, noticeable improvement in respiratory function and other parameters was seen.[44]

In another study, 29 patients with covid-19 received high-dose IV Anakinra (5 mg/kg twice daily) and 16 covid-19 patients received standard treatment. After Anakinra therapy, 21 patients showed respiratory function improvement, 5 of them needed mechanical ventilation, and 3 died. In the standard treatment group, in 8 patients improvement of respiratory function was observed, and 7 patients died.[45]

Therapeutic Benefits of Interleukin 6 Inhibitors in Covid-19

IL-6 is an important multifunctional cytokine that modulates the immune reaction and inflammation. Almost all stromal cells and immune system cells can produce IL-6, including macrophages, dendritic cells, monocytes, B-lymphocytes, T-lymphocytes, mast cells, etc. Also, IL-1β and TNFα play a central role in IL-6 expression induction.[20]

High expression of IL-6 was observed in approximately all pathological and physiological inflammatory conditions and also in autoimmune diseases.[11] However, IL-6 plays a key role in cytokine release syndrome and can be a possible mechanism for treatment in severely ill patients.[46] Plasma levels of IL-6 in covid-19 infection are higher than what is commonly seen in severe (bacterial) infection. In addition, higher levels of IL-6 are closely related to critical lung injury and strong indicator of mortality.[13]

Several lines of evidence showed that in critically ill covid-19 patients the levels of IL-6 are associated with the disease severity and death. In support of this observation, studies of other coronavirus infections such as SARS and influenza A infection have shown that IL-6 levels are linked to the severity of disease and mortality.[47] In addition to the central role of IL-6 inhibitors in the defense system response in covid-19 patients, possibly the beneficial effects of tocilizumab on the coagulation abnormality system of covid-19 patients are also applicable.[10, 47]

Numerous patients with severe coronavirus infection exhibited and developed coagulopathy that is closely related to high risk of death and mortality.[47, 48] FDA approved tocilizumab, sarilumab, and siltuximab for use in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. In view, IL-6 plays a pivotal role in the pathogenesis of critically ill patients with covid-9 infection, so therapeutic effects of these drugs against IL-6 may be considered.[18, 49]

Tocilizumab (Actemra)

Tocilizumab is a IL-6 receptor antagonist that is approved by Food and Drug Administration (FDA)

to treat moderate-to-severe rheumatoid arthritis, autoimmune disorder, systemic juvenile idiopathic arthritis, giant cell arteritis, and cytokine release syndrome (CRS).[50, 51]

In coronavirus patients with acute infection, CRS and IL-6 marker associated with CRS were elevated. Lou et al. found that more than half of coronavirus patients (15 severe ill patients) decreased acute phase reaction level after starting Tocilizumab administration.[46, 52] Xu and colleagues investigated 21 ill patients with acute coronavirus infection. In their study, 20 out of 21 ill patients improved 2 weeks after receiving tocilizumab with no adverse drug effects.[53]

In another study, six patients with severe coronavirus infection and respiratory failure treated with tocilizumab showed a significant decline in D-dimer and C-reactive protein (CRP) production level together with gradual increases in the platelet and lymphocyte.[54] Based on data from a large observational study on 1229 covid-19 patients, tocilizumab therapy was closely related to lower mortality in covid-19 patients with high levels of CRP or ICU admission.[55] Meleveedu et al. included 31 severely ill patients with covid-19 and pulmonary impairment in tocilizumab therapy; they observed a significant improvement in symptoms related to patients, such as CRP level, temperature, oxygen requirement, and IL-6.[56]

Capra et al. included 85 severe covid-19 patients, and 62 patients received tocilizumab. They observed a lower death rate (2 out of 62 patients) in the group treated with tocilizumab compared with 11 out of 23 patients in the untreated group.[49] In another study, it was revealed that 51 patients with severe coronavirus infection after receiving tocilizumab showed a major decrease in body temperature and CRP production level.[57]

Limitation

In this review, we discussed the possible therapeutic benefits of anti-inflammatory agents on acute and recovery phase of illness and their implications for potential covid-19 treatments. The limitation of this study was that the most efficient anti-inflammatory agent in covid-19 treatment has not been specified. This is possible by meta-analysis of a large number of studies, that was not performed in this study; should it is suggested that this type of analysis be reviewed in future studies.

Conclusion

In conclusion, severely ill patients with coronavirus disease may develop extensive inflammatory cytokine release syndrome which include a wide spectrum of cytokine and chemokines. It seems that IL-1/IL-6 axis plays an important role in this scenario, and the use of anti-IL-1/IL-6 drug seems beneficial. Early clinical outcome demonstrated dysregulation of the immune system associated with coagulopathy and sequences disorder which causes critical condition that needs ICU admission. Indeed, in non-survivor patients, the levels of IL-6, IL-1, and D-dimer are higher than those in survivor coronavirus patients.

The interplay between immune system responses and coagulation pathway was observed in pathological condition of coronavirus patients, leading to abnormal condition of clot formation, increased incidence of strokes with a poor clinical prognosis, and high rate of mortality after a few days of covid-19 symptoms onset, even after recovery.

Hyperactivity of coagulation pathway plays a key role in inflammation, and anticytokine drugs are an important target for therapeutic purposes in hospitalized patients with severe coronavirus infection and prevention risk of strokes.

Authors' Contribution

Authors have read and agreed to the published version of the manuscript.

Ethical Approval

Our study did not require an ethical board approval because ethical approval is needed for experimental studies on human or animal.

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