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Cytokine storms caused by novel coronavirus 2019 and treatment for cardiac injury

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Abstract. – Since December 2019, an outbreak of a new coronavirus, COVID-19, infection has been taking place. At present, COVID-19 has spread to most countries worldwide. The latest evidence suggests that cytokine storm syndrome (CSS) is an important cause of the transition from mild to critical pneumonia and critically ill patients' death. The sudden exacerbation of COVID-19 may be related to a cytokine storm. Therefore, early identification and active treatment of CSS may play very important roles in improving the patients' prognosis, and these tasks are given attention in the current treatment of new Coronavirus pneumonia. However, there is still no specific medicine for this purpose. This article reviews cytokine storms and conducts an exploratory review of pharmacotherapy for cytokine storms to provide a reference for clinical treatment.

Key Words:
Coronavirus, Severe acute respiratory syndrome, Inflammatory storm, Cytokine storm, Drug therapy.

Introduction

Since December 2019, an outbreak of a new type of coronavirus disease (coronavirus disease 2019, COVID-19) has been occurring. It has been reported that some patients with COVID-19 have milder symptoms in the early stage but suddenly worsen in the later stage and die within hours. This clinical process is very similar to a "cytokine storm". As a result, cytokine storm syndrome (CSS) in patients with COVID-19 began to attract the attention of frontline clinicians and gradually entered public awareness. An "inflammatory storm" refers to the unregulated and excessive release of inflammatory factors in the body. Since inflammatory factors belong to the category of cytokines, the essence of an "inflammatory storm" is a cytokine storm. As early as 2005, Huang et al[1] found that cytokine storms have an important role in acute respiratory distress syndrome (ARDS) caused by severe acute respiratory syndrome coronavirus (SARS-CoV) infections. A recent investigation[2] that analyzed 41 patients with COVID-19 in Wuhan from December 16, 2019 to January 2, 2020 indicated that critical illness in patients with COVID-19 may be related to cytokine storms. Another retrospective study of 99 patients with COVID-19 showed that lymphocyte levels decreased in most patients. It is speculated that COVID-19 may mainly affect lymphocytes, spread through the respiratory mucosa and infect other cells. The main symptoms of COVID-19 include fever, interstitial and alveolar pneumonia, and large amounts of inflammatory secretions in the alveoli, which lead to rapid hypoxia, shock, dyspnea, respiratory and multiple organ failure in some patients. Based on the current literature, this article defines a cytokine storm and conducts an exploratory review of the pharmacotherapy of cytokine storms to provide a reference for the treatment of cytokine storms caused by COVID-19.

Definition of Novel Coronavirus

Novel coronavirus pneumonia is a new infectious disease that is mainly characterized by lung infections and lesions and its pathogen is a new type of coronavirus (COVID-19). COVID-19 is different from the pathogenic viruses of severe acute respiratory syndrome (SARS) that were first seen in 2003 and Middle East respiratory syndrome (MERS) in 2012. Genetic screening for COVID-19 has shown that the COVID-19 and SARS-CoV genomes have a homology of 86.9% based on their nucleotide sequences[3].

Cytokine Storm Syndrome

Cytokines are a group of small proteins secreted by cells and are used mainly for signal

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transmission and communication between cells and include interleukins (ILs), interferons (IFNs), tumor necrosis factor (TNF), colony-stimulating factors, chemotaxis factors, and growth factors. Different inducements, such as bacterial or viral infections, sepsis, malignant tumors, rheumatic diseases, or the administration of immunotherapy drugs can cause the immune response to become uncontrolled and cause a series of self-amplifying cytokines to activate a cascade reaction which quickly produces large numbers of cytokines that clinically manifest as systemic inflammation, hyperferritinemia, hemodynamic instability, shock, diffuse intravascular coagulation, and multiple organ failure that are known as CSS which, if not treated in time, often lead to the patient's rapid deterioration and even death.

The pathogenesis of CSS has not been fully elucidated. At present, the main mechanisms are considered to have the following two characteristics. (1) Genetic factors during the cellular immune response, cytotoxic T lymphocytes and natural killer cells act on target cells (e.g., infected cells and tumor cells) by releasing perforin and encode perforin for transport and release. Gene mutations in the proteins necessary for this process cause the target cells to clear checkpoints and thereby continuously activate T lymphocytes and macrophages, release large numbers of cytokines, and produce multiorgan inflammation and cytokine storms. (2) Cytokine storm, when the immune system fights pathogens, cytokines normally send signals to the immune cells, which allow them to go to the infection site. At the same time, cytokines continue to activate these cells and stimulate the production of additional cytokines. Usually, this feedback loop is controllable. However, in the case of infection, tumors, or use of drugs, this inflammatory response becomes uncontrollable, large numbers of immune cells are activated and secrete additional cytokines, and these additional cytokines recruit additional immune cells and thus form an out-of-control cascade, but the exact cause of this loss of control is not completely clear.

Cytokine Storms

The main functions of cytokines help control cell proliferation and differentiation, angiogenesis, and the regulation of immune and inflammatory responses[4]. Many cytokines promote or restrict each other in the body and form a very complex cytokine regulatory network[5]. If the body is severely infected, the balance of cytokine-promoted immune and anti-immune mechanisms becomes out of balance and leads to a cytokine storm.

Cytokine storms and cytokine release syndrome (CRS), cytokine cascades or hypercytokinemia are the same concepts[6]. In 1989, the OKT3 anti-T cell antibody was found to produce a series of uncomfortable symptoms in patients after the first treatment, such as elevated temperature, headache, and release of large numbers of cytokines. These symptoms can be alleviated with glucocorticoid treatment. The concept of CRS has also been formally proposed[7]. In 1993, Ferrara et al[8] first proposed the concept of a cytokine storm in graft-versus-host disease. Beginning with SARS in 2003, cytokine storms were found to cause multiple organ failure, which led to extremely high mortality rates, which gradually attracted great attention[9]. In recent years, with the rapid development of immunotherapy represented by chimeric antigen receptor T (CAR-T) cells, cytokine storms have been widely considered as the most common adverse reaction of CAR-T therapy.

The Potential Mechanism of Cytokine Storms

At present, the cause of cytokine storms is not very clear. It is generally believed that the immune system overreacts to new and highly pathogenic pathogens. Namely, an imbalance in the immune regulatory network, lack of negative feedback, and constant self-amplification of positive feedback cause a variety of cytokine levels to be abnormally elevated and eventually lead to a cytokine storm[6]. When the body is infected or injured, its immune system generates an immune response with the goal of eliminating or destroying the antigen. When a pathogen invades the body, the body's innate immune system functions first, the epithelial cells infected by the pathogen produce a small amount of cytokines, such as IFN-α/β and IL-1β, and the natural killer (NK) cells that are stimulated by IFN-α/β release a small amount of IFN-γ to activate macrophages. These activated macrophages release large amounts of cytokines, such as TNF-α and IL-12, that in turn activate NK cells. As a result, positive feedback occurs between NK cells and macrophages, and cytokine levels increase dramatically[10]. At the same time, the pathogen's innate immune system processes, antigen presentation, and the adaptive immune system, which

is composed of B cells and T cells, also begin to function. Large amounts of IL-12 and IFN-γ that are released by T helper-1 (Th1) cells can both stimulate their own division and proliferation and stimulate the activation of macrophages to further activate the innate immune system, which can also produce positive feedback[11].

Under normal circumstances, once the body has controlled the invading pathogen *via* the positive feedback regulation, the signal presented by the antigen signal to the adaptive immune system weakens, cytokine release begins to decrease, and the inflammatory response gradually weakens, thereby forming a negative feedback adjustment. Moreover, some suppressive cytokines in the immune system, such as IL-10, TGF-β, and 1-phosphate sphingosine (S1P), act on vascular endothelial cells and regulate excessive immune responses, namely, negative feedback adjustment[4].

However, when the body is subjected to violent virus attacks, such as the currently raging SARS-CoV-2 infections, the human immune system releases large amounts of cytokines under the action of positive feedback and the cytokine signal is greatly amplified. If the negative feedback regulation is too weak and too late, this may lead to an imbalance in the body's immune regulation network and cause a cytokine storm and disease deterioration. The levels of IL-17, IP-10, IL-6, G-CSF, GM-CSF, and other cytokines were significantly increased in the serum of patients with severe SARS-CoV, H1N1 influenza virus or avian influenza virus infections. Although the highly pathogenic mechanisms of SARS-CoV and MERS-CoV (Middle Eastern respiratory syndrome coronavirus) are not fully understood, early studies have shown that increases in the numbers of proinflammatory cytokines in serum are associated with lung inflammation and are widely related to lung injury. The amounts of IL-1B, IL-6, IL-12, MCP-1, and other cytokines increase significantly in SARS patients and MERS-CoV infection and induce increased IFN-γ, TNF-α, IL-15, IL-17, and other proinflammatory cytokine levels.

Patients with COVID-19 also have large amounts of IL-1B, IFN-γ, IP-10, and MCP-1, which may activate Th1 cells. In addition, critically ill patients have higher G-CSF, IP-10, MCP-1, MIP-IA, and TNF-α concentrations, which suggests that cytokine storms are associated with disease severity[2]. However, SARS-CoV-2 infections also lead to increased secretion of T helper-2 (Th2) cytokines (such as IL-4 and IL-10) that suppress inflammation, which is different from what occurs for SARS-CoV infections. Further investigations are needed to describe the Th1 and Th2 responses in SARS-CoV-2 infections and elucidate its pathogenesis.

Due to excessive secretion of cytokines and recruitment of additional immune cells, the vascular permeability of the diseased site is increased, which allows the pathogens at the targeted site to more easily enter blood vessels and accelerate the extravasation of fluid in the blood vessels, thereby destroying their organization. Some reports have suggested that cytokine storms are the underlying cause of ARDS. Inflammatory reactions in the lung are uncontrolled and excessive immune responses activate immune cells[6]. The abnormally elevated cytokine levels and overactivated immune cells cause diffuse damage to pulmonary capillary endothelial cells and alveolar epithelial cells and large exudates accumulate to block the airway and eventually lead to the occurrence of ARDS. At the same time, severe lung injury coupled with damage to the body's immune function and systemic cytokine storms caused by cytokines in the circulatory system can cause further dysfunction of systemic organs[12]. This condition is likely to be one of the important reasons for the sudden worsening and even death seen in some COVID-19 patients.

Cardiovascular Diseases Affected by COVID-19

Clinical Evidence

An earlier observation of 41 cases with COVID-19 showed that five patients (12%) had myocardial injury and severe heart disease that were related to viral infections, such as fulminant myocarditis, cardiogenic shock, and heart failure symptoms[13]. Recent clinical studies have shown that, when compared with those of survivors, high-sensitivity cardiac troponin levels of patients are significantly higher and continue to increase along with disease progression. Univariate analysis showed increased in-hospital mortality in patients with diabetes or coronary heart disease[14]. The histopathology of patients with COVID-19 showed that lung tissues and other organ tissues had severe inflammatory reactions. Fifty-two percent of patients with COVID-19 had elevated IL-6 levels and 86% of patients had elevated C-reactive protein levels[15]. After

COVID-19 invades, inflammatory factors, such as MCP-1, TNF-α, IFN-α, IFN-β, IL-1, and IL-6 are activated and excessively produced cytokines cause myocardial cells to undergo apoptosis in a cascading manner, which can lead to myocardial injury and heart failure.

Angiotensin-Converting Enzyme 2 (ACE2)

Angiotensin-converting enzyme 2 (ACE2) can be expressed in many tissues and organs, such as the lung, heart, kidney, and gastrointestinal tract. ACE2 mediates viral infections and directly participates in the process of cardiopulmonary injury after viral infections because of its important regulatory role in the renin-angiotensin-aldosterone system (RAAS). ACE2 is a metalloproteinase whose active domain is exposed on the cell surface, which is beneficial for cleaving the polypeptide in the cycle. ACE2 can cleave angiotensin I to produce inactive angiotensin 1-9 peptide[16], which can be further converted in vasodilating blood vessels by ACE or other peptidases into angiotensin 1-7 (Ang 1-7) peptide. In addition, ACE2 can directly metabolize angiotensin II (Ang II) into the Ang 1-7 peptide[17]. ACE2 and Ang-(1-7) have effects on cardiomyocyte hypertrophy, interstitial fibrosis hyperplasia, the inflammatory response, and oxidative stress caused by Ang II[18-19].

These results from animal experiments suggest that after myocardial infarction, rat myocardial tissue overexpresses the ACE2 gene, expression of AngII in the myocardial tissue surrounding the infarct region decreases, and the expression of Ang-(1-7) increases, which can prevent ventricular remodeling[20]. The experimental results of animal models treated with Ang-(1-7) have also indicated that Ang-(1-7) can inhibit ventricular remodeling in an AngII-dependent or AngII-independent manner[21]. Crackower et al[22] found that ACE2 gene knockout mice had increased AngII levels in their plasma and myocardial tissues, myocardial contractility decreased, and severe heart failure occurred. In the ACE2 knockout rat myocardial infarction model, the expression level of Ang II in infarction-related areas increased and the expression level of Ang-(1-7) decreased[23]. These results suggest that the downregulation of ACE2 expression in rat myocardial tissue increases the response of inflammatory factors and oxidative stress and leads to an aggravation of myocardial damage. Based on these results, it is speculated that in patients with COVID-19, binding to ACE2 will reduce the expression of ACE2, increase expression of AngII in plasma and local tissues of the myocardium, and reduce expression of Ang-(1-7) and the inflammatory response. Oxidative stress induces myocardial damage, which in turn leads to a decrease in myocardial contractility.

Myocardial damage that is caused by infection of cardiomyocytes with ACE2 receptors plays an important role in the entire process of COVID-19 and pathogenesis[24]. Both *in vitro* cell models and *in vivo* studies have confirmed that ACE2 is a functional receptor for SARS-CoV infections in human cells and allows SARS-CoV into the human tissue pathway[25]. Electron microscopy imaging results have found that, after human infection with COVID-19, the virus can directly attack the ACE2 receptors on the surface of the lung and heart[26]. Oudit et al[27] found through animal experiments and autopsy studies on SARS patients that SARS-CoV infections not only can cause lung injury but can also cause myocardial injury, which is accompanied by a significant decrease in ACE2 expression. Thirty-five percent of patients with SARS-CoV infection have detectable SARS-CoV nucleic acids.

As SARS-CoV binds to the ACE2 protein, the extracellular part of ACE2 will be cleaved; the transmembrane part will be transferred into the cell, which mediates fusion of the viral double-layer phospholipid and human cell membrane; and the virus enters the cell[17]. Xu et al[28] found that similar to SARS-CoV, COVID-19 has a high affinity for ACE2 and infects cells by binding to ACE2 receptors. The virus invades myocardial cells and replicates in these cells. The virus released by cell lysis continues to infect other myocardial cells and tissues and causes myocardial degeneration, necrosis and dysfunction, and the affinity of COVID-19 and ACE2 is higher than the affinity of SARS-CoV and ACE2 by up to 10-20 times. Therefore, it is speculated that the severity of the myocardial injury caused by COVID-19 is much higher than that caused by SARS-CoV.

Myocardial Damage Caused by Hypoxemia

Clinical observations have shown that patients with severe COVID-19 often have dyspnea and/or hypoxemia 1 week after onset. In severe cases, such patients can quickly progress to acute respiratory distress syndrome, septic shock, and recalcitrant metabolic acidosis, as well as coagulation dysfunction and multiple organ failure.

Hypoxemia can lead to oxidative stress and inflammatory reactions. Hypoxemia can also cause myocardial edema by regulating the expression of aquaporins in myocardial tissue. Furthermore, large numbers of cytokines are released due to virus-induced damage to tissues. Patients with COVID-19 have atrioventricular block, ventricular fibrillation and other malignant arrhythmias and cardiac arrest. The inflammatory response affects the stability of coronary arterial plaques, leads to weakened plaque stability, increases the risk of plaque rupture, and induces events, such as angina pectoris and acute myocardial infarction.

Effects of Fever and Lung Infections on the Myocardium

Fever leads to an increased heart rate and aggravates the burden on the heart. Furthermore, pulmonary inflammation causes varying degrees of hypoxia and CO_2 retention, which cause pulmonary vasospasms and lung lesions, such as massive destruction of the pulmonary capillary bed, which increases resistance to pulmonary circulation. Hypoxia, acidosis and hyperkalemia weaken the contractility of the myocardium. The release of various exotoxins and endotoxins from pathogenic microorganisms activates endogenous inflammatory mediators and aggravates myocardial damage. Infected cells that are damaged by free radicals increase the synthesis and release of endothelin (ET), decrease synthesis of nitric oxide (NO), dysregulate atrial natriuretic peptide (ANP), and increase the release of tumor necrosis factor (TNF). These factors that contribute to the occurrence of heart failure have important physiological and pathological roles.

Treatment for COVID-19

There is currently no effective drug for COVID-19 or cytokine storms. The drugs that are recommended in the "New Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Version 7)" are mainly for antiviral treatments. Only a few drugs, such as glucocorticoids and convalescent plasma, may have certain effects on cytokine storms. In addition, intravenous injection of gamma globulin may have some effect. Combining the mechanism of cytokine storms and the pharmacological characteristics of various drugs, especially the treatment experience of cytokine storms caused by other factors, such as CAR-T immunotherapy, combining drugs that may be used for cytokine storms caused by COVID-19 provides a reference for clinical treatment. Antiviral therapy is a CSS-based treatment for viral infections. Unfortunately, there are currently no specific drugs for COVID-19 and various new drugs are still being actively explored and experimentally applied. The effects are yet to be evaluated.

IL-6 Antagonist

In CAR-T therapy and patients with severe influenza virus infection, IL-6 and other cytokines are released excessively, which can cause cytokine storms. The more severe the cytokine storm is, the higher the peak IL-6 serum concentration[29]. Maude et al[30] suggest that targeted IL-6 drugs can effectively control CRS without affecting the efficacy of CAR-T cells. Tocilizumab is an anti-IL-6 receptor monoclonal antibody that can bind to both IL-6R and sIL-6R and thereby block downstream signaling[31]. Stutuzumab is a drug that directly targets IL-6, which can directly bind to IL-6 and then neutralize the biological effects caused by IL-6[32]. Accumulating clinical researches have shown that tocilizumab can be widely used to treat refractory chronic immune-mediated diseases and acute severe inflammatory diseases, such as cytokine storms[33]. Alvi et al[32] have shown that the shorter the time is from CRS onset to the application of tocilizumab after CAR-T treatment, the lower the incidence of cardiotoxicity and cardiovascular events. In addition, some investigations have shown that tocilizumab use for early prevention can reduce the incidence of severe (grades 3-4) CRS in high-risk groups. In children, tocilizumab treatment can reverse CRS-related hemodynamic or respiratory instability[34]. The efficacy of these two drugs in cytokine storms caused by COVID-19 still needs further clinical trials for verification.

Glucocorticoids

At present, glucocorticoids have been widely used to treat refractory cytokine storms for which IL-6 receptor antagonists are ineffective[35]. After glucocorticoids enter the blood, most of them combine with cortisol-binding protein and albumin to form a complex. A small amount of free hormones diffuses into the cytoplasm through the cell membrane and, after binding to the glucocorticoid receptor, they enter the nucleus to induce inhibition inflammation-related gene expression and exert anti-inflammatory effects[6]. Glucocorticoids are widely used in the treatment of SARS and MERS. In the SARS-CoV-2 epidemic, they

have also been used in combination with other drugs in the treatment of patients. However, Russell et al[31] pointed out that glucocorticoids should not be used to treat SARS-CoV-2-induced lung injury or shock, except in the context of clinical trials. Although corticosteroids can inhibit lung inflammation, they also inhibit the immune response and the immune system's elimination of viruses. Due to the methodological limitations of the current evidence, glucocorticoid use remains controversial. High-dose glucocorticoids in patients with novel coronavirus pneumonia do have risks of secondary infection, long-term complications, and prolonged detoxification. However, for critically ill patients, lung injury caused by a large number of inflammatory factors may cause rapid disease progression. In short, glucocorticoids are a double-edged sword. Their pros and cons need to be carefully weighed before using glucocorticoids.

Other Cytokine Blockers

Etanercept is a tumor necrosis factor-alpha (TNF-α) inhibitor, which is a dimer of TNF-α receptor 2, and can competitively bind TNF-α and inhibit its biological activity. Among this class of drugs, etanercept has been used alone or in combination with tocilizumab for CRS after CAR-T therapy[36]. It is suggested that etanercept may also have certain effects on CRS in patients with new coronavirus infections. Preclinical studies of other cytokine blockers for CRS are also ongoing. GM-CSF and IL-1 blockers have shown good effects in the treatment of CRS in animal experiments and the IL-1 blocker, anakinra, has been used in the treatment of CAR-T cell-associated encephalopathy syndrome (CRES). It also shows better efficacy than the IL-6R blocker tocilizumab[37,38]. Therefore, these cytokine blockers may also be used in cytokine storms caused by SARS-CoV-2 infections.

Catecholamine Modifiers

Staedtke et al[39] demonstrated in animal models of CRS that cytokine release is related to catecholamines, such as epinephrine and that limiting their synthesis can effectively control the occurrence of cytokine storms. Studies have found that prophylactic administration of catecholamine modulators, such as atrial natriuretic peptide (ANP) and α-methyltyrosine (MTR), can reduce cytokine levels *in vivo* without affecting antitumor effects. ANP is a small protein that is secreted by cardiomyocytes that can maintain electrolyte balance. Studies have found that mice injected with ANP have reduced cytokine levels and at the same time, the levels of catecholamines, such as epinephrine, norepinephrine, and dopamine also decreased. MTR is a key catecholamine synthesis rate-limiting tyrosine hydroxylase enzyme inhibitor that can further reduce catecholamine levels in the body. However, the questions of how immune activation causes increased catecholamine levels and how catecholamines promote cytokine production need to be further explored. The efficacy of such drugs still needs further clinical verification and registration of clinical trials may be considered if necessary.

Sphingosine Analogs

One potential approach to cytokine storms is to limit the host's immune response. The use of corticosteroids to comprehensively suppress the host's immune response is largely unsatisfactory. Cattley et al[5] have shown that the S1P receptor signaling pathway can significantly inhibit the immune pathological damage caused by the host's innate and adaptive immune responses and thereby achieve the goal of reducing cytokine storms. Among the S1P receptor modulator drugs, siponimod was approved for marketing in 2019 for the treatment of multiple sclerosis. Whether it can be an ideal drug for treating cytokine storms still needs further verification in clinical trials.

Ulinastatin

Ulinastatin is a natural anti-inflammatory substance. It protects the vascular endothelium by inhibiting the production and release of inflammatory mediators. It is widely used in clinics for treating pancreatitis and acute circulatory failure. Current studies have shown that ulinastatin can reduce the levels of proinflammatory factors, such as TNF-α, IL-6 and IFN-γ and increase the anti-inflammatory factor level of IL-10[40] which can promote a balance between proinflammatory and anti-inflammatory responses by interrupting cytokine storms that are triggered by the vicious cycle of the inflammatory response. Some researches have shown that high-dose ulinastatin has an anti-inflammatory effect comparable to that of hormones. However, unlike glucocorticoids, ulinastatin does not inhibit immune function and it is extremely unlikely to cause sequelae, such as femoral head necrosis. This drug has very promising application prospects in clinical settings.

Treatment of COVID-19 in Patients With Cardiovascular Diseases

ACEI and AT blockers may accelerate the entry of COVID-19 into cells and cause damage to multiple organs, such as the lung, heart and kidney. Myocardial injury occurs in patients with COVID-19. The main treatments include basic treatment, oxygen inhalation and respiratory support to ensure sufficient oxygenation and to prevent and treat complications. For patients with both COVID-19 and heart disease, it is recommended to continue to treat coronary heart disease as a secondary prevention strategy. How should the myocardial injury deal with in patients with COVID-19? There are no effective preventive drugs. Therefore, application of antioxidants and anti-free radicals and improvement of myocardial energy metabolism may be beneficial. Vitamin C can inhibit oxidative stress reactions after pulmonary inflammation, reduce excessive inflammatory reactions, and activate excessive inflammatory reactions. It can be applied when the level of inflammatory factors may decrease significantly after use.

How should ACEI and ARB be applied? Theoretically, ACEI and AT blockers can reflexively increase the expression of ACE_2, which may accelerate the entry of COVID-19 into cells and result in damage to multiple organs, such as the lungs, heart, and kidneys. However, at the same time, the increased expression of ACE_2 can inhibit the RAAS, which has a beneficial effect. To date, for patients with COVID-19 combined with hypertension and heart failure, there is no unified opinion on whether to stop ACEI and ARB. However, considering that ACEI and ARB are the basis for treating hypertension and heart failure, continued application of these therapies is recommended and their clinical efficacy remains to be determined via observation research.

Conclusions

Since December 2019, due to the rapid spread of COVID-19, cytokine storms have once again entered people's awareness. The cause of cytokine storms is not clear. It is generally believed that the immune system overreacts to new and highly pathogenic pathogens, which causes an imbalance in the immune regulatory network, a lack of negative feedback and a continuous self-amplification of positive feedback. Cytokine levels are abnormally elevated. Cytokine storms are likely to play an important role in ARDS caused by COVID-19, but we do not currently have a specific treatment. Based on the mechanism of cytokine storms and the pharmacological characteristics of various drugs, this article addresses the experience of cytokine storms that are caused by other factors, such as CAR-T immunotherapy and addresses the possible cytokine storms caused by COVID-19. Currently, IL-6 antagonists, such as tocilizumab and stuzumab, glucocorticoids and cytokine blockers, such as etanercept and anakinra, and atrial natriuretic peptide and α-methyltyrosine are used. Eculizumab, an inhibitor of the activated residue of C5 (C5a), plays important roles in the treatment of severe cases of COVID-19. Ongoing SOLID-C19 trial will provide further information about the efficacy of eculizumab[41]. Catecholamine modulators, sphingosine analogs such as siponimod, ulinastatin, and plasma from recovered patients have potential therapeutic effects but additional evidence-based data are still needed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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