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Immunomodulatory Approaches in Mechanisms and Treatments for SARS-CoV-2-Associated Cytokine Storm

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease affecting primarily the lung. It was initially discovered in late 2019, caused by a new pathogen called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and rapidly spread throughout the world. Acute respiratory distress (ARDS), which is triggered by the excessive release of cytokines (cytokine storm) during viral infection, is responsible for a significant number of deaths in SARS-CoV-2 patients. This paper aimed to explore the mechanism of some specific cytokines in the cytokine storm during the SARS-CoV-2 infection and also the related treatments for it. The treatments include the use of inhibitors or antagonists for several upregulated cytokines. The purpose is to provide several vital information and feasible treatment approaches that could possibly be deployed to alter the disease course in critically ill COVID-19 patients.

Keywords

SARS-CoV-2; COVID-19; cytokine storm; therapies for COVID-19.

1. INTRODUCTION

Late in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, and caused coronavirus disease 2019 (COVID-19). This disease spreads rapidly and caused a worldwide pandemic. By Aug 16th, 2020, there were 21.2 million cases confirmed infected and 761,000 lethal cases [1], among which 13.8% showed severe courses and 6.1% showed critical courses [2]. The virus shows a latent period of approximately two weeks. Before that, some people are asymptomatic. Within 11.5 days, 97.5% of all patients developed symptoms, including 75% infected patients hospitalized show a mild symptom and require supplemental oxygen, while 5% patients (20% of those patients are hospitalized) experience severe symptoms and need intensive care [3].

The SARS-CoV-2 is a large, enveloped, and single-stranded RNA virus. It can be found in some mammals, for instance, humans, dogs, pigs. Some birds and fish can also be infected by this virus [3]. The virus is the seventh member of the coronavirus family that can cause human infections. The other two well-known coronaviruses that caused severe disease in humans are SARS-CoV

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and MERS-CoV [4]. The transmission pathway of SARS-CoV-2 is the airborne pathway. Data shows that droplets during close face-to-face contact (coughing, laughing, etc.) are the most common ways to transmit SARS-CoV-2 [3].

Pathological manifestations vary across different COVID-19 patients. Initially, patients show symptoms that resemble common flu, such as fever, dry cough, fatigue, or muscle soreness. However, infected patients could develop to critically ill and even resulting in death. The acute respiratory distress syndrome (ARDS), pneumonia, and some organ dysfunction are believed to be some of the severe clinical manifestations of COVID-19 progression [5, 6].

In the work, we demonstrated the pathogenesis of the cytokine storm in SARS-CoV-2 infection and explored the potential treatment for it. Cytokine storm is known as the over-releasing of cytokines [5]. In the early phase of COVID-19 infection, most patients show mild symptoms, which suddenly worsen in the later stage of infection [7]. The cytokine storm is considered to be the cause of ARDS and organ failure [8]. Therefore, the potential treatment for severe cases will primarily focus on reducing excessive cytokine levels in the host and mitigating their damaging effects by blocking receptors, with the hope that more patients could be saved by this new approach [9].

2. RESULTS

The results section will first break down the severity of SARS-CoV-2 into three main levels: paucisymptomatic, pneumonia, and ARDS, based on the different stages of infection. Then the cause of the severe stages of infection will be analyzed and evaluated and concluded with hypothetical reasoning of the development of ARDS--the dysregulation of the cytokines. The article then would cover some specific cytokines such as the IFN, TNF, and interleukins that caused the cytokine storm in patients. As a result, T-cell counts are decreased in COVID-19 patients. Towards the end, the article will provide some future therapeutic approaches in treating the dysregulation of the cytokines.

2.1. Host Defense, and Breakdown of SARS-CoV2 Patients by Disease Severity

2.1.1 Host defense Against SARS-CoV-2

After the host encounters the virus, SARS-CoV-2 targets the bronchial epithelial cells and pneumocytes through the spike protein binding to the angiotensin-converting enzyme 2 receptor or ACE2 receptor. The host cell presents the type 2 transmembrane serine protease (TMPRSS2) which "promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein, which then mediates coronavirus entry into host cells" [3]. After the virus enters the host cell through endocytosis, it releases its RNA and replicates itself to assemble more virions [10]. In the early stages of COVID-19, it behaves like other respiratory viral diseases in which lymphopenia might occur: the infection of bronchial epithelial cells, type I and II alveolar pneumocytes, and capillary endothelial cells. As a result, cytokines such as TNFs and interleukins are released which then enhances the inflammatory response. As the inflammatory response becomes worse, it damages lymphopoiesis and promotes lymphocyte apoptosis [11]. In the later stages of infection, endothelial barrier disruption, dysfunctional alveolar-capillary oxygen transmission, and damaged oxygen diffusion capacity will be triggered as viral replication accelerates. As a result, alveolar interstitial thickening, increasing vascular permeability, and edema [3].

2.1.2 Breakdown of SARS-CoV-2 Severity

The severity of SARS-CoV-2 is varied widely depending on the different stages of patients. Some patients would show asymptomatic and appear mild conditions such as fever, fatigue, and dry cough similar to flu-like symptoms. While others could develop into critical illness then resulting in death [12]. Therefore, having a scale of the severity of Covid-19 for the infected

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patients would not only help to treat the patients with different therapies but also help scholars analyze to manipulate immunity to propose new therapies and vaccines. The severity of SARS-CoV-2 can be broken down into three levels: Pauci-symptomatic, Pneumonia, and Acute respiratory distress syndrome (ARDS) reflecting different phases of the infection [13]. Most Covid-19 patients are only considered to be paucisymptomatic, i.e. having only mild symptoms such as fever and dry cough. Patients falling into this category are likely to recover spontaneously without requiring hospitalization or other medical intervention. However, there are about 15% of patients with severe pneumonia, and about 5% develop ARDS, for which effective therapies and hospitalization are urgently required [14]. The pathogenic mechanism of SARS-CoV-2-induced pneumonia can be explained by the production of excessive immune reactions in the host. The released cytokines will then promote the differentiation of B cells, promote or inhibit the growth of different cells which would impair the functionality of the central nervous system and promote more inflammatory diseases [13]. The most severe stage is when patients develop ARDS. It accounts for a significant number of deaths with estimated mortality being 40%. ARDS is regarded as the "hallmark immune-mediated clinical consequence" of SARS-CoV-2 and is also defined as bilateral lung infiltrates and severe hypoxemia. Its pathogenesis will lead to respiratory insufficiency due to the inflammatory injury to alveolar and its capillary membrane, resulting in increased lung permeability and the leaking of edema fluid into air spaces [15].

2.2. Cytokine Storm Is Found to Be the Cause of ARDS

2.2.1 Severe COVID 19 disease is associated with dysregulation of numerous cytokines

According to clinical statistics derived from severe patients of COVID-19, conditions of ARDS are associated with the significant skyrocketing of cytokine levels in the body, which is also termed as cytokine release syndrome (CRS) or cytokine storm, a condition manifested by excessively strong activation of the immune system [5]. The cytokine storm will recruit immune cells which later attack the host body. As a result, infection by SARS-CoV-2 will cause ARDS and organ failure [16]. Usually, the release of cytokines is conducive to eliminate pathogens in the body by enhancing inflammatory responses. Nevertheless, extremely high levels of cytokines will dampen the adaptive immune system and trigger many observable symptoms in COVID-19. As a result, the cytokine storm caused by infections will favor the proliferation of pathogens, in this case, the SARS-CoV-2.

Researches have demonstrated that, in the early stages of COVID-19 infection, delayed release of cytokines and chemokines occurs. In later phases, interferons (IFNs) were produced at a low level and various cytokines are produced excessively, which can attract inflammatory cells to lungs, resulting in excessive infiltration into lung tissue and causing lung injury [5,17]. The cytokine storm can also jeopardize the condition by rendering the T cells apoptosis, favoring the virus reproduction [18].

2.2.2 The cytokine storm in COVID-19 Patients is characterized by low concentrations of type I and III interferon (IFN) and high concentrations of chemokines

In SARS-CoV patients, ARDS is the severe result of a cytokine storm for some critical cases, in which the release by inflammatory cells of profuse amounts of pro-inflammatory cytokines and chemokines infiltrates and triggers the critical systemic inflammation in tissues. In general, cytokines involved in the ARDS include interferon, interleukin, and TNF families; involved chemokines encompass CCL and CXCL families [19,20].

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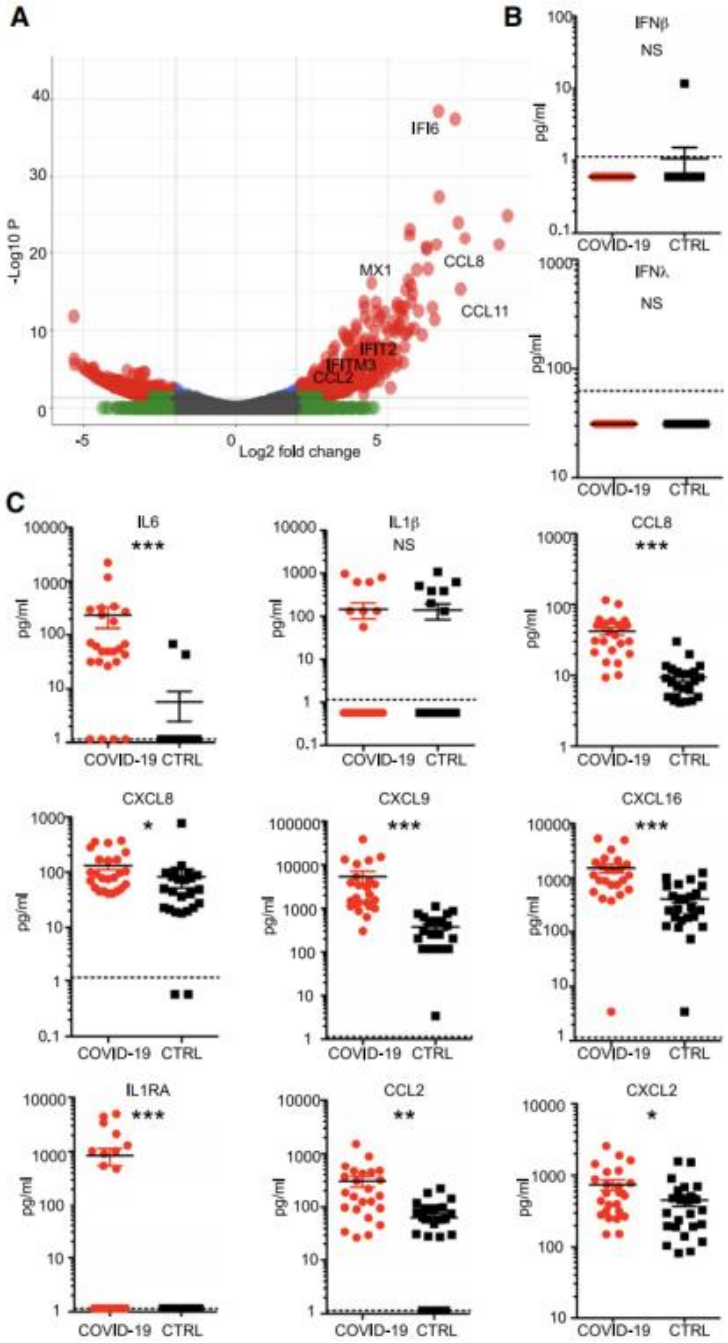

Fig 1. [7] Transcriptional and Serological Profile of Clinical COVID- 19 Patients

To further justify the increment in cytokine levels, researchers compared and contrast several lung biopsy specimens from COVID-19 patients with ones taken from healthy individuals. The result justified enhanced innate and humoral immune responses. SARS-CoV-2 triggers profuse amounts of chemokines including CCL2, CCL8, and CCL11(Fig.1 A) [7].

Next step, to further validate discoveries, a larger population of patients took serological tests, in which researchers want to detect circulating cytokines in blood serum caused by SARS-CoV-2 pathogens. To this end, researchers examine serological samples from two groups of people in the Kaiser Santa Clara testing facility (Clara, CA). These samples all present low levels for Interferon-b and the Interferon-I family (Fig.1 B). In addition, detection of high levels of cytokines and chemokines in serum specimens justified the escalation of inflammatory responses in COVID-19 patients, as shown by a stark increment in circulating the Interleukin

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family of cytokines and several chemokines (Fig.1 C). Among these, CXCL9 and CXCL16 will recruit T cells and NK cells, respectively; CCL8 and CCL2 will attract macrophages to tissues; CXCL8 can attract neutrophils [7].

To put it into a nutshell, infections by SARS-CoV-2 can result in increased levels of cytokines and chemokines in both lungs and blood serum. The induced cytokine storm will jeopardize the host, triggering an array of harmful pathological manifestations, as shown by the ARDS.

2.3. IL-6, IL-10, and TNF-α Are Vastly Upregulated

2.3.1 Functions & role of IL-6 and TNF

IL-6 is a lymphoid factor produced by fibroblasts and activated T cells. Synergistic colony-stimulating factor promotes the growth and differentiation of primitive bone marrow cells and enhances the lytic function of natural killer cells. IL-6 is essential to acute inflammatory responses and cytokine networks. IL-6 has a relatively late clinical application, but it is of great value in the early diagnosis and prognosis assessment of inflammation and infection [21].

The researchers found that SARS-COV-2 RNA (RNAemia) detected in the serum of COVID-19 patients was related to increased IL-6 concentration and poor prognosis. As the elevation of IL-6 as part of a larger cytokine storm may worsen outcomes, IL-6 may be a potential therapeutic target for critically ill patients with excessive inflammation [22]

When COVID-19 infuses the upper and lower respiratory tract, it can cause mild or high acute respiratory syndrome, accompanied by the discharge of pro-inflammatory cytokines. Inflammation is caused by IL-1, IL-6, and other factors. Tumor necrosis factor and initiation. IL-1 is the most studied cytokine, and its properties are associated with a variety of inflammatory diseases, including viral infection. Complex synthesis and release of inflammatory IL-1 occur after COV-19 binds to toll-like receptors (TLR). [23].

TNF antibody has been used in inflammatory bowel disease, rheumatoid arthritis, and other serious autoimmune diseases for more than 20 years. The U.S. Food and Drug Administration has accepted 10 indications for anti-TNF therapy and four indications for off-label therapy in 2019. Numerous studies have shown that TNF is an effective target for the treatment of a variety of inflammatory diseases. TNF is present not only as an inflammatory amplifier in almost all acute inflammatory diseases but also in the blood and infected tissues of coVID-19 patients. Therefore, the researchers recommend that patients be evaluated for TNF at admission in case they need intensive care for future treatment [24].

2.3.2 The counts of T-cells are found decreased in patients suffering from COVID-19

The T-cell is a kind of lymphocyte. It is an important cell in the immune system. The CD4 and CD8 receptors on the cell-surface bind with the MHC complex to make an effective response to the antigen [25]. Therefore, less T-cell counts mean that the immune system would be less activated and would become a harmful threat to health. One of the syndromes of COVID-19 is the low CD3+T-cell counts, CD4+T-cell counts, or CD8+T-cell counts but almost normal CD16+CD56+ cell (natural killer cells) counts [26, 27]. Unlike T-cells, an increase in other immune cells, monocytes, and B-cells was found [28]. The group of Xiaonan Zhang used the Kruskal-Wallis test to analyze the lymphocyte counts in COVID-19 patients. Among all the patients, asymptomatic patients have almost normal lymphocyte counts as normal people do. When it comes to T-cells, an obvious decline of CD3+ T-cell counts in the first 14 days after the onset of symptoms in all patients (mild, severe, and critical) was seen (Fig.2 a). This trend was also observed in the CD4+ T-cell counts and CD8+T-cell counts (Fig.2 b,c). However, no significant changes were found in natural killer cells (NK cells) and B-cells (Fig.2 d,e). Further tests were taken in later days. The result was interesting. There was a recovery of these T-cells and the counts eventually went back to normal range.

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A difference among the amounts of the same cell type was also found. For instance, critical patients have fewer CD3+T-cell counts than severe patients, and severe patients have fewer CD3+ T-cell counts than mild patients (Fig. 2 a) [29]. The same conclusion can also be made in T-cells with CD4 receptors and CD8 receptors. (Fig.2 b,c) Therefore, it can be speculated that the T-cell counts negatively correlates with the severity of symptoms in COVID-19.

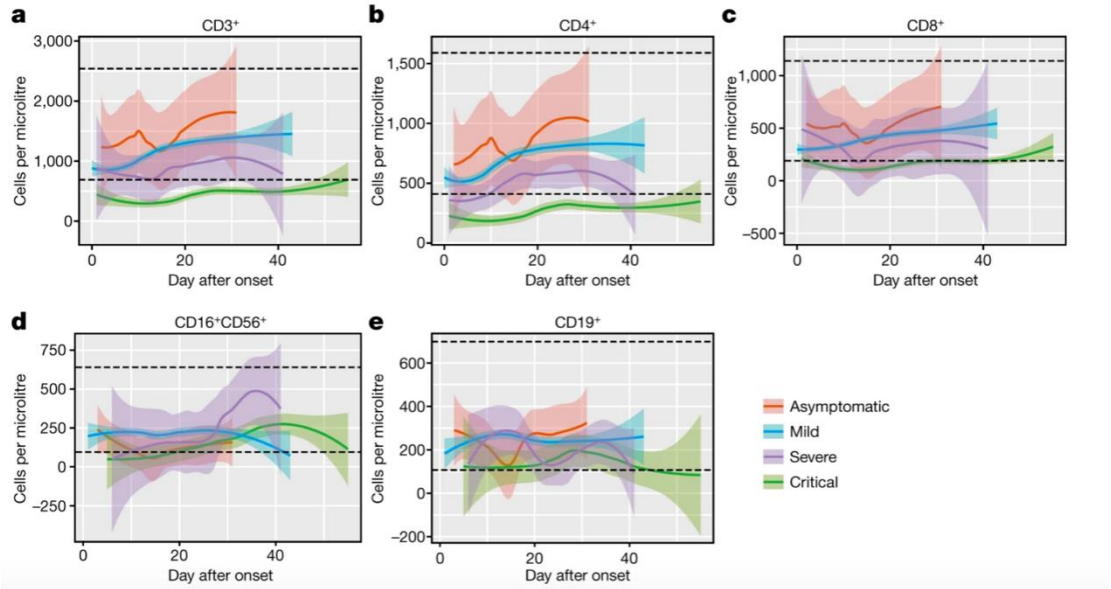

Fig 2. [30] Lymphocytes permicrolitre of asymptomatic, mild, severe and critical patients. a) CD3+ T-cells; b) CD4+ T-cells; c) CD8+ T-cells; d) CD16+CD56+cells (natural killer cells); d) CD19+ cells (B-cells) Method: the Kruskal-Wallis test

2.3.3 Dysregulated TNF-alpha, IL-6, and IL-10 suppress T-cells counts

As the decline of T-cells, the TNF-alpha, IL-6, and IL-10 concentrations were found increasing, which leads to the cytokine storm [27]. On the contrast, the level of IFN-gamma, IL-2, and IL-4 was not elevated and stayed on the normal range [27]. The concentration of TNF-alpha, IL-6, and IL-10 correlates with the severity of the patient (Fig.3 A), which is completely different from the amounts of T-cells in these two different types of patients. Further tests on the concentration of TNF-alpha, IL-6, and IL-10 in the serum samples were done and a decrease was found in the disease resolution period than the illness period. Simultaneously, T-cell counts were also found to recover in the disease resolution period. (Fig.3 C). Therefore, we can discover that the concentration of TNF-α, IL-6, and IL-10 is negatively correlated with the T-cell counts (Fig.3, B). This leads to the conclusion that the dysregulation of cytokines (TNF-alpha, IL-6, and IL-10) suppressed T-cell counts in COVID-19 patients.

2.4. Therapeutic Approaches

2.4.1 TNF inhibitors

Cytokine storm is mainly caused by TNFs which are always used as a target to mediate the cytokine storm. Anti-TNF therapy showed effectiveness in increasing survival possibilities in patients with sepsis according to a report [31]. It has also gained prominent outcomes when treating patients with atherosclerosis and other non-infectious diseases [32]. There is also another report showing the effectiveness of this therapy in COVID-19 challenged mice, it performed well in impairing T cell response and treating acute lung injury. Generally, suppression of TNF activity can increase the survival rate and recovering rate in patients with SARS-CoV [33]. However, TNFs haven't been found patients' serum at a later stage of infection [5]. Also, until now, there are not any clinical outcomes data to show the effective use of anti-

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TNF therapy in Covid-19 patients. Thus, the efficacy of using the TNF blocker requires further research and experiment.

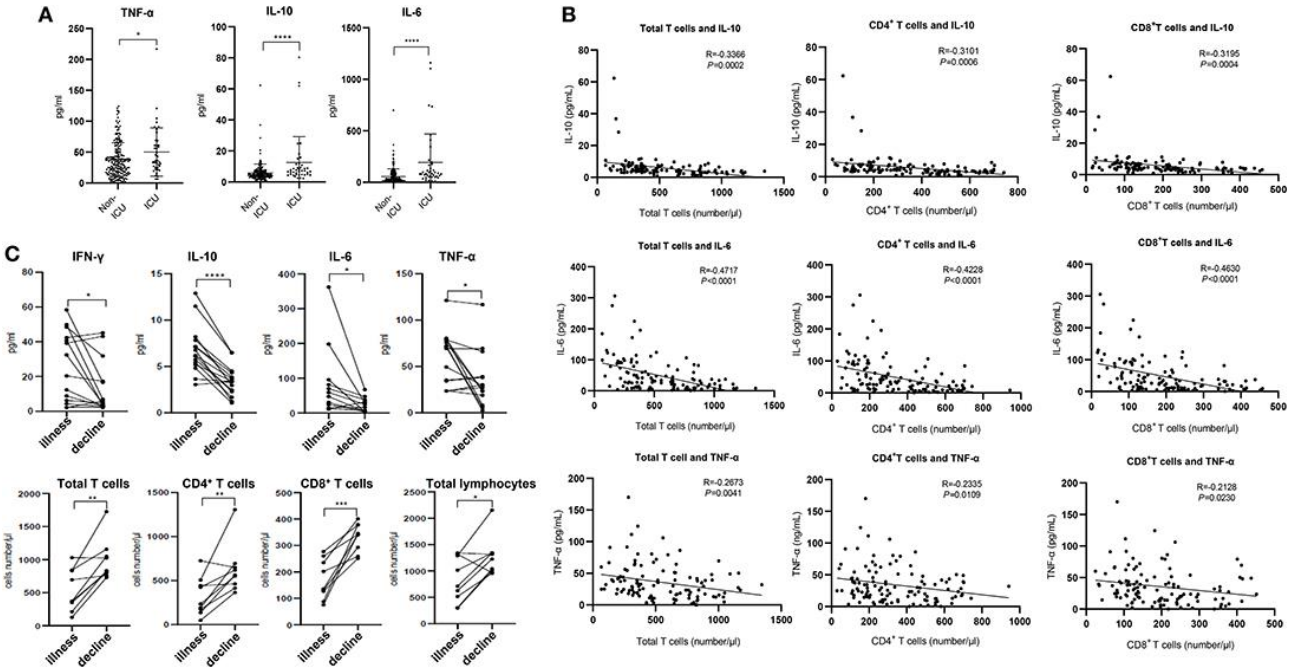

Fig. 3 [27] A) Concentration of TNF-alpha, IL-10 and IL-6 in none-ICU and ICU patients; B) Relationship between total T-cells and IL-10,CD4+T-cells and IL-10, CD8+ T-cells and IL-10 (Line 1), T-cells and IL-6, CD4+T-cells and IL-6, CD8+ T-cells and IL-6 (Line 2), T-cells and TNF-alpha,CD4+T-cells and TNF-alpha, CD8+ T-cells and TNF-alpha (Line3). (Shown in Cartesian coordinate system; horizontal axis: T-cell counts(number/μl); vertical axis: cytokines concentrations(pg/mL)); C) Trend of T-cell counts (total T-cell counts, CD4+ T-cell counts, and CD8+ T-cell counts) and cytokines concentration (TNF-alpha, IL-6, and IL-10) in illness period and decline period (disease resolution period).

2.4.2 Suppression of JAK1/JAK2

Baricitinib, showing apparent benefits when treating patients with rheumatoid arthritis (RA), can intracellularly inhibit the inflammatory signals of cytokines by suppressing JAK1/JAK2. It can prevent the assembly of SARS-Cov-2 into the target cells mediated by the ACE2 receptor as well as treating the cytokine storm caused by COVID-19 [34]. More than 10 clinical trials of Baricitinib registered in the U.S National Library of Medicine showed that the respiratory function of those patients improved a lot during the first two weeks in the baricitinib-treated group, compared to the baseline-treating group [35]. However, not the whole population can use the Baricitinib, for example, older people may get renal function repaired. Clinical trials and data of baricitinib are still quite limited. Further experiments are required to verify the applicable patients, dose requirements, and risks of the drug.

2.4.3 IFN- alpha and beta inhibitors

IFN alpha and beta can prevent viral replication by expressing the IFN-stimulated gene, IFN-alpha, and beta deteriorate the diseases by improving the macrophage and other innate immune cells' function [5]. There is a report shown that the early interferon response has a positive effect on mice infected with SARS-CoV but a delayed IFN alpha and beta expression can cause the imbalanced host response which drives to the development of COVID-19 [7]. This important finding indicates the importance of timing when using IFN treatment. Thus, the IFN-

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alpha/beta-blockers should be applied in the later stages of COVID-19 to stop the development of disease [36].

2.4.4 IL-1 family antagonists

IL-1 beta, IL-18, and IL-33 are the most influential cytokines in the IL-1 family during the cytokine storm [37]. Among the three of them, IL-1 beta plays the most important role. an antagonist of IL-1 beta, Anakinra, can be used to treat the cytokine storm caused by infection and it significantly increased the survival possibilities of patients with severe sepsis [38]. However, there is no clinical trial or result about using IL-1 family antagonists to treat patients with COVID-19. Further experiments and effects should be evaluated in the future.

2.4.5 IL-6 antagonists

IL-6 plays a key role in the pathology of COVID-19, and also is one of the main inflammatory cytokines. Tocilizumab, for now, as one often main cure for autoimmune diseases such as rheumatoid arthritis, is used to restrain the function of immune response and reduce the serum IL-6 level [39]. Experimental and clinical cases have proved that serum IL-6 level is remarkably rising in severe cases. Tocilizumab shows highly efficient in treating severe patients with extensive bilateral lung lesions, whose IL-6 level has already increased, in China. Tocilizumabis suggested to be intravenously injected, and the first dose is four to eight mg/kg. It is recommended dose of four hundred mg was diluted to one hundred ml with 0.9 percent saline solution, and the infusion time should be for more than an hour. An additional dose may be applied at 12 hours (the previous dose is the same), with the maximum two cumulative doses, in patients with poor response to the first dose [5].

3. CONCLUSION

This work reviewed the mechanism and the therapy of cytokine storm in COVID 19. Here, we focused especially on IFN, TNF, and certain interleukins which have been shown to be dysregulated in multiple independent studies. The upregulated IL-6, IL-10, and TNF-α may cause T-cell suppression and is one of the pathogenesis of COVID-19. Therapies including inhibitors and antagonists targeting IFN, TNF, interleukins, and the JAK1/JAK2 were discussed.

The immune system's daily job is to protect us from infection, but if the immune system is activated to the limit or gets out of control, it can harm the host, and the cytokine storm is an example. Immune cells communicate with each other through cytokines into the bloodstream that allow them to rush to the site of infection, while they can also devour damaged cells and even penetrate the walls of blood vessels. One severe example of dysregulated cytokines is the one the work discussed. Therefore, it is necessary to explore the mechanisms and the treatment for the cytokine storm in order to cure COVID-19.

IFN, TNF, and interleukins were discussed in this article. They are all cytokines. But what caused the pathogenesis of COVID-19 is not only cytokine storm but also chemokine storm. Chemokines like CXCL10, CXCL8, CXCL9, CCL2, CCL3, CCL5 [7] are also found greatly upregulated in COVID-19 patients. Further investigation on those chemokines should also be done.

Besides, all treatments for COVID are still needed further exploration to be introduced to general patients. Although Baricitinib is regarded as a potential drug for RA, its efficacy, risks, and dose control for COVID-19 patients remain unknown, especially for special groups - pregnant women and/or older individuals. Anti-TNF therapy has already achieved satisfying results in SARS-CoV- infected mice by curing acute lung injury and impairing the T-cell response. However, its feasibility of implementation needs more detailed clinical trial results to be verified. Tocilizumab, an IL-6 antagonist, has already been used in treating with COVID-19 patients in China and shows efficiency in treating severe patients with extensive bilateral lung lesions

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resulting from an elevated level of IL-6. Intravenous injection is recommended to use this drug. However, its side effect needs to be explored through more clinical trials.

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