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SARS-CoV-2 infection: Role of IL-6 and inflammatory cascade

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Abstract

Since December 2019, a novel coronavirus that represents a serious threat to humans' lives has emerged. There is still no definite treatment for the severe cases of the disease caused by this virus, named COVID-19. One of the most considered treatment strategies targets the exaggerated immune regulator, and IL-6 is a crucial pro-inflammatory mediator. Severe SARS-CoV-2 cases show an elevated high level of IL-6 related to the disease severity. IL-6 activity can be inhibited in these parts: IL-6 itself, IL-6 signaling pathways such as JAK-STAT, gp130, IL-6R, and downstream activated ILs, such as IL-17 and IL6 cytokine. Currently, according to these studies and their results, IL-6 blockade with anti-IL6- or its receptor antibodies such as tocilizumab in COVID-19 is beneficial in severe cases and may reduce the mortality rate. JAK-STAT inhibitors Ab inhibit the cytokine storm by inhibiting several crucial pro-inflammatory mediators such as TNF-α and IL-6 and have shown various results in clinical trials. IL-6 induces IL-17 secretion, and IL-17 is involved in the pathogenesis of inflammatory processes. Clinical trials of anti-IL-17 drugs are currently recruiting, and anti gp130 antibody is preclinical. However, this agent has shown positive effects of inflammatory bowel disease clinical trials and could be tested for SARS-CoV-2. This study aimed to review IL-6 role in the cytokine storm and studies regarding IL-6 and its inflammatory

pathways blockade in COVID-19 to find out if any of these agents are beneficial for COVID-19 patients.

Key Words: Anti-interleukin -6; COVID-19; Inflammation; Interleukin-6; Interleukin-6 receptor; SARS-CoV-2

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Core Tip: One of the most considered treatment strategies is targeting the immune response and pro-inflammatory cytokines such as IL-6. Severe SARS-CoV-2 individuals show an elevated level of IL-6 and it is related to the disease severity. Currently, according to studies IL-6 blockade by anti-IL-6 or its receptor antibodies such as tocilizumab is beneficial in severe cases and may reduce the mortality rate. Moreover, combination of anti-inflammatory agents is more effective than single therapy.

INTRODUCTION

In December 2019, an epidemic of secretive pneumonia started from Wuhan city, Hubei province, China, and quickly spread into many other countries and finally turned to a pandemic [1]. The causative agent, Severe Acute Respiratory Syndrome-Corona Virus 2 (SARS-CoV-2), is a single-stranded enveloped RNA virus belonging to Nidovirales and the family Coronaviridae. The SARS-CoV-2 genome structure analysis has presented that this virus is related to the beta-coronavirus genus, containing bat SARS-identical coronavirus and two previous invasive coronaviruses Middle East Respiratory Syndrome-Corona virus (MERS-CoV) and SARS-CoV [2]. Universally, as of September 2021, there have been 226,844,344 recognized cases of SARS-CoV-2, including 4,666,334 victims [3]. Disease caused by the novel coronavirus, Corona Virus Disease 2019 (COVID-19), is similar to those previous ones, mainly causes pulmonary involvement

dieses [4], and all of them have a zoonotic origin. In addition to the pulmonary involvement, various organs such as the kidney, gastrointestinal system, nervous system, liver, and coagulation system, can be targets of the virus, leading to serious complications such as acute kidney injury (AKI), acute pulmonary failure, and disseminated intravascular coagulation (DIC) that may lead to death [5]. Currently, this virus is a serious global concern with enormous social and economic damages to all societies worldwide [6].

Moreover, the fatality rate is high in severe cases [7]. As of now, we do not have any definite treatment for severe cases of this disease, and the management of severe SARS-CoV2- patients is still challenging. Therefore, various treatment options are assumed according to the different viral pathogenesis levels, including viral entry, replication, and effects of the virus on the target cells. The anti-viral agent remdesivir is the only treatment with a federation of drug and food administration agency (FDA) approval for this disease, and dexamethasone is the only one revealed to reduce mortality in hospitalized patients with decreased oxygen saturation but not in others [8]. Albeit the World Health Organization (WHO) has suggested mortality trials for some repurposed anti-viral drugs, including lopinavir, interferon beta 1a (INF-β-1a), and hydroxychloroquine in hospitalized patients with SARS-CoV-2 [9].

In this regard, IL-6 is known as a crucial inflammatory mediator with essential roles in the pathogenesis of inflammatory diseases in addition to several chronic disorders such as diabetes mellitus [10]. This cytokine is widely expressed by different immune cells and affects immune function [11]. In this regard, the disease has a wide range of symptoms. Clinical deterioration in COVID-19 is mainly due to the effects of inflammatory cytokines like IL-1, Interleukin-6 (IL-6), IFN-α, and tumor necrosis factor (TNF) that are increased in the cytokine storm phase, and also the role of immune cells including neutrophils [12–15]. In this process, when a neutrophil encounters a pathogen, the extensive release of cytokines such as IL-1 and IL-6 may become harmful to the body and lead to multi-organ damage [13]. In this rationale, targeting the cytokine release

syndrome (CRS) symbolizes a possible therapeutic goal in managing SARS-CoV-2 related cytokine storms, and one of the significant known cytokines as IL-6 [16].

In this study, we aim to review IL-6 roles, the rationale of IL-6 blockade in COVID-19, and the results of recent studies that have been done in this regard so far to find out whether any available anti-IL6 agents or any other drugs with the ability to inhibit inflammatory pathways induced by this cytokine has shown efficacy in improving the patient's prognosis in SARS-CoV-2.

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2. METHOD OF STUDY

PubMed, Google Scholar, Scopus, and the science web were searched with the following keywords or their combinations, without any time limits: COVID-19, Interleukin-6, Interleukin-6 Receptor, SARS-CoV-2, Anti-IL-6, Inflammation. Related articles of any type were reviewed and selected. Extracted information included: SARS-CoV-2 pathophysiology and characteristics, IL-6 activities in the immune system and associated pathways, examples of studies focused on the concept of anti-IL-6 antibodies in the treatment of COVID-19, and other ways of IL-6 inhibition (Janus Kinase and Signal Transducer and Activator of Transcription (JAK-STAT) inhibition and anti-IL-17 therapies) and are discussed further.

3. SARS-COV-2 PATHOPHYSIOLOGY AND CHARACTERISTICS

In the last two decades, the third most common coronavirus to cause a pandemic of acute respiratory disease in humans is SARS-CoV-2. These viruses enter the body through respiratory aerosols and are attached to the nasal or paranasal epithelial cells

[17]. Angiotensin-converting enzyme 2 (ACE-2) is the major receptor for these viruses to enter host cells, which is more expressed in nasal epithelial cells [18,19].

The virus, along with the infection of the ciliated cells in the airways, undergoes local replication and dissemination. This stage lasts a few days, and a slight immune response is produced during this process. Despite having a low viral load at this time, infected individuals are highly contagious, and the virus can be identified with a nasal swab [20].

3.1 VIRUS ENTRANCE TO THE HOST CELL

Through its spike (S) protein, the virus enters the host cell *via* binding to ACE-2 on the cellular surface. Transmembrane serine protease 2 (TMPRSS2), protease then mediates S protein cleavage, and the virus enters the cell [21]. A high virus infectivity rate is associated with mutations in the binding domain of the receptor and the acquisition of a furan cleavage site in the S protein. The association of the virus with ACE-2 can decrease anti-inflammatory function and increase angiogenic activity [22]. The virus migrates from the nasal epithelium to the upper respiratory tract within the conducting airways [23]. The disease presents various signs and symptoms such as fever and dry cough due to the involvement of the upper respiratory tract [24].

During this point, a higher immune response is risen from the virus-infected cells and results in the secretion of C-X-C motif chemokine ligand 10 (CXCL-10) and interferons (IFN-β and -λ). As a result of the sufficient immune response to control the spread of infection, the majority of patients do not advance beyond this point [25]. About one-fifth of infected individuals advance to this point and may experience severe symptoms. The virus, *via* the host receptor ACE-2, targets the alveolar epithelial cells of type 2 and continues to undergo replication to create more and more viral nucleocapsids [26].

Many distinct cytokines and inflammatory markers are now produced by virus-laden pneumocytes such as interleukins (IL-1, IL-6, IL-8, and IL-12), tumor necrosis factor-alpha (TNF-α), IFN-λ and IFN-β, monocyte chemoattractant protein-1 (MCP-1), CXCL-10, and macrophage inflammatory protein-1 alpha (MIP-1α). This 'cytokine storm'

serves as a chemoattractant to neutrophils, CD4 helper, and CD8 cytotoxic T cells, and these cells then get sequestered in the pulmonary tissue [27,28]. In addition to being crucial in fighting the virus, these cells cause inflammation and damage to the lungs and other organs. The host cell undergoes apoptosis by releasing new viruses, which will then infect the neighboring type 2 alveolar epithelial cells in the same way. Diffuse trauma to the alveoli eventually results in an acute respiratory syndrome and finally respiratory distress, owing to the recurrent injuries triggered by the sequestered immune cells and viral replication, contributing to both type 1 and type 2 pneumocytes annihilation [29,30].

The COVID-19 virus spreads mainly by transmitting respiratory droplets from person to person and occurs when someone is in close contact with an infected individual with coughing or sneezing violently. This happens as the host's mucosal surfaces, i.e., the eyes, nose, and mouth, are exposed to the infected respiratory droplets [31]. Virus transmission may also occur by fomites, such as bedsheets, towels, kitchen utensils, thermometers, and stethoscopes, used by or used on the infected person. Airborne transmission of COVID-19 can occur especially in situations where aerosol-generating procedures are conducted, i.e., endotracheal intubation, bronchoscopy, open suction, oxygen nebulization, bronchodilators, or steroids, ventilation using the bag, and mask, tracheostomy, and cardiopulmonary resuscitation [32]. In this way, the incubation time for SARS-CoV-2 (between the onset of symptoms and exposure to the virus) is about 5 to 6 days. However, it can reach up to 14 days. During this time, also known as the 'pre-symptomatic' phase, the affected individual can be contagious and transmit the virus to the healthy population [33,34]. The most frequent symptoms include fever, muscle aches, shortness of breath, malaise, and a dry cough.

While patients can remain asymptomatic or develop a mild, moderate, or severe illness, gastrointestinal manifestations such as stomach pain, vomiting, and loose stools can also occur. Many of the complications seen in SARS-CoV-2 infected individuals are attributed to cytokine release syndrome [35,36].

3.2. CYTOKINE STORM

Cytokine storm was historically referred to as an influenza-like syndrome from a historical standpoint that occurred during systemic diseases such as sepsis and after immunotherapies such as toxins from Coley. *Yersinia pestis* (causative agent of plague or black death) infection has led to extreme pandemics; it induces alveolar macrophages to produce disproportionate quantities of cytokines, resulting in the storming of cytokines and subsequently has caused massive pandemics [37]. Intensive inflammatory response and fast release of various cytokines (such as TNF-α-1,2, IL-6, and IFN-γ) to the circulation are activated by the pathogen infection (Figure 1). Patients with viral infections are especially vulnerable to acute respiratory failure due to the cytokine storm [38]. For instance, in other extreme coronaviruses (SARS and MERS), cytokine cascades and low lymphocytes are positively linked to the course and severity of the disease. Latest experiments have supported this conclusion in most cases of SARS-CoV-2, indicating low lymphocyte counts and heightened levels of inflammatory mediators [12,39]. Furthermore, it has been shown that pro-inflammatory cytokines such as IL-6 play an essential role in the progression of COVID-19 disease.

4. IMMUNE SYSTEM AND ROLES OF IL-6

IL-6 is a soluble mediator with various functions in the immune system [40]. For example, controlling the differentiation and migration of the immune cells, apoptosis of target cells [41], and assembly of acute-phase proteins such as C-reactive protein (CRP), haptoglobin, and fibrinogen. In contrast, IL-6 reduces the production of other proteins such as albumin. Human IL-6 comprises 212 amino acids (28-amino-acid signal peptide), and its controlling gene is located on chromosome 7p21 [40]. This interleukin is contributed to the hypothalamic-pituitary-adrenal axis regulation and glucose homeostasis. It induces the differentiation of T-helper cells, which secret IL-17. These cells are related to the pathogenesis of chronic inflammatory diseases [42]. IL-6 is produced in the immune system by different cells and endothelial cells and contributes to the pathogenesis of chronic inflammatory diseases like rheumatoid arthritis,

atherosclerosis, and systemic lupus erythematosus [41]. This cytokine acts through binding to its receptor on the target cells that are consisted of CD126 (IL-6 Receptor-α) and glycoprotein 130 (gp130). Therefore, it activates signaling pathways such as JAK/STAT [43] and mitogen-activated protein kinase [11]. Conformational alterations in the gp130 cytoplasmic domain after IL-6 bound to IL-6 receptor induces JAK/STAT to become activated [43], and JAK/STAT signaling pathway activation leads to cytokine release [44]. However, these signaling pathways downregulate IL-6 expression [11].

While the membrane-bound receptor (IL6-Rα) is expressed only on the surface of a small number of cells such as leukocytes and hepatocytes (known as IL6- classic signaling), IL-6 can affect many other cells through its soluble receptor (sIL-6Rα). Endothelial cells also have recently been discovered that express IL-6R. This receptor forms a complex with IL-6 that binds to gp130. Then this complex mediates a signal known as IL-6 trans-signaling through which pro-inflammatory responses are mainly mediated. In contrast, the classic signaling pathway is related to the anti-inflammatory pathways [41]. Furthermore, IL-6 is produced by the innate immune cells after encountering a pathogen and is critical in the body's defense against the respiratory syncytial virus and influenza virus in the early infection phases [45]. However, in CRS, IL-6,5 can induce coagulation cascade and complement system over-activation, capillary leakage, hypotension, and myocardial dysfunction [46].

In the severe SARS-CoV-2 infection, there are high levels of pro-inflammatory mediators, such as IL-6. While one study showed the role of monocytes as a source of IL-1β and IL-8, the exact source of IL-6 remains unclear [47]. In the presence of the immune dysregulation, in addition to a non-sufficient anti-viral response, we have a continuous secretion of pro-inflammatory mediators such as IL-6 that resemble the macrophage activation syndrome and lead to multi-organ damage [45]. Also, in COVID-19, multifocal interstitial pneumonia is the chief reason for pulmonary failure and death. In this process, there are inflammatory infiltrates in the interstitial tissue of the lungs, which lead to alveolar damage [48]. These infiltrates consist of mononuclear cells that will be called after the pro-inflammatory pathways are activated by trans-signal

transduction of IL-6 [45]. In this way, One study showed that patients with high levels of ACE-2 expression experience more severe tissue damage by IL-6 and cytokine storm after being infected with SARS-CoV-2. These individuals also have a suppressed immune system to fight against the virus [7]. In summary, IL-6 is crucial in both pro-inflammatory and anti-pathogen responses, and trans-signaling is the critical pathway of inflammatory processes conducted by IL-6. A diagram of its significant roles and location in the immune cascade is summarized in Figure 2.

5. DRUGS AVAILABLE TO INHIBIT IL-6 ACTIVITY

According to the signaling pathways induced by IL-6 and its components, IL-6 activity can be inhibited in these parts: IL-6 itself, IL-6 signaling pathways such as JAK-STAT, gp130, IL-6R, or IL-6/sIL-6R complex [49]. Two main drugs in the class of IL-6 receptor blockers include tocilizumab (TCZ) and slumab, which are monoclonal antibodies FDA approved in rheumatoid arthritis, while the first one is also approved in juvenile idiopathic arthritis (JIA) and giant cell arteritis [50].

TCZ blocks both soluble and membrane-bound receptors and accordingly blocks the signal transduction *via* JAK/STAT [51]. JIA, chimeric antigen receptor (CAR)-T cell-induced CRS, giant cell arteritis, rheumatoid arthritis, and Still's disease are examples of the conditions in which tocilizumab has been used to control the disease [52]. Siltuximab is an anti-IL6 agent that has shown more effectiveness than TCZ in some aspects, and although it is not FDA approved, it is used in CRS refractory cases. Data regarding Siltuximab in COVID-19 are currently restricted [46].

The specific gp130FC named Olamkicept specifically blocks the trans-signaling pathway. In animals, it showed more effectiveness in controlling the hyper-inflammatory status due to sepsis than anti-IL-6 antibodies. Significantly, it didn't impair anti-inflammatory responses of IL-6 *via* classic signal-transduction [45]. JAK/STAT inhibition is another option. Some of these agents are currently on COVID-19 clinical trials, such as ruxolitinib. A list of these drugs is summarized in table-1.

6. EXPERIENCE OF IL-6 BLOCKADE IN COVID-19

Cytokine storm is shown to be associated with the disease intensity in SARS-CoV-2, as it was also indicated in SARS-CoV-1 and MERS-CoV. Although reports from different studies focused on IL-6 blockade in COVID-19 are inconsistent, it was first shown to reduce the mortality rate in critically ill patients [53].

Considering the presence of lymphopenia in SARS-CoV-2 patients, administration of immunosuppressive agents might increment the risk of secondary fungal or bacterial infections [54]. Besides, in a previous study, tocilizumab induced necrotizing fasciitis and candidemia [55]. Accordingly, the exact place for immunosuppression and anti-IL-6 agents in COVID-19 is crucial. The idea of the possible effects of tocilizumab on the management of the COVID-19 related cytokine storm first originated from observational studies that showed it to be effective in the clinical improvement of COVID-19 patients [56]. In a recent clinical trial, the effect of a single dose of 8mg/kg tocilizumab administration *via* the intravenous route in addition to the standard of care in the management of COVID-19 was investigated. In this study, 46 adult patients who were positive for SARS-CoV-2 and had multifocal interstitial pneumonia in the imaging studies were enrolled soon after showing clinical worsening. The drug was influential in the clinical improvement of severely ill patients and patients in the early clinical worsening status. However, it didn't show any significant efficacy in reducing the mortality rate and was accompanied by adverse effects [48].

According to a recent observational study, having a more than 30 pg/mL level of IL-6 is related to the disease severity and need for respiratory support in COVID-19 patients. This study showed the positive effects of tocilizumab on patients with higher IL-6 Levels at baseline, but no positive trends were seen in the group with a low IL-6 Level [51].

A recent case series showed the efficacy of subcutaneous TCZ in three severely ill COVID-19 patients in reducing the inflammatory-related indices and improving the clinical condition [57]. The results of a prospective phase two cohort study (TOCIVID-19) showed that tocilizumab effectively reduced the mortality rate at 30 days, especially in

severe patients who didn't need mechanical ventilation. This effect was independent of corticosteroids and was not accompanied by any significant adverse events [58].

One of the concerns about using anti-immune drugs in SARS-CoV-2 is that they may interfere with the proper immune response to the virus. Cytokines, especially IL-6, play a significant role in the host's fight against the viruses through the humoral and cellular responses by affecting helper and cytotoxic T cells. Accordingly, a cohort study was conducted in Spain in which it was found that these drugs do not pose a problem in the body's fight against the virus. Although the study found that patients treated with anti-cytokines had a longer viral clearance time, they initially had higher virus levels, and their disease was more severe [59]. A preprint study that showed an unexpected increase of inflammatory mediators after TCZ administration supports the fact that IL-6 blockade alone may not work in the management of COVID-19 [60]. Recently, two studies showed a transient elevation in the D-dimer level in SARS-CoV-2 patients receiving TCZ [61,62]. A recent meta-analysis also demonstrated that IL-6 blockade alone does not lower the mortality rate, although it may effectively reduce the risk of respiratory failure in hospitalized patients [63]. According to one other study, administration time is another crucial factor, and treatment with TCZ after ten days of disease onset is more beneficial [64]. In contrast, other studies, including the recovery trial, have shown that early administration of TCZ in severe cases before ICU admission and the need for mechanical ventilation is effective in reducing the mortality rate, [65,66] and after the patient needs mechanical ventilation, it will not have much effect [66,67]. In general, different methods and inclusion criteria in studies do not find a sole result. A list of recent studies in this regard is summarized in Table 2. According to some clinical trials, tocilizumab, when added to a corticosteroid, reduces the mortality rate remarkably compared with corticosteroids (CSs) alone. Treatments that include agents to target more ILs in addition to IL-6 have more efficacy than the sole IL-6 blockade [63,68]. IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF, IL-1, and IL-8 are the primary inflammatory mediators that could be targeted in CRS. IL-1 is proximal to IL-6 in the inflammatory cascade, and its blockade has recently been

considered. A recent study compared the effectiveness of IL-1 and IL-6 blockade and also with the standard of care, and it was observed that IL-1 inhibition is more effective in reducing the mortality rate, while positive effects of IL-6 antibodies were restricted to a group of severely ill patients with high CRP levels [50]. One other clinical trial of tocilizumab in COVID-19 patients with a hyperinflammatory state also stopped recruiting as it failed to reach its primary endpoints (improving the patient's clinical status or reducing the mortality rate) [69]. In general, despite the effect that IL-6 blockade has on the suppression of inflammation, it cannot completely control the inflammation because it doesn't affect the distal inflammatory pathways [70]. However, in severe and critical SARS-CoV-2 patients with a hyperinflammatory state, IL-6 blockade with monoclonal antibodies seems to be effective in reducing the mortality rate, reducing the risk of mechanical ventilation, and improving the clinical condition [67,71–74]. Although all of these studies have been performed in adult patients, the effect of tocilizumab in the treatment of COVID-19 in children is also being investigated in the RECOVERY trial [67].

As of now, several clinical trials have failed to show the efficiency of tocilizumab in COVID-19 treatment. However, the RECOVERY trial and some other clinical trials showed positive results [67,75,76]. Although meta-analysis had previously demonstrated an 11% reduction in 28-day mortality from tocilizumab use in severe patients with SRS-CoV-2, this reduction was significant when the results of the recovery trial were added [67]. In conclusion, this drug can effectively improve the prognosis in extreme cases.

As we know, tocilizumab inhibits both classic and trans-signal transductions through IL-6, thus interfering with this cytokine's anti- and pro-inflammatory functions. As mentioned previously, IL-6 signaling pathways involve the JAK-STAT that could be targeted with drugs such as ruxolitinib, a JAK 1 and 2 inhibitors. This drug lowers the levels of IL-6 and is currently being evaluated for SARS-CoV-2 and had positive effects in one previous study [77]. However, RUXCOVID, a clinical trial of phase 3 of ruxolitinib, revealed no significant efficacy in reducing the death rate and serious complications [78]. The other JAK inhibitor is baricitinib. A recent clinical trial (ACTT2)

that have evaluated baricitinib in hospitalized patients with SARS-CoV-2 indicated that it reduced the recovery time when added to remdesivir, compared with remdesivir alone [79,80]. Another study also investigated the potency of the anti-myeloproliferative agent ruxolitinib and included the patients needing supplementary oxygen but not with respiratory failure. This study found that inflammatory mediators significantly went down after using ruxolitinib and improved clinical conditions. These successes were not accompanied by any severe effects [81]. Another potency of JAK inhibitors to hamper the cytokine storm is related to TNF, the other crucial inflammatory mediator in the cytokine storm formation that uses JAK signaling and will be inhibited by JAK inhibitors. One recent study evaluated the concurrent administration of an IL-1 blocker antibody and ruxolitinib in critical patients with SARS-CoV-2. The preliminary report of this study demonstrated that this combination was beneficial in clinical improvement, and also, the lymphocyte count grew after the treatment [82]. Besides, they didn't observe any treatment-related severe complications. Tofacitinib is another JAK inhibitor that was shown to reduce adverse outcomes and mortality in COVID-19 treatment in a previous retrospective cohort study [83]. Another exciting intervention for IL blockade with positive effects in patients on ECMO in the previous research was extracorporeal cytokine adsorption which showed a significant IL-6 decrease in treated patients [84,85]. Other agents with anti-IL6 properties have not entered clinical trials of COVID-19 yet. However, targeting the trans-signaling pathway seems more efficient than non-specific IL-6 blockade with monoclonal anti-bodies.

7. IL-6 INDUCES TH17 LINEAGE DIFFERENTIATION

Th17 is shown to be related to the inflammatory processes. As mentioned in figure-2, after the IL-6-sIL-6R complex reaches CD4+ T cells, it causes them to differentiate into Th17 cell lineage. This action is mediated through the JAK/STAT signaling pathway (IL-6 recruits JAK 1 and 2). These cells can secret IL-17, 21, and 22 and GM-CSF, and therefore, they are contributed to the pathogenesis of inflammatory processes and chronic diseases. Viral diseases also promote Th17 related responses, and severe cases

show higher Th17-related cytokines. Accordingly, the Th17 blockade seems to be another way to fight against COVID-19, especially in extreme cases. One study showed that fedratinib reduced the Th17 related cytokines in mouse models. This drug is a JAK 2 inhibitor [86].

It is shown that the Th17 subgroup of T cells is increased relative to the other subgroups in COVID-19 severe cases. The role of these cells is revealed in lung injuries of SARS-CoV-2 patients. Drugs with anti-IL17 activities are ixekizumab, secukinumab, and brodalumab, and they are used in moderate to severe cases of psoriasis [87,88]. Ixekizumab is an anti IL17 antibody currently on a recruiting COVID-19 clinical trial. Inclusion criteria in this study are having high serum levels of IL-6 and not being intensive care unit (ICU) admitted [89]. When IL17 is secreted from Th17 cells, it causes target cells to produce inflammatory mediators, including IL-6, TNF- α, chemokine C-C motif 2 (CCL2), and IL-1β. These procedures lead to CRS and clinical worsening in SARS-CoV-2 [87]. IL-17 is also related to the cutaneous manifestations of COVID-19 [90]. However, recent evidence has shown undetectable quantities of IL-17A expression in COVID-19 patients [91]. In a previous study, Secukinumab, an anti-IL-17A selective antibody, was accompanied by clinical improvement in severe SARS-CoV-2 patients [92].

CONCLUSION

According to the all mentioned above, IL-6 blockade alone with anti-IL6R monoclonal antibodies has no significant benefits on improving the prognosis of patients, except for patients with a critical condition and at the hyper-inflammatory state before mechanical ventilation. Many factors are related to a patient's response to IL-6 blockades, such as baseline IL-6 Level and disease severity. It may also be associated with some worrying side effects. According to recent data, a combination of anti-inflammatory agents is more effective than any one alone. Other ways to IL-6 inhibition, such as selective trans-signaling pathway and JAK/STAT inhibition, should be more investigated.

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