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REVIEW

Cytokine release syndrome: inhibition of pro-inflammatory cytokines as a solution for reducing COVID-19 mortality

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ABSTRACT. Coronavirus disease (COVID-19) reached pandemic proportions at the beginning of 2020 and continues to be a worldwide concern. End organ damage and acute respiratory distress syndrome are the leading causes of death in severely or critically ill patients. The elevated cytokine levels in severe patients in comparison with mildly affected patients suggest that cytokine release syndrome (CRS) occurs in the severe form of the disease. In this paper, the significant role of pro-inflammatory cytokines, including IL-1, IL-6, and TNF-alpha, and their mechanism of action in the CRS cascade is explained. Potential therapeutic approaches involving anti-IL-6 and anti-TNF-alpha antibodies to fight COVID-19 and reduce mortality rate in severe cases are also discussed.

Key words: Corona virus, COVID-19, cytokine release syndrome, treatment

INTRODUCTION

Coronavirus disease 2019 (COVID-19), an epidemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has already reached pandemic proportions in 2020, affecting individuals in almost all countries and regions of the world [1-3].
It is estimated that the COVID-19 fatality rate is about 4%, which might not be a big number compared to other lethal viruses. However, due to the high transmission capability, the overall number of deaths is very high. It has been found that severe cases of COVID-19 occur mostly in the elderly population or individuals with underlying diseases [4, 5]. Studies have demonstrated that severe cases of COVID-19, who presented with acute respiratory distress syndrome (ARDS), had higher levels of inflammatory cytokines. The clinical observation of high levels of pro-inflammatory cytokines, which is often caused by infectious diseases like COVID-19, is described as cytokine release syndrome (CRS) [6-8]. CRS is an acute reaction of the immune system that results from T lymphocyte activation and an increased level of cytokines that are released from myeloid cells such as macrophages and monocytes due to their activation by corona virus. The high grades of CRS can lead to serious symptoms in severe cases. Interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) are the three major cytokines found in CRS activation [8-10].
Deaths from COVID-19 are primarily attributed to diffuse alveolar damage with pulmonary edema, hyalin membrane formation, and interstitial mononuclear inflammatory infiltrate associated with early-stage adult respiratory distress syndrome (ARDS). Prevention of ARDS and death in COVID-19 patients is an urgent health emergency. Owing to the significant role of IL-1, IL-6, and TNF-α in CRS activation, it is hypothesized that by blocking these cytokine pathways, CRS activation and its extreme manifestations that lead to patient death could be lessened. Tocolizumab is an anti-IL-6 monoclonal antibody drug which has shown promising results. In addition to Tocolizumab, anti-TNF therapeutic antibodies like Infliximab or Adalimumab could also be studied for COVID-19 treatment [11, 12].

COVID-19 SEVERE CASES

Recent studies have demonstrated that severe cases of COVID-19 occur mostly in the elderly population or

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individuals with underlying diseases [13]. Based on the standard criteria for case stratification applied in China and other countries, a COVID-19 case is considered as *severe* if the patient has the following manifestations:
(i) tachypnea (respiration rate $\geq$ 30 per minute);
(ii) oxygen saturation $\leq$ 93% or;
(iii) arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO2/FiO2 ratio) is less than 300 mm Hg.

Moreover, a critical case is defined as a patient who suffers from the following conditions:
(i) respiratory failure in which respiratory intubation is indicated;
(ii) septic shock, or other organ failures that need hospitalization in an intensive care unit (ICU) [14].

According to epidemiological studies, up to 20% of SARS-CoV-2 cases can be classified as severe or critical cases. Due to the higher morbidity and mortality rate in these subgroups, they impose a much higher burden on health systems around the globe [15].
Based on various studies, the SARS-CoV2 Receptor Binding protein (RBP) binds to Angiotensin Convertase Enzyme 2 (ACE2) as its main receptor for entrance into various cells [16]. ACE2 is mainly expressed in cardiac and alveolar cells, but it also can be found in several hematopoietic cell types, including macrophages and monocytes [15]. The infection of hematopoietic cells with SARS-CoV2 can lead to cell activation and secretion of pro-inflammatory cytokines like IL-6, IL-1, and TNF-α into the systemic blood circulation, which can result in severe manifestations of the disease. As one example, increased vascular permeability caused by these pro-inflammatory cytokines can lead to infiltration of blood cells and plasma into the alveoli, which can lead to respiratory symptoms like dyspnea or ARDS in these patients [17].
A study by Chen *et al.* demonstrated that severe cases of COVID-19, who presented with acute respiratory distress syndrome (ARDS), had higher levels of inflammatory cytokines, including IL-6, TNF-α, and IL-2R compared to moderate cases [7]. CRS was also suggested to be one of the leading causes of morbidity in infections with SARS-CoV and the Middle East respiratory syndrome-related coronavirus (MERS-CoV), which showed significant similarities with the present SARS-CoV2 in terms of their pathogenicity mechanisms [18, 19].
In a study by Wan *et al.* 123 patients with a confirmed diagnosis of SARS-CoV-2 were enrolled for the analysis of their serum cytokine levels. They were divided into two subgroups of moderate and severe, based on the standard criteria. The analysis of serum cytokines in these two groups of patients demonstrated a high level of IL-6 in 30% of patients in the moderate subgroup, while the IL-6 level was above the normal range in 76% of the severe group patients [20]. The data analysis showed a significant difference for IL-6 level ($p < 0.0001$) between mild and severe cases of COVID-19. Moreover, a significant correlation between higher levels of IL-6, TNF-α, and severe cases of COVID-19 has recently been observed [20, 21].

AN INTRODUCTION TO CYTOKINE RELEASE SYNDROME

The cytokine storm or CRS development is a potentially fatal immune disorder, characterized by rapid proliferation and hyperactivation of T cells, macrophages, natural killer cells, and overproduction of more than 150 different inflammatory cytokines and chemical mediators that are secreted by immune or nonimmune cells [21-23]. CRS is initially characterized by definitive fever and several types of organ damage. CRS can be caused by various factors such as specific drugs, some infections, therapeutic antibodies, and chimeric antigen receptor (CAR) T cell therapy. It has been proposed that some viruses, like influenza and coronavirus (COVID-19), might also trigger the onset of the CRS cascade [24-26].
CRS is categorized into four grades ranging from grade one, which is the mildest where the patient presents flu-like symptoms, to grade four where the patient suffers from serious illness and requires ICU care (*figure 1*). Weakness, headache, skin rash, arthralgia, and myalgia are associated with grade-1 CRS. On the other hand, severe CRS or Grade three and four patients present with a high-grade fever, which leads to uncontrolled cytokine release with vascular leakage and multiple end organ damage such as renal failure, heart failure, or pulmonary edema. In these cases, disseminated intravascular coagulation (DIC), and other laboratory disorders such as cytopenia, high levels of CRP, creatinine, and liver enzymes might occur as well [27].
The pathophysiology of CRS is not completely understood. CRS is usually due to on-target effects caused by the binding of a bispecific antibody or the receptor on CAR-T cells to its antigen and the subsequent activation of existing immune cells and also nonimmune cells, such as endothelial cells. Activation of the bystander cells results in the massive release of a number of cytokines like IL-1, IL-6, and TNF-α. Our knowledge about the initial T-cell activation that results in cytokine release and systemic inflammation is limited [28-30].
There is evidence that the cytokine cascade is TNF-dependent. Therefore, if TNF-α is inhibited, there is an immediate (i.e. <12 h) decrease in IL-6 and IL-1 concentrations in patients with active systemic inflammatory disease. Relevantly, the loss of adhesion molecules and the secretion of vascular endothelial growth factor, often known as vascular permeability factor, suggest its role in the capillary leakage. In fact, decreased leukocyte transport occurs in inflamed tissues due to reduced adhesion molecules and chemokines, with diminished cell content in the exudate [31-34].

ROLE OF PRO-INFLAMMATORY CYTOKINES IN CYTOKINE RELEASE SYNDROME

CRS pathogenesis depends on the activation of various cytokines like IL-1, IL-6, and TNF-α. Although these cytokines play a pro-inflammatory role intended to defend the host against several infectious agents, their

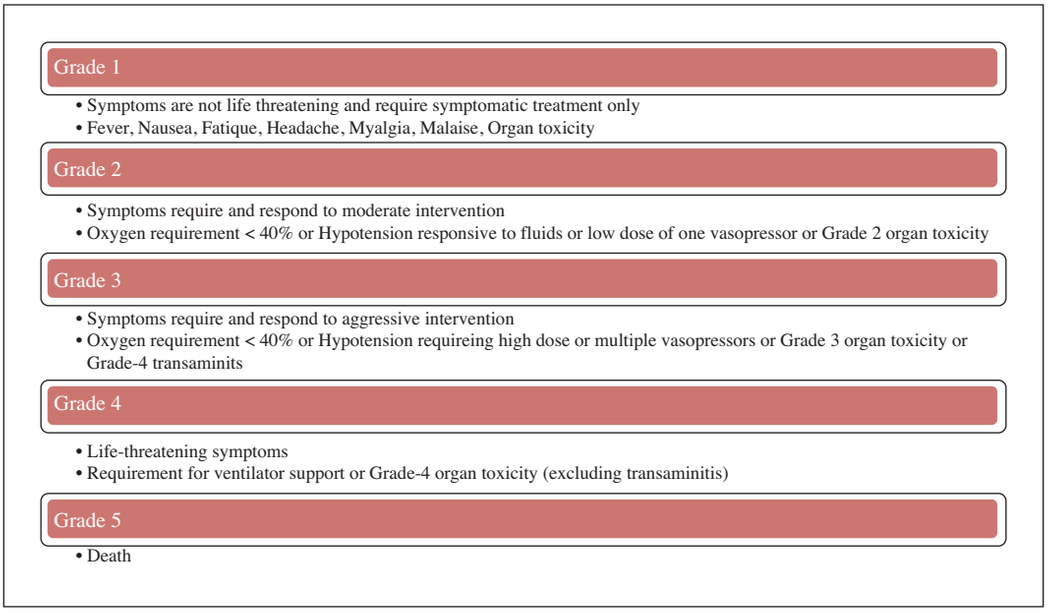

Figure 1
CRS grading.

excessively high levels can become a life-threatening factor leading to systemic CRS [35].

Epithelial cells are the first barriers against viral respiratory infections. As the viral load increases, due to the proximity of epithelial cells and tissue macrophages, macrophages become infected. These activated macrophages initiate the cytokine release, and can even activate a biochemical cascade that leads to the secretion of other cytokines. IL-1, IL-6, and TNF-α not only activate the release of other cytokines, but also have its own destructive properties, including inflammation, fever, and fibrosis. All these responses are related to danger-associated molecular patterns (DAMPs) present in the structure of viruses, which are

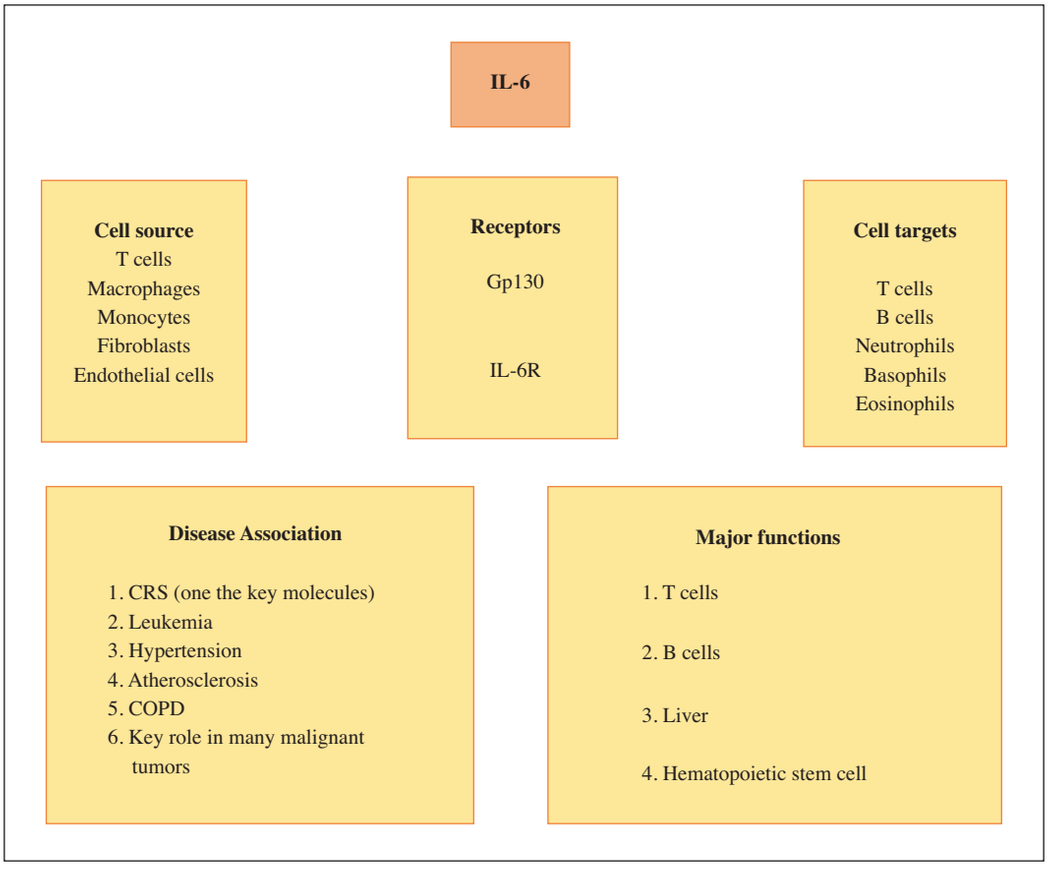

Figure 2
Brief introduction of IL-6.

recognized by "pattern recognition receptors" (PRRs) of the innate immune system. Toll-like receptors are a subgroup of PRRs that are activated by binding to viral targets and cause the release of inflammatory cytokines such as IL-1β. [18]. A brief summary of the functions of IL-1, IL-6, and TNF-α is shown in *figures 2, 3 and 4*.

PRO-INFLAMMATORY CYTOKINES: STRUCTURE, SIGNALING PATHWAYS, AND BIOLOGICAL FUNCTIONS

Structure and characteristics

IL-1 was initially named "pyrexin" or "endogenous pyrogen." Later, it was discovered that it had many biological functions such as being a lymphocyte activating factor or PGE2 inducer. IL-1 is divided into two subtypes α, and β [36]. These proteins are encoded by two genes located on chromosome 2. IL-1β is mainly produced by monocytes, macrophages, neutrophils, and hepatocytes that have been stimulated, and has a structure consisting of a β trefoil fold made up of 12 β strands connected by 11 loops and containing 269 amino acids [37, 38]. When pro-IL-1β is produced, it is inactive and has to be converted to its active form. When cells such as macrophages, monocytes, and neutrophils are induced to make IL-β, Caspase-1 cleaves the pro-inflammatory cytokine pro-interleukin to an active secreted version [39]. Like many other cytokines, the IL-1β activation pathway is stimulated by various endogenous substances, such as monosodium urate, or exogenous substances, such as microbes and their components [40].

IL-6 was once known by different names such as B-cell stimulatory factor 2 (BSF-2), hepatocyte-stimulating factor (HSF), or interferon (IFN)-b2, and is a four-helical cytokine and member of the IL-6 cytokine family that collectively share glycoprotein 130 kDa (gp130) as a subunit of their receptors. Human IL-6 is a glycosylated protein composed of 184 amino acids in addition to a signal peptide of 28 amino acids. The genomic location for this 24-kDa interleukin is on chromosome 7p15 [41, 42].

Both immune cells, like neutrophils, monocytes, macrophages, and T-cells and stromal cells such as endothelial cells, mesenchymal cells, fibroblasts, and many others can express and secrete IL-6 in response to diverse stimuli [42]. The production of IL-6 is strictly controlled by different mechanisms including gene polymorphism, modification of chromatin architecture, at transcriptional and post-transcriptional stages [43]. This is due to the fact that this cytokine acts as a warning mediator, influencing the whole body at the

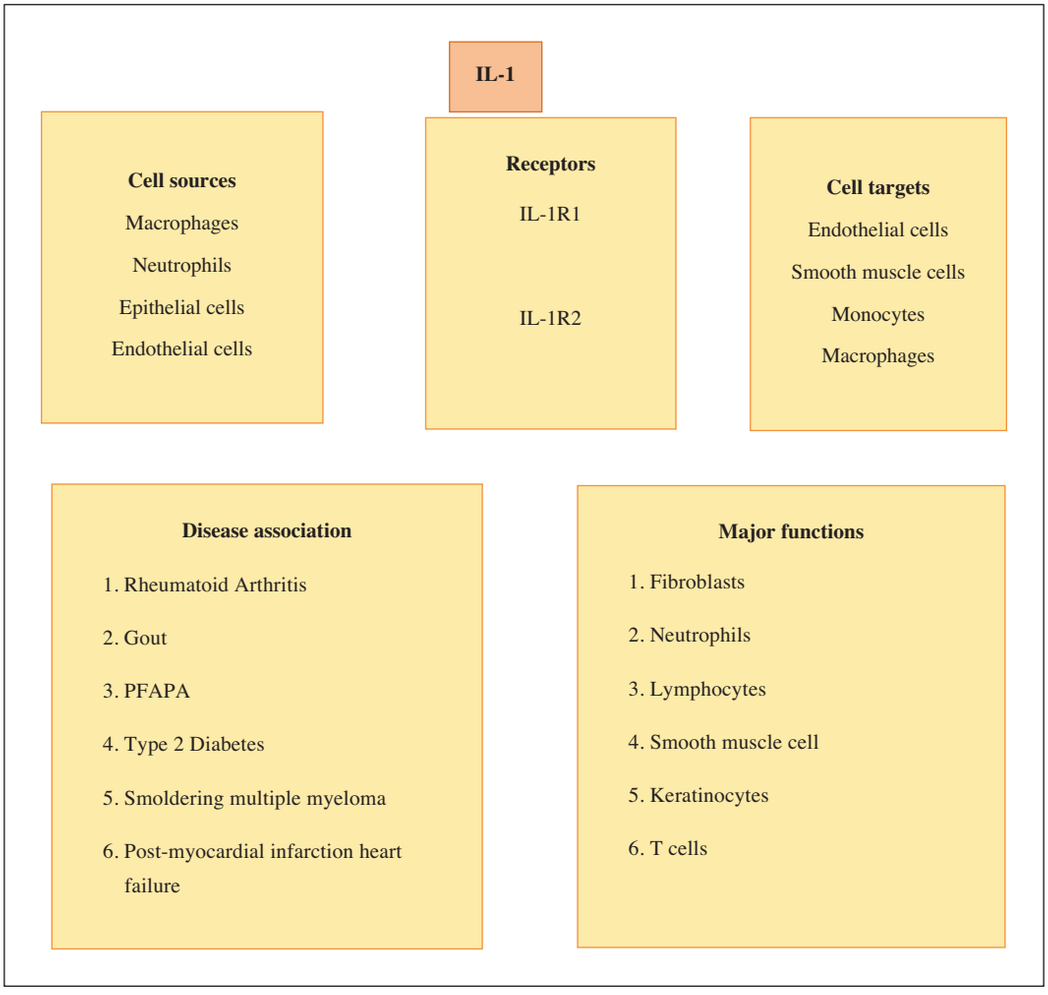

Figure 3
Brief introduction of IL-1.

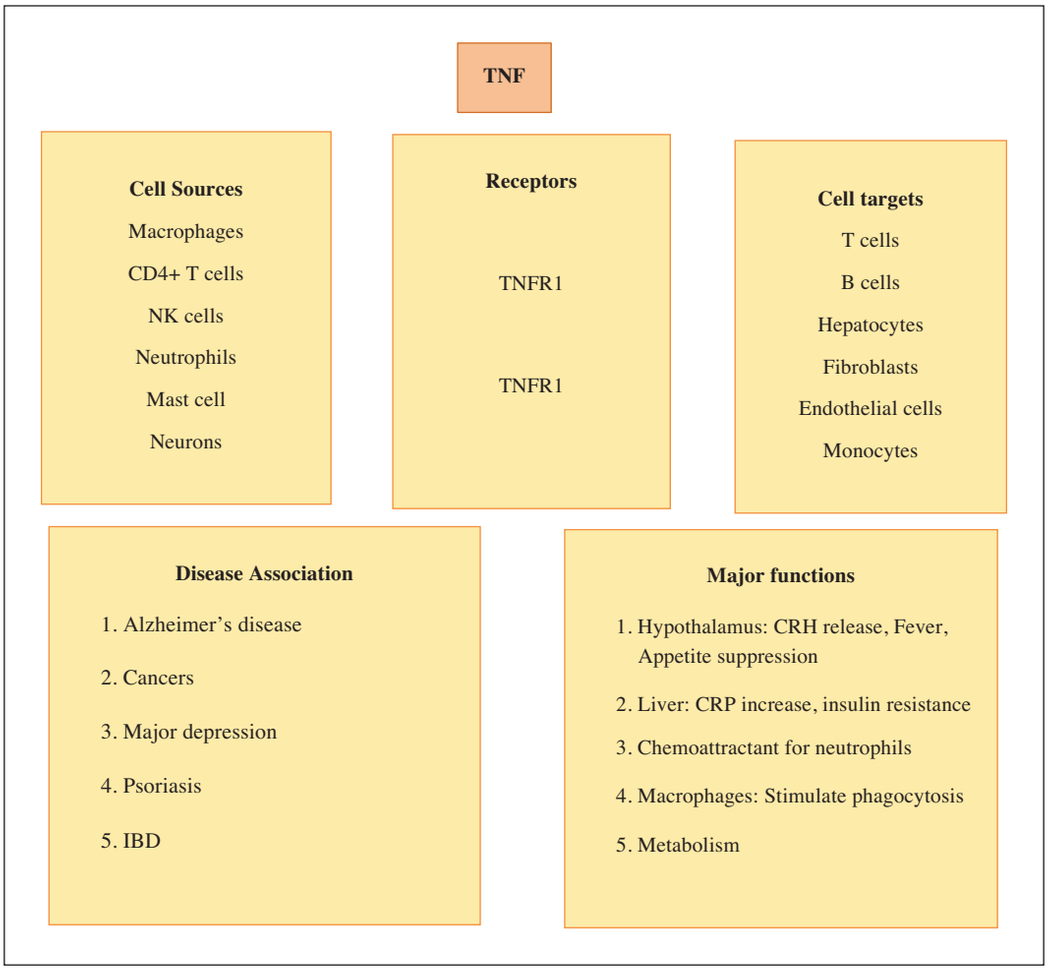

Figure 4
Brief introduction of TNF.

beginning of pathological states like inflammation, neoplasia, or infection [42]. In this regard, it was shown that the average concentration of IL-6 in a healthy human (1 pg/ml) can rise as high as 150 ng/ml in patients with rheumatoid arthritis [44].

Recognition of pathogen-associated molecular patterns by Toll-like receptors (TLRs) or other relevant receptors on immune cells can initiate signaling pathways such as nuclear factor (NF)-kB that upregulates the synthesis of inflammatory cytokines including IL-1β, IL-6, and TNF-α. Nevertheless, IL-1β and TNF-α are also primary activators of IL-6 production. Moreover, danger signals prompted by sterile inflammation like burns or major trauma can increase IL-6 levels [42].

The transcription of IL-6 can be regulated by microRNAs (e.g., let-7a), RNases (e.g., regnase-1), and RNA-binding proteins (e.g., Arid5a) [45]. Interestingly, several hormone receptors like estrogen and the glucocorticoid receptors can suppress IL-6 expression [42].

Tumor necrosis factor-alpha (once known also as lymphotoxin or cachectin) is a member of the TNF-α superfamily which comprises 19 members that all have a trimeric structure containing a TNF-α homology domain, and bind to 29 different receptors related to this family [46-48]. This 17-kDa cytokine contains 157 amino acids in its mature human form, and is initially a transmembrane protein that is transformed into a soluble form after cleavage by a metalloproteinase named TNF-α converting enzyme (TACE) [49]. The TNF gene is located on the short arm of the 6th human chromosome [50].

The origin of this Janus-faced cytokine was originally thought to be macrophages; however, it was later discovered that a wide range of other immune cells like lymphocytes, neutrophils, and NK cells, as well as nonimmune cells such as adipocytes, endothelial cells, and astrocytes, could secrete TNF-α [49]. Just like the previously discussed cytokines, various exogenous and endogenous stimuli, including cytokines, lipopolysaccharides (LPS), tissue plasminogen, and reactive oxygen species, can trigger the production of this pleiotropic cytokine [51]. NF-kB and nuclear factor of activated T-cells (NF-AT) are the main regulators of TNF-α expression that act at the transcriptional level [52]. Treffkorn et al. showed that prostaglandin E2 can inhibit the LPS-induced expression of IL-1 and IL-6, whereas it could increase IL-6 in murine models [53].

Signaling pathways

IL-1 has one of the simplest signaling mechanisms in the innate immune system. It is capable of sensing an infection and triggering an inflammatory response [54]. The IL-1 superfamily receptors have a closely similar

architecture, composed of three Ig-like domains, and an intracellular Toll/IL-1R (TIR) domain that is also found among Toll-like receptors. Induction of cytokine signaling requires two types of receptors, a primary specific receptor, called IL-1 receptor Type I (IL-1RI) for IL-1β signaling, and an accessory receptor, called Il-1R accessory protein (IL-1RAcP) also binding IL-1β, that can be shared in some cases [55]. Binding of each cytokine to its receptor results in a ternary signaling complex, which leads to the dimerization of the TIR domains of the two receptors. This activates mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which initiate intracellular signaling. This signaling pathway activates inflammatory responses such as the activation of cyclooxygenase Type 2, an increase in adhesion molecules, and the synthesis of NO (Nitric Oxide) [56].

As mentioned above, the primary specific receptor for IL-1β is IL-1R1. Its antagonist, IL-1Ra, is usually synthesized by the same cells, which produce IL-1β, meaning monocytes, macrophages, epithelial cells, etc. This inhibitor does not cause any conformational changes in its receptor (which is interestingly IL-1R1). IL-1Ra competes with its antagonist (IL-1β) for the binding to IL-1R1, and so it inhibits IL-1β. However, for the inhibition to be efficient, the IL-1Ra concentration has to be up to 100-fold higher compared to IL-1β [57] (*figure 5*).

IL-6 is among the most important cytokines involved in inflammatory responses, especially the cytokine storm. Accordingly, IL-6 can play diverse roles in different phases of inflammation, at first promoting detrimental reactions within the tissue, then contributing to resolving the inflammation, and finally helping to start tissue repair in the late stages [58]. This interleukin carries out its activity through several unique signal transduction pathways: classic signaling; trans-signaling, cluster-signaling; and intracellular signaling [43, 59].

Membrane-bound IL-6 receptor (mIL-6R) is a protein that requires to bind to homodimeric signal-transducing component gp130 to become functional in the classical signaling pathway [60]. Unlike GP-130 that is universally expressed on all immune and nonimmune cells, mIL-6 appears only on some cells, such as leukocytes, megakaryocytes, and hepatocytes, making other cells unable to carry out the classical signal transduction [45, 61]. However, in the trans-signaling system, IL-6R can lose its intracytoplasmic segment by proteolytic cleavage of mIL-R (carried out by a metalloprotease called ADAM17) or alternative splicing of related mRNA and can form soluble IL-6R (SIL-6R). The three components, IL-6, SIL-6R, and membrane-bound gp130 (mgp130) bind together, forming a complex able to trigger most cells within the human body [62]. It is noteworthy that the soluble form of gp130 (sgp130), which is present in higher concentrations than mgp130, selectively inhibits the

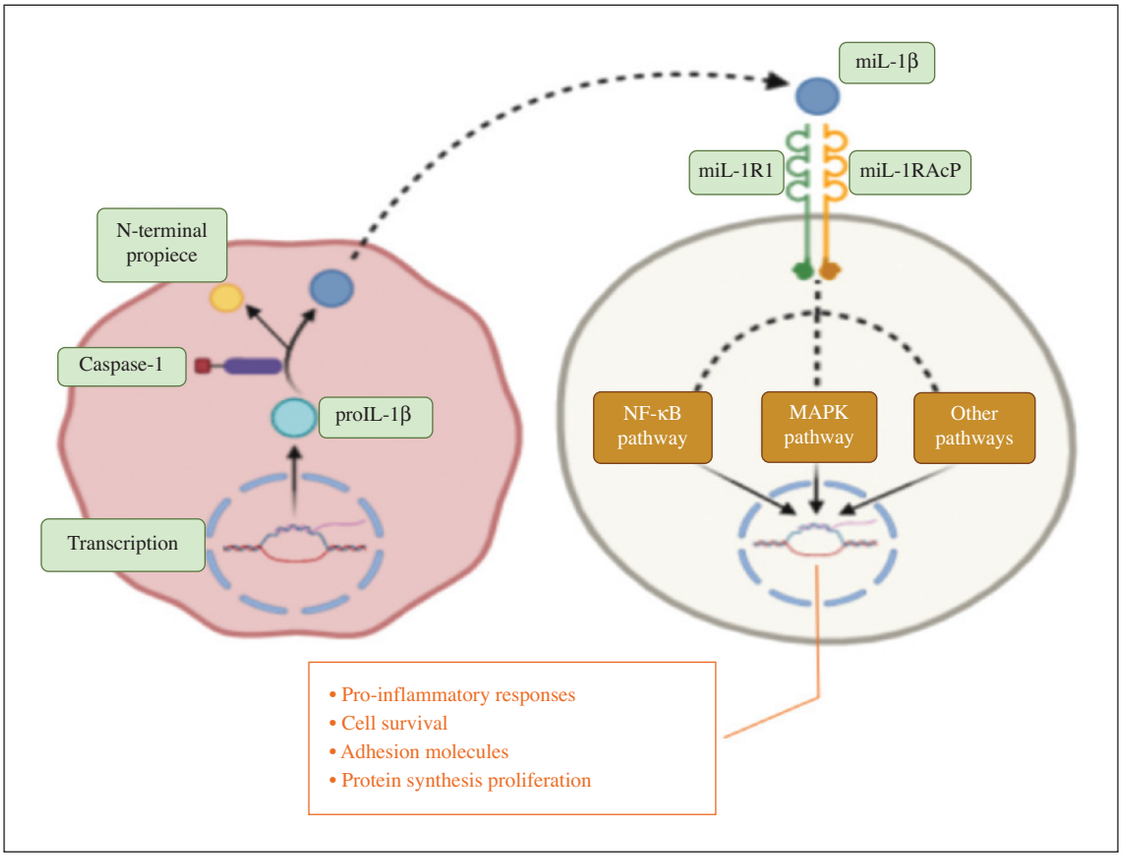

Figure 5

IL-1β production and signaling pathways. When certain cells are activated, IL-1β's production is induced, resulting in activation of caspase 1 and the production of the activated IL-1b(mIL-1b). This protein then connects to its specific receptor and activates different pathways as seen in the figure.

trans-signaling complex [63]. Heink *et al.* described another mechanism for IL-6 signaling called "cluster signaling." In this process, the IL-6-IL-6R complex expressed on the membrane of transmitter cells (e.g., dendritic cells) can be recognized by mgp-130 expressed on receiver cells (e.g., T cells) [64]. Notably, cluster signaling induces different responses in target cells from those caused by classic IL-6 signaling [59]. Furthermore, IL-6 intracellular signal transduction can occur either by autocrine mechanisms in IL-6-producing cells with IL-6R and gp130 on their membrane, or in the Golgi apparatus or endoplasmic reticulum before secretion [65].

The pleiotropic influence of IL-6 on immunity, inflammation, hematopoiesis, etc. takes place by binding to its receptors, thus initializing specific signaling pathways [66]. Activation of gp130 activates intracellular tyrosine kinases, especially Janus kinase (JAK) 1 and JAK2, that then activate the transcription factors, signal transducer, and activator of transcription (STAT) 1 and STAT3 [67, 68]. Other cascades that can be activated by IL-6 include SHP-2/ERK MAPK, PI3K-AKT-mTORC1, and SRC-YAP-NOTCH pathways [69-71]. Nevertheless, these signaling pathways can be further inhibited or promoted by regulatory molecules. For instance, suppressor of cytokine signaling 3 (SOCS3) has an essential inhibitory effect on the JAK-STAT3 pathway [72] (*figure 6*).

TNF-α has two types of receptors, TNFR1 and TNFR2, and can activate different signaling pathways simultaneously in a single-cell type (*figure 7*). These receptors, similar to TNF-α, have to be activated by the TACE molecule. TNFR1 can interact with both soluble and membrane-bound TNF-α; however, TNFR2 has a higher affinity toward membrane TNF-α. Both receptors have similar extracellular regions containing four homogenous cysteine-rich domains, but the intracellular domains (ICD) are structurally different [73]. TNFR1 is found on almost all the cells of the body, but TNFR2 is typically found only on immune system cells. TNF-R2 induces gene expression by its own signaling mechanism, and also by simultaneous interactions with TNF-R1. TNF-R1 and TNF-R2 both activate MAPKs, caspases, and the NF-κB pathway, but TNFR1 can also induce necrosis and apoptosis in target cells because it contains a so-called Death Domain within its ICD [74].

When TNF-α binds to TNF-R1 on the cell surface, it activates the receptor and exposes the intracellular domain of TNF-R1. This intracellular domain recruits a death-domain containing an adaptor protein called TRADD by homophilic interactions. TRADD, which acts as a scaffold protein, allows TRAF2 and RIPK1 to form a complex, which is called complex 1. Complex 1 is believed to play an essential role in NF-κB activation. Complex 1 eventually dissociates from the receptor and integrates with a protein called FADD and procaspase8 to form a complex, which is called complex 2. Activated CASP8 activates CASP3 and, therefore, triggers apoptosis. CASP8 activates apoptotic signaling through another mechanism involving cleavage of BID to truncated BID (tBID). tBID increases the outer membrane permeability in the mitochondria, therefore releasing cytochrome c and killing the cell. Reactive oxygen species (ROS) increase

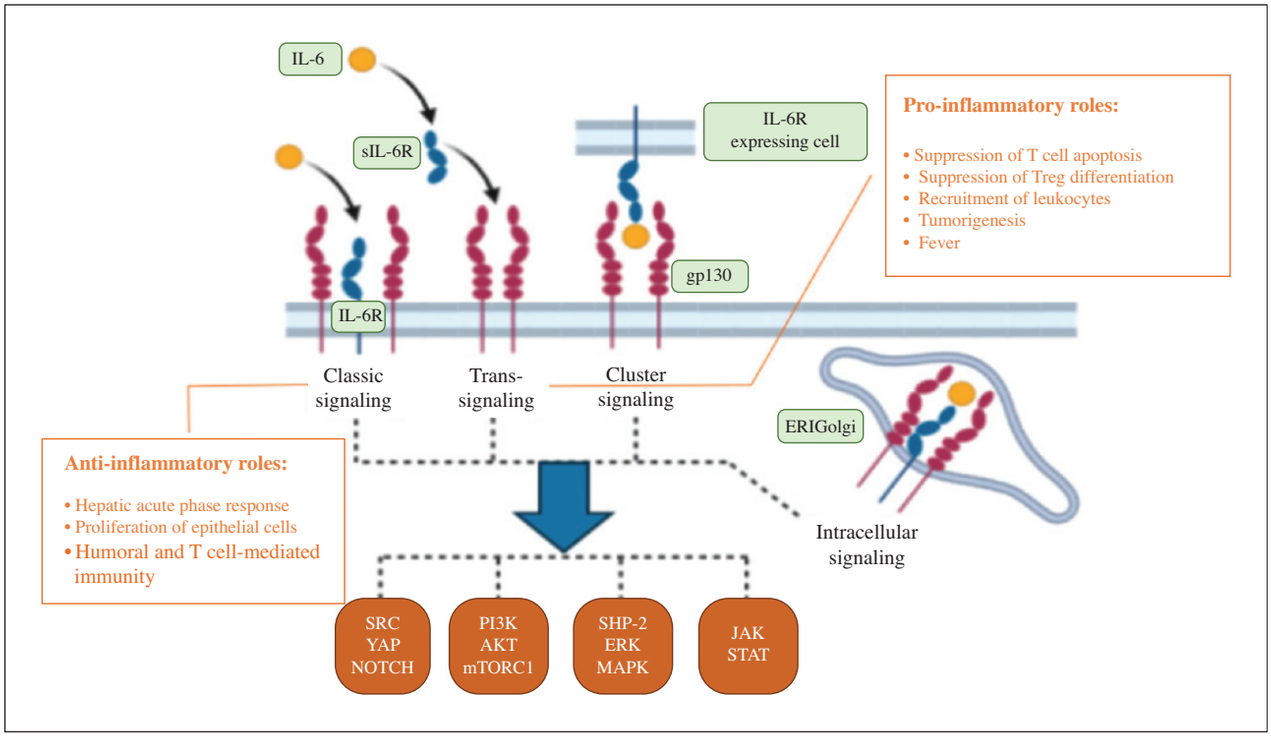

Figure 6

IL-6 signaling pathways. This interleukin implements its actions through several unique signal transduction pathways comprising: Classic signaling, trans-signaling, cluster-presentation, and intracellular signaling. Consequently, Ligand-receptor complex activates pathways like JAK-STAT, SHP2-ERK-MAPK, PI3K-AKT-mTORC1, and SRC-YAP-NOTCH that leads to various biological responses in different contexts. While activation of classic IL-6 signaling pathway promotes anti-inflammatory, protective, and regenerative reactions, trans-signaling pathway induces rather pro-inflammatory responses.

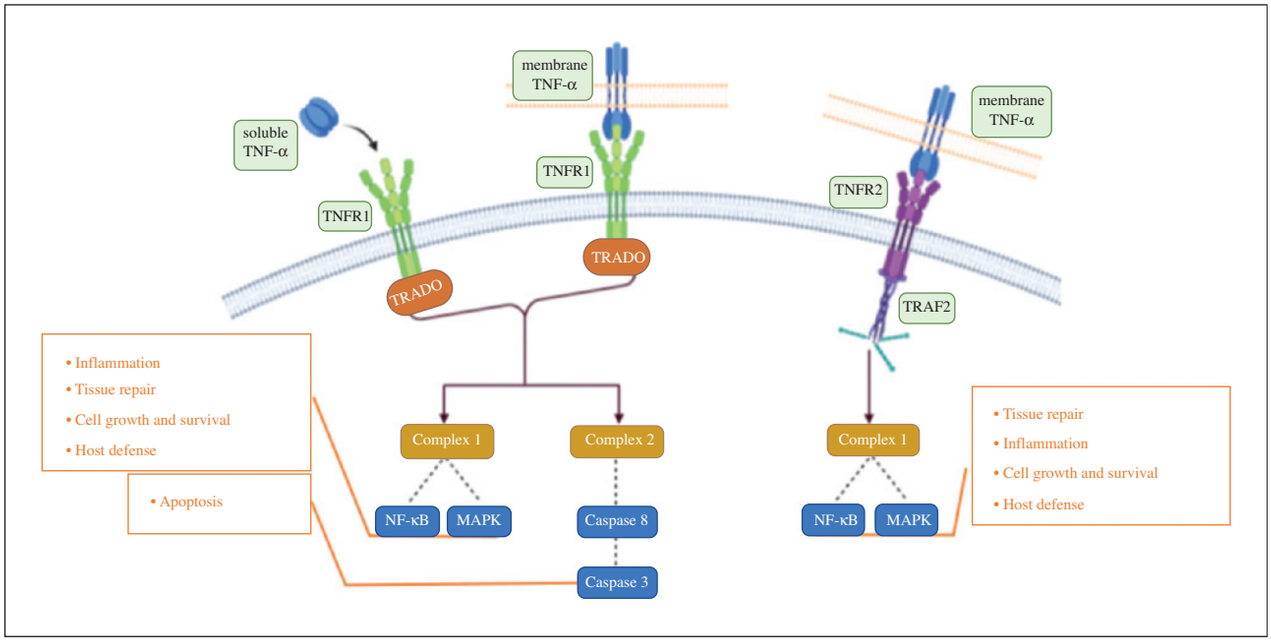

Figure 7
TNF signaling pathways. Two different types of TNF-α can induce each cell; soluble TNF-α and membrane TNF-α. The receptors (TNFR1 and TNFR2) each have their own specific activation pathways which at the end result in tissue repair, inflammation, apoptosis, etc.

during or after the formation of complex 1 and 2 to help with apoptosis. TRAF-2 in complex 1 also induces the MAP kinase cascade that activates JNK, which mediates both apoptosis and necrotic cell death [73, 74].

Biological functions

The IL-1 family consisting of IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-36ra, IL-37, and IL-38 includes members with both pro-inflammatory and anti-inflammatory functions. However, IL-1β is an agonist of inflammation [75]. IL-1β is an activator that induces myeloid progenitor cells from the bone marrow and increases the number of neutrophils in the body. It also increases the expression of pro-inflammatory cytokines and chemokines and upregulates the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2. IL-1 can set off multiple cascades, such as those involving MAPKs and NF-κB. IL-1β also activates mast cells, and so increases the production of TNF-α, IL-13, IL-3, IL-5, and IL-6. The IL-1β produced by antigen-presenting cells induces the proliferation of naive, memory, and effector T cells. This is achieved by activating IL-2R, PI3K, and NF-κB pathways. It has also been shown that IL-1β induces fever in the body when needed to fight infections [76].

IL-1β is also involved in the drop in vascular blood pressure during lipopolysaccharide (LPS)-induced endotoxemia. IL-1β increases JAK-STAT3 signaling, calcium sensitivity within blood vessels, and decreases Rho and PKC kinase [76]. Another function of IL-1β is its role in the induction of pain and the maintenance of chronic pain. It also has critical homeostatic functions in human behavior, such as the regulation of feeding, sleep, and temperature [77].

IL-6 acts as a two-faced cytokine regarding inflammation. In other words, the biological functions of this cytokine in each organ are dependent on the ongoing pathological state [43]. Activation of the classic IL-6 signaling pathway promotes anti-inflammatory, protective, and regenerative functions, including hepatic acute phase response, proliferation of epithelial cells, and fosters humoral and T-cell-mediated immunity against bacterial and viral infections. Contrariwise, the trans-signaling pathway induces pro-inflammatory responses like suppressing T-cell apoptosis, blockade of Treg differentiation, recruitment of leukocytes, tumorigenesis, fever, and so on. A balance between these contrasting effects of IL-6 is moderated by metalloprotease ADAM17 [44]. Regarding the biological functions of IL-6, it is well documented that IL-6 can impact the immune system, liver, muscles, hematopoiesis, cardiovascular system, kidney, and can even affect emotions and the brain [58, 66, 78].

Owing to the wide variety of biological functions reported to be caused by IL-6, this review will discuss some in more detail. Firstly in the immune system, IL-6 can affect both innate and adaptive immunity. It can induce a transition from neutrophils to monocytes as infiltrating cells in sites of acute inflammation, increase macrophage differentiation, and decrease the production of dendritic cells [79, 80]. Bringing adaptive immunity into consideration, IL-6 stimulates the transformation of immature B cells into antibody-producing plasma cells [81]. Furthermore, the IL-6-related STAT3 pathway can activate the differentiation of naive CD4+ cells into Th17 cells that are capable of producing IL-17 [82]. In contrast, IL-6 inhibits differentiation of Th17 into Treg cells and blocks Treg function [83].

In the cardiovascular system, IL-6, along with other inflammatory cytokines, causes vascular permeability [84]. This vascular permeability is exacerbated when the complement cascade is activated, and hypoalbuminemia in the liver also occurs as a consequence of IL-6 secretion [85]. Moreover, IL-6 seems to have a significant role in the hypercoagulability and cardiomyopathy that are also seen in CRS [27, 86].

For a long time, the liver had been supposed to be a primary target for IL-6. Activation of classical signaling in hepatocytes leads to a burst in the production and secretion of a wide range of proteins, collectively called acute phase proteins. These comprise C-reactive protein (CRP), haptoglobin, hepcidin, serum amyloid A (SAA), fibrinogen, and thrombopoietin; however, IL-6 suppresses the levels of albumin and cytochrome P450 in the liver [42, 43]. Additionally, IL-6 can augment the regenerative capacity of hepatocytes and prevent them from undergoing apoptosis [87].

When the expression of TNF-α is induced by activation of macrophage TLRs, there is a delicate balance with IFN-γ that can activate other macrophages to respond to TNF-α, resulting in migration of these rapid response immune cells to encounter pathogens and phagocytose them. Furthermore, TNF-α also has a crucial role in the apoptosis, proliferation, and differentiation of macrophages [52]. In addition to the pivotal role of TNF-α and macrophages in pro-inflammatory immune responses, this cytokine also upregulates the cyclooxygenase and lipoxygenase pathways [88].

Even though early studies suggested that TNF-α may act principally as an anti-tumorigenic factor, extensive research on this cytokine in the recent two decades has revealed many additional and even contrasting roles for it in neoplasia, inflammation, apoptosis, and proliferation. Moreover, the contribution of TNF-α to the pathogenesis of a vast range of disorders such as autoimmune, neurologicical, cardiovascular, and metabolic diseases has also come under significant scrutiny [46-48]. The biological functions of TNF-α in normal physiologic context have been investigated in TNF-deficient mouse models. These include its decisive role in immune response against infections, the formation of germinal centers in lymphoid organs, granulomatous reactions, and repairing tissue damage [46]. Nonetheless, TNF-α, in combination with other proinflammatory cytokines such as IL-1 and IL-6, has been shown to induce destructive responses in inflammatory and autoimmune diseases, paving the way for TNF-blockade to be proposed as a therapy for disorders like RA, Crohn's disease, and psoriasis [89]. In relation to cancer, TNF-α has been shown to act as a double-edged sword, because while TNF-α has antitumor activity mainly through triggering apoptosis, it can also encourage tumorigenesis by inhibiting DNA repair mechanisms, or help tumor cells to proliferate either directly via the NF-kB pathway in cancer cells, or indirectly via a vicious circle resulting in increased survival, growth, invasion, angiogenesis, and metastasis in the tumor environment [48, 90-92].

DRUGS THAT INHIBIT PRO-INFLAMMATORY CYTOKINES AND THEIR THERAPEUTIC ROLE

Human studies on SARS-CoV and MERS, which are two analogous infectious diseases to the current SARS-CoV-2 virus pandemic, have revealed that these viruses affect the body not only with direct cytotoxic mechanisms but also by triggering cytokine storms that cause severe grade-4 manifestations [18]. Considering the important role of IL-6 and TNF-α in CRS, and since studies have demonstrated a correlation between these cytokines and severe or critical cases of COVID-19, we could hypothesize that anti-IL-6 and anti-TNF antibodies could be effective for reducing COVID-19 mortality. In the following section, we will discuss two different anti-IL-6 antibodies, Tocilizumab and Myoinositol, and then continue by discussing two anti-TNF antibodies.

Tocilizumab

Tocilizumab was the first marketed IL-6 monoclonal antibody, which had very good results in treating patients suffering from rheumatoid arthritis (RA) [2]. In a study by Xiaoling *et al.,* 21 patients from two hospitals in China who had been classified as severe or critical cases of COVID-19 were recruited and administered Tocilizumab therapy in addition to standard care for COVID-19 including antiviral therapy, oxygen therapy, and symptom relief. The results of the Tocilizumab subgroup showed significant improvements in their symptoms, including fever, respiratory function, and requirement for oxygen therapy. Moreover, computed tomography (CT) scan results showed the lessening of lung opacities in 19 patients, and 19 out of 21 patients were discharged on average 13.5 days after therapy, while the other two patients remained in a stable condition; moreover in this study, there were no reports of adverse drug reactions to Tocilizuma [3].

In a retrospective study by Pan *et al.*, fifteen confirmed COVID-19 cases from one hospital in Wuhan city of China, including two moderate, six severe, and seven critical cases, were enrolled. Five patients received more than one dose of Tocilizumab, and the remaining ten received one dose of Tocilizumab plus methylprednisolone. The C-reactive protein (CRP) level of all patients was above the normal range at the beginning. The trial demonstrated that post Tocilizumab therapy, the CRP level of 11 patients showed a rapid decrease, four critically ill patients who received one dose of Tocilizumab did not demonstrate symptom relief, and despite all the efforts, 3 of them died and the 4th patient did not show any reduction in CRP level and the symptoms worsened. In 10 patients, the IL-6 level spiked initially and then significantly decreased, but in the 4 critical patients who received one dose Tocilizumab and whose treatment failed, the IL-6 level remained unchanged or even increased. Therefore, based on this study, it was recommended to administer 2 doses of Tocilizumab in critically ill patients [4]. The efficacy of Tocilizumab was also investigated in a case report study in which a 42-year-old man with a history

of metastatic renal cell carcinoma was hospitalized due to fever and cancer management. During his hospitalization period, the patient was suspected to have SARS-CoV2 infection, and his PCR-test confirmed this. They started routine therapy, but he did not show any significant improvements in symptoms; and on the 8th day of his hospitalization, his symptoms worsened and he developed dyspnea and low oxygen saturation, and then received two doses of Tocilizumab intravenously. Afterward, he experienced considerable improvement in symptoms, his fever improved, and his oxygen therapy requirement reduced gradually up to the 12th day. Moreover, his chest CT scan on 12th day revealed apparent regression of lung opacities. The patient recovered completely [5].

A similar case report described a 60-year-old man with multiple myeloma history who was diagnosed with COVID-19 and was classified as a severe case. He was suffering from chest tightness and ground-glass opacities were detected in the chest CT scan. After intravenous administration of one dose of Tocilizumab on the 9th day of his hospitalization, his chest tightness began to improve until day 12, and in the chest CT scan conducted on day 19 the range of lung opacities was visibly decreased. The patient recovered completely and was discharged [6].

Although Tocilizumab has demonstrated no significant adverse effects in COVID-19 cases, some studies suggested that there was a correlation between Tocilizumab and osteonecrosis of the jaw [7]. Overall the present studies on COVID-19 show that Tocilizumab could be effective in alleviating COVID-19 symptoms, especially in severe and critical cases, but further studies including randomized control trials (RCT) are suggested to confirm its effectiveness.

Myoinositol

Myoinositol has been used to treat newborn respiratory distress syndrome and is believed to reduce IL-6 and to reduce the cytokine storm; therefore, it is hypothesized that it might have promising results in COVID-19 patients [8].

Infliximab and adalimumab

Anti-TNF antibodies have been used for more than 20 years in serious cases of chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, or ankylosing spondylitis [93]. Since TNF-α acts as an amplifier of inflammation, it was proposed that these anti-TNF therapies should be evaluated in severe COVID-19 patients. In a study by Hussell *et al.*, the effectiveness of anti-TNF therapy on viral lung diseases caused by respiratory syncytial virus or influenza virus was examined in mouse models, and the results showed reduced weight loss, shorter disease duration, and less cell and fluid infiltration in the lungs [94]. This work suggested a possible justification for the use of anti-TNF therapy in viral pneumonia, especially given the known mechanism of action of TNF-α and the reversal of TNF-induced immunopathology in multiple diseases [95].

The effects of anti-TNF therapy in COVID-19 patients can be inferred from the results of a study on COVID-19 infection in patients with inflammatory bowel disease (IBD) or rheumatoid arthritis, who were also on anti-TNF therapy. As of May 6, 2020, on SECURE-IBD, a COVID-19 and inflammatory bowel disease (IBD) database with a register of outcomes of IBD patients with COVID-19, there were 283 patients on anti-TNF therapy alone, 227 (80%) of whom were outpatients and recovered without hospitalization, 55 patients (19%) were hospitalized and three (1%) patients died. By contrast, about half (52%) of 261 patients on sulfasalazine/mesalamine recovered without hospital admission and 21 patients (8%) died [96]. Thus, IBD patients with COVID-19 on anti-TNF therapy do not do worse than those treated with other medications, but there are insufficient data to draw conclusions about a better outcome.

TNF-antibodies seem to be promising for the treatment of COVID-19 severe cases; however, the data on the side effects of these drugs and the exact benefit obtained are still limited.

Metronidazole

Studies have suggested that metronidazole is capable of reducing the levels of inflammatory cytokines, such as IL-6 and IL-1β, which are known to be released in CRS [9].

Overall there are several drugs other than Tocilizumab, including Myoinositol and Metronidazole, which according to studies, could have the potential to suppress inflammatory storm and may be helpful for treating COVID-19, but their efficacy in COVID-19 requires further investigation.

CONCLUSIONS

COVID-19 is a newly emerged infectious disease which has spread all over the world during a short period of time and has no definitive treatment. The virus attaches to Angiotensin Convertase Enzyme 2 (ACE2) receptor for entrance into cells [16]. ACE2 mainly exists in cardiac and alveolar cells, but it also can be found in several hematopoietic cells, including macrophages and monocytes [17]. Hematopoietic cell infection with SARS-CoV2 can lead to cell activation and secretion of pro-inflammatory cytokines such as IL-6 into the systemic blood circulation, which can result in severe manifestations of this disease. IL-1 and IL-6 are two major cytokines that have significant roles in CRS activation and inflammation cascade. In severe and critical COVID-19 cases who are suffering from acute respiratory distress syndrome and/or end organ damage, it has been observed that they have higher levels of cytokines that leads to cytokine release syndrome (CRS), which is a leading cause of fatality in infected individuals [97].

It is hypothesized that by inhibiting the CRS cascade, these patients may have a better chance of survival. Lately, some cytokine antagonists like Tocolizumab have been investigated, and they are showing promising early results. However, we still need RCT trials in

order to arrive at a better understanding of their effectiveness and their probable side effects [14].

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