Received: 20 January 2022 | Revised: 2 May 2022 | Accepted: 10 May 2022

DOI: 10.1002/rmv.2372

REVIEW

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The role of cytokines and their antagonists in the treatment of COVID-19 patients

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Abstract

The coronavirus disease 2019 (COVID-19) has various presentations, of which immune dysregulation or the so-called cytokine storm syndrome (COVID-CSS) is prominent. Even though cytokines are vital regulators of body immunoinflammatory responses, their exaggerated release can be harmful. This hyperinflammatory response is more commonly observed during severe COVID-19 infections, caused by the excessive release of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, tumour necrosis factor, granulocyte-macrophage colony-stimulating factor, and interferon-gamma, making their blockers and antagonists of great interest as therapeutic options in this condition. Thus, the pathophysiology of excessive cytokine secretion is outlined, and their most important blockers and antagonists

Abbreviations: ANC, absolute neutrophil count; ARDS, acute respiratory distress syndrome; CLS, capillary leakage syndrome; COVID-19, coronavirus disease 2019; COVID-CSS, COVID-19-related cytokine storm syndrome; CRP, C-reactive protein; CT scan, computed tomography scan; GCA, giant cell arteritis; GI, gastrointestinal; GM-CSF, granulocyte-macrophage colony-stimulating factor; HBV, hepatitis B virus; HCV, hepatitis C virus; HGF, hepatocyte growth factor; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; IFN-γ, interferon-gamma; IGRA, interferon-gamma release assay; IKK, IκBα kinase; IL-1, interleukin 1; IL-10, interleukin 10; IL-17A, interleukin 17A; IL2RA, soluble interleukin-2 receptor alpha chain; IL-6, interleukin 6; IL-6R, interleukin-6 receptor; IL-8, interleukin 8; IVIG, intravenous immunoglobulin; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-alpha; JAK/STAT, Janus kinase/signal transducer and activation of transcription; LDH, lactate dehydrogenase; LFT, liver function test; LT, lymphotoxin; MCD, multicentric Castleman disease; MERS, Middle East respiratory syndrome; MIS-C, multisystem inflammatory syndrome in children; MOF, multi-organ failure; MRONJ, medication-related osteonecrosis of the jaw; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK cell, natural killer cell; PPD, purified protein derivative; rIL-2, recombinant human IL-2; SAA, serum amyloid A; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA score, sequential organ failure assessment score; TB, tuberculosis; TNF, tumour necrosis factor; ULN, upper limit of normal.

are discussed, mainly focussing on tocilizumab, an interleukin-6 receptor blocker approved to treat severe COVID-19 infections.

KEYWORDS
COVID-19, cytokine, SARS-CoV-2, tocilizumab

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) has various presentations, from a flu-like illness to acute respiratory distress syndrome (ARDS), multi-organ failure (MOF), and death.[1–3] Some of these life-threatening manifestations are the symptoms of immune dysregulation or the so-called COVID-19-related cytokine storm syndrome (COVID-CSS),[4] which results in long-hauler syndrome and multisystem inflammatory syndrome in children (MIS-C).[5] Even though cytokines are vital regulators of our immunoinflammatory response, their excessive release can be harmful.[6] This hyperinflammatory response is most commonly observed during severe SARS-CoV-2 infection, caused by the excessive release of pro-inflammatory cytokines, such as interleukin 1 (IL-1), IL-6, IL-8, tumour necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon-gamma (IFN-γ).[7] COVID-CSS is defined by presence of the following criteria: (1) COVID-19 pneumonia needing mechanical ventilation; (2) fever (T > 38°C); (3) C-reactive protein (CRP) > 100 mg/L; and (4) serum ferritin > 1000 μg/L.[8] Frequently, we expect patients with this condition to have elevated serum IL-6 concentrations exceeding 80 pg/ml. It has been found that an IL-6 level >80 pg/ml on admission is associated with poor prognosis, with mortality rates exceeding 20% in 14 days.[9] Thus, blockers and antagonists of these cytokines are expected to have therapeutic effects in those at risk of CSS.[10]

2 | CONDITIONS INCREASING CYTOKINE LEVELS

IL-6 affects B and T lymphocytes, hepatocytes, and hematopoietic stem cells and is also involved in immune-mediated disorders and cardiovascular diseases.[11] IL-6 levels are likely to increase in COVID-19 and other inflammatory conditions, such as sepsis, capillary leakage syndrome (CLS), ARDS, hemophagocytic lymphohistiocytosis (HLH), myelofibrosis, organomegaly (TAFRO) syndrome, multicentric Castleman disease (MCD), and giant cell arteritis (GCA).[12–14] Moreover, it has been shown that higher serum levels of these inflammatory cytokines are correlated with disease severity and the need for admission into an intensive care unit in COVID patients.[15] Despite the 2–100 fold increase in IL-1, IL-10, and TNF levels in COVID-CSS, IL-6 concentrations can be elevated even more substantially, sometimes more than 1000 times the upper limit of normal (ULN).[16]

3 | CYTOKINE CASCADE INVOLVED IN COVID-CSS

Immune dysregulation due to COVID-19 infection can lead to a life-threatening condition known as COVID-CSS. This highly aggressive inflammatory response is mainly caused by the secretion of pro-inflammatory cytokines in large quantities.[17] A serum-cytokine-analysis study on 207 COVID-19 cases showed that cytokines like TNF, IL-6, IL-10, and IL-1β increased so early in patients with severe conditions.[18] However, as mentioned before, IL-1, IL-6, IL-8, TNF, GM-CSF, and IFN-γ are the most important pro-inflammatory cytokines released excessively in severely-infected patients.[7] Besides, immune cells also play an important role in the pathophysiology of COVID-CSS. The most important innate cells participating in this phenomenon are natural killer (NK) cells, macrophages, and neutrophils. For example, neutrophil extracellular traps (special networks of fibres) can associate with thrombogenesis and the over-production of cytokines. Interestingly, it has been reported that high amounts of IL-6 could impair NK cells' function through a reduction in granzyme and perforin production.[19]

Although previous studies have partially determined the underlying relations between cytokines participating in autoimmune-caused cytokine storms, Interactions among the preceding cytokines can establish a perplexing cascade that requires future studies to be focussed on this area to detect the undiscovered prospects of the COVID-19 induced cytokine storm syndrome. Nevertheless, it is possible to describe some of the previously-introduced interactions as a part of the COVID-CSS cytokine cascade.

The TNF superfamily is one of the most influential cytokine groups, playing important roles in inflammatory reaction promotion.[20] This superfamily includes 19 types II transmembrane proteins (able to act as cytokines after being released by extracellular proteolytic cleavage), among which TNF plays a crucial role in COVID-19 induced cytokine storm syndrome. A TNF's relative cytokine called lymphotoxin (LT), which shares one of its receptors, was characterised[21] and cloned[22] before TNF itself. Until 1985, when TNF began to be referred to as TNF-α and LT as TNF-β, these two acronyms were used interchangeably. While extensively used, this nomenclature was questioned because LT was the preceding molecule. Following that, two LT variants known as LT-α and LT-β were found, succeeding TNF-β and rendering TNF-α an orphan name. As a result, despite its widespread use, TNF-α today has no meaning other than the original word, TNF, and thus, should be abandoned.[23]

Many cells and tissues can produce TNF, including macrophages, neutrophils, endothelium, smooth muscle cells, activated lymphocytes, and adipose tissue.[24] The fact that TNF inhibition could decrease the level of IL-1, IL-6, IL-8, and GM-CSF, revealed that there must be an underlying cascade among these cytokines.[25] Accordingly, it has been reported that TNF could trigger IL-1 and IL-6 production through IκBα kinase (IKK) and the NF-κB pathway. First, TNF activates IκB via the IKK complex. Then, this reaction leads to polyubiquitination and degradation of IκB, which results in the release of NF-κB from IκB. Finally, the discharged NF-κB can transfer to the nucleus and promote the transcription of genes like IL-1, IL-6, and TNF itself.[26,27] Moreover, several studies have shown that TNF could increase IL-8 gene transcription by enhancing histone acetylation at the NF-κB binding site within the IL-8 promoter, which could enhance NF-κB binding to this sequence.[28,29]

4 | THE APPLICATIONS OF CYTOKINES EVALUATION

Prognostic biomarkers, such as significant lymphocytopenia, elevated CRP, lactate dehydrogenase (LDH), ferritin, D-dimer, serum amyloid A (SAA), procalcitonin, and IL-6, are valuable markers for assessing the severity of COVID-19 and in helping physicians to determine the appropriate management of these patients.[30] Moreover, research has shown that serum IL-6 levels are superior to CRP, ferritin, fibrinogen, D-dimer, and liver function tests (LFTs) for predicting patient outcomes and helping the physicians with patient management.[16,31] For example, increased baseline levels of IL-6 are positively correlated with more severe chest problems, as determined by computed tomography (CT) scans,[32,33] and it can also be used to indicate higher SARS-CoV-2 viral loads.[34] Moreover, unfortunately, a favourable response to IL-6 inhibitors could not necessarily be observed in these patients.[35]

It is important to note that changes in the balance of cytokines can predict disease progression. Therefore, the Dublin-Boston score was defined based on changes in the IL-6 to IL-10 ratio to identify more severely infected hospitalised COVID-19 patients with higher risks of morbidity and mortality.[36] Furthermore, IL-6 levels can be used for patients' follow-up and monitoring, decreasing and increasing significantly during the disease remission and exacerbation phases, respectively.[37] In addition, it is believed that vascular dysfunction and thromboembolic events are directly mediated by immunoinflammatory cytokines, such as IL-6 and IL-17A.[38] Furthermore, significantly increased CRP, LDH, ferritin, and IL-6 levels are associated with liver damage in severely infected SARS-CoV-2 patients.[39] Interestingly, the loss of smell and taste symptoms (ageusia and anosmia) in COVID-19 patients are associated with elevated IL-6 levels rather than the central nervous system or direct viral injury to the neurons.[40] Moreover, IL-6 is thought to cause long-term neuropsychiatric manifestations in these patients, including fatigue, insomnia, anxiety, and depression.[41]

Even though serum IL-6 concentrations indicate severe COVID-19 infection, serum IL-8 levels have been correlated with mild SARS-CoV-2 infections. Interestingly, compared with IL-6, IL-8 levels are a better reflector of the overall clinical disease scores at the different infection phases of a particular patient.[42] Soluble interleukin-2 receptor alpha chain (IL2RA, or CD25) and hepatocyte growth factor (HGF) are also associated with hyper-inflammation and organ failure in COVID-19 patients.[43] IL-10 is another inflammatory cytokine that is elevated during COVID-19-CSS, which may increase even earlier than IL-6.[44,45] IL-10 is thought responsible for some COVID-related headaches[46] and has conflicting effects in COVID-19 patients. Despite being protective against early immune-mediated lung damage, it can interfere with viral clearance, leading to further viral spread.[47] IL-17A can accelerate the progression of SARS-CoV-2 lung involvement to pulmonary fibrosis. Hence, medications antagonising this mediator may have a positive therapeutic effect on this condition.[48] As $CD4^+$ T-cells diminish during a severe SARS-CoV-2 infection, it has been suggested that IL-2, IL-18, and IL-4, may be helpful during the recovery phase of these patients. Therefore, a recombinant human IL-2 (rIL-2) can be beneficial as an immunomodulator therapeutic option in severe cases.[49] Thus, considering the responsible biomarkers for the cytokine storm and the hyperinflammatory state in SARS-CoV-2 infections, different therapeutic options can be administered to manage the condition.

5 | USE OF IMMUNOMODULATORS IN THE TREATMENT OF SARS-COV-2 INFECTION

Corticosteroids are commonly used to reverse the course of severe COVID-19 infections.[50] These agents have immunosuppressive effects and can block pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-17.[51,52] However, there is conflicting evidence regarding the benefits of corticosteroids in treating SARS-CoV-2 infections. Past evidence from the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) epidemics indicated increased mortality and delayed virus clearance when using corticosteroids.[53] Nevertheless, in the current pandemic, primarily low-dose dexamethasone, glucocorticoids are particularly beneficial in reducing mortality,[54] whereby the highest efficacy is achieved when administered prior to critical illness and admission to an intensive care unit (ICU). Therefore, corticosteroid therapy dose, duration, and timing should be carefully planned to avoid harming susceptible patients unwittingly. [41]

Several other agents have also been proposed to counteract the hyperinflammatory response to SARS-CoV-2 infection. Cytokine-blocking biological agents have been popular therapeutic options since the beginning of the pandemic. However, recently, they have gained much more attention, as several studies have confirmed their efficacy in treating SARS-Co2 infections. IL-1, IL-6, and interleukin-6 receptor (IL-6R) inhibitors were the most commonly used medications. Examples of IL-6R and IL-6 inhibitors include tocilizumab (Actemra), sarilumab (Kevzara), and siltuximab (Sylvant), while anakinra (Kineret) is a prominent IL-1 blocker. Anakinra is an IL-1 receptor antagonist approved for treating autoimmune disorders,

mainly rheumatoid arthritis, and less commonly for macrophage activation syndrome and septic shock.[55–57] Tocilizumab and sarilumab are monoclonal antibodies blocking IL-6R, approved for treating rheumatoid arthritis, ankylosing spondylitis, GCA, noninfectious uveitis, and malignancies.[58–62] Interestingly, elevated CRP or LDH levels suggest a relatively good response to these agents, resulting in reduced mortality, ARDS, and hyper-inflammation.[63] Studies have demonstrated that acute-phase reactants levels, such as CRP, drop rapidly following tocilizumab administration (Table 1).[64]

So far, studies have shown conflicting results regarding the effectiveness of these agents, with some concluding that IL-1 inhibitors were more effective than IL-6 blockers. Several studies have found that IL-6 inhibitors do not affect mortality,[65,66] while others have shown the beneficial effect of this agent on the inflammation-induced hypercoagulable state.[67] Nevertheless, the RECOVERY trial showed that using this agent reduced mortality among COVID-19 patients.[68] These disparities may be explained by differences in the timing of treatment initiation or concomitant use of glucocorticoids.[69] Janus kinase/signal transducer and activation of transcription (JAK/STAT) inhibitors (e.g., ruxolitinib) can also block many inflammatory mediators, such as IL-6. Moreover, they have the advantage of a shorter half-life than tocilizumab, facilitating treatment monitoring.[70,71] Recently, bazedoxifene, an oestrogen analogue used primarily for managing postmenopausal osteoporosis, has been introduced with an anti-IL-6 activity and has been suggested to be a less expensive and more convenient option for treating COVID-19-related lung issues.[72]

Although no agent with anti-IL-10 characteristics has been introduced yet, this would be a promising target for improving the prognosis of patients with severe COVID-19.[73,74] Previous studies had acknowledged the role of this cytokine in coronavirus-induced encephalomyelitis, making such agents helpful in avoiding this complication during the current pandemic.[75] IL-7 immunotherapy has also been proposed for restoring lymphocyte counts during COVID-19 infection.[76,77] TNF inhibitors, including Infliximab, and Adalimumab, can also be considered for preventing cytokine-induced lung injury during a SARS-CoV-2 infection.[78] However, the risk of opportunistic severe bacterial and fungal infections and latent tuberculosis (TB) reactivation should be considered when administering these medications.[79]

Nevertheless, it should be reminded that in previous studies, TNF inhibitors brought about adverse effects after a long-term period of administration [e.g., in Galloway et al. (2011) study,[80] the risk of serious infectious diseases was maximum during the first 6 months of treatment] not an acute one. Therefore, it has remained a controversial idea whether short-term use of these medications could lead to common, life-threatening adverse effects or not. Thus, future studies should aim to clarify the disputable idea that the short-term administration of TNF inhibitors could lead to highly life-threatening conditions or not. Anti-IFN-γ (e.g., Emapalumab) and anti-GM-CSF antibodies (e.g., lenzilumab) are other therapeutic options for reversing the COVID-CSS (Figures 1 and 2).[81,82]

6 | WHO SHOULD RECEIVE IMMUNOMODULATORS?

It is not yet known which patients benefit the most from therapy using immunomodulators. IL-6 inhibitors are not necessarily effective in all COVID-19 patients. Some studies recommend these agents according to the percentage of lung consolidation so that patients

TABLE 1 The advantages and disadvantages of the most important medications for COVID-19 hyperinflammatory responses

Medication	Advantages	Disadvantages
Dexamethasone Methylprednisolone	• Good efficacy in stabilising hemodynamics • Shortening ICU stay and duration of mechanical ventilation	Higher mortality rate when steroids are used in virus-induced acute lung injury
Tocilizumab	• Improving or stabilising clinical conditions in COVID-19 patients • Reduction in ICU admissions and mechanical ventilation use	• The common adverse reactions of tocilizumab include infection, increased serum cholesterol, ALT and AST, and injection-site reaction • According to the FDA, possible serious post-administration infections lead to hospitalisation or death due to tuberculosis, bacterial, invasive fungal, viral, and other pathogens
Sarilumab	• Reduction in CRP levels • A positive trend in clinical outcomes only in patients with critical disease	According to the FDA, possible serious post-administration infections lead to hospitalisation or death due to tuberculosis, bacterial, invasive fungal, viral, and other pathogens
Baricitinib	• Reduction in mortality rate • Reduction in the risk of progression to invasive ventilation or ECMO	Baricitinib is expected to cross the placenta, and animal studies show teratogenic effects at high doses

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; ICU, intensive care unit.

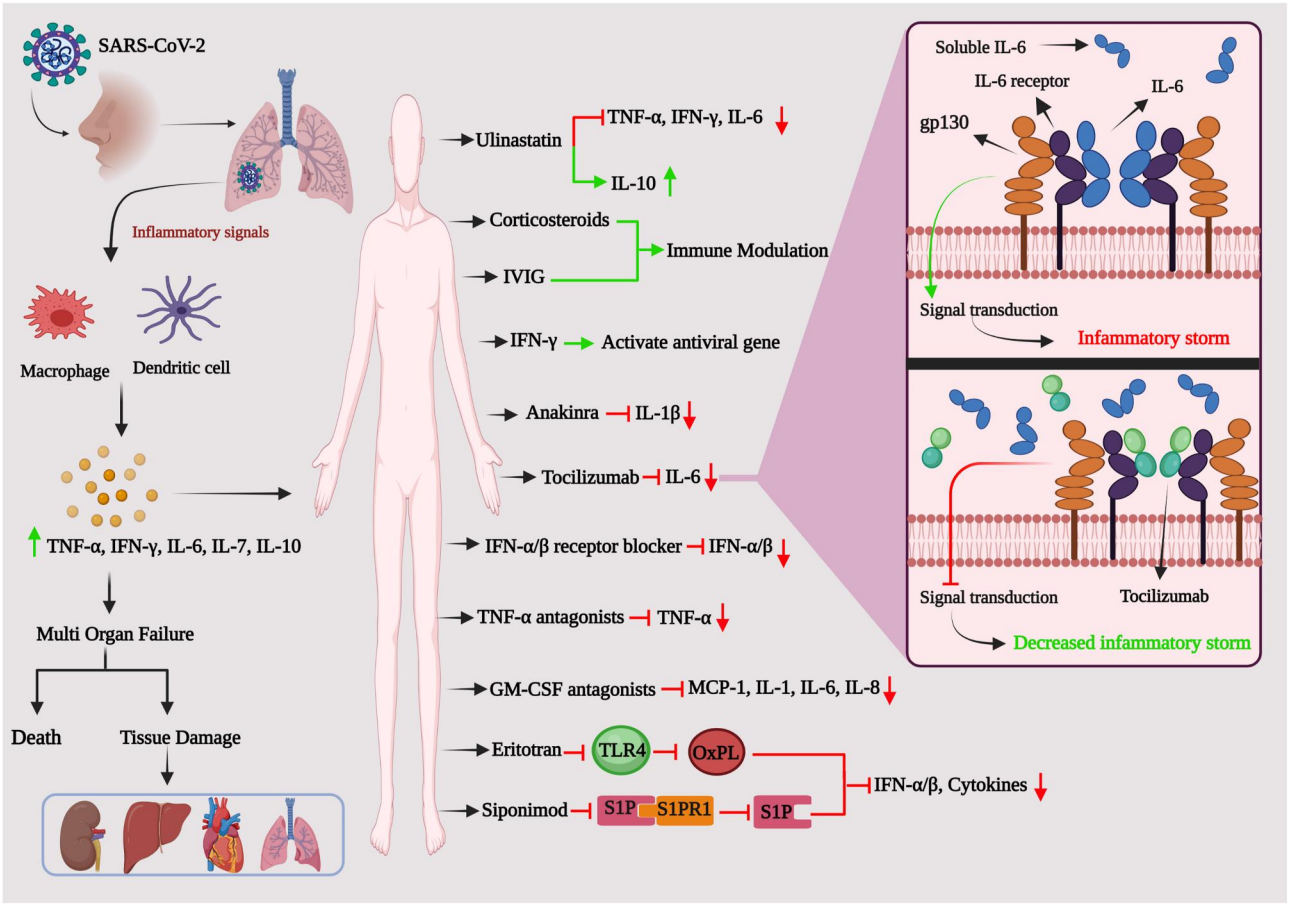

FIGURE 1 The role of cytokines and their antagonists in COVID-CSS pathophysiology. After the entry of the SARS-CoV-2 into the respiratory tract, APCs, such as macrophages, and dendritic cells, phagocytose these pathogens, and initiate a cascade of events, resulting in over secretion of pro-inflammatory cytokines, including TNF-α, IFN-γ, IL- 6, IL-7, and IL-10. This cytokine storm, commonly known as COVID-CSS, can cause multi-organ failure or even death via autoinflammatory pathways. Thus, administration of these cytokines' antagonists and blockers may play a crucial role in inhibiting such catastrophic adverse events and saving the patient's life. Among these agents, tocilizumab, an IL-6 antagonist, is proven to be beneficial, especially in the moderate-severe forms of the disease. This medication exerts its anti-IL-6 effect via occupying the IL-6 receptors, thus, inhibiting its pro-inflammatory actions. APCs, antigen-presenting cells; COVID-CSS, COVID-19 cytokine storm syndrome; GM-CSF, granulocyte-macrophage colony-stimulating factor; gp130, glycoprotein 130; IFN-α/β, interferon-alpha/beta; IFN-γ, interferon-gamma; IL-1β, interleukin-1beta; IL-6, interleukin-6; IL-7, interleukin-7; IL-8, interleukin-8; IL-10, interleukin-10; IVIG, intravenous immunoglobulin; MCP-1, monocyte chemoattractant protein-1; OxPL, oxidised phospholipids; S1P, sphingosine-1-phosphate; S1PR1, sphingosine-1-phosphate receptor 1; TLR4, toll-like receptor 4; TNF-α, tumour necrosis factor-alpha. *Source*: Created with BioRender.com

with less severe lung involvement would be the best candidates for this therapy.[83] To date, the most remarkable efficacy of IL-6 antagonists has been observed among patients with severe COVID-19 infections requiring supplemental oxygen therapy through high-flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation.[84,85] Some physicians are even recommending preventive tocilizumab treatment in COVID-19 patients with evidence of sepsis (using their SOFA scores) or among those who have not yet become critically ill or are requiring high levels of oxygen but are expected to progress.[86,87] This is because tocilizumab administration improves patients' outcomes before FiO_2 falls below 45%. Although there have been concerns about these immunomodulatory agents' virological and immunological burden, studies have shown that while these agents do not impair anti-viral antibody responses, they may delay viral clearance.[88] Similarly, some studies deny the beneficial role of these agents, considering the increase in opportunistic infections.[89] In contrast, other studies have concluded that tocilizumab decreases mortality and severe complications but has no effect on clinical improvement or the duration of hospitalisation.[90]

Tocilizumab administration is allowed in individuals >2-years old with severe CRS.[91] However, it is important to know that IL-6 levels are not routinely assessed in most hospitals. Therefore, alternative biomarkers, such as CRP, ferritin, D-dimer, and fibrinogen can decide which patients should be started on tocilizumab therapy. The best time to initiate tocilizumab therapy is after the clinical worsening, rather than following the infection period. It is unknown how many tocilizumab doses would be sufficient in a specific COVID-19 patient since it depends on their clinical condition and response. Nonetheless, the

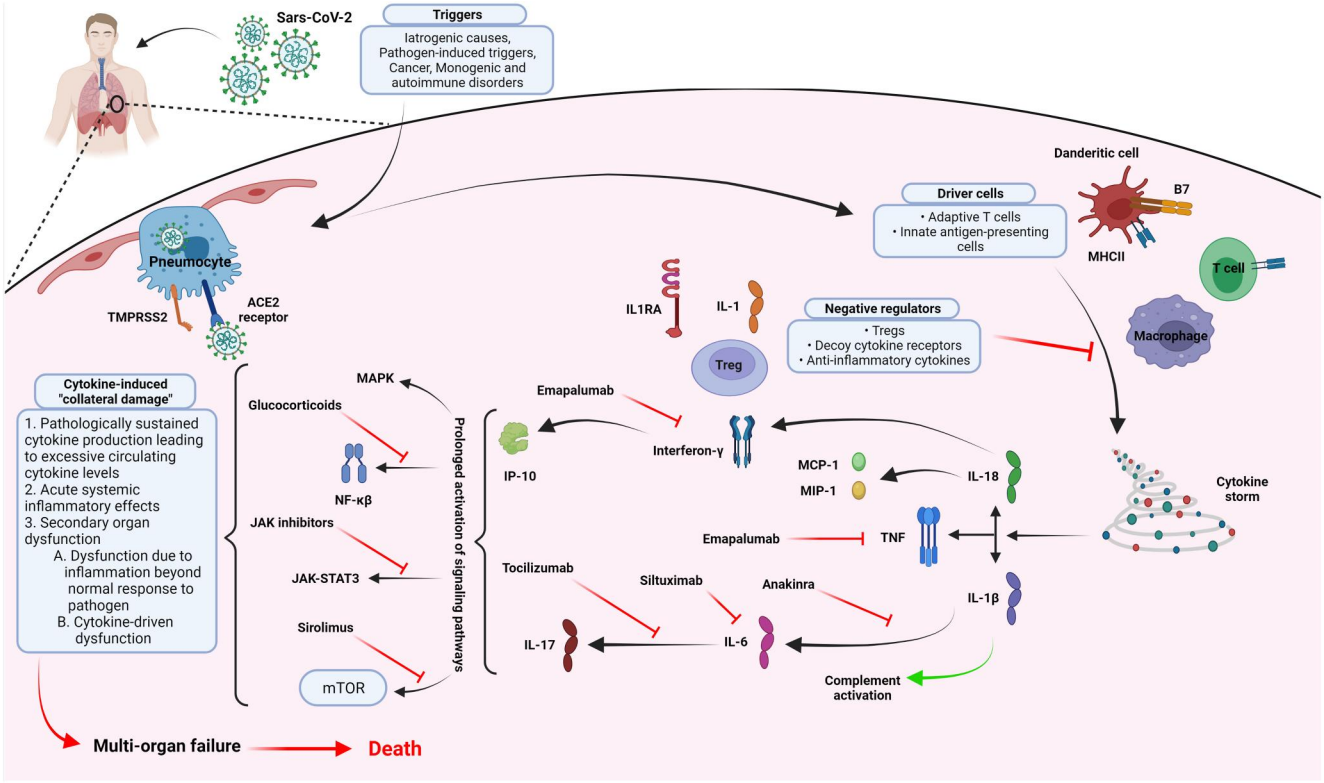

FIGURE 2 The features of cytokine cascades in the COVID-CSS. Various stimuli can enter the body, activate the immune system, and trigger a cytokine storm. Also in this path are cells and cytokines that control this storm. In the aftermath of this storm, many different cytokines are activated, each of which stimulates the activation of the other cytokine. The MAPK, JAK STAT3, NF-κβ, and mTOR signalling pathways are activated for a long time. These pathways can also be controlled. Prolonged activation of these pathways increases circulating cytokine levels, leading to acute systemic inflammation and secondary organ dysfunction. Which eventually leads to multi-Organ failure and death. ACE2, angiotensin-converting enzyme 2; COVID-CSS, COVID-19 cytokine storm syndrome; IL-1, interleukin 1; IL-17, interleukin 17; IL-18, interleukin 18; IL-1Ra, interleukin 1 receptor antagonist; IL-1β, Interleukin 1β; IL-6, interleukin 6; IP-10, interferon-inducible protein-10; JAK/STAT3, Janus kinase/signal transducer and activator of transcription-3; MAPK, Mitogen-activated protein kinase; MCP1, monocyte chemotactic protein-1; MHC, major histocompatibility complex; MIP1, Macrophage inflammatory protein-1; mTOR, mammalian target of rapamycin; NF-κβ, nuclear factor kappa light chain enhancer of activated B cells; TMPRSS2, transmembrane serine protease 2; TNF, Tumour necrosis factor; Treg, regulatory T lymphocyte. *Source*: Created with BioRender.com

current recommendation is to administer two 5–8 mg/kg doses of tocilizumab at 12–24-h intervals. However, some studies have suggested using up to three additional doses in patients not responding to therapy, with intervals of at least 8-h. Only intravenous injections are allowed, and the infusion duration should not be less than 1-h. Doses over 800 mg per infusion are not recommended. At least 2 weeks of monitoring is mandated to prevent adverse events caused by the relatively long half-life of tocilizumab (2- to 3-weeks).[70] This therapy method can be the last-line therapeutic option in patients with immunomodulation-refractory ARDS needing extracorporeal membrane oxygenation (ECMO), intravenous immunoglobulin (IVIG), and selective cytapheresis by cytokine-adsorption devices.[92]

7 | SAFETY ISSUES TO BE CONSIDERED DURING TOCILIZUMAB THERAPY

The most concerning issue in applying tocilizumab has been the increased risk of bacterial and fungal superinfections, particularly in critically ill COVID-19 patients in an ICU, due to its innate immunity weakening properties.[93,94] The main concern is that some believe this agent can diminish short-term mortality at the expense of increasing long-term mortality.[95] Other adverse events that are likely following tocilizumab therapy include LFTs elevation, absolute neutrophil count (ANC) and a reduction of platelets, infusion-related adverse reactions, anaphylaxis, acute hypertriglyceridemia, increased risk of latent TB reactivation, hepatitis B virus (HBV) reactivation, complications of the hepatitis C virus (HCV), hypotension, gastrointestinal (GI) perforation, and dyspnoea.[96–101] Recently, medication-related osteonecrosis of the jaw (MRONJ) was identified as a rare complication of tocilizumab therapy.[102] Nonetheless, it should be reminded that in previous studies, tocilizumab was administered for a long-term period [e.g., 48 weeks in Khanna et al. (2016) study[103]], not an acute one. Thus, it has still remained controversial whether short-term use of tocilizumab could demonstrate common, life-threatening adverse effects or not. Thus, future studies should aim to clarify this disputable idea that the short-term administration of tocilizumab can lead to highly life-threatening conditions, including bacterial and

fungal superinfections, latent TB and HBV reactivation, and complications of the HCV.

8 | TOCILIZUMAB THERAPY CONTRAINDICATIONS

Tocilizumab should be administered with caution in patients with severe bacterial and fungal infections, cytopenia, and liver abnormalities.[104] Treatment should be withheld if severe infections occur during tocilizumab therapy until the infection has subsided.[98] Due to the risk of latent TB reactivation, a purified protein derivative (PPD) skin test or the interferon-gamma release assay (IGRA) test should be performed to rule out this infection.[105] This agent is also contraindicated in patients with ANC <500/μl, platelet counts <50,000/μl, or liver function tests exceeding five times the ULN.[106,107] Moreover, its use in pregnancy and the elderly (>65 years old) is not recommended. In addition, individuals with non-severe COVID-19 or those with multi-organ failure are less likely to benefit from these agents, and therefore it is better not to administer tocilizumab to these patients, as it may harm them.

9 | CONTROVERSY OF CCS IN COVID-19

There is no doubt that scepticism exists about the concept of hypercytokinaemia as a pathological issue to be addressed. The most prominent critics of the CCS theory for COVID-19 believe that increased cytokine activity may be necessary for effective viral clearance.[108] Their reasoning for this stance is the observation that average serum IL-6 concentrations are not high in COVID-19 patients, and therefore, this infection is a hypo-inflammatory vasculopathy rather than a hyperinflammatory state. In this scenario, immunomodulatory therapy would have little effect on the course of the COVID-19 infection.[109,110] The consequence of introducing an ambiguous pathophysiological term, such as CCS, into the COVID-19 management arena without confirmation through a tangible biological diagnosis is the potential for mismanagement and resultant sub-optimal treatment outcomes.[109] Therefore, until further research is undertaken to strengthen the evidence base in either direction for immunomodulator therapy in COVID-19, their use in clinical practice needs to be undertaken with caution and the understanding that a limited evidence base exists.

10 | CONCLUSION

Modulation or blockage of the hyper-inflammatory state resulting from the cytokine release storm may aid medical management among specific sub-groups of COVID-19 patients, such as those requiring supplemental oxygen therapy. In some cases, physicians use immunomodulator therapy as a prophylactic measure, particularly among individuals with sepsis. There is some evidence to suggest that treatment may result in reduced ICU admissions, length of hospital stay, the need for mechanical ventilation, and reduced mortality. However, scepticism exists due to vagueries in the current evidence base. Therefore, after carefully considering and evaluating the patients, administering these agents may be the last therapeutic option for severe COVID-19 patients. Moreover, more studies on newer biologic agents to antagonise and further block other pro-inflammatory cytokines are needed.

AUTHOR CONTRIBUTIONS

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ACKNOWLEDGEMENTS

The authors would like to thank the Clinical Research Development Center of Imam Reza Hospital, Kermanshah University of Medical Sciences, and the Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences for their kind support.

CONFLICT OF INTEREST

Terence T. Sio reports that he provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure, Inc. and also as a member of the Advisory Board to Galera Therapeutics, which are not in any way associated with the content or disease site as presented in this manuscript. All other authors have no relevant financial interests to be declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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How to cite this article: Mohseni Afshar Z, Barary M, Babazadeh A, et al. The role of cytokines and their antagonists in the treatment of COVID-19 patients. *Rev Med Virol*. 2022; e2372. https://doi.org/10.1002/rmv.2372