

Review Article

Inflammation in COVID-19: from pathogenesis to treatment

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Abstract: The coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020 by the World Health Organization (WHO). To date, there were > 163 million confirmed cases of COVID-19 and the disease has claimed > 3.3 million lives globally. As with many other diseases, inflammation is a key feature of COVID-19. When inflammation is overwhelming, it may lead to unfavorable outcomes or even death. Scientists all over the world are working tirelessly in search of therapeutic strategies to suppress or modulate inflammation in COVID-19. This review gives an overview of the role of inflammation in COVID-19. It also critically examines the various treatment approaches that target the immune system and inflammation in COVID-19, as well as highlights the key findings in the numerous studies conducted thus far.

Keywords: COVID-19, SARS-CoV-2, inflammation, cytokine storm, pharmacotherapy

Introduction

In December 2019, there were an increasing number of pneumonia cases in Wuhan, a city in China's Hubei Province. However, the cause of the disease was unclear at that time. A month later, the Chinese Centre for Disease Control and Prevention announced the isolation of a novel coronavirus (CoV) from a patient with pneumonia in Wuhan [1]. The virus was different from severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle-East Respiratory Syndrome coronavirus (MERS-CoV) previously reported in the published literature. This newly isolated CoV was initially called 2019-nCoV and is now widely known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This was followed by the declaration of COVID-19 as a pandemic by the WHO two months later, in March 2020 [2]. Since its emergence, COVID-19 has spread uncontrollably across the globe and SARS-CoV-2 has infected people in nearly every country in the world. As of 17th May 2021, there were > 163 million confirmed cases of COVID-19 with > 3.3 million people losing their lives to the disease (<https://www.worldometers.info/coronavirus/>).

Although pharmacotherapy plays a pivotal role in the treatment of many infectious diseases, the process of developing new drugs is usually very time-consuming, challenging and costly. Under normal circumstances, up to 15 years are needed from the development of the original idea to the drug reaching the patient [3]. In addition, pharmaceutical companies usually have to spend millions of dollars before promising results can be reached. Therefore, there is an urgent need to come up with a quick solution to treat patients with COVID-19, while researchers continue the quest for a curative treatment.

One of the key features of COVID-19 is the overwhelming inflammation observed in some patients, especially those who develop severe illness. An exaggerated immune response mediated by an array of cytokines plays a role in the pathogenesis of the disease. Studies have demonstrated that several types of immune cells and inflammatory mediators are involved in the disease process [4, 5]. Hence researchers from all over the world have explored several anti-inflammatory and other pharmacotherapeutic agents to combat the

deadly inflammation. This review gives an overview of the role of inflammation in the pathogenesis of COVID-19, critically examines the pharmacologic agents that target inflammation and the immune system in the treatment of COVID-19, as well as consolidates the important findings from the numerous studies carried out thus far.

Inflammation in COVID-19

There is increasing evidence that points to the association between one's immune response and progression of disease in COVID-19, and abnormalities in immune cells, inflammatory markers and the cytokine storm have been implicated in disease severity and outcome. In addition, cytokine storm, hyperinflammation, and multi-organ failure have also been indicated in patients with severe disease. This section discusses the role of inflammation in COVID-19 from these perspectives.

Overview of pathogenesis of COVID-19

A basic understanding of the pathogenesis of COVID-19 and the immune response in SARS-CoV-2 infection is crucial in the understanding of the role of inflammation in COVID-19. SARS-CoV-2 is a coronavirus belonging to the Coronaviridae family and Coronavirinae sub-family. SARS-CoV-2 is an RNA virus. Its RNA is positive sense and single-stranded and the genome size of SARS-CoV-2 is 29.9 kb [6]. The structure of the virus has been widely studied since its emergence. The genetic materials of the virus are surrounded by an envelope. The structural proteins that are associated with SARS-CoV-2 include nucleocapsid (N) protein, envelope (E) protein, spike (S) protein, membrane (M) protein, and sixteen non-structural proteins (nsp1-16) [7].

The mechanisms of how SARS-CoV-2 enters the cells have been described. SARS-CoV-2's entry into host cells requires the use of its spike protein. The virus first attaches its receptor binding domain (RBD) to the human angiotensin-converting enzyme 2 (hACE2) receptor with the help of human proteases. Research has found that the RBD of SARS-CoV-2 has a stronger binding affinity for hACE2 in comparison with that of SARS-CoV. However, the more potent RBD is less exposed to hACE2 than that of SARS-CoV. Pre-activation of the spike by

furin (a proprotein convertase) also plays a role in cell entry. These features contribute to efficient cell entry and help explain why the virus is highly infectious and is capable of spreading rapidly in the community [8].

In the respiratory system, the two main types of cells that SARS-CoV-2 targets are ciliated bronchial epithelial cells and type 2 pneumocytes. However, hACE2 is widely found in many other bodily systems such as the cardiovascular-, renal-, and gastrointestinal systems. Endothelial cell binding of SARS-CoV-2 may result in systemic vasculitis, disseminated intravascular coagulation and thromboembolism, whereas epithelial cell binding may result in diarrhea [9]. The virus replicates itself after gaining entry to cells before it becomes recognized and attacked by the immune system. **Figure 1A** and **1B** shows the structure and the mechanism by which SARS-CoV-2 enters the host cell.

Immune response in SARS-CoV-2 infection

The human body reacts to SARS-CoV-2 infection in two main phases. The first phase is called the innate immune response, which acts as a first line of immune defense. During this phase, innate immune cells secrete interferons and cytokines, which in turn, initiate the adaptive immune response. The innate immune response occurs in not just SARS-CoV-2 infection but any viral infections [10]. During this phase, the infected person may present with symptoms such as fever, muscle aches, and malaise. One of the factors that affects the severity of COVID-19 lies in the differential innate immune response. A delayed production of type I interferons in older patients, for instance, may lead to increased recruitment of inflammatory cells such as macrophages, monocytes and neutrophils, which in turn, leads to overwhelming inflammation [11].

As the adaptive immune response sets in, CD8⁺ cytotoxic T cells play a role in targeting the virus-infected cells while the CD4⁺ helper T cells stimulate B cells to produce antibodies that specifically target the virus [10]. Studies have shown that a maladaptive immune response, with an increase in innate immune cell lineages and reduction in lymphocytes (lymphopenia) are associated with more

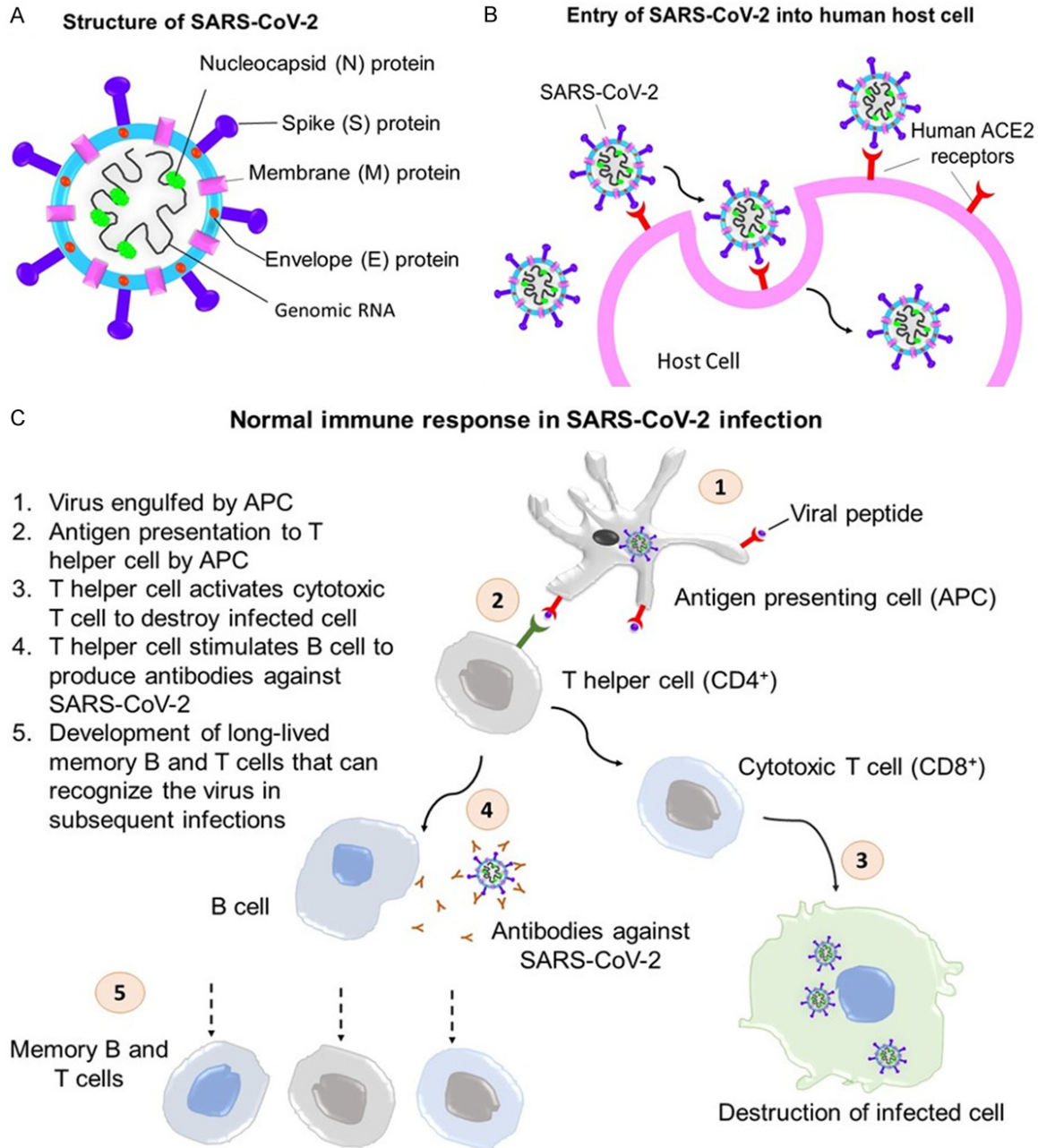


Figure 1. (A) Structure of SARS-CoV-2, (B) entry of SARS-CoV-2 into human host cell and (C) normal immune response in SARS-CoV-2 infection.

severe disease and poorer outcomes [4, 5, 12]. A delayed type I interferon response during the innate response phase may be the explanation for uninterrupted initial viral replication and delayed priming of the adaptive immune response. Therefore, the viral load becomes too high and severe disease that requires intensive intervention results, which is accompanied by a high risk of intubation and mortality [13].

During the adaptive response phase, CD4⁺ T cell response appears to be more prominent than the CD8⁺ T cell response as circulating CD8⁺ T cells specific to SARS-CoV-2 were detected in 70% of convalescent patients whereas circulating CD4⁺ T cells were detected in 100% of patients. CD4⁺ T cells mainly respond to S protein, whereas the N, S, and M proteins are each responsible for 11% to 27% of the total CD4⁺ response [14]. Tan *et al* demonstrated

that an early induction of T cell immunity against SARS-CoV-2 was associated with viral clearance and a mild disease [15]. As for B cell immunity, many patients infected with SARS-CoV-2 were found to be seroconverted within 5 to 15 days and a 90% seroconversion was detected by the 10th day post symptom onset. The S protein is the main target of the neutralizing antibodies, with > 90% of them targeting the RBD of the S protein [16], although other antigens are also targeted. This partly explains why the development of many vaccines revolves around S protein. The normal innate and adaptive responses in viral infections are summarized in **Figure 1C**.

Cytokine storm in COVID-19

Although many infected patients are asymptomatic or having only mild to moderate symptoms, a small minority of patients have severe to life-threatening disease [17]. This is because the effects of the overactive immune response are more destructive than that of the infection itself, which result in massive and irreversible damage to the organs. This overwhelming immune response in COVID-19 has been linked to what is termed as a cytokine storm.

In general, cytokines are small proteins that are released by cells, especially immune cells that regulate the immune response to diseases or inflammation. They include a broad array of chemicals e.g. chemokines (which play a role in chemotactic activities), lymphokines (cytokines released by the lymphocytes), interleukins (IL) (cytokines released by white blood cells that act on other white blood cells), and monokines (cytokines released by the monocytes). Other examples of cytokines include tumour necrosis factors (TNF) and interferons (IFN). Cytokines may act on the cells that secrete them (autocrine effect), neighboring cells (paracrine effect) or cells that are distant from the site of secretion (endocrine effect). Some cytokines are pro-inflammatory while others are anti-inflammatory [18].

A cytokine storm (CS) refers to uncontrolled and massive cytokine release (or hypercytokaemia) by the innate immune system in the presence of infectious or non-infectious stimuli. Although the concept of a cytokine storm may have started before the coining of the term, the

first mentioned of term cytokine storm can be dated back to 1993, in an article on graft-versus-host disease [19]. Cytokine storms are not uncommon in viral infections caused by MERS-CoV, SARS-CoV, influenza, and other viruses [20, 21]. Impaired and delayed viral clearance, delayed type I interferon response, increased neutrophil extracellular traps (NETS) and pyroptosis are some proposed underlying mechanisms for CS in COVID-19 [22].

On the other hand, cytokine storm syndrome (CSS) encompasses a diverse set of conditions and were formerly known as familial or primary hemophagocytic lymphohistiocytosis (HLH) and secondary HLH. Other terms under the umbrella of CSS include macrophage activation syndrome (MAS), cytokine release syndrome (CRS), malignancy-associated haemophagocytic syndrome (MAHS), infection-associated haemophagocytic syndrome (IAHS) and cytokine storm (CS) [23].

Research has shown that CS contributes to hyperinflammation in the lungs and results in acute respiratory distress syndrome (ARDS). Postmortem findings of lungs affected by ARDS in COVID-19 demonstrated diffuse alveolar damage, bilateral interstitial mononuclear inflammatory infiltrates with a dominance of lymphocytes, accompanied by reduced peripheral blood levels of CD8⁺ and CD4⁺ T cells, as well as increased levels of proinflammatory Th17 helper cells [24]. Minimally invasive autopsies revealed a dominance of macrophages and monocytes in the alveolar infiltrates with moderate multinucleated giant cell infiltration and minimal neutrophil, eosinophil and lymphocyte infiltration. Other findings include increased proliferation of type II alveolar cells, congestion, edema and widening of alveolar septal blood vessels, presence of hyaline thrombi in microvessels, pulmonary interstitial fibrosis and lung tissue focal hemorrhages [25].

CS is also one of the chief causes of multi-organ damage in COVID-19. Other than the lungs, cytokine-induced injuries can occur in the heart, liver, kidney, and other organs of COVID-19 patients [26] whereas pathological changes have been observed in the spleen, heart, kidney, liver, blood vessels during autopsies [25]. If not treated, multi-organ damage may lead to multi-organ failure followed by

death. The uncontrolled release of cytokines also causes vascular injury and leads to platelet activation, which partly explains the hypercoagulable states in many COVID-19 patients with severe disease [27]. The underlying mechanisms of cytokine storm and pathogenesis of multi-organ failure are summarized in **Figure 2**.

Association between immune cells/inflammatory markers and disease outcome

In general, abnormalities in immune cell counts and marked increase in proinflammatory markers are more frequently seen in patients with severe COVID-19. Qin *et al* demonstrated that patients with COVID-19 had a lower level of B cells, T cells and natural killer (NK) cells [5]. Comparing the severe and non-severe groups, the former tended to have an even lower level of these cells. On the other hand, the neutrophil lymphocyte ratio (NLR), leukocyte and neutrophil counts were observed to be higher in the former, while a lower percentage of basophils, eosinophils and monocytes was observed. For the T cells, both the suppressor T cells and helper T cells were affected. A couple of infection-related and inflammatory markers were demonstrated to be higher in the severe COVID-19 cases, which included procalcitonin, C-reactive protein (CRP), serum ferritin, interleukin (IL)-2R, IL-6, IL-8, tumor necrosis factor (TNF)- α [5]. Similar findings were also shown in another study by Tan *et al* in which an overall lower level of B cells, NK cells and T cells (both CD4⁺ and CD8⁺ cells) and more marked levels of IL-6, IL-10, and CRP were detected in severe cases of COVID-19 [4].

Severe inflammation is not only associated with disease severity but also disease outcome. In a study with 283 patients with RT-PCR confirmed COVID-19, three inflammatory markers, i.e. serum CRP (86.36% sensitivity; 88.89% specificity), lactate dehydrogenase (LDH) (90.91% sensitivity; 80.56% specificity), and ferritin (95.45% sensitivity; 86.57% specificity) were shown to be useful in predicating mortality [28]. Zeng *et al* on the hand, showed that an array of inflammatory markers such as serum soluble IL-2 receptor, IL-6, IL-8, IL-10, TNF- α , procalcitonin, ferritin, LDH, high-sensitivity CRP, and high sensitivity CRP to lymphocyte ratio were all elevated in critically ill COVID-

19 patients. IL-6 and LDH were independent predictors in disease severity whereas an early decline in inflammatory markers yielded better outcomes. Among the critically ill and deceased patients, no significant decline in inflammatory cytokines and markers was observed throughout the course of disease [29].

Therapeutic strategies that target the immune system and inflammation in COVID-19

While as many as 80% of the patients present with mild to moderate illness and probably do not need any therapy, it is important that treatment is started early and not until the patients are severely ill, especially when adverse outcomes are predicted in some cases. To date, there is no cure for COVID-19. Neither is there a drug that is specifically used for the disease. For patients in respiratory distress, supportive treatment such as oxygen therapy is the mainstay of patient management. Both non-invasive and invasive mechanical ventilation have been used in these patients and intensive care plays a crucial role in severe cases. Researchers have explored therapeutic options such as passive immunity by convalescent plasma transfusion, the use of corticosteroids and other agents to suppress the overwhelming inflammation in COVID-19. This section discusses the various strategies that target the immune system and inflammation in SARS-CoV-2 infection.

Convalescent plasma therapy

Some researchers have suggested that the convalescent plasma of those who have recovered from COVID-19 may be a potential treatment option. In convalescent plasma therapy, the acellular portion of the blood of a recovered individual is transfused to a patient with the infection. There are several possible explanations for why convalescent plasma may work in COVID-19. The antibodies (mainly IgM and IgG) contained in the convalescent plasma exert their antiviral effects by binding to the antigenic parts of the virus, particularly the S protein. These antibodies, together with anti-inflammatory cytokines from healthy donors who have recovered from COVID-19, also exert immunomodulatory effects such as neutralization of cytokines, autoantibodies, and complement and regulation of the hypercoagulable state, all

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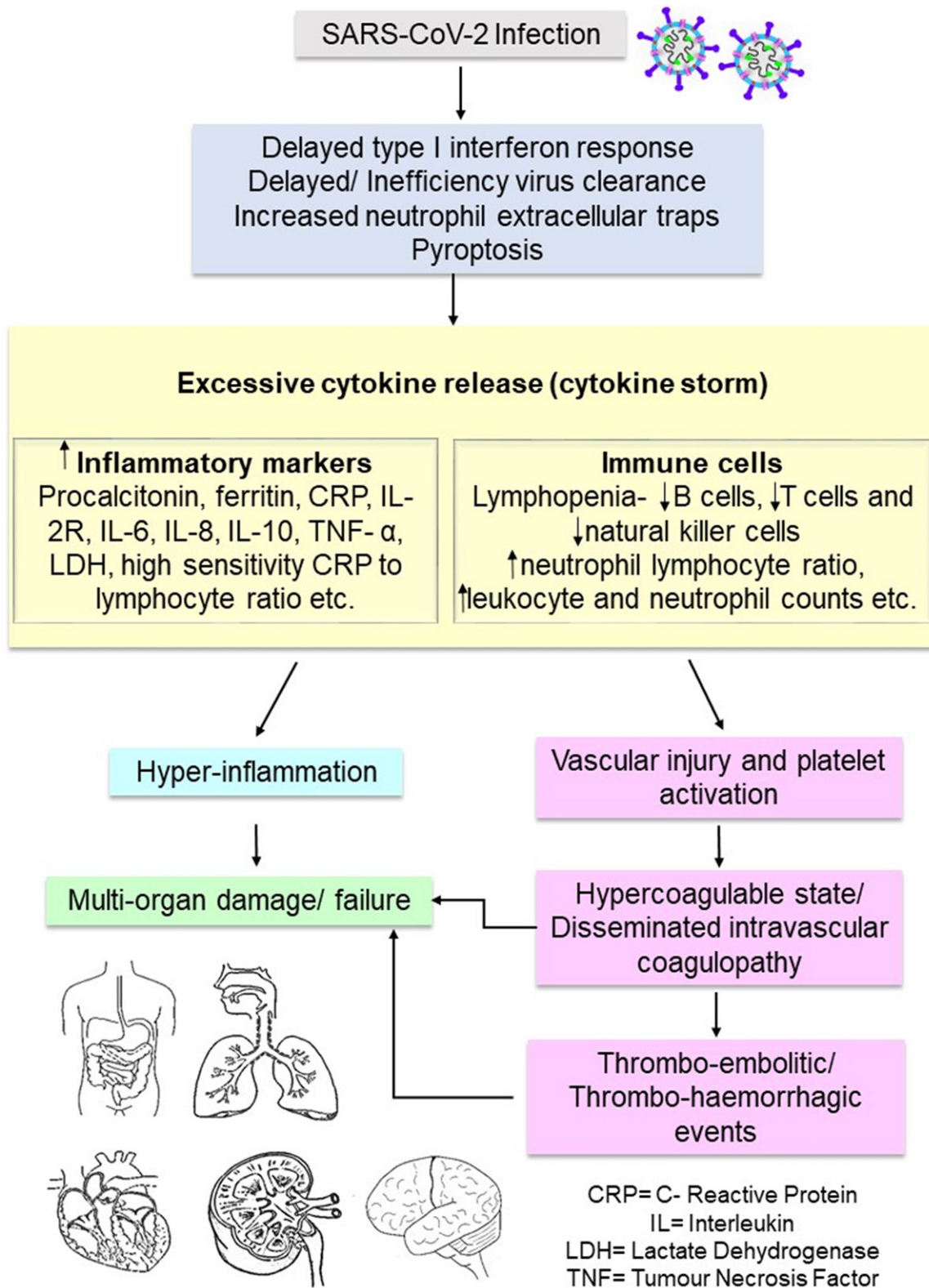


Figure 2. Underlying mechanisms of cytokine storm and pathogenesis of multi-organ failure.

of which are responsible for the heightened inflammation (reviewed by Rojas *et al*) [30].

It is noteworthy that both convalescent plasma and steroids had been used in the previous

SARS-CoV outbreak. Soo *et al* reported in a retrospective study that patients who received ribavirin-steroid therapy and convalescent plasma (n=19) had a shorter duration of hospitalization (P=0.001) and a lower mortality (P=0.049) compared to patients who received ribavirin and methylprednisolone. Nevertheless, the sample size was small in this study and the fact that the control group received further pulsed methylprednisolone instead of convalescent plasma might have confounded the findings [31].

Joyner *et al* conducted a study on the safety of convalescent plasma transfusion in 5000 hospitalized patients whose condition was at risk of progressing to severe or life-threatening COVID-19 [32]. There were 36 reported serious adverse events (or < 1% of all transfusions) within the first four hours. Over the first 7 days, 602 mortalities were reported with an overall 7-day mortality rate of 14.9% (95% CI: 13.8%, 16.0%), which was no higher than the case fatality rate reported in the published literature for hospitalized patients (about 15-20%) [33, 34] and patients who received intensive unit care (57%) [35]. The study concluded that given the deadly nature of the disease and the enormous number of patients with severe disease and comorbidities, the mortality rate in the study did not appear to be excessive and there was no indication of toxicity beyond the expected toxicity of plasma use in critically-ill patients.

On the other hand, Duan *et al* transfused 200 ml of convalescent plasma with neutralizing antibody titres of > 1:640 to 10 COVID-19 patients with severe disease, as an additional treatment on top of antiviral drugs and maximal supportive treatment. A median time of 15.5 days from illness onset to transfusion was recorded. In five patients, the neutralizing antibody level rapidly increased up to 1:640 post transfusion whereas four other patients were able to maintain a high level of neutralizing antibodies of 1:640 post transfusion. Within 3 days of transfusion, an improvement of clinical symptoms was observed with an increase in oxyhaemoglobin saturation, accompanied by an increase in lymphocyte count, a reduction in C-reactive protein, and radiologic improvement within 7 days. Seven patients with previous viremia demonstrated undetect-

able viral load post transfusion and no patient reported severe adverse effects due to transfusion [36].

In a randomized trial in which older adult COVID-19 patients were given either convalescent plasma containing high IgG titers against SARS-CoV-2 or placebo within 72 hours of the onset of mild symptoms, it was reported that 16% (13 out of 80) of patients given convalescent plasma and 31% (25 out of 80) patients given placebo developed severe respiratory disease (P=0.03). When patients (n=6) who reached primary end point prior to infusion of either placebo or convalescent plasma were excluded, a larger effect size was observed, suggesting that COVID-19 progression in mild disease was reduced by high-titer IgG convalescent plasma against SARS-CoV-2. The trial ended early at 76% of its targeted sample size due to reducing confirmed case number of COVID-19 in the trial region [37].

Monoclonal antibodies

Monoclonal antibodies are synthetic proteins that behave like antibodies in the immune system. Depending on how they are produced, they are divided into four main types, namely a) murine monoclonal antibodies (synthesized from mouse proteins with the drug name ending with “-omab”), b) chimeric monoclonal antibodies (synthesized from both mouse and human proteins with the drug name ending with “-imab”), c) humanized (synthesized from a small part of mouse protein, attaching to a human protein, with the drug name ending with “-zumab”) and human (synthesized from purely human proteins, with the drug name ending with “-umab”) (<https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/monoclonal-antibodies.html>).

Chen *et al* investigated the effects of LY-CoV-555 (bamlanivimab), a neutralizing antibody in a single intravenous (IV) infusion (using either 700 mg, 2800 mg or 7000 mg) versus placebo in 452 patients with mild or moderate COVID-19. The primary outcome assessed was the change of viral load from baseline at day 11. Findings of the interim analysis showed a significant difference in log viral load (-0.53) from baseline in the group receiving 2800 mg LYCoV555 and placebo (P=0.02). For the group

receiving 700 mg and 7000 mg LYCoV555 versus placebo, the differences were -0.20 ($P=0.38$) and 0.09 ($P=0.70$) respectively. Less severe symptoms were observed in patients receiving LYCoV555 than those receiving placebo whereas less patients in the LYCoV555 group (1.6%) required hospitalization compared to the placebo group (6.3%). The study concluded that 2800 mg IV infusion of LYCoV555 appeared to speed up the natural decrease in viral load in mild or moderate COVID-19 cases [38].

Similar findings were reported by Weinreich *et al* in a study that investigated the effects of a neutralizing antibody cocktail, REGN-COV2 (consisting of imdevimab and casirivimab) on viral load in COVID-19 patients who were not hospitalized. The percentage of patients who required at least one medically-related visit among patients in the treatment group and placebo group was also analyzed. REGN-COV2 was demonstrated to lower viral load especially in patients with a high baseline viral load whereas the percentage of those required at least one medically-related visit was 6% for the placebo group and 3% for the treatment group [39]. Notably, the Food and Drug Administration (FDA) has authorized bamlanivimab and combination of casirivimab and imdevimab for emergency use in mild to moderate COVID-19 [40].

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial explored the efficacy and safety of tocilizumab, which is a monoclonal antibody used in treating rheumatoid arthritis. It binds to the IL-6 receptor and reduces inflammation. The clinical outcomes evaluated included mortality and need of invasive mechanical ventilation. Altogether, 4116 adult patients were enrolled in the trial, with 2022 patients treated with usual care plus tocilizumab and 2094 treated with usual care alone. It was reported that 31% ($n=621$) of the patients in the tocilizumab group and 35% ($n=729$) of the patients in the control group died within a period of 28 days ($P=0.007$). A significant mortality benefit was observed, especially in patients given systemic corticosteroids. A statistically significant difference in the likelihood of being discharged alive from the hospital between the tocilizumab group (57%, $n=1150$) and the control group (50%, $n=1104$; $P <$

0.0001) was reported. The patients in the tocilizumab group (35%, $n=619$, out of 1754) were also significantly less likely to require invasive mechanical ventilation or die when compared to the control group (42%, $n=754$, out of 1800; $P < 0.0001$). The study concluded that tocilizumab was beneficial in improving survival and clinical outcome, in addition to the beneficial effects of systemic corticosteroids [41].

Corticosteroids

Research on corticosteroid administration in COVID-19 patients has yielded contradicting findings. In one study that investigated the effects of a short course of methylprednisolone given early in moderate to severe cases of COVID-19, a significantly shorter duration of median hospital stay was reported in patients who received methylprednisolone (5 days) when compared to those in the control group (8 days; $P < 0.001$) [42] whereas another study showed that corticosteroid treatment was not associated with virus clearance time, duration of hospital stay or symptom duration [43]. Yang *et al* conducted a meta-analysis using 15 studies with a total of 5270 patients infected with coronavirus (including MERS-CoV, SARS-CoV and SARS-CoV-2) and revealed that corticosteroids therapy is more likely to be used in critical patients and that its use is associated with a higher mortality, longer duration of hospitalization, and higher rate of bacterial infection [44].

A randomized trial on the use of inhaled budesonide in 146 COVID-19 patients recently has its data published. Patients with mild COVID-19 within 7 days of symptom onset were either assigned inhaled budesonide or usual care. The primary end point included emergency visit, assessment or hospitalization. With the budesonide group, one participant reached the primary outcome whereas the usual care group had 10 patients reaching the primary end point ($P=0.004$). The clinical recovery time for the budesonide group was significantly shorter than the usual care group (7 days vs 8 days; $P=0.007$). At day 14 and day 28, the proportion of those with fever or persistent symptoms was lower in the budesonide group. Therefore, the study concluded that inhaled budesonide decreased the probability of the need for emer-

gency care and recovery time in patients in early COVID-19 [45].

The REMAP-CAP trial consisted of several arms (e.g. corticosteroids, antiviral drugs or immunoglobulin). There were 614 patients with COVID-19 (either suspected or confirmed) enrolled into at least one arm of the trial. For the corticosteroid arm, there were 137 patients randomized to a 7-day fixed-dose intravenous hydrocortisone, 146 patients to a shock-dependent course of hydrocortisone and 101 patients to no hydrocortisone (after excluding patients who withdrew). Within a timeframe of 21 days, the fixed-dose group and shock-dependent dose group gave a 93% and 80% probability of superiority respectively, in terms of the odds of improvement in the number of days that were organ-support free. The results were inconclusive as the trial was terminated early without any treatment meeting any of the predetermined statistical superiority criteria [46].

Non-steroidal anti-inflammatory drugs (NSAIDs)

Numerous studies have investigated the acute or chronic use of NSAIDs in COVID-19. Thus far, there is no evidence to suggest NSAIDs are related to less favourable clinical outcomes in COVID-19. A study on the use of NSAIDs among patients with COVID-19 demonstrated no increased mortality risk associated with acute ibuprofen use (n=40) or chronic NSAID use (n=96) when compared to non-NSAID users (n=357). Acute ibuprofen or chronic NSAID users also did not demonstrate a significant higher risk of hospitalization, severe COVID-19 or oxygen support compared to non-NSAID users [47]. Another study reported similar findings and suggested that ibuprofen use did not worsen clinical outcomes in COVID-19 with regards to mortality and the need for oxygen support [48]. Wong *et al* (2020) reported that there was no statistical difference in COVID-19 related death risk between current -and non-users of NSAIDs in the general population or patient with osteoarthritis or rheumatoid arthritis [49].

Other treatment strategies

Mesenchymal stem cells (MSCs) are known for their immunomodulatory properties. MSCs have been used in COVID-19 patients and dem-

onstrated some beneficial effects. In China, intravenous injection of ACE2-negative and TMPRSS2-negative MSCs in seven patients with severe COVID-19 has demonstrated improvement in pulmonary symptoms and functions. An increase in peripheral lymphocyte count, a decline in proinflammatory markers and overactivated immune cells, as well as an increase in anti-inflammatory markers were reported in patients receiving MSC treatment in comparison with the placebo group [50]. On the other hand, human umbilical cord mesenchymal stem cells (hUM-MSCs) were given three times at three-day intervals to a 65-year-old severely ill COVID-19 patient. Laboratory- and CT-evident remission of inflammation was observed with good tolerance of the hUC-MSCs [51]. However, much is still unknown about the role of MSC treatment in COVID-19 and it should be used with caution under investigational situation. **Table 1** gives a summary of the key findings regarding treatment strategies that target the immune system and inflammation in COVID-19.

Conclusions

Given the high number of reported cases and deaths on a daily basis, there is a desperate need to come up with effective treatment strategies for patients with COVID-19. Although supportive and intensive care play a crucial role, especially in severe cases, it is important that the overwhelming inflammation associated with severe and critical cases is addressed, as there are no specific or curative drugs for COVID-19 thus far. The therapeutic options that target inflammation and the immune system discussed in this review are some of the many examples of strategies that have been investigated and used for the treatment of COVID-19. While some of these strategies have shown promising results, others have been found to be ineffective.

In a study that aimed to examine the potential drugs for COVID-19 through large-scale compound repurposing, nearly 12,000 clinical-stage or FDA-approved small molecules have been screened. Among these, 100 molecules were identified to exhibit viral replication inhibition and 21 out the 100 molecules are known drugs demonstrating dose-response relationships [52]. These findings suggest that there is

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Table 1. Summary of key findings on therapeutic strategies targeting the immune system and inflammation in COVID-19

Therapeutic option	Key findings	Reference
Convalescent plasma therapy	Mortality rate did not appear to be excessive and no indication of toxicity beyond the expected toxicity of plasma use in critically-ill patients.	[32]
Convalescent plasma therapy	Improvement of clinical symptoms and viral load in severe cases of COVID-19.	[36]
Convalescent plasma therapy	COVID-19 progression in mild disease was reduced by high-titer IgG convalescent plasma against SARS-CoV-2.	[37]
Bamlanivimab (LY-CoV555)	IV infusion of single dose of 2800 mg LYCoV555 appeared to speed up the natural decrease in viral load in patients with mild or moderate COVID-19.	[38]
REGN-COV2 (combination of casirivimab and imdevimab)	Reduced viral load especially in patients with a high baseline viral load.	[39]
Tocilizumab	Beneficial in improving survival and clinical outcome, in addition to the beneficial effects of systemic corticosteroids (RECOVERY trial).	[41]
Methylprednisolone	A significantly shorter median hospital stay compared to control group.	[42]
Corticosteroids	Not associated with virus clearance time, duration of hospital stay, or symptom duration.	[43]
Corticosteroids	More likely to be used in critical patients. Its use was associated with a higher mortality, longer duration of hospitalization and higher rate of bacterial infection.	[44]
Inhaled budesonide	Decreased the probability of the need for emergency care and recovery time in patients in early COVID-19.	[45]
Intravenous hydrocortisone	Results were inconclusive. Trial was terminated early without any treatment meeting any of the prespecified criteria for statistical superiority (REMAP-CAP trial).	[46]
Non-steroidal anti-inflammatory drugs (NSAIDs)	No significant higher risk of mortality, hospitalization, severe COVID-19 or oxygen support was demonstrated among acute ibuprofen and chronic NSAID users when compared to non-NSAID users.	[47]
Ibuprofen	Use of ibuprofen did not worsen clinical outcomes in COVID-19 patients in terms of mortality and need for oxygen support.	[48]
NSAIDs	No difference in COVID-19 related death risk between current- and non-users of NSAIDs in general population and patients with osteoarthritis or rheumatoid arthritis.	[49]
Mesenchymal stem cell (MSC) injection	Improvement of pulmonary symptoms and functions, reduction in proinflammatory markers and overactivated immune cells and increase in anti-inflammatory markers in seven COVID-19 patients given IV MSC injection.	[50]
Human umbilical cord MSCs	Laboratory- and CT-evident remission of inflammation in a case of severe COVID-19.	[51]

still much room for further research into pharmacologic treatment for COVID-19, amidst the race to break the chain of transmission through the global vaccination campaigns. Having said that, combating inflammation in COVID-19 remains an important aspect of the management of COVID-19. Future research should focus on the underlying mechanisms of these anti-inflammatory strategies used in COVID-19.

Disclosure of conflict of interest

None.

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