Review

Turk J Immunol 2021;9(1):1-11
DOI: 10.5222/TJI.2021.92486

Hyperinflammation Syndrome in COVID-19 Disease: Pathogenesis and Potential Immunomodulatory Agents

COVID-19 Hastalığında Hiperenflamasyon Sendromu: Patogenez ve Potansiyel İmmünomodülatuvar Ajanlar

Moulid Hidayat[1], Diah Handayani[2], Fariz Nurwidya[2], Sita Laksmi Andarini[2]

[1]Faculty of Medicine, University of Mataram, Indonesia.
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia-Persahabatan Hospital Jakarta, Indonesia

Cite as: Hidayat M, Handayani D, Nurwidya F, Andarini SL. Hyperinflammation syndrome in COVID-19 disease: Pathogenesis and potential immunomodulatory agents. Turk J Immunol 2021;9(1):1-11.

Received: 03.01.2021 **Accepted:** 29.01.2021 **Publication date:** 30.04.2021

Corresponding Author: Moulid Hidayat, Faculty of Medicine, University of Mataram; Jl. Pendidikan No.37, Mataram, Indonesia, 83125.
moulid@juntendo.ac.jp

Abstract

The coronavirus disease 2019 (COVID-19) pandemic caused by infection of the SARS-CoV-2 virus has affected millions of people in the world. The pathogenesis and clinical manifestations of COVID-19 disease are tightly influenced by the host immune response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. In some condition, the immune response might be uncontrolled, giving rise to hyperinflammatory conditions marked by excessive release of proinflammatory cytokines (cytokine storms) in severe COVID-19 patients, which then can cause acute respiratory distress syndrome (ARDS), multiorgan failure, and death. Furthermore, treatment using immunomodulator agents including immunostimulatory and immunosuppressive agents can be an option in achieving successful treatment. In this review, we discuss the pathogenesis of the disease, including host immune responses to SARS-CoV-2 virus infection, and immune mechanisms which contribute to the disease severity and death as well as several potential immunomodulatory agents which can be used in the management of hyperinflammatory syndrome of severe COVID-19.

Keywords: hyperinflammation syndrome, coronavirus disease 2019 (COVID-19), immunomodulatory treatment, cytokine storm

Öz

SARS-CoV-2 virüsü enfeksiyonundan kaynaklanan koronavirüs hastalığı 2019 (COVID-19) pandemisi, dünyada milyonlarca insanı etkilemiştir. COVID-19 hastalığın patojenezi ve klinik seyri, şiddetli akut solunum yolu sendromu koronavirüsü 2'ye (SARS-CoV-2) karşı konak immün cevabından (SARS-CoV-2) etkilenir. Bazı durumlarda immün cevap, şiddetli COVID-19 hastalarında proenflamatuvar sitokinlerin (sitokin fırtınaları) fazla salımıyla hiperenflamatuvar durumlara yol açarak kontrol edilemeyebilir, bu da daha sonra akut solunum sıkıntısı sendromu (ARDS), çoklu organ yetmezliği ve ölüme yol açabilir. Ayrıca immünostimulatuvar ve immünosupresif ajanlar da dahil olmak üzere immünomodülatör ajanların kullanıldığı tedavi, başarılı bir tedavinin sağlanmasında bir seçenek olabilir. Bu makalede, SARS-CoV-2 virüsü enfeksiyonuna konak immün tepkileri ve hastalığın şiddetine ve ölüme etkisi olan bağışıklık mekanizmaları ve şiddetli COVID-19 hiperenflamatuvar sendromunun tedavisinde kullanılabilecek birkaç potansiyel immünomodülatör ajan dahil olmak üzere hastalığın patogenezi tartışılmaktadır.

Anahtar kelimeler: hiperinflamasyon sendromu, koronavirüs hastalığı 2019 (COVID-19), immünomodülatör tedavi, sitokin fırtınası

Introduction

The first case of coronavirus disease 2019 (COVID-19) occurred in China in December 2019 which was likely a zoonotic transmission from wild animals sold in the seafood market, Wuhan.[1] The cause of this disease is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which then can be transmitted from human to human.[2] In March 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic, and until June 14, 2020, global COVID-19 sufferers reached around 7.6 million confirmed cases associated with a number of around 420 thousand deaths.[3] Meanwhile, the number of sufferers in Indonesia reached around 37 thousand confirmed cases associated with a number of nearly 2 thousand deaths.[3]

Acute respiratory distress syndrome (ARDS) and multi organ failure caused by a hyperinflammatory response characterized by increased levels of proinflammatory

ORCID: M. Hidayat 0000-0001-5526-2700, **D. Handayani** 0000-0002-3647-2670, **F. Nurwidya** 0000-0002-8379-9510, **S.L. Andarini** 0000-0002-9108-6641

cytokines are associated with high mortality rates in severely ill COVID-19 patients.[1] The increasing number of new cases and deaths which occur every day in each country encourages efforts to treat the disease, and prevent its spread completely so that excellent knowledge about the pathogenesis of COVID-19 can be used as an insight in managing of COVID-19 cases. This review aims to summarize the current understanding of COVID-19 disease including its pathogenesis, host immune responses to viral infections in general, and several immunomodulatory agents that can be used as a treatment modality for hyperinflammatory syndrome in COVID-19.

PATHOGENESIS COVID-19

Coronavirus is a virus that causes disease in humans and animals.[4] Most of these viruses are types of human coronaviruses which are not highly infective pathogens (human coronavirus 229E, NL63, OC43, and HKUI1) that infect the upper respiratory tract and cause mild symptoms.[4] Besides, three types of coronaviruses are highly infective pathogens, which can replicate in the lower airway, cause pneumonia, and can sometimes end up with a severe and fatal disease. There are 3 types of coronavirus infections are severe acute respiratory coronavirus syndrome (SARS-CoV), Middle East coronavirus respiratory syndrome (MERS-CoV) and SARS-CoV-2.[5]

Severe acute respiratory syndrome coronavirus-2 is a new virus from the genus betacoronavirus that can infect humans.[2] SARS-CoV-2 is genetically similar to human coronavirus SARS-CoV with about 79% similarity and about 98% identical to the RaTG13 coronavirus that infects bats.[2] Transmission of this virus was originally thought to be from animals to humans[6], but then it has been found that the SARS-CoV-2 virus can be transmitted from human to human through close contact and with droplets from the airways when sick individuals cough and sneeze.[7] There are also reports that the transmission can be through fecal-oral route but this route of transmission has not been established.[8] Furthermore, whether the asymptomatic individuals can transmit the virus remains controversial and there is no adequate evidence so far.[9]

The median incubation period for COVID-19 disease until the onset of symptoms is about 4 to 5 days.[10] The majority of symptomatic patients (97.5%) develop clinical symptoms within 11.5 days[10], whereas in other studies the incubation period ranged from 2 to 14 days.[11] In general, the clinical symptoms and laboratory findings of COVID-19 patients are the same as findings in those who suffer SARS-CoV and MERS-CoV.[12] Patients usually experience fever, dry cough, shortness of breath, myalgia, fatigue, diarrhea, loss of taste and smell, headaches and very rarely can cough up blood.[12,13]

The penetration process of the SARS-CoV-2 virus into the host cell is the same with the SARS-CoV virus which began with the binding of spike glycoprotein or S protein of SARS-CoV-2 with its target receptor, namely angiotensin-converting enzyme 2 (ACE-2).[14] However, there is a difference between two viruses in terms of the binding affinity of S protein to ACE2 receptors.[14] The binding affinity of S protein to ACE-2 receptors in COVID-19 is greater than the binding of homologous protein in SARS-CoV so that the SARS-CoV-2 has a greater virulent potential.[14] Expression of ACE-2 receptors is abundant on the surface of alveolar epithelial cells, type 2 pneumocyte cells, epithelial cells of the airway, vascular endothelium, and macrophages in the lungs.[8,15] The binding process of S protein to ACE2 receptors is followed by entry of the virus into the cytoplasm of cells and resultant formation of new virus particles by releasing ribonucleic acid (RNA) genomes and replicating RNA.[15]

The infection of SARS-CoV-2 and the destruction of pulmonary cells stimulate local immune responses.[8] The local immune response begins with the process of introducing viral antigens with the help of antigen-presenting cells played by major tissue histocompatibility complex (MHC), which then presents the virus antigens to natural killer (NK) and CD8-positive cytotoxic T cells.[15] This process then stimulates innate and adaptive immunities which turn out in the release of large amounts of proinflammatory cytokines and chemokines.[15] In some cases, immune dysfunction can occur and lead to excessive immune response and end up in the development of cytokine storms which cause uncontrolled inflammation, multiorgan failure, involving cardiac, hepatic, and renal systems.[8,15]

INTERACTIONS BETWEEN IMMUNE SYSTEMS AND VIRUSES

SARS-CoV-2 viruses, like most of the cytopathic viruses, has the ability to induce injury and death of infected cells and tissues as part of the viral replication cycle.[8] The process of infection and viral replication in the target cell is then lead to a condition known as pyroptosis that is an inflammatory form of programmed cell death which often occurs in infection caused by an intracellular pathogen.[16] This condition of pyroptosis has the potential to trigger further inflammatory responses.[8,16] Generally in the innate immune system, pattern recognition receptors (PRRs) expressed by macrophages, monocytes, dendritic cells, and neutrophils play a pivotal role in detecting pathogen-associated molecular patterns (PAMPs) expressed by infectious agents in the form of RNA viruses.[8,17] Toll-like receptors (TLRs) are one of the most common PRRs which recognize PAPMs in extracellular and

intracellular environments.[15] This signaling process then triggers the expression of NF-ϰB which is a transcription factor inducing proinflammatory cytokines and activates interferon regulatory factors which mediate the type I interferon-dependent antiviral response.[15,17]

Another type of pathogen recognition sensor is a nod-like receptor (NLR) which can detect the presence of damage-associated molecular patterns (DAMPs) expressed in cells, including molecules of adenosine triphosphate (ATP) and deoxyribonucleic acid (DNA).[8,15] The binding process of DAMPs then activates the NLR protein and eventually triggers the formation of inflammasome which converts procaspase-1 to the active form of caspase-1.[17] The caspase-1 then plays a role in the formation of an important proinflammatory cytokine, altering pro-interleukin 1 (IL-1) beta (pro-IL-1β) to IL-1β.[17] Immune cells in blood such as monocytes, and T lymphocytes from the blood are then attracted to the site of infection as a result of the secretion of proinflammatory cytokines and chemokines.[17]

Recruitment of immune cells from the blood into the lung along with lymphocyte infiltration causes a decrease in blood lymphocytes (lymphopenia) and an increase in the value of the neutrophil-lymphocyte ratio (NLR) as seen in the majority of COVID-19 patients.[18] Pathogen-associated molecular patterns of the virus in the form of nucleic acids bind to endosomal toll-like receptors 3 (TLR-3), toll-like receptors 7 (TLR-7), and cytosolic receptors including retinoic acid-induced gene I (RIG-I)-like receptors (RLR).[15] The binding process between viral RNA and RLR causes the activation of genes that encode type-1 interferon which has an important role in coordinating the cellular immune response in the form of antiviral immunity against viral infections.[19]

In general, when a viral infection occurs, the innate immune cells in the form of NK cells and adaptive immune cells represented by CD8-positive cytolytic T-cells will destroy the infected cells.[15] Besides, several other studies have also showed the involvement of CD4-positive T- cells along with the CD8-positive cytolytic T-cells which represent the response of the type 1 helper T cells.[8] The CD4-positive T cells are involved in the recruitment of immune cells and cytokine production in patients with SARS and COVID-19 disease.[8] The role of type 2 helper T-cells in COVID-19 disease is manifested with the existence of serum levels of IL-4 and IL-10, which are cytokines produced by type 2 helper T-cells.[20] Likewise, Roncati L, et al.[21] found evidence of immune response induced by type 2 helper T-cells immune response in the peripheral blood cells of COVID-19 patients requiring intensive care unit (ICU) treatment.[21] In addition to the T-cell immune response, there is also a B cell immune response in COVID-19 patients which becomes manifest about 1 week after the onset of symptoms.[22] In SARS patients, this response appears initially as a response to protein nucleocapsid (N-protein), and then after 4-8 days of initial clinical symptoms, antibodies respond to S-protein.[23]

Natural killer cells and CD8-positive cytolytic T-cells destroy the infected cells by using granulysin secretion mediated by perforin.[15] However, the inadequacy of the destruction process may occur due to defects in the ability of cytolytic lymphocytes which can be caused by genetic or acquired disorders.[15] This condition causes an increase and prolongation of interaction between innate and adaptive immunity resulting in the excessive and uncontrolled release of the proinflammatory cytokines, including tumor necrosis factor (TNF), interferon-γ (IFN-γ), IL-1, IL 2, IL-6, IL-7, IL-10, IL-18, and IL-33 which can cause cytokine storms, extensive lung inflammation, ARDS, and multiorgan failure.[12,15]

PATHOGENESIS OF HYPERINFLAMMATION SYNDROME

Cytokine storm is a process of releasing excessive, and uncontrolled proinflammatory cytokines.[24] Clinically, it appears as systemic inflammation, multiorgan failure, escalation of inflammatory parameters, and secondary hemophagocytic lymphohistiocytosis (sHLH) (often referred to as macrophage activation syndrome (MAS)).[25] This condition can be caused by a variety of diseases, including infectious diseases, rheumatic diseases, and as consequences of tumor immunotherapy.[24,25] Some evidence suggest that there is an escalation of the production of proinflammatory cytokines and ferritin in severely ill COVID-19 patients.[26] The same process was revealed in SARS and MERS patients specifically increased levels of serum IL-6, IL-8, IL1β, IFN-α, IFN-induced protein 10 (IP-10), chemokine (C-C motif) ligand 2 (CCL2), CCL3, CCL5, chemokine (C-X-C motif) ligand 8 (CXCL8), and CXCL-10 are detected in these patients.[26-28]

As stated earlier, in COVID-19 disease concentrations of several proinflammatory cytokines, and especially of IL-6 cytokines significantly increase in SARS and MERS.[24] This increase in proinflammatory cytokines is a major cause of morbidity and is related to respiratory failure, ARDS, and declining of clinical conditions.[24] Furthermore, in a multicenter, retrospective cohort study, there was an increase in serum IL-6 levels in patients who died compared to patients who survived.[29] Similar results were obtained from several studies that showed elevated serum IL-6 levels in critically ill COVID-19 patients.[30] In severe infections, there was also an increase in the biological marker C-reactive protein (CRP), whose expression is influenced by the increased expression of IL-6.[25,30]

Monocytes, macrophages, and dendritic cells infected

by betacoronavirus are then activated and secrete IL-6 and other inflammatory cytokines.[25] IL-6 has prominent proinflammatory property, it can signal through two main pathways specifically the classic cis signaling pathway and the trans pathway through its binding with membrane-bound IL-6 receptor (mIL6-R) and soluble form of IL-6 receptors (sIL-6R).[25] The signal transduction of the two signaling pathways are mediated by janus kinase (JAK) and signal transducer and activator of transcription 3 (STAT3). The final product of activation of cis- signaling that exerts pleiotropic effects on both the acquired immune system (B-cells and T-cells) as well as the innate immune system including neutrophils, macrophages, and NK cells, which can contribute to cytokine release.[31]

In the trans-signaling pathway, the interaction process among IL-6, the soluble form of IL-6 receptor, and JAK-STAT3 then causes cytokine storms which involve secretion of vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), IL-8, and the increased IL-6 concentration, and decreased of E-cadherin expression in endothelial cells.[32] Increased vascular permeability and plasma leakage are the consequences of decreased expression of E-cadherin and VGEF secretion, which are involved in pulmonary dysfunction and hypotension in ARDS.[25]

Secondary hemophagocytic lymphohistiocytosis is a hyperinflammatory syndrome characterized by cytokine storms, cytopenia, and multiorgan failure.[33,34] CD163-positive macrophages which is a source of ferritin is involved in sHLH.[35] This type of macrophage is involved in the process of reticuloendothelial iron signaling pathway so that when the sHLH happens, then the increase in the level of serum ferritin is likely.[35] In addition to high serum ferritin levels, fever, elevated triglyceride levels, pancytopenia, fibrinolytic consumptive coagulopathy, liver dysfunction, pulmonary involvement including ARDS and splenomegaly can also be found.[34,36] Furthermore, besides the involvement of CD163-positive macrophages, CD25-positive macrophages are also involved in the process with decreasing in NK cell activity, and the occurrence of hemophagocytosis, which explains the decrease in the number of blood cells in this condition.[33]

There are several suggestions on the predisposing factors for the occurrence of sHLH and cytokine storms in COVID-19 disease, namely there is a failure of virus clearance due to the ability of the virus to avoid the host immune system.[37,38] This ability is obtained by inhibiting the mechanisms of induction and signaling INF-I, and also by producing double-membrane vesicles which lack PRRs, thus weakening the introductive ability of host immune systems fighting against PAPMs found in viruses.[37,38] Another mechanism involves presence of genetic or acquired defects in the host immune system.[15] Failure in the eradication of the virus then causes sHLH and improper immune system activation which then results in ARDS and multiorgan failure.[15]

In severe COVID-19 disease, the activation of the coagulation process which has the potential to cause disseminated intravascular coagulation (DIC) occurs.[39] This condition is closely related to the pathophysiological process involving pulmonary endothelial cells.[39] Hyperinflammation in patients with severe COVID-19 disease can speed up activation and endothelial inflammation processes (endotheliitis). The process of endotheliitis is characterized with dysfunction (damage of vascular integrity), lysis and death of endothelial cells.[39] The coagulation cascade is then activated after the endothelial cell is exposed to thrombogenic basement membranes due to endothelial dysfunction and cell death.[40]

Endothelial cells activated by TNF and IL-1β subsequently express P-selectin, fibrinogen and von Willebrand factor that binds to platelets.[41] The endothelial cells then increase the expression of tissue factors (the main activator of the coagulation cascade) through the stimulation of VEGF produced by platelets.[41] In addition, the complement system is also considered to be associated with microvascular lesions and development of thrombosis in severely ill COVID-19 patients.[42] Furthermore, endothelial activation and dysfunction are thought to be involved in the worsening of cytokine storms and tissue damage.[39] This condition occurs because endothelial cells facilitate the extravasation and accumulation of leukocytes through the expression of leukocyte adhesion molecules.[41] The worsening of cytokine storms can be induced by the complement activation due to pulmonary vascular denudation.[39]

Another type of hyperinflammatory syndrome is what has been termed as multisystem inflammatory syndrome in children (MIS-C).[43] The clinical manifestations of MIS-C are persistent fever, headache, diarrhea, rash, conjunctivitis, and edema of extremity, which are often associated with severe illness including shock, myocardial dysfunction and respiratory failure.[43-45] The pathogenesis underlying MIS-C is still unknown. Some early studies linked it to Kawasaki disease, but recently several studies have confirmed that the two conditions are different.[43] The inflammatory mediators and T-cell subsets involved in MIS-C are different from those of the hyperinflammatory syndrome in patients with severe COVID-19 and Kawasaki disease.[44] In Kawasaki disease, IL-17a plays an important role, whereas in MIS-C, the IL-17a levels are very low or even absent.[44]

One hypothesis is that MIS-C occurs depending on the time the interferon responds to SARS-CoV 2 infection.[46] The interferon response times may vary depending on viral load and genetic differences in the host.[46] Mild infection occurs when viral load is low, where an interferon response

can increase viral clearance.[46] Conversely, severe infection can occur if the viral load is high and the host has genetic defect impairing antiviral response.[46] As a result the virus replicates freely and inhibits the interferon type-I and type-III response and the occurrence of a cytokine storm before the adaptive response eradicates the virus, which ensues in a severe disease condition including MIS-C.[47,48]

In contrast to the hyperinflammatory syndrome in adults that appears after about a week following an initial onset which is often called pulmonary phase II, MIS-C is most likely to occur post-infection in either symptomatic or asymptomatic COVID-19 infection (hyperinflammation phase III).[43] Some recommended managements of MIS-C patients include use of several immunomodulators, namely corticosteroids, anankira, tocilizumab, and IVIG.[43] The goals of treatment are to reduce systemic inflammation and restore organ function.[43]

IMMUNOMODULATORY AGENTS USED IN COVID-19 DISEASE

Management of COVID-19 patients consist of eradication of the virus using antiviral and supportive therapies including immunomodulatory agents (either immunostimulatory or immunosuppressive agents).[49] In severe cases, cytokine storm is common so that the use of immunomodulatory agents is expected to prevent further damage. Until now there has been no specific antiviral drug and vaccine that has proven to be effective and available for the management of COVID-19 disease.[15] The presence of hyperinflammation in COVID-19 disease, enable the use of immunosuppressive agents such as chloroquine and hydroxychloroquine, corticosteroids, inflammatory cytokine antagonists (such as IL-6R monoclonal antibodies, TNF inhibitors, IL-1 antagonists, JAK inhibitors).[50] In addition, the use of immunostimulatory agents in severe cases of COVID-19 disease can also be considered.[49]

Nevertheless, the decision to use immunosuppressive agents in patients with severe and critical symptoms needs careful consideration as these agents have benefits but also have a weakening effect on the antimicrobial immune system, especially interferon type I antiviral immunity.[51] Furthermore, consideration of the timing and duration for the administration of immunosuppressive and immunostimulatory agents is also important in achieving treatment success. In this literature review, we limit the discussion to the use of immunomodulatory agents including corticosteroids, chloroquine/hydroxychloroquine, anti-IL-6 receptor antibodies and anti-IL-6 antibody, IL-1 antagonists, convalescent plasma, Intravenous immunoglobulin (IVIG), and mesenchymal stem cells (Table 1).

Type 1 interferons

As mentioned earlier, IFN-I has a very crucial role as an antiviral agent.[38] However, some evidence shows that in COVID-19, SARS-CoV2 is able to evade the immune system by inhibiting IFN-I production and decreasing the activity of T lymphocyte cells.[52] Several recombinant interferons such as IFN-α2a, IFN-α2b, IFN-β1a and IFN-β1b have been previously used *in vitro* for MERS, Sars-CoV1, and Sars-CoV2 with mixed success rates.[53] The use of these recombinants failed to reduce viral load and mortality in MERS patients.[54] This may be due to the timing of administration.

Tumor necrosis factor blockers

Use of anti-TNF agents to control cytokine storms has been of concern. Its use is based on the results of studies that show an increased survival rate in septic patients after

Table 1. Potential immunomodulatory agents used in COVID-19.

Immunomodulatory agent	Function
Corticosteroids	Suppress the inflammation process
Tocilizumab	Targets signaling of IL-6R to decrease inflammation
Sarilumab	Blocks anti-human IL-6R
Intravenous immunoglobulin (IVIG)	Inhibits activation and differentiation of T and B lymphocytes and neutralizes cytokines and antibodies
The IL-1 family antagonist	Inhibits the inflammation process
Chloroquine and Hydroxychloroquine	Enhances antigen processing, and the work of regulatory T-cells, and inhibits the production of proinflammatory cytokines
Neutralizing antibody and convalescent plasma	Antibodies from convalescent plasma bind to the S protein of the virus and inhibit viremia
Mesenchymal stem cell	Inhibits the release of proinflammatory cytokines including IL-1, TNF-α, IL-6, IL-12, and IFN-γ

using anti-TNF.[55] The results of this study are in line with the role of TNF, an important inflammatory factor in the occurrence of cytokine storms.[55] In the mice model, TNF contributes to decreased T cell potency and is involved in acute lung injury in SARS-CoV, and loss of TNF expression prevents morbidity and mortality.[56] Based on these findings, the use of anti-TNF in COVID-19 disease can be considered. However, further research is needed regarding the efficacy of anti-TNF in COVID-19 patients.[57]

Corticosteroids

Corticosteroids are anti-inflammatory drugs with steroid groups which are generally used to suppress the inflammation process[58]. Corticosteroids were used as immunosuppressive agents during the SARS epidemic in 2003.[58,59] Timely use of corticosteroids in an appropriate time can provide good clinical outcomes as shown in a retrospective study conducted by Chen Rc, et al.[60] who found that corticosteroid administration in severely ill SARS patients could reduce mortality and shorten hospital stay.[60] However, several other studies such as those conducted by Auyeung TW, et al.[59] found that the use of corticosteroids in SARS-CoV infection had a detrimental effect in the form of an increase in plasma viral load and worsening of disease.[59]

Although there is not much evidence from randomized controlled trials supporting the use of systemic corticosteroids in COVID-19 patients, the use of systemic corticosteroids in COVID-19 patients is currently administered in patients with severe clinical symptoms to suppress ARDS, and multiorgan failure as a manifestation of cytokine storms.[61,62] The use of methylprednisolone for a short term (3-15 days) at a dose of 1-2 mg/kg per day can be recommended in patients with ARDS1, however, most of the evidence shows that the side effects of using systemic corticosteroids are more numerous as compared to the benefits obtained.[1] Data obtained from Russel et al.[63] show that the use of systemic corticosteroids in COVID-19 patients with pulmonary injuries is not supported by sufficient clinical evidence.[63]

Furthermore, meta-analyses have shown that corticosteroid administration is associated with high mortality rates in patients with SARS-CoV-1, MERS-CoV, and SARS-CoV-2 infections.[64] In the absence of conclusive scientific evidence, the regular use of corticosteroids in COVID-19 patients with pneumonia or ARDS is not suggested by WHO unless indicated for other conditions, such as asthma, exacerbation of chronic obstructive pulmonary disease (COPD), or septic shock.[65,66] The majority of data on corticosteroid use in COVID-19 patients is based on observational research data so large scale randomized controlled trials are needed to understand the risks and benefits of corticosteroid use in these patients.

Anti-IL-6 receptor antibodies and anti-IL-6 antibody

As noted earlier, the role of IL-6 as a proinflammatory cytokine is quite prominent and important in the pathogenesis of hyperinflammatory syndrome in COVID-19 patients so that the use of anti-IL-6 receptor antibody or anti-IL-6 antibody is expected to overcome the hyperinflammatory problem.[25] This is also supported by previous evidence that the use of anti-IL-6 and anti-IL-6R antibody has good efficacy in cytokine storm and sHLH conditions due to infection or iatrogenic administration of chimeric antigen receptor T-cell (CAR-T).[67] The anti-IL-6 receptor antibody used currently is tocilizumab which works by binding to the sIL-6R receptor on trans signaling and mIL6-R receptor on cis signaling, thus causing a suppressing effect on the IL-6 signaling transduction process.[25,68] Besides there are other anti-IL-6 receptor antibody namely sarilumab, and anti-IL-6 antibody, siltuximab.[25]

Promising preliminary results were obtained in a cohort study using tocilizumab in severe COVID-19 patients in China.[69] The study showed clinical improvement of fever and several other objective features such as decrease in pulmonary opacity on computed tomography scans (CT scans) and recovery of lymphocyte counts in the majority of patients in a short period.[69] Besides, there was a significant decrease in oxygen demand in three-quarters of the patients.[69] Another study conducted by Roumier et al.[70] found that there was a decrease in ICU treatment rates and the use of mechanical ventilators in severely ill COVID-19 patients who received tocilizumab.[70] Several clinical studies on the efficacy and safety of anti-IL-6R antibodies and anti-IL-6 antibodies in severely ill COVID-19 patients using various methodologies have been conducted so far.[71] However, the use of an antibody against IL-6 receptor and its ligands needs to be carefully considered. The reduction in virus clearance is one of the adverse effects of its use.[25]

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is a type of immunomodulatory therapy that contains polyclonal immunoglobulin G (IgG) derived from healthy donor plasma.[20] The benefits of IVIG consists of immunostimulation, anti-inflammation, and immune substitution.[20,68] So far, the use of IVIG has often been given to patients with immune deficiency, and systemic autoimmune diseases.[72] The anti-inflammatory effect of IVIG is obtained through its ability to bind to complement factors, to inhibit Fcγ receptors, inhibit activation and differentiation of T and B lymphocytes and to neutralize cytokines and antibodies.[73]

Two possible side effects can arise in IVIG administration, namely: 1) the occurrence of transfusion (immunoglobulin) -related acute lung injury (TRALI) which can

result in ARDS, and 2) the occurrence of thrombosis in the blood vessels.[74,75] Therefore, its usage in severely ill COVID-19 patients requires vigilance and good judgment. The side effects related to thrombosis in IVIG administration can be precluded by giving adequate anticoagulation and hydration.[15] So far, the use of IVIG in COVID-19 patients is still controversial and a further clinical trial with good research design needs to be done.[68,76]

The IL-1 family antagonist

An alternative immunosuppressive agent for the management of severely ill COVID-19 patients is the use of IL-1 antagonist with the generic name anakinra.[77] This is based on the finding that all three important cytokines from the IL-1 family such as IL-1β, IL-8, and IL-33 were found to be involved in cytokine storms.[77] This agent is a recombinant of the interleukin 1 receptor antagonist (IL-1Ra) protein, naturally secreted by macrophages and monocytes and selectively binds to IL-R.[68] It has been used in sepsis, autoimmune disease, and malignancy and it has been shown to suppress the inflammatory response.[78,79] Furthermore, the use of anakinra in sepsis has been reported to increase survival rates without significant side effects.[80,81] There are currently no reports of using this agent in COVID-19 patients, but based on its effectiveness in suppressing inflammation in sepsis, its use in severely ill COVID-19 patients with hyperinflammatory syndrome may be considered.

Chloroquine and Hydroxychloroquine

Chloroquine and its derivative, hydroxychloroquine are antimalarial agents and immunomodulatory agents in the management of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.[50] The use of chloroquine and hydroxychloroquine as antiviral agents in COVID-19 disease is based on their effectiveness as an antiviral agents in patients with SARS-CoV-1 infection.[71,82,83] Chloroquine enhances the effectiveness of MHC class I and MHC class II in antigen processing, inhibits endosomal TLR7 and TLR9, and enhances the work of regulatory T-cells.[73,84] Chloroquine and hydroxychloroquine can prevent the virus from entering the host cell by several mechanisms, namely: 1) These two substances accumulate in the lysosome thereby increasing the acidity level of endosomes[82]; 2) they weaken the glycosylation of the ACE-2 receptor so that the SARS-CoV-2 virus cannot bind effectively to the receptor.[85] Besides, they can also prevent ARDS by inhibiting the production of proinflammatory cytokines including IL-6.[15]

A study showed that the use of chloroquine and hydroxychloroquine in infected cells before and after onset of infection can reduce viral load. This study shows that both agents can be effectively used either as a prophylactic or therapeutic treatment.[86] A small scale open-label, non-randomized study, revealed that the combination of hydroxychloroquine and azithromycin can be beneficial in COVID-19 patients with severe clinical symptoms by reducing viral load on the 6th day of illness.[87] Several studies are currently underway on the efficacy of these two drugs[71] and whether they have beneficial in terms of antiviral and immunomodulatory effects in COVID-19 patients is a controversial issue and needs further investigation.

Neutralizing antibody and convalescent plasma

Neutralizing antibody

Two approaches can be implemented in the treatment of using neutralizing antibodies (nAbs) in SARS-CoV-2 virus infections, namely: 1) by stimulating the host immune system to actively produce nAbs against the SARS-CoV-2 virus by vaccination, and 2) by passively accepting nAbs from the outside body as a therapeutic approach. The second approach has been previously applied in the management of SARS and MERS and proved effective.[88,89] This source of nAbs can be obtained naturally through infection and from animals.[71] The mechanism of action of nAbs involves preventing binding of S-protein of virus to the ACE2 receptors of cells and thus inhibiting the fusion between the virus and the host cell membrane by binding the S-protein.[90]

Neutralizing antibodies from patients who have recovered from SARS-CoV-2 infection can be used as a source of recombinant nAbs.[91] Besides, the development of effective nAbs against SARS-CoV-2 derived from animal models has also been carried out.[71] Furthermore, a shred of interesting evidence indicates that nAbs from SARS patients has the potential to be used to treat COVID-19 patients as shown by Pinto et al.[92] who found that the memory B-cell recovered previously from the convalescent serum of the patients with SARS infection can neutralize SARS-CoV-2 virus.[92] This phenomenon can happen because the SARS-CoV-1 and SARS-CoV-2 viruses have a genetic similarity up to about 79%.[5]

Convalescent plasma

The principle of giving convalescent plasma is the same as giving recombinant nAbs, namely by conferring passive immunization through titer of nAbs produced by patients who were previously infected and have recovered.[71] Convalescent plasma can be given as prophylaxis to infected patients or individuals who have a susceptibility of contracting an infection.[90] The nAbs titers which will be used are the highest titers produced by recovered individuals.[71,90] Immunity gained from convalescent plasma is temporary and has a short duration.[90] Compared to recombinant nAbs, which requires a lot of time and costs a lot, convalescent plasma can be produced in a relatively short

time and is relatively inexpensive.[71]

Administration of convalescent plasma has been applied previously and showed good results in the pandemics of Spanish influenza in 1918, SARS, Argentine hemorrhagic fever, and H1N1 influenza.[90,93-96] Similar to recombinant nAbs, antibodies from convalescent plasma act by binding to the S-protein of the virus.[90] However, it is also important to note that the administration of the antibodies may conversely exert adverse effects known as antibody-dependent enhancement (ADE). In ADE the virus binds to non-neutralizing antibodies which increases the ability of the virus to invade host immune cells.[90,97]

Several studies have shown that the administration of convalescent plasma in severely ill COVID-19 patients is quite effective, and safe.[90-92] The administration of convalescent plasma on the 14th day was also reported to be quite efficient based on previous evidence accumulated in influenza and SARS.[90,95,96] In general, the administration of this plasma is acceptable, safe, and shows effective performance.[90] But several important things such as timing and duration of administration, and the required amount of convalescent plasma to be given need to be determined.[90] Besides, further research on this issue should be conducted with perfectly designed randomized controlled clinical trials.

Stem cell therapy

Mesenchymal stem cell (MSC) is a type of stem cell which not only have multipotency and self-renewal abilities but also have strong anti-inflammatory ability.[20] The use of MSC as a treatment of severely ill COVID-19 patients is considered to effectively relieve hyperinflammatory/cytokine storm conditions as it can inhibit the release of proinflammatory cytokines which including IL-1, TNF-α, IL-6, IL-12, and IFN-γ.[98] Also, MSC can also repair damaged pulmonary alveolar cells, increase alveolar fluid clearance, and prevent pulmonary fibrosis by secreting IL-10 and several growth factors such as hepatocyte growth factor, keratinocyte growth factor, and VEGF.[99] Recently, several clinical studies have been conducted to assess the efficacy of stem cell therapy.[100] Thanks to its many favourable effects, it is expected that the use of MSC can be applied as an effective immunomodulatory agent in the management of severe COVID-19 disease.

CONCLUSION

Interaction between the SARS-Cov-2 virus and the host immune system is very important in the development of COVID-19 disease. This interaction then contributes to the development, and severity of the disease. Host immune response begins with the process of introduction of viral antigens, followed by the activation of the innate and acquired immune systems, and may end in either virus destruction or even failure in virus elimination. In some cases, SARS-CoV-2 virus infection may further progress to severe illness and generating the condition of hyperinflammatory syndrome characterized with the release of excessive proinflammatory cytokines (cytokine storms), systemic inflammation, and ends in ARDS conditions, multiorgan failure, and death.[25] The failure in the process of eliminating viruses due to the weakening of the immune system by viruses as well as genetic or acquired defects in the immune system is considered to be a predisposing factor for the occurrence of the hyperinflammatory syndrome[15,37]

Besides antiviral agents, several immunomodulatory agents have been used recently as the treatment of choice in COVID-19 patients with hyperinflammatory syndrome.[49] Timeliness in applying the immunomodulatory agents might be very important in efforts to improve treatment success and reduce mortality even though until know there is no encouraging data that clarify this issue and for this reason it still need further investigation. Nevertheless, it needs a good consideration by balancing the risk and benefit ratio before using an immunomodulatory agent. Finally, further understanding of the host immune response to SARS-CoV-2 infection, and introduction of a more comprehensive immunopathological mechanism regarding the development of hyperinflammatory syndrome is needed in formulating better management strategies for the treatment of severely ill COVID-19 patients.

Conflict of Interest: The authors have not declared any conflicts of interest.

Funding: None declared.

REFERENCES

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395(10223):507-13. **[CrossRef]**
2. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3. **[CrossRef]**
3. World Health Organizarion. Coronavirus disease (COVID-2019) situation reports [Internet]. 2020 [June 14, 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
4. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1-23. **[CrossRef]**
5. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nature Reviews Microbiology. 2009;7(6):439-50. **[CrossRef]**
6. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. New England Journal of Medicine.

2020;382(13):1199-207. [CrossRef]

7. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020;395(10223):514-23. [CrossRef]
8. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-74. [CrossRef]
9. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. Journal of Infection and Public Health. 2020;13(5):667-73. [CrossRef]
10. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020;172(9):577-82. [CrossRef]
11. Linton NM, Kobayashi T, Yang Y, Hayashi K, Akhmetzhanov AR, Jung SM, et al. Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data. J Clin Med. 2020;9(2). [CrossRef]
12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. [CrossRef]
13. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020;382(18):1708-20. [CrossRef]
14. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clinica Chimica Acta. 2020;507:167-73. [CrossRef]
15. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clinical rheumatology. 2020:1-10. [CrossRef]
16. Fink SL, Cookson BT. Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. Infect Immun. 2005;73(4):1907-16. [CrossRef]
17. Schnappauf O, Chae JJ, Kastner DL, Aksentijevich I. The pyrin inflammasome in health and disease. Front Immunol. 2019;10:1745. [CrossRef]
18. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clinical Infectious Diseases. 2020. [CrossRef]
19. Stetson DB, Medzhitov R. Type I Interferons in Host Defense. Immunity. 2006;25(3):373-81. [CrossRef]
20. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-13. [CrossRef]
21. Roncati L, Nasillo V, Lusenti B, Riva G. Signals of T(h)2 immune response from COVID-19 patients requiring intensive care. Ann Hematol. 2020;99(6):1419-20. [CrossRef]
22. Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nature medicine. 2020;26(4):453-5. [CrossRef]
23. Wu HS, Hsieh YC, Su IJ, Lin TH, Chiu SC, Hsu YF, et al. Early detection of antibodies against various structural proteins of the SARS-associated coronavirus in SARS patients. J Biomed Sci. 2004;11(1):117-26. [CrossRef]
24. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393. [CrossRef]
25. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science (New York, NY). 2020;368(6490):473. [CrossRef]
26. Min C-K, Cheon S, Ha N-Y, Sohn KM, Kim Y, Aigerim A, et al. Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. Scientific reports. 2016;6(1):25359. [CrossRef]
27. Jiang Y, Xu J, Zhou C, Wu Z, Zhong S, Liu J, et al. Characterization of cytokine/chemokine profiles of seven acute respiratory syndrome. American journal of respiratory and critical care medicine. 2005;171(8):850-7. [CrossRef]
28. Reghunathan R, Jayapal M, Hsu L-Y, Chng H-H, Tai D, Leung BP, et al. Expression profile of immune response genes in patients with Severe Acute Respiratory Syndrome. BMC Immunology. 2005;6(1):2. [CrossRef]
29. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054-62. [CrossRef]
30. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. The Journal of Clinical Investigation. 2020;130(5):2620-9. [CrossRef]
31. Kang S, Tanaka T, Narazaki M, Kishimoto T. Targeting Interleukin-6 Signaling in Clinic. Immunity. 2019;50(4):1007-23. [CrossRef]
32. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016;8(8):959-70. [CrossRef]
33. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. Frontiers in Immunology. 2019;10(119). [CrossRef]
34. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020;395(10229):1033-4. [CrossRef]
35. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-8. [CrossRef]
36. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet (London, England). 2014;383(9927):1503-16. [CrossRef]
37. Snijder EJ, van der Meer Y, Zevenhoven-Dobbe J, Onderwater JJM, van der Meulen J, Koerten HK, et al. Ultrastructure and Origin of Membrane Vesicles Associated with the Severe Acute Respiratory Syndrome Coronavirus Replication Complex. Journal of Virology. 2006;80(12):5927-40. [CrossRef]
38. Channappanavar R, Fehr AR, Zheng J, Wohlford-Lenane C, Abrahante JE, Mack M, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. The Journal of Clinical Investigation. 2019;129(9):3625-39. [CrossRef]
39. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol. 2020;20(7):389-91. [CrossRef]
40. Nachman RL, Rafii S. Platelets, petechiae, and preservation of the

vascular wall. The New England Journal of Medicine. 2008;359(12):1261-70. [CrossRef]

41. Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. Nat Rev Immunol. 2007;7(10):803-15. [CrossRef]

42. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res. 2020;220:1-13. [CrossRef]

43. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management. Children (Basel). 2020;7(7). [CrossRef]

44. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell. 2020. [CrossRef]

45. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, et al. Multisystem Inflammatory Syndrome in Children During the Coronavirus 2019 Pandemic: A Case Series. Journal of the Pediatric Infectious Diseases Society. 2020;9(3):393-8. [CrossRef]

46. Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. Nat Rev Immunol. 2020;20(8):453-4. [CrossRef]

47. Park A, Iwasaki A. Type I and Type III Interferons - Induction, Signaling, Evasion, and Application to Combat COVID-19. Cell Host Microbe. 2020;27(6):870-8. [CrossRef]

48. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell. 2020;181(5):1036-45.e9. [CrossRef]

49. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20(4):400-2. [CrossRef]

50. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clinical Immunology. 2020;214:108393. [CrossRef]

51. Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? The Lancet. 2020;395(10230):1111. [CrossRef]

52. Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19: Immunology and treatment options. Clin Immunol. 2020;215:108448. [CrossRef]

53. Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clinical Infectious Diseases. 2019;70(9):1837-44. [CrossRef]

54. Channappanavar R, Fehr AR, Zheng J, Wohlford-Lenane C, Abrahante JE, Mack M, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. The Journal of Clinical Investigation. 2019;129(9):3625-39. [CrossRef]

55. Qiu P, Cui X, Sun J, Welsh J, Natanson C, Eichacker PQ. Antitumor necrosis factor therapy is associated with improved survival in clinical sepsis trials: A meta-analysis. Critical Care Medicine. 2013;41(10):2419-29. [CrossRef]

56. McDermott JE, Mitchell HD, Gralinski LE, Eisfeld AJ, Josset L, Bankhead A, III, et al. The effect of inhibition of PP1 and TNFα signaling on pathogenesis of SARS coronavirus. BMC Systems Biology. 2016;10(1). [CrossRef]

57. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-13. [CrossRef]

58. Ho JC, Ooi GC, Mok TY, Chan JW, Hung I, Lam B, et al. High-Dose Pulse Versus Nonpulse Corticosteroid Regimens in Severe Acute Respiratory Syndrome. American journal of respiratory and critical care medicine. 2003;168(12):1449-56. [CrossRef]

59. Auyeung TW, Lee JSW, Lai WK, Choi CH, Lee HK, Lee JS, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. Journal of Infection. 2005;51(2):98-102. [CrossRef]

60. Chen R-C, Tang X-P, Tan S-Y, Liang B-L, Wan Z-Y, Fang J-Q, et al. Treatment of Severe Acute Respiratory Syndrome With Glucosteroids: The Guangzhou Experience. Chest. 2006;129(6):1441-52. [CrossRef]

61. Chan KW, Wong VT, Tang SCW. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese-Western Medicine for the Management of 2019 Novel Coronavirus Disease. The American Journal of Chinese Medicine. 2020;48(03):737-62. [CrossRef]

62. Sun P, Lu X, Xu C, Sun W, Pan B. Understanding of COVID-19 based on current evidence. Journal of Medical Virology. 2020;92(6):548-51. [CrossRef]

63. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395(10223):473-5. [CrossRef]

64. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect. 2020;81(1):e13-e20. [CrossRef]

65. obaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA, et al. Therapeutic management of patients with COVID-19: a systematic review. Infection Prevention in Practice. 2020;2(3):100061. [CrossRef]

66. Mareev VY, Orlova YA, Pavlikova EP, Matskeplishvili ST, Krasnova TN, Malahov PS, Samokhodskaya LM, Mershina EA, Sinitsyn VE, Mareev YV, Kalinkin AL, Begrambekova YL, Kamalov AA. Steroid pulse -therapy in patients With coronAvirus Pneumonia (COVID-19), sYstemic inFlammation And Risk of vEnous thRombosis and thromboembolism (WAYFARER Study). Kardiologia. 2020 Jul 7;60(6):15-29. [CrossRef]

67. Serling-Boyd N, Stone JH. Recent advances in the diagnosis and management of giant cell arteritis. Current Opinion in Rheumatology. 2020;32(3):201-7. [CrossRef]

68. Alijotas-Reig J, Esteve-Valverde E, Belizna C, Selva-O'Callaghan A, Pardos-Gea J, Quintana A, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. Autoimmunity reviews. 2020;19(7):102569. [CrossRef]

69. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences. 2020;117(20):10970-5. [CrossRef]

70. Roumier M, Pauler R, Groh M, Vallee A, Ackermann F. Interleukin-6 blockade for severe COVID-19. medRxiv. [CrossRef]

71. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al. Immunology of COVID-19: Current State of the Science. Immunity. 2020;52(6):910-41. [CrossRef]

72. Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19:

Immunology and treatment options. Clin Immunol. 2020;215:108448. [CrossRef]

73. Hoffmann JHO, Enk AH. High-Dose Intravenous Immunoglobulin in Skin Autoimmune Disease. Frontiers in Immunology. 2019;10:1090. [CrossRef]

74. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect. 2020;9(1):687-90. [CrossRef]

75. Reddy DR, Guru PK, Blessing MM, Stubbs JR, Rabinstein AA, Wijdicks EF. Transfusion-Related Acute Lung Injury After IVIG for Myasthenic Crisis. Neurocrit Care. 2015;23(2):259-61. [CrossRef]

76. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Crit Care. 2020;24(1):91. [CrossRef]

77. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. Journal for ImmunoTherapy of Cancer. 2018;6(1):56. [CrossRef]

78. Hedrich CM, Bruck N, Fiebig B, Gahr M. Anakinra: A safe and effective first-line treatment in systemic onset juvenile idiopathic arthritis (SoJIA). Rheumatology International. 2012;32(11):3525-30. [CrossRef]

79. Sönmez HE, Demir S, Bilginer Y, Özen S. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. Clinical Rheumatology. 2018;37(12):3329-35. [CrossRef]

80. Calabrese LH. Molecular differences in anticytokine therapies. Clinical and Experimental Rheumatology. 2003;21(2):241-8.

81. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 Receptor Blockade Is Associated with Reduced Mortality in Sepsis Patients with Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Critical Care Medicine. 2016;44(2):275-81. [CrossRef]

82. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virology Journal. 2005;2(1):69. [CrossRef]

83. Keyaerts E, Vijgen L, Maes P, Neyts J, Ranst MV. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochemical and biophysical research communications. 2004;323(1):264-8. [CrossRef]

84. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020;16(3):155-66. [CrossRef]

85. Qiu, T.; Liang, S.; Dabbous, M.; Wang, Y.; Han, R.; Toumi, M. Chinese Guidelines Related to Novel Coronavirus Pneumonia. Preprints 2020, 2020040207. 86. Clementi N, Criscuolo E, Diotti RA, Ferrarese R, Castelli M, Burioni R, et al. Combined prophylactic and therapeutic use maximizes hydroxychloroquine anti-SARS-CoV-2 effects in vitro. bioRxiv. 2020:2020.03.29.014407. [CrossRef]

87. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents. 2020:105949. [CrossRef]

88. Cao Z, Liu L, Du L, Zhang C, Jiang S, Li T, et al. Potent and persistent antibody responses against the receptor-binding domain of SARS-CoV spike protein in recovered patients. Virology Journal. 2010;7(1):299. [CrossRef]

89. Jia W, Channappanavar R, Zhang C, Li M, Zhou H, Zhang S, et al. Single intranasal immunization with chimpanzee adenovirus-based vaccine induces sustained and protective immunity against MERS-CoV infection. Emerging Microbes & Infections. 2019;8(1):760-72. [CrossRef]

90. Abraham J. Passive antibody therapy in COVID-19. Nat Rev Immunol. 2020;20(7):401-3. [CrossRef]

91. Ju B, Zhang Q, Ge J, Wang R, Sun J, Ge X, et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. Nature. 2020. [CrossRef]

92. Pinto D, Park Y-J, Beltramello M, Walls AC, Tortorici MA, Bianchi S, et al. Structural and functional analysis of a potent sarbecovirus neutralizing antibody. bioRxiv. 2020:2020.04.07.023903. [CrossRef]

93. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus. 2016;14(2):152-7.

94. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med. 2006;145(8):599-609. [CrossRef]

95. Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis. 2011;52(4):447-56. [CrossRef]

96. Wong VW, Dai D, Wu AK, Sung JJ. Treatment of severe acute respiratory syndrome with convalescent plasma. Hong Kong Med J. 2003;9(3):199-201.

97. Kulkarni R. Antibody-Dependent Enhancement of Viral Infections. Dynamics of Immune Activation in Viral Diseases. 2019:9-41. [CrossRef]

98. Uccelli A, de Rosbo NK. The immunomodulatory function of mesenchymal stem cells: mode of action and pathways. Annals of the New York Academy of Sciences. 2015;1351(1):114-26. [CrossRef]

99. Lee JW, Fang X, Krasnodembskaya A, Howard JP, Matthay MA. Concise review: Mesenchymal stem cells for acute lung injury: Role of paracrine soluble factors. Stem cells. 2011;29(6):913-9. [CrossRef]

100. Golchin A, Seyedjafari E, Ardeshirylajimi A. Mesenchymal Stem Cell Therapy for COVID-19: Present or Future. Stem Cell Reviews and Reports. 2020;16(3):427-33. [CrossRef]