Review Article

SARS-CoV-2: Cytokine Storm and Therapy

Mir Ibrahim Sajid[1], Javeria Tariq[2], Shehar Bano Awais[3], Zehra Naseem[4], Samira Shabbir Balouch[5], Sajid Abaidullah[6]

[1]Student, Medical College, Aga Khan University, Stadium Road, Karachi, Pakistan; [2]Student, Medical College, Aga Khan University, Stadium Road, Karachi, Pakistan; [3]Student, Medical College, Aga Khan University, Stadium Road, Karachi, Pakistan; [4]Student, Medical College, Aga Khan University, Stadium Road, Karachi, Pakistan; [5]Assistant Professor, Oral & Maxillofacial Surgery, Neela Gumbad, Lahore, Pakistan; [6]Professor & Head of North Medicine Department, KEMU/ Mayo Hospital, Lahore

Abstract

SARS-CoV-2 can vary on a spectrum of an asymptomatic disease process, to a severe stage characterized by a "Cytokine Storm". This phenomenon is a pro-inflammatory state marked by an intricate interplay of a cocktail of chemokines and cytokines. An excessively raised serum levels of cytokines and chemokines can lead to the development of acute respiratory distress syndrome. This article highlights the pathophysiologic mechanisms responsible for creating this cytokine havoc and delves into potential therapeutic interventions

Corresponding Author | Prof. Dr. Sajid Abaidullah, Professor & Head of North Medicine Department, KEMU/ Mayo Hospital, Lahore **Email:** sajidabaidullahemw@hotmail.com

Keywords | SARS-CoV-2, Cytokine Storm, Cytokines, Chemokines, Therapy, Anti-Viral Therapies, Anti-Inflammatory Therapies, Review

Introduction

The novel coronavirus (n-CoV) stemmed as a local epidemic in the Wuhan City of China and presented as viral pneumonia of unknown etiology. Once the nasopharyngeal samples were utilized to do a reverse transcriptase-polymerase chain reaction (RT-PCR) testing, it became evident, that this was a mutated version of the notorious Coronavirus family.[1] What started as a Wuhan endemic disease, soon spread to other parts of the world and was declared as 'pandemic' by the World Health Organization on 12th March 2020.[2] To date, 16th July 2020, this virus infected more than 8.1 million people with >440,000 deaths (mortality rate: 5.3%).

Before SARS-CoV-2 was the talk of the town, the Coronavirus family has been responsible for two major epidemics and several minors. The major ones being, the SARS-CoV-1 and the Middle Eastern Respiratory Syndrome (MERS). Surprisingly, the SARS-CoV-1 was too identified as a respiratory pathogen in China in the province of Guangdong, in 2002.[3] Even though SARS-CoV-1 was a fatal virus, resulting in a case fatality ratio of 11%, almost double to that SARS-CoV-2,[4] the transmission rate (Ro) was significantly lower. This decreased infection potential prevented the major spread of the virus, and the viral illness was successfully managed at homes and hospitals, without taking a toll on the healthcare systems.

MERS was isolated in 2012, when people in the Middle East started developing respiratory symptoms, especially in Saudi Arabia.[5] This particular virus was expected to be a mutated version of the human coronavirus, with dromedary camels being the primary zoonotic reserve. MERS reported a significantly higher mortality rate of approximately 50% in 2012; however, it was effectively contained by the end of 2013.

The SARS-CoV-2 infection has resulted in symptoms which vary considerably, from asymptomatic forms to acute bilateral pneumonias that requires hospitalization. The milder version of the disease presents as fatigue, fever and dry cough, with characteristic lymphopenia and elevated levels of lactate dehydrogenase.[6] Computed Tomography (CT) scan of the lung field displays distinctive patterns of bilateral homogenous, ground-glass opacities.[2] Patients who lie on the severe spectrum of the disease process may develop acute respiratory syndrome (ARDS) and require intensive care support with mechanical ventilation. A subset of these patients would experience a 'cytokine storm', whereby an elevated level of pro-inflammatory cytokines, render the patient prone to a rapidly progressive and fatal multiorgan failure.[7]

Cytokine Storm

Cytokine storm refers to a hyper exaggerated, uncontrolled, and generalized inflammatory response to a foreign antigen.[8] This term was coined after a vigorous immune response was generated in hosts who underwent graft surgery.[9] The cytokine storm has since been used to describe immensely powerful immune responses to both infectious and non-infectious diseases, especially the respiratory infection caused by the H5N1 influenza virus.[10]

The presence of cytokine storm can be responsible for the development of life-endangering ARDS, which can account for up to 40% of mortalities, in the setting of induced hypoxemia and interstitial lung infiltrates.[11]. ARDS can occur in clinical vignettes of severe sepsis, pneumonia of multiple etiologies, and incompatible blood transfusions. ARDS pathogenesis entails inflammatory disruption to the alveolo-capillary membrane, leading to greater permeability of the lung and deposition of protein-rich pulmonary edema fluid into the airspace, resulting in respiratory failure.

As shown in the pathogenesis and immune response studies of SARS-CoV-1 and MERS,[12] a higher circulating level of cytokines and chemokines (C&C) are responsible for inflammation of the lungs. Similarly, studies[1] have shown that SARS-CoV-2 also exhibits an exaggerated pro-inflammatory milieu of C&C, such as CCL 2, IL-1B, CXCL 10 and IFNγ, rendering patient more prone to developing the severe form of the diseases, requiring intensive care support and mechanical ventilation. The presence of these mediators suggests activation of Th1 subset of T-Helper Cells, however, it's of interest to note that as opposed to the SARS-CoV-1 infection, in addition to Th-1 cells, Th-2 Cells are also upregulated.[13] This subset of T-Helper Cells entails IL-4 and IL-10, which are responsible for suppressing an inflammatory response.

This intricate interplay between these families of C&C has dictated the severity of the disease process in SARS-CoV-2. In this review, we highlight the critical role of these pro-inflammatory mediators and discuss various immune-modulating therapies which have either shown to or hypothesized to, play a vital role in attenuating this storm.

Chemokines: Chemokines- as their namesake, hold the ability to strongly attract immune cells- by creating an effective chemical gradient[14] and aid immune cells migration from intravascular compartments into the site of inflammation. Apart from this role in immunology, the chemokines are a key player in the generation of innate and adaptive immunity and cancer metastasis.[15] In response to viral or microbial infections, they are promptly secreted by a variety of cells.[16]

An example here is of CXCL10, whose role has been illustrated in human and animal models. In these experimental models, it has shown to play an essential part in the onset of ARDS.[17] In vitro, following experimental infection of the subject, levels of CXCL10 have shown to increase exponentially, followed by microvascular damage and ARDS-typical pulmonary edema.[18] This rise in CXCL10 levels, in part, have been attributed to the increase in neutrophils, who release this particular cytokine, which in turn recruits more neutrophils- thereby creating an autocrine loop leading to the development of severe inflammation of the lungs. Mice models predict that once CXCL10 levels are neutralized with their respective antibodies, the chances of developing extensive lung damage can decline.[19]

Apart from CXCL10, the vital role of CXCL8 in the development of ARDS has been explored.[20] In the settings of ARDS, this chemokine's elevated levels in the blood[21,22] and broncho-alveolar lavage[23] are

evidence of its involvement in the pathogenesis of the respiratory distress syndrome.

Interleukins: Interleukins play an essential role in activating immunomodulatory cytokines and driving differentiation between various cell types. These mediators, especially IL-6, direct immune cells to the locus of infection, especially during the acute phase of inflammation- stimulating the epithelial cells and facilitating the production of secondary cytokines.[24] IL-1β and tumor necrosis factor (TNF-α) facilitate the increase in production of IL-6,[25] from cells such as B&T lymphocytes, mast cells and fibroblasts,[26] among others, which in turn activates Th-17.[27] In patients tested positive for SARS-CoV-2, higher Th-17 levels have been visualized,[28,29] which can be a possible stimulant for an increase in IL-6, thereby accounting for higher IL-6 levels in these patients.[30] Given the ability of IL-6 to stimulate multiple genes and activate a cocktail of C&C; the plasma levels of this interleukin have shown to be directly related to the severity of the disease.

Colony Stimulating Factors (CSF): These proteins are associated with inflammatory conditions and are components of an amplification cascade that ultimately increases the production of cytokines by macrophages at inflammatory sites. Studies in animal models have demonstrated that depletion of CSF's can provide a therapeutic advantage in inflammatory conditions, such as SARS-CoV-2.

Tumor Necrosis Factor α (TNF-α): Tumor necrosis factor is a cytokine released from immune cells in the acute inflammation and infection phase and remains a central cytokine in viral diseases. It's relation to the pathogenesis of several chronic inflammatory, and autoimmune diseases have been expressed over the years.

Interferons: Interferons belong to a class of immune mediators which have shown to play a pivotal role in the generation of innate immunity following a viral infection. This phenomenon entailsbinding to specific host receptors and expressing genes which encode for proteins responsible for the production of antiviral and immune-modulating responses. Perhaps for this very reason, interferons have been used over the years in the treatment of viral (e.g. chronic hepatitis) and non-viral infections such as lymphoma and multiple sclerosis.

Therapeutic Interventions

Interferon-λ: Interferon- λ (IFN- λ) belongs to the family of interferons (alpha, beta and gamma) and is involved in both antiviral and immunomodulatory actions. IF N- λ is known to have a wide range of effects on both cancerous and non-cancerous cells, and hence considered as a pleiotropic cytokine. It binds to its receptor on target cells and mediates its actions via JAK-STAT signaling pathway.

SARS-CoV-2 primarily targets the epithelial cells of the alveolus. IFN- λ is beneficial in immune responses against viruses, tumors and other pathogens; and recently has proved effective in "Cytokine storm" when given earlier in the course of infection. IFN- λ mediates the following actions preventing the overactivation of humoral immune response and thus improving symptoms in a COVID patient:

1. It regulates the action of mononuclear phagocytes inhibiting the inflammatory action of IFN-αβ, which is mediated by macrophages.
2. It exerts its antiviral actions on alveolar epithelial cells via the JAK-STAT pathway leading to activation of several antiviral genes
3. Inhibits the recruitment of neutrophils at the inflammatory site

However it isn't known to reduce the mortality and is only used to reduce viral load during the early manifestation of the disease since its usage in a later course isn't beneficial as high serum levels of IFN- λ are associated with severe ARDS;

1. It increases the production of IL-6 by monocytes
2. It up-regulates the expression of MHC class I and II on various leukocytes and epithelial cells.

Corticosteroid Therapies: Corticosteroids (particularly glucocorticoids) are steroid hormones used mainly to suppress inflammation in several diseases like asthma, allergy, septic shock rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis. They are widely used to alleviate lung injury caused by severe community-acquired pneumonia because of their anti-inflammatory actions, and hence also administered in COVID patients presenting with associated pneumonia leading to ARDS.

However the therapeutic role of glucocorticoids for viral pneumonia caused by H1N1, MERS, SARS[30] remains controversial due to their adverse effects such as; (osteoporosis, skin atrophy, diabetes, abdominal obesity, glaucoma, cataracts, avascular necrosis and secondary infection, growth retardation, and hypertension); which seemingly outweigh the potential beneficial effects. Although corticosteroids served as the prime immunomodulator during the SARS-CoV-1 epidemic in 2003 where it markedly reduced the mortality rate; its usage is based on dosage, duration and timing of intervention of glucocorticoid therapy.

When used earlier in the course of SARS-CoV-2 infection, Corticosteroids (CS) enhance the viral load in plasma by decreasing the clearance of virus due to early immune-suppression; thus leading to worsening of the disease. Hence, CS is used in critically ill patients trapped in a cytokine storm (such as ARDS, acute cardiac injury, renal failure, and patients with higher serum levels of D-Dimer); whereby it prevents pulmonary fibrosis and occurrence of severe ARDS via its anti-inflammatory effects. Therefore appropriate use of low-dose CS administered timely and given for short duration, is known to increase the survival rate of severely ill patients with SARS-CoV2, shortens the stay in ICU and minimizes the need for ventilator support.

Recently conducted randomized clinical trials didn't yield a conclusive positive effect, and hence WHO did not recommend the usage of systemic glucocorticoids in SARS-CoV-2 patients. However, evidence suggests that methylprednisolone 1–2 mg/kg per day no more than 7 days, along with to TCZ treatment, proved beneficial during cytokine storm.

Intravenous Immunoglobulins:IVIG consists of a pool of IgG obtained from the blood of thousands of healthy donors and is not only used to treat several autoimmune and inflammatory diseases such as dermatomyositis, Kawasaki disease, multiple sclerosis, lupus, chronic lymphocytic leukemia, and idiopathic thrombocytopenic purpura; but also used to suppress several viral and bacterial infections[(21)]. The immunomodulatory role of IVIG in immunosuppressed individuals led to several studies and interventions on SARS-CoV-2 patients yielding positive results with good tolerance. Hence it's suggested to use a high dose of IVIG (0, 3– 0, 5 g/kg) for 5 days in critically ill SARS-CoV2 infected patients during the earlier course of the disease. Chen and colleagues found that 27% of 99 Wuhan patients who recovered from SARS-CoV-2 received IVIG treatment[(30)]. Experiments conducted by Jawhara in Wuhan suggested the effective usage of IVIG which neutralizes SARS-CoV-2 virus; with a much greater efficacy if IgG pool is collected from the plasma of donors who are residents of the same city and are previously infected by COVID to yield a specific immune response. In an experiment conducted by Diez using IVIG products, significant cross-reactivity was noted to S1 protein of SARS-CoV2, which is responsible for the binding of the SARS virus to host cell.

IVIG mediates its immune response via multiple mechanisms:

1) It blocks the cocktail of pro-inflammatory cytokines and leukocyte adhesion molecules, thereby ameliorating the Th1 and Th17 T-Helper subsets and suppressing the levels of autoantibodies.
2) It induces COX-2 dependent PG-E2 production in the dendritic cells
3) Reduction of IL-6 levels and promotion of anti-inflammatory cytokines such as IL-10
4) Upregulating the expressions of PPARγ, which mediates anti-inflammatory responses in degrading inflammation in the body. Similarly, TLR-4 expression, which mediates the inflammatory response, was found to be reduced.

Given the ability of CS in amplifying passive immunity and altering systemic inflammatory responses, a high dose IVIG may be considered an excellent choice in patients who worsening in the initial stages of SARS-CoV-2.

The IVIG was widely used as an alternative in the treatment of serious influenza-related pneumonia, although there are concerns about its therapeutic effect on SARS-CoV-2 pneumonia, given the inclusion of the seventh version of the guidelines specifying that it can be recommended for use in patients with acute illness and critical condition. Clinical intravenous immunoglobulin administration has enabled rapid clinical improvement, as demonstrated by the need for short respiratory support with CPAP, improved blood &gas levels and radiological imaging.

Briefly, following IVIG treatment, the health and respiratory status of all patients enhanced, and the oxygen saturation levels increased, resulting in the patients being extubated earlier with noticeably better chest radiographs[50]. Eventually, immunotherapy combined with resistant IgG and antiviral therapies may provide effective treatment against SARS-CoV-2. By enhancing the immune response in newly infected patients, these antibody IgG antibodies obtained from recovering patients should help treat patients with SARS-CoV-2[24].

IL-1 Family Antagonists:IL-1 family consists of IL-1β, IL-18, and IL-33 that play a key role in favoring inflammation during the cytokine storm[51]. IL-1 signaling is involved in the acute phase of infection and also affects the differentiation of lymphocytes, particularly Th17 cells. The isoform IL-1β is known to play a role in SARS-CoV2 infection, particularly aggravating lung-related pathology, i.e. ARDS and cause pyroptosis via IL-1β[28].

Hence IL-1β antagonists can be used to treat the cytokine storm, thereby increasing survival in SARS-CoV2 patients, especially those suffering from severe sepsis. Anti- IL-1β therapy is based on the inhibition of different mechanisms that mediate IL-1β signaling. These include:

1) **Anakinra:** A modified IL-1 receptor antagonist with a half-life of 4-6 hours, used especially in COVID patients with sepsis. Anakinra's prescribed adult dosage ranges from 100 to 200 mg daily to 100 mg three days a week; whereas, in the pediatric population, the drug dosage is recommended at 1 mg/kg daily. Empirical information has demonstrated that tocilizumab-refractory CRS with clinical characteristics similar to HLH / MAS secondary to CAR T cell therapy is effectively modulated by Anakinra.
2) **Rilonacept*:** A receptor trap
3) **Canakinumab*:** An anti-IL-1β antibody

*Use of Rilonacept and Canakinumab so far haven't been seen in the treatment of SARS-CoV-2.

Anti-IL-1β treatment is safe and is strongly correlated with a reduction in neutrophils count that can be clinically significant as a high NLR (neutrophil to leukocyte ratio) predicts poor SARS-CoV-2 prognosis.

IL-6 Antagonists: IL-6 receptor antagonist, Tocilizumab (TCZ) is a monoclonal antibody that inhibits the inflammatory response mediated by IL-6 via binding to soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). It is not only used for autoimmune rheumatic diseases (e.g., Rheumatoid arthritis) but also for treating Cytokine release syndrome (CRS) induced by chimericantigen receptor T-cell (CART) therapy[13]. Since serum IL-6 levels are markedly elevated in critically ill SARS-CoV-2 patients suffering from cytokine storm and ARDS; TCZ has potential therapeutic effects in SARS-CoV2 infection. Retrospective studies conducted by Wei Haiming in China demonstrated that usage of TCZ enhanced oxygenation, reduced fever, resolved lung lesions and improved blood lymphocytes and serum CRP levels[21]. Hence, TCZ is used to treat critical cases of SARS-CoV2 because of its high efficacy in CRS. However, it could also lead to several adverse effects like hepatotoxicity, hypertriglyceridemia and opportunistic bacterial or fungal infections. To treat CRS associated with SARS-CoV-2, a dosage of 8 mg/kg IV is recommended per day.

TNF-α Blockers:TNF-α is a key inflammatory cytokine obtained mainly from the monocytes, fibroblasts and endothelial cells. TNF mediated immune response is vital for several viral infections like influenza, smallpox; however, markedly raised levels as seen in SARS-CoV-2 patients have been associated with lung injury or ARDS. TNF-α blockers are often used for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis[21]. Multiple TNF-α inhibitors used in studies involving animal models showed the potential role of Anti-TNF therapy in lung injury and ARDS, thus reducing SARS associated mortality in mice; however, its efficacy in humans is still not conclusive. Evidence supporting the success of TNF-α receptor trap (Etanercept) in treatment of CRS secondary to CART is also documented; however, trials regarding its use in SARS-CoV-2 associated cytokine storm didn't yield positive results yet. TNF-α inhibitors are also used for TEN (Toxic epidermal necrolysis) and due to similarities of TEN with severe SARS-CoV-2 infection, in terms of the pathogenesis and clinical features; usage of TNF-α inhibitors is suggested for SARS-CoV-2 infection.

Janus Kinase (JAK) Inhibitors: SARS-CoV-2 is known to mediate its effects by binding to an ACE-2

receptor present on cell-surface in heart, alveoli of lungs, kidneys and blood vessels. It thenenters the cell via endocytosis which is regulated by AP2-associated protein kinase I (AAK1). Baricitinib (a JAK/STAT inhibitor) is also an AAK1 inhibitor and hence can suppress the COVID symptoms by hindering the entry of the virus into the cell. However, JAK inhibitors also inhibit the production of IFN, which is needed for anti-viral actions, thus suppressing immunity. Therefore, further investigation is required regarding the safe usage of JAK inhibitors in SARS-CoV-2 infected patients.[22]

Neutrophil-Elastase Inhibitors (NES): Patients severely infected with SARS-CoV-2 usually suffer from CRS and ARDS. The infection has shown to induce lymphocytopenia; however, due to increased inflammatory response, a simultaneous increase in neutrophils resulting in a high Neutrophil-to-Lymphocyte ratio has been observed.[22] Neutrophils produce ROS (Reactive oxygen species) and proteases (mainly Elastase which activates the S protein on SARS-CoV-2), leading to ARDS. Hence NES would result in inhibition of Neutrophil Elastase production, preventing damage to alveoli and thus preventing ARDS. Also, it inhibits the activation of S protein and hence hindering the binding of SARS-CoV-2 on the host cell. However, clinical trials are needed to provide supportive evidence for the usage of NES as a potential therapeutic agent in SARS-CoV-2 infection.

Interferon- αβ inhibitors: Interferon- αβ works as an immune modulator via the JAK/STAT pathway, by inducing interferon production- which leads to the recruitment of macrophages and other cells of the innate immune system,leading to an anti-viral host response. However, studies on Influenza virus have shown that an excessive release of Interferon αβ further into the disease process, leads to apoptosis of T cellsand alveolar epithelial cells through Fas-Fas ligand and Death receptor-5- thereby preventing viral clearance. In addition to the inability of generating effective viral clearance, the apoptosis of epithelial cells may damage the tissues and vessels of the lungs.[22]

Early release and moderate levels of Interferon- αβ are shown to be effective against viruses. Conversely, high levels of INF αβ enhance apoptosis but do not have any other anti-viral effects. Hence, the use of Interferon αβ-inhibitors may not be as straightforward and is highly dependent on the time it is given. If used early on in the disease process, it may decrease the body's immune response to the viral load, which may be harmful instead of beneficial. Therefore, the use of INF- αβ inhibitors may only be helpful if used later in the disease timeline.

Chloroquine: Chloroquine-an orally administered antiviral drug, previously used for infections such as Malaria, has been recently suggested as a possible treatment for SARS-CoV-2. The drug has significant infiltration into various organs of the body, including the lungs. It works by:

1. Inhibiting virus-endosome fusion by increasing the endosomal pH
2. Inhibiting the production of pro-inflammatory cytokines (IL-6 and TNF α)
3. Interfering with the glycosylation of certain cellular receptors.

All of these processes may prevent the development of ARDS, which has shown to occur in SARS-CoV-2 patients. The use of Chloroquine stems from studies done on cells infected with SARS-CoV-1. These studies have demonstrated a prophylactic and therapeutic role of Chloroquine in the viral disease [(23)].

Multiple clinical trials in China have led to an expert consensus on the use of Chloroquine in individuals aged 18-65. However, this drug is contraindicated in combination with other drugs that have shown to prolong the QT interval and in pregnant women. Overall, Chloroquine is a safe, old and well-researched drug which can potentially be used to treat patients with SARS-CoV-2.

Ulinastatin: Ulinastatin (Urinary trypsin inhibitor) is a naturally occurring protease inhibitor which is present in our bodies and works by phosphorylating the nuclear factor-NF-kB. In this manner, it helps remove oxygen free radicals from the body and play an anti-apoptotic role necessary to treat infections such as acute pancreatitis. This drug has also shown to aid in the release of IL 10- helping generate an anti-inflammatory response.[23]

In hospitalized patients with SARS-CoV-2 infection; a treatment regimen consisting of high dose Ulinas-

tatin has shown it be a safe-to-use drug with multiple advantages. All of these patients have shown a various degree of resolution in terms of primary lung lesions, with approximately 66.7% of them no longer requiring oxygen therapy. With no adverse effects reported, Ulinastatin can potentially be a likely treatment option for SARS-CoV-2.

Oxidized Phospholipids (OxPL): During infections, the local production of reactive oxygen species can lead to oxidation of phospholipids in the lungs, including unsaturated phosphatidylcholine (present in the surfactant) and the subsequent formation of oxidized phospholipids (OxPL). OxPL have been shown to increase the production of pro-inflammatory cytokines through increased activation of the TLR-4-TRIF-TRAF6 signaling cascade, leading to cytokine storm and subsequently, an acute lung injury. This phenomenon was seen in individuals infected with SARS-CoV-1 and H1N1, whereby an accumulation of OxPL has been seen in the lungs, in the setting of a cytokine storm.[23]

Etirovan, a TLR -4 inhibitor has been revealed to block not only the cytokine storm but also the further production of OxPL, decreasing the rate of acute lung injury and mortality in mice infected with Influenza virus. Similarly, the accumulation of OxPL in patients with SARS-CoV-2 may be a plausible mechanism in causing acute lung injury. Therefore, the use of TLR-4 inhibitors or OxPL can prove to be beneficial in preventing lung injury in those infected with SARS-CoV-2.

Sphingosine-1-phosphate receptor 1 agonist therapy: Sphingosine-1-phosphate-receptor 1 (S1P1) after binding to its receptor on pulmonary endothelial cells, inhibits the release of excessive pro-inflammatory C&C, preventing the damage that results from a cytokine storm. The use of Sphingosine -1-phosphate receptor agonists in mice has shown to shield the lung against injury caused by the Influenza Virus. They do so by inhibiting cytokine storm, migration of dendritic cells and T cell proliferation.

On that account, since the same cells of the lung are involved in SARS-CoV-2, and the same pro-inflammatory cytokines are released (IL-6, TNF- α) which cause lung injury, Sphingosine-1 phosphate receptor 1 agonists may be further studied as potential therapies for SARS-CoV-2.

Stem Cell Therapy: Mesenchymal stem cells (MSCs) although preferred from the bone marrow, can be acquired from different human tissues, for example, peripheral blood, adipose tissues and birth associated tissues (placenta, umbilical cord, amniotic fluid).

MSCs are capable of secreting Keratinocyte growth factor, Hepatocyte growth factor, epidermal growth factor, angiopoietin-1, IL-1 receptor antagonist (IL-1RA), and prostaglandin E2. These factors have shown to heal injured lung tissue, resist fibrosis and cause an increased surfactant production. MSCs also bring about the release of IL-10 by activating Th-2 subset, which has anti-inflammatory properties.[24]

Studies have assessed the therapeutic use of MSCs in acute lung injury. Laboratory tests and imaging of a woman infected with SARS-CoV-2 has showed very effective results after 21 days of treatment with stem cell therapy. Another study in Beijing in February 2020 was successful in improving the clinical symptoms of all patients after only two days of the intervention. While stem cell therapy looks promising, more clinical trials on humans will be necessary to determine the optimal dose and route of delivery as well as the patients who can be selected for this therapy.[25]

Plasma Therapy: Treatments aiming at the reduction of the inflammatory cascade and its associated mediators have also been initiated, primarily during the initial period of this disease's pathogenesis. The primary aim of such treatment regimens involves cleansing the serum via interchanging a person's plasma or by blood filtration to control uncontrolled inflammation by inhibiting the 'cytokine storm' by changing the levels of pro and anti-inflammatory cytokines.[25,26] Moreover, patients suffering from coronavirus experience imbalances in their fluid homeostasis, involving ionic and acid-base imbalance. Thus, performing plasma exchange proved to be efficacious in improving the fluid balance, particularly among those having a severe illness.[26]

Sepsis and its associated system-wide inflammatory cascade, negatively alters the blood flow through capillary beds, resulting in organ ischemia and failure.[26] Thus, patients experiencing sepsis or septic

shock can receive renal replacement therapy through adsorption of inflammatory cytokines and pathogenic proteins via sorbents composed of polystyrene copolymer beads.[27] Studying this treatment modality, a study by Zuccari and colleagues[28] demonstrated that IL-8 decreased considerably in the first day following a plasma exchange, while procalcitonin reaches lower levels after the first day. In addition to this small vessel circulation with regards to vascular density and blood flow in the sublingual region also improved.

A prior meta-analysis on plasma therapy in coronavirus patients has shown promising results as it leads to early discharged and decreased case fatality rates if initiated during the period of initial symptoms. Moreover, viral burden decreases significantly post plasma therapy. Further benefits of this treatment include the low risk of severe complications, with fever and shivering being the currently reported consequences.[28] In addition to this, plasma from treated coronavirus patients and plasma therapy can be used to provide passive immunity to currently infected symptomatic patients or serve as post-exposure prophylaxis.[29] Shen and colleagues[30] also demonstrated an increase in coronavirus-specific immunoglobulin levels and resolution of ARDS among patients, while Bloch and colleagues also included evidence of disease termination in imaging.

Concluding Remarks

Clinical and laboratory findings have led to therapeutic interventions based on the course of the disease, and while some treatment options seem to be beneficial in a particular stage; it might be equally devastating in another stage. Early recognition and timely control of SARS-CoV2 infection via appropriate treatment such as immunomodulators, cytokine antagonists, anti-viral and anti-inflammatory drugs can help reduce the morbidity and mortality. This table summarizes the potential interventions at each stage of disease:

Table 1: *Comparison of Predictive Values (Bishop Score vs. Cervical Length)*

Stage of disease	Characteristic Features	Treatment options
Initial acute phase	Marked by viremia	Mild disease: IFN- λ, NES inhibitors, Chloroquine Severe disease: Intravenous Immunoglobulins (IVIG), Stem cell therapy, Plasma cell therapy Prevent Cytokine storm: S1P1 antagonists, Oxidized Phospholipids
Acceleration phase	Inflammation and involvement of other organs like heart, lung, Gastrointestinal tract progressing to complications such as "Cytokine storm" marked by progressive lymphocytopenia and elevated serum cytokines	In cytokine storm: IFN- αβ inhibitors, IL 1β antagonists, IL-6 antagonists, TNF- α blockers, JAK inhibitors Ulnistatin In severely ill patients with ARDS: Corticosteroids
Final Recovery phase	Resolution of symptoms	Continuation of the therapy with dose adjustments

References And Notes

1. C. Huang YW, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
2. Sajid M, Awais S, Salar K, Sherwani M, Abaidullah S, Kamal N, et al. Impact of COVID-19 on pregnancy and childbirth: a systematic review of recent evidence. Biomedica2020;36:145-57.
3. J.S. Peiris KYY, A.D. Osterhaus, K. Stöhr. The severe acute respiratory syndrome. N Engl J Med. 2003; 349(25):2431-41.
4. Chan-Yeung M, Xu R. SARS: epidemiology. Respirology 2003;8(9):14.
5. A.M. Zaki SvB, T.M. Bestebroer, A.D. Osterhaus, R.A. Fouchier. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367(19):1814-20.
6. BE Fan VC, SS Chan, GH Lim, KG Lim, GB Tan, SS Mucheli, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020; 95(6): 131-4.
7. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth F R. 2020.
8. J.R. Tisoncik MJK, C.P. Simmons, J. Farrar, T.R. Martin, M.G. Katze. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012;76(1):16-32.
9. J.L. Ferrara SA, D.G. Gilliland. Cytokine storm of graft-versus-host disease: a critical effector role for

interleukin-1. Transplant Proc. 1993;25(1):1216-7.

10. K.Y. Yuen SSW. Human infection by avian influenza A H5N1. Hong Kong Med J. 2005;11(3):189-99.
11. M. Bhatia RLZ, S. Jeyaseelan. Role of chemokines in the pathogenesis of acute lung injury. Am J Respir Cell Mol Biol. 2012;46(5):566-72.
12. R. Channappanavar SP. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529-39.
13. C. Zhang ZW, J.W. Li, H. Zhao, G.Q. Wang. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020.
14. R.L. Zemans SPC, G.P. Downey. Transepithelial migration of neutrophils: mechanisms and implications for acute lung injury. Am J Respir Cell Mol Biol. 2009;40(5):519-35.
15. M. Rotondi LC, S. Romagnani, M. Serio, P. Romagnani. Role of chemokines in endocrine autoimmune diseases. Endocr Rev. 2007;28(5):492-520.
16. S. Sozzani PA, A. Vecchi, J. Van Damme, A. Mantovani. Chemokine receptors: interaction with HIV-1 and viral-encoded chemokines. Pharm Acta Helv. 2000;74(2-3):305-12.
17. L.F. Neville FA, P.M. McDonnell, P.R. Young, G.Z. Feuerstein, R. Rabinovici. Mob-1 expression in IL-2-induced ARDS: regulation by TNF-alpha. Am J Physiol. 1995;269(6):884-90.
18. R. Rabinovici DZ, Y. Su, X. Luo, Q. Zhao, J.H. Yang. MOB-1 and TNF-alpha interact to induce microvascular lung injury. Shock. 2002;18(3):261-4.
19. S. Lang LL, X. Wang, J. Sun, X. Xue, Y. Xiao, M. Zhang, T. Ao, J. Wang. CXCL10/IP-10 neutralization can ameliorate lipopolysaccharide-induced acute respiratory distress syndrome in rats. PLoS One. 2017;12(1).
20. M.I. García-Laorden JAL, C. Flores, A.S. Slutsky, J. Villar. Biomarkers for the acute respiratory distress syndrome: how to make the diagnosis more precise. Ann Transl Med. 2017;5(14):283.
21. R.D. Fremont TK, C.S. Calfee, W. Wu, L.A. Dossett, F.R. Bossert, D. Mitchell, et al. Acute lung injury in patients with traumatic injuries: utility of a panel of biomarkers for diagnosis and pathogenesis. J Trauma. 2010;68(5):1121-7.
22. I.P. Aisiku JMY, P. Doshi, J.S. Benoit, S. Gopinath, J.C. Goodman, C.S. Robertson. Plasma cytokines IL-6, IL-8, and IL-10 are associated with the development of acute respiratory distress syndrome in patients with severe traumatic brain injury. Crit Care. 2016; 20:288.
23. R.B. Goodman RMS, D.P. Martin, K.P. Steinberg, J.A. Milberg, R.J. Maunder, S.L. Kunkel, et al. Inflammatory cytokines in patients with persistence of the acute respiratory distress syndrome. Am J Respir Crit Care Med. 1996;154(3):602-11.
24. C. Brocker DT, A. Matsumoto, D.W. Nebert, V. Vasiliou. Evolutionary divergence and functions of the human interleukin (IL) gene family. Hum Genomics. 2010;5(1):30-55.
25. C.A. Hunter SAJ. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015;16(5):448-57.
26. J. Scheller SR-J. Interleukin-6 and its receptor: from bench to bedside. Med Microbiol Immunol. 2006; 195(4): 173-83.
27. A. Kimura TK. IL-6: regulator of Treg/Th17 balance. Eur J Immunol. 2010;40(7):1830-5.
28. L. Chen HGL, W. Liu, J. Liu, K. Liu, J. Shang, Y. Deng, S. Wei. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43(0).
29. Hamilton JA. Colony-stimulating factors in inflammation and autoimmunity. Nat Rev Immunol. 2008; 8(7):533-44.
30. E.A. Carswell LJO, R.L. Kassel, S. Green, N. Fiore, B. Williamson. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci U S A. 1975;72(9):3666-70.