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Open Access Journal of Pulmonary & Respiratory Sciences
ISSN: 2642-1143

Potential Anti-Inflammatory Approaches for the Management of SARS-CoV2 Infections

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Review Article

Volume 5 Special Issue 1

Received Date: May 22, 2020

Published Date: May 28, 2020

Abstract

The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was declared as a global pandemic by WHO in March 2020. COVID-19 infection has had a devastating impact on human health and world economy. Currently, it has affected more than 4,000,000 individuals worldwide with more than 300,000 deaths. COVID-19 is most commonly associated with pneumonia and acute respiratory distress syndrome. As the number of infected individuals increases, we are learning that not only lungs, but other organs can be affected by the virus causing multi-organ failure and sepsis. It has been proposed that the severity and mortality rates of the susceptible population infected by SARS-CoV2 is related to a cytokine storm, in which an exaggerated production of pro-inflammatory substances are released into the pulmonary microenvironment over a short period of time. Here we review some of the key pro-inflammatory molecules that are being targeted for therapy of COVID-19 multi-organ failure.

Keywords: Anti-Inflammatory; COVID-19; Alpha-1; SARS-CoV-2; IL-6

Introduction

The severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a novel enveloped RNA beta coronavirus that emerged in December of 2019 in Wuhan, China. COVID-19 is the term used to define the infection caused by SARS-CoV-2. The infection with the novel virus manifests in multiple organ systems as pneumonia, myocarditis, acute renal injury and skin manifestations. The symptoms for COVID-19 typically manifest between 5 and 14 days after infection occurs. Symptoms of COVID-19 range in severity from mild to severe, and include fever, cough, shortness of breath, fatigue, myalgia and at times diarrhea. Due to the involvement of multiple organ systems, the illness can go from mild to severe in a short period of time.

Discussion

The available data at this time indicates that patients with COVID-19 have an increased risk for the development of pneumonia and acute respiratory distress syndrome (ARDS). These patients tend to be hospitalized and have more severe reactions to the virus. Approximately 20 to 30 percent of hospitalized patients with COVID-19 and pneumonia have required intensive care for respiratory support. There are currently no specific treatments for COVID-19.

The excessive immune response to the COVID-19 infection has been incriminated in the pathogenesis of the respiratory distress syndrome and multiorgan system failure observed in the COVID-19 patients. Activation of multiple pathways by viral proteins leads to the production of cytokines, chemokines, and activation of the coagulation cascade. Structural proteins of SARS-CoV-2, mainly the spike (S) glycoprotein, induce immune and inflammatory responses which contribute to development of ARDS and organ failure. Several studies have indicated a "cytokine storm" with release of IL-6, IL-1, IL-12, and IL-18, along with tumor necrosis factor alpha (TNFα) and other inflammatory mediators which is called the cytokine release syndrome (CRS). CRS is a common immunopathogenesis underlying many pathological processes, such as ARDS, sepsis, and primary and secondary hemophagocytic lymphohistiocytosis (HLH) which were seen in SARS-CoV1 and MERS patients. In addition, there is dysregulated coagulation which provides a feed forward mechanism to infection. Increase in D-dimer, ferritin, LDH, ESR and other inflammatory markers have been detected in patients with SARS-CoV2. The increased pulmonary inflammatory response comprising of inflammation with micro-clots which result in decreased alveolar-capillary gas exchange, making oxygenation difficult in patients with severe illness. The cytokine storm with the novel corona virus is associated with high levels of inflammatory markers including LDH, serum ferritin, CRP, D-dimer and IL-6. Some patients with COVID-19 quickly develop septic shock. These patients appear to be deteriorating faster than patients with septic shock from other organisms. The severity of inflammation along with the cytokine storm related to COVID-19 is believed to directly relate to the quick deterioration in these patients.

The CDC has recently issued a health advisory to health care providers across the country to be on the lookout for a new syndrome that affects children and may be associated with COVID-19 infection. The syndrome called "multisystem inflammatory syndrome" manifested with a fever of at least 100.4 for at least 24 hours, severe illness requiring hospitalization, problems affecting at least two organs that could include the heart, kidneys, lung, skin or the nervous system. The children with this syndrome have elevated inflammatory markers in blood tests.

Clinical management of hospitalized patients with COVID-19 primarily includes supportive therapy such as supplemental oxygen therapy to improve oxygen saturation levels, mechanical ventilation and empirical antimicrobials. Some clinicians have added antiviral therapy to their treatment regimen.

The routine use of systemic corticosteroids is not recommended by the World Health Organization (WHO) for the treatment of COVID-19 pneumonia or ARDS, although, in practice, corticosteroids are reported to be used in patients with severe COVID-19. The use of glucocorticoids for the treatment of acute respiratory distress syndrome and the cytokine storm could prolong the shedding of the COVID-19 virus and increase the risk of secondary infections. The Surviving Sepsis Campaign suggests a short course of steroids for moderate to severe ARDS related to the viral infection. The use of glucocorticoids may help shorten the need for vasopressor in shock state (hydrocortisone at a dose of 200mg daily by means of infusion or intermittent dosing) [1].

IL-6 Inhibitors

A better understanding of the pathogenesis underlying CRS may facilitate the design of novel immunotherapies and anti-inflammatory approaches. Emerging evidence suggests that high levels of C reactive protein and IL-6 are observed in patients infected with COVID-19. Currently, there are two available drugs based on human monoclonal antibodies against IL-6 receptor, tocilizumab and sarilumab. IL-6 receptor inhibitors are currently licensed for several autoimmune disorders and are considered well tolerated and safe in general. Tocilizumab is a recombinant humanized monoclonal anti-IL-6R antibody which is approved for use in Rheumatoid arthritis and other autoimmune diseases. Anecdotal reports from China and Italy of use of IL-6 blockade which showed beneficial effects has led investigators to study the role of IL-6 inhibition in patients with severe COVID-19 infections with ARDS and multi-organ failure.

A retrospective uncontrolled study of 21 patients with severe COVID-19 symptoms as defined by prespecified criteria examined the effect of IL-6 blocker Tocilizumab. All patients had ground glass opacities on chest imaging and required supplemental oxygen. Within 24 hours of starting tocilizumab therapy, fever and elevated C-reactive protein levels resolved, and the level of the proinflammatory markers declined. The need for supplemental oxygen and length of mechanical ventilation improved. The study has limitation since it enrolled a small number of patients and was uncontrolled; however, it sheds important light on the role of the cytokine storm in the pathogenesis of the acute lung injury in patients infected with COVID-19. Patients treated with tocilizumab are at increased risk for infections, some progressing to serious infections leading to increased morbidity and mortality. These infections have included bacterial infections, tuberculosis, invasive fungal and other opportunistic infections. This has the potential to further complicate the clinical course of COVID-19 infected patients who are already at increased risk for secondary bacterial infection and sepsis. Thus, this study suggests that in patients with COVID-19 inhibition of IL-6 with tocilizumab appears

to be efficacious and safe, the results of several ongoing clinical trials should be awaited to better define the role of tocilizumab in COVID-19 prior to routine clinical application. Large well-designed randomized control trials will define the role of IL-6 blockade in COVID-19 infections.

Pegylated Interferon

A phase 2, multi-center, open-label, randomized trial in adults with COVID-19 that were hospitalized in one of six major hospitals in Hong Kong was recently published in The Lancet. The study showed early triple combination of interferon beta-1b, Lopinavir-ritonavir, and ribavirin was safe and superior to Lopinavir-ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19 [2].

Pegylated interferon lambda (PEG-IFN-lambda) is a potent antiviral cytokine that acts to generate an antiviral state within many cell types. There have been commercially available, injectable versions of IFN, approved by the FDA for use in treatment of chronic hepatitis C and certain forms of cancer. A new investigator-initiated trial led by Dr. Raymond Chung at Massachusetts General Hospital will evaluate the use of the PEG-INF lambda to treat these patients. Compared to the more commonly used alpha and beta interferons, lambda has a more restricted receptor distribution in epithelial cells but not immune or bone marrow cells, and is therefore associated with fewer systemic side effects. Interferons could induce an excessive immune response in cases that might already be hyperactivated; therefore, the safety of this treatment should first be established in clinical trials [3].

Immune-Based Agents	Availability	Rationale	Clinical Data
BTK Inhibitors (acalabrutinib, ibrutinib, rilzabrutinib)	FDA-approved for some hematologic cancers	Immunomodulation-targeting cytokines	Clinical trials in progress
Convalescent Plasma	Investigational; FDA single-patient emergency IND; expanded-access program for persons ineligible for or unable to participate in clinical trials	Use in other viral illnesses, including H1N1 influenza, SARS, and MERS	Limited: small, uncontrolled cohort studies suggested benefit, but confirmation required; randomized, controlled trials in progress
Glucocorticoids	FDA-approved for multiple indications	Broad immunomodulation	Limited: retrospective, nonrandomized cohort study showed association with lower mortality among patients with severe COVID-19 and ARDS, but concern for survivor treatment bias; randomized clinical trials involving patients with influenza, MERS, or SARS did not show benefit and suggested possible harm (increased viral shedding and increased mortality)
Interleukin-1 Inhibitors (anakinra, canakinumab)	FDA-approved for some autoimmune diseases	Immunomodulation; activity in macrophage activation syndrome	Clinical trials in progress
Interleukin-6 inhibitors (sarilumab, siltuximab, toxilizumab)	FDA-approved for some autoimmune diseases and cytokine release syndrome (tocilizumab)	Immunomodulation; activity in cytokine release syndrome	Limited: in a small cohort study, a majority of patients who received siltuximab had an improved or stabilized condition; randomized controlled trials in progress
JAK inhibitors (baricitinib, ruxolitinib)	FDA-approved for rheumatoid arthritis (baricitinib) and myelofibrosis and polycythemia vera (ruxolitinib)	Broad immunomodulation	Clinical trials in progress

Table 1: Immune-Based Therapy for COVID-19 [1].

Immunomodulating agents currently being evaluated for severe COVID-19 include convalescent plasma, IVIG and Interleukin-1 inhibitors, Interleukin-6 inhibitors, JAK inhibitors and BTK inhibitors. Refer to Table 1 for more detailed information on immune-based therapies.

Alpha-1 Antitrypsin

Another option in the treatment of COVID-19 that could directly combat the inflammatory response would be alpha-1 infusion therapy. The alpha-1 infusion will help inhibit IL-6 and the tumor necrosis factor, which drives the inflammatory response in these patients. By reducing the inflammatory response, we can reduce the severity of shock and decrease the need for hemodynamic support, in addition to reducing the risk of DIC and coagulopathy. The alpha-1 infusion therapy is also likely to improve and promote quicker healing of the lungs due to the neutrophil elastase effect. Quicker healing of the lungs will directly correlate to the amount of time the patients will require mechanical ventilation. The alpha-1 infusion therapy is not expected to increase the risk of secondary infection as is expected with steroids and IL-6 inhibitors, and has a very low risk of anaphylaxis, making this treatment option relatively safe to the COVID-19 patients.

As a member of the serine protease inhibitor (SERPIN) family of proteins, Alpha-1 Antitrypsin (AAT) inhibits different proteinases and also is known as alpha one-antiprotease. AAT is primarily produced and secreted by hepatocytes and is locally secreted by epithelial cells, alveolar macrophages, and neutrophils [4-6]. The protein circulates to the lung through the blood stream where its principle activity is to protect the lungs from damage induced by the protease enzyme neutrophil elastase (NE). As part of the normal physiologic response to infection and inflammation, NE degrades components of the extracellular matrix in the clearance of damaged tissue and may have other antibacterial and proinflammatory effects. In healthy individuals, AAT protects the alveoli from the proteolytic effects of NE by maintaining a balanced milieu between anti and proinflammatory proteins in the lower respiratory tract. It also inhibits other neutrophil proteases, such as protease-3 and cathepsin-G, and counteracts the cytotoxic effects of neutrophil defensins [7].

There are several lines of evidence implicating AAT as a participant in the immune response. In addition to NE, AAT is an acute-phase reactant. Upregulation of AAT occurs in response to infection and tissue injury to aid in tissue repair, in a mechanism that is mediated by interleukin 6 and TNF-α. AAT also inhibits various lymphocyte cytotoxic reactions, including T-cell, natural killer cell, and antibody dependent cell-medicated processes. Moreover, AAT is thought to decrease the ability of natural killer cells to bind to their target cells.

The various modulatory effects of AAT are illustrated in Figure 1 wherein the thickness of the arrow reflects the perceived depth of knowledge (thicker indicates more data available).

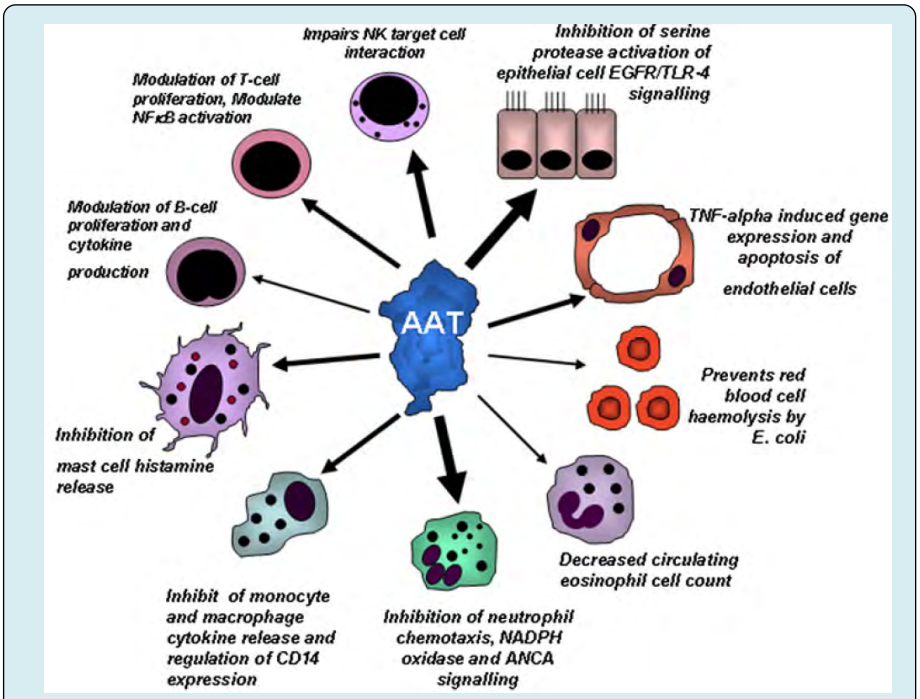

Figure 1: AAT modulation of different cell types during inflammation [8].

In addition to in vitro results, in vivo models of anti-inflammatory properties and reported modulating effects of AAT are shown in Figure 2. In murine models, exogenous human AAT protected islet cell allografts from rejection and increased survival in an allogeneic marrow transplantation model [9]. In other models AAT therapy protected against tumor necrosis α (TNF-α) / endotoxin induced lethality, cigarette smoke induced emphysema and inflammation and appeared to suppress bacterial proliferation during infections [10]. Furthermore, human AAT given to mice during renal ischemia–reperfusion (I/R) injury lessened tissue injury and attenuated organ dysfunction.

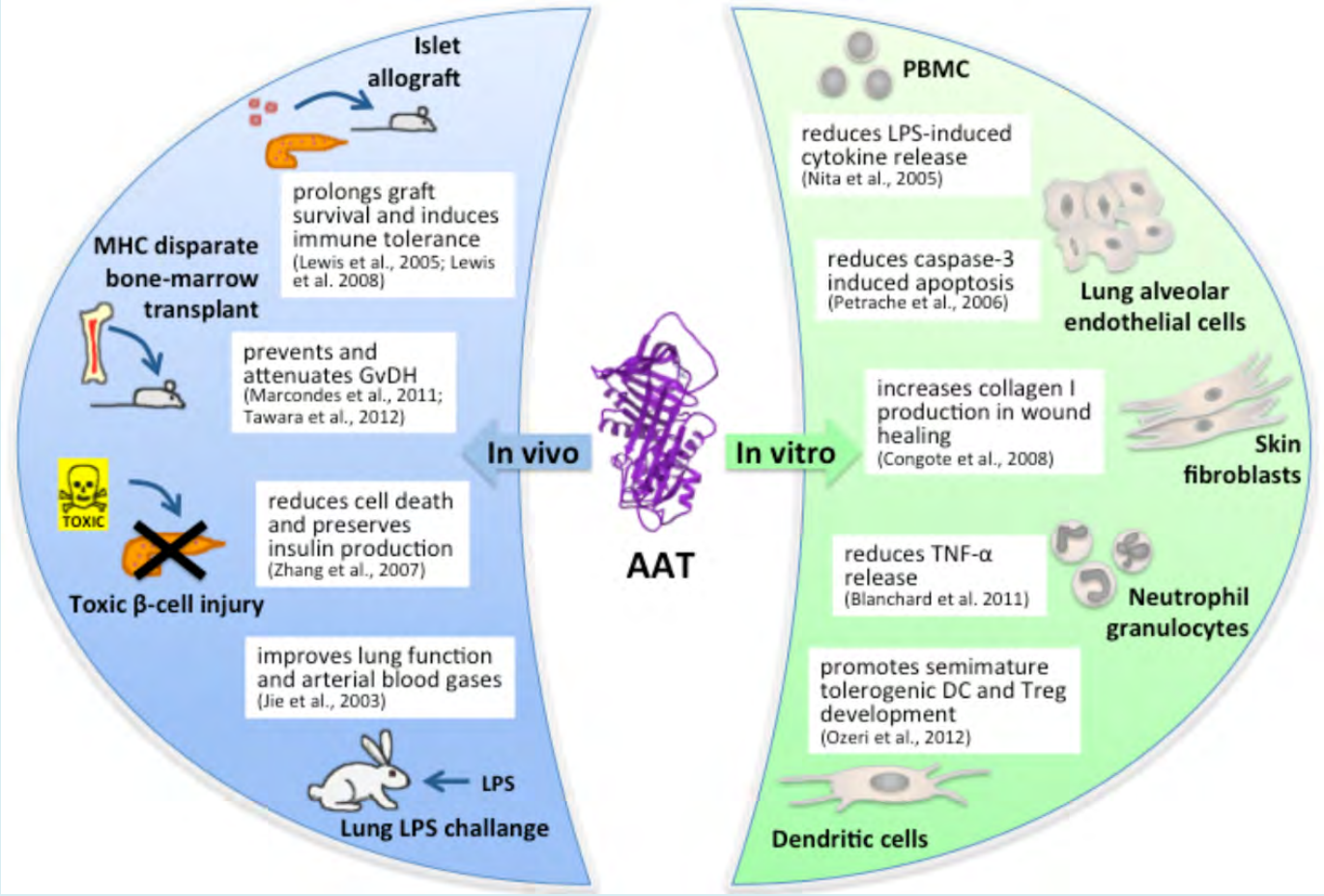

Figure 2: Selected anti-inflammatory and immunoregulatory activities of AAT [9].

There is an urgent need to test new anti-inflammatory and immunomodulatory therapies for this devastating infection. We believe the combination of antiviral treatment (Remdesivir or anti-retroviral therapy) with anti-inflammatory agents is the best approach to treat moderate to severe cases of COVID-19. We propose high-dose alpha-1 infusion treatment due to the wide spectrum of anti-inflammatory effects to counteract the cytokine storm. This will reduce acute lung injury and multisystem organ failure, without increasing the risk of a secondary bacterial infection or anaphylaxis. We suggest a loading dose of 120 mg/kg on the first day, to be followed by daily intravenous infusions of 60 mg/kg for three to five days depending on the clinical progression of the patient. Clinical trials to examine the safety and efficacy of this approach will need to be conducted on an urgent basis.

Conclusion and Future Directions

Defining mechanisms by which SARS-CoV2 induces lung injury and impairs innate immunity within the lung are urgent imperatives in the pandemic response. From an immunopathological standpoint, coronaviruses such as SARS-CoV-2 induce increased levels of pro-inflammatory cytokines and chemokines with intense inflammation and pro-coagulation. This vicious cascade of activation of pro-inflammatory cytokines and coagulation pathways results in lung injury and multi-organ failure. Activation of

multiple pathways by SARS-Cov2 leads to the production of cytokines, chemokines, complement, and lipid mediators. Recent studies have highlighted the role of IL-6, TNF-alpha, and IL-23 in SARS-CoV2 infection. Therefore, approaches to curtail inflammation and rescue organ function are imminently needed to decrease the morbidity and mortality due to COVID-19 pneumonia and lung injury. However, immunomodulatory strategies will need to be approached with caution, in combination with anti-viral medications. Ongoing studies with anti-inflammatory approaches and anti-viral medications will provide novel therapeutic strategies to rescue organ function for this devastating disease.

Acknowledgment

Grant Funding: VA Merit Award I01 BX001786 (RTS) NIH R01 HL144478 (RTS)

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