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Cytokine storm intervention in the early stages of COVID-19 pneumonia

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ABSTRACT

Clinical intervention in patients with corona virus disease 2019 (COVID-19) has demonstrated a strong upregulation of cytokine production in patients who are critically ill with SARS-CoV2-induced pneumonia. In a retrospective study of 41 patients with COVID-19, most patients with SARS-CoV-2 infection developed mild symptoms, whereas some patients later developed aggravated disease symptoms, and eventually passed away because of multiple organ dysfunction syndrome (MODS), as a consequence of a severe cytokine storm. Guidelines for the diagnosis and treatment of SARS-CoV-2 infected pneumonia were first published January 30th, 2020; these guidelines recommended for the first time that cytokine monitoring should be applied in severely ill patients to reduce pneumonia related mortality. The cytokine storm observed in COVID-19 illness is also an important component of mortality in other viral diseases, including SARS, MERS and influenza. In view of the severe morbidity and mortality of COVID-19 pneumonia, we review the current understanding of treatment of human coronavirus infections from the perspective of a dysregulated cytokine and immune response.

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially identified in Wuhan China in December 2019, has led to a global pandemic that has not been witnessed for more than a century. At the time of editing this article (April 24, 2020), the current estimate of global disease burden (Johns Hopkins University - https://coronavirus.jhu.edu/map.html) is over 2.7 million infections and almost 200,000 deaths worldwide. Social distancing in cities and countries around the world remains the only means available to limit the impact of virus transmission. At the same time, an unprecedented response from the world's biomedical research community seeks to identify treatments for COVID-19 that include antiviral drug and vaccine development.

Current clinical observations indicate that SARS-CoV2 infection can range from an inapparent non-symptomatic infection, to a respiratory illness presenting with spiking fever and dry cough, accompanied by a high rate of human-human transmission. One of the most serious complications of Corona virus disease (COVID-2) is the development of an atypical upper respiratory tract pneumonia that poses a major challenge to clinicians in terms of disease management. An abnormal and uncontrolled production of cytokines has been observed in critically ill patients with COVID-19 pneumonia [1] and the ensuing uncontrolled cytokine storm in COVID-19 patients is centrally involved in the exacerbation of symptoms and disease development, and represents a major factor contributing to COVID-19 mortality. In this sense, COVID-19 disease shares similarities with other viral diseases such as SARS, MERS and influenza, where the development of a cytokine storm is a warning sign of disease escalation.

In support of the above observations, a retrospective study of 41 patients with COVID-19 [2] showed that most SARS-CoV-2 infected patients present clinically with mild symptoms, while a minority of patients progressively declined from the infection and eventually died of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MOD). Guidelines for the diagnosis and treatment of SARS-CoV-2 infected pneumonia were first published on January 30th 2020, and recommended for the first time that cytokine monitoring be applied to improve the curative rate and reduce

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mortality [3]. In view of the severe morbidity and mortality of COVID-19 pneumonia, here we review the current understanding of treatment of human coronavirus infections from the perspective of a dysregulated immune response.

1. The role of cytokine storm in the pathogenesis and progression of COVID-19 pneumonia

The emerging and re-emerging viruses (Ebola, Zika, Chikungunya, H1N1, dengue, SARS, MERS) have led to numerous global public health crises in recent years and continue to threaten public health and security. Unfortunately, these viruses are often difficult to control due to the lack of approved antiviral drugs and vaccines. In addition to SARS-CoV2, two other novel coronaviruses have emerged as global health threats since 2002, namely severe acute respiratory syndrome coronavirus (SARS-CoV in 2002) that was transmitted to 37 countries, and the Middle East respiratory syndrome coronavirus (MERS-CoV in 2012) that was transmitted to 27 countries. Severe pneumonia caused by pathogenic human coronaviruses (HCoV) are often associated with induced hypercytokinemia, also termed cytokine storm, in immunocompetent individuals; uncontrolled overproduction of inflammatory cytokines contributes to acute lung injury and acute respiratory distress syndrome (ARDS).

The secretion of multiple cytokines, also termed Cytokine Release Syndrome (CRS), is closely related to development of clinical symptoms; for example, IFN-γ can cause fever, chills, headaches, dizziness, and fatigue; TNF-α can cause flu-like symptoms similar to IFN-γ, with fever, general malaise, and fatigue, but can also cause vascular leakage, cardiomyopathy, lung injury, and acute-phase protein synthesis [4]. IL-6, which is an important target in CRS induced by adoptive cell therapy, can lead to vascular leakage, activation of complement and the coagulation cascade, leading to the characteristic symptoms of severe CRS, such as diffuse intravascular coagulation (DIC) [5,6]. It is noteworthy that IL-6 is likely to cause cardiomyopathy by promoting myocardial dysfunction, which is often observed in patients with CRS [7]. In addition, activation of endothelial cells may also be one of the hallmarks of severe CRS. Endothelial dysfunction can lead to capillary leakage, hypotension, and coagulopathy [8] (Fig. 1). Taken together, these studies argue that the virus-induced immunopathological events play a crucial role in the fatal pneumonia observed after HCoV infections [9].

The development of a cytokine storm is a potentially fatal immune condition characterized by rapid proliferation and hyperactivation of T cells, macrophages, natural killer cells and the overproduction of more than 150 inflammatory cytokines and chemical mediators released by immune or nonimmune cells [10,11]. In viral infections, the aberrant release of pro-inflammatory factors leads to lung epithelial and endothelial cell apoptosis which damages the lung microvascular and alveolar epithelial cell barrier, leading to vascular leakage, alveolar edema and hypoxia. The uncontrolled production of pro-inflammatory factors, containing IL-6, IL-8, IL-1β, and GM-CSF, and chemokines such as CCL2, CCL-5, IP-10, and CCL3, together with reactive oxygen species cause ARDS leading to pulmonary fibrosis and death [12].

In SARS-CoV infected patients, high levels of serum pro-inflammatory cytokines (IFN-γ, IL-1, IL-6, IL-12, and TGFβ) and chemokines (CCL2, CXCL10, CXCL9, and IL-8) were detected in cases of severe disease compared to patients with uncomplicated SARS [13]. In MERS infection, high levels of serum pro-inflammatory cytokines (IL-6 and IFN-α) and chemokines (IL-8, CXCL- 10, and CCL5) were likewise observed in severe disease, compared to mild or moderate disease [14]. In contrast to SARS and MERS, doctors in Wuhan Central South Hospital found that the levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1a and TNF α were significantly elevated in the blood of severely ill patients, compared to patients with mild illness [2]. The level of IL-6 in the blood of the severe group was 76 % higher than that of the mild group (30 %) [15]. Furthermore, histological examination and biopsy samples obtained from a patient who died from severe SARS-CoV-2 infection showed an increased concentration of highly proinflammatory CCR4 + CCR6 + Th17 + CD4 T cells, suggesting that T cell hyperactivation contributed in part to the severe immune injury in this patient [16]. Pulmonary examination in other patients with early phase SARS-COV-2 pneumonia also revealed patchy inflammatory cell infiltration; however, the pathological results in early stage of SARS-

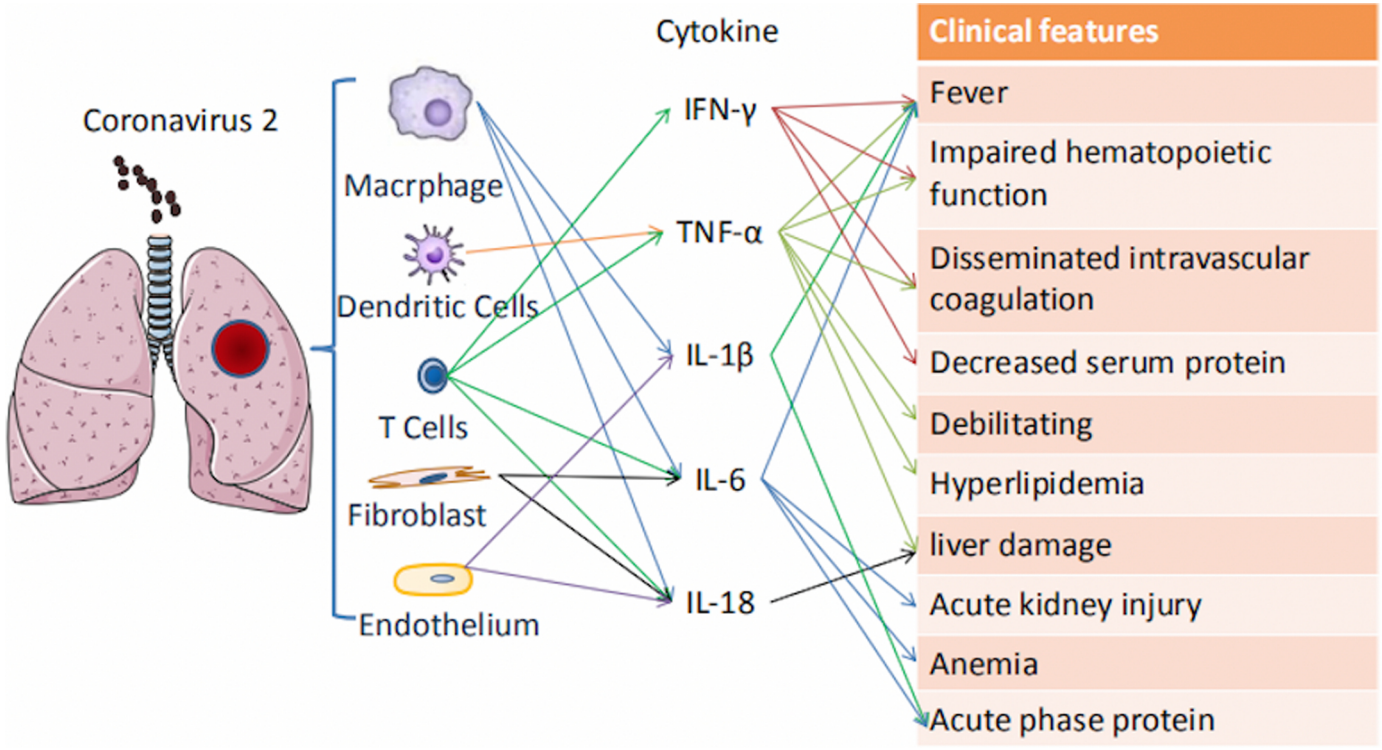

Fig. 1. Schematic representation of clinical features versus pathogenic inflammatory cytokine response in SARS-CoV-2 infections.

COV2 pneumonia require further confirmation [17]. In short, aberrant release of multiple cytokines appears to trigger a cytokine storm that produces immunopathogenic damage to tissues and organs, even while the immune response seeks to suppress and eradicate the virus (Fig. 1).

2. Treatment of the cytokine storm in COVID-19 pneumonia

2.1. Current management strategies for COVID-19

In view of the above observations, therapeutic strategies to treat the cytokine storm in the pathogenesis of severe COVID-19 pneumonia deserve special attention. In accordance with current WHO guidance [18], supportive therapy remains the most important management strategy for this pneumonia, including supplemental oxygen therapy, conservative fluid management and empiric antimicrobial application in the time of need. It is noteworthy that the use of glucocorticoids remains controversial. Current WHO guidance recommends that corticosteroids should not be used in SARS-CoV2-induced lung injury or shock, except in the setting of a clinical trial. However, in clinical settings, front-line physicians in China tend to use corticosteroids prudently at a low to moderate dosage in patients with SARS-CoV2 infection [19].

In the period of SARS epidemic (2002–2003), corticosteroids were generally used by clinicians for immunomodulatory treatment, and according to clinical feedback, could bring early beneficial changes including a decline in fever, resolution of radiographic lung infiltrates, and the improvement of oxygenation [20,21]. However, further studies indicated opposite clinical outcomes and a systematic review in SARS, MERS and influenza infections indicated no survival benefit and possible harm (avascular necrosis, psychosis, diabetes, delayed viral clearance and secondary infections) with corticosteroids [22]. In our opinion, the use of corticosteroids is not recommended for patients with HCoV infections, although corticosteroids may be used prudently in critically ill patients.

2.2. Immunotherapeutic strategies in COVID-19 pneumonia

In the treatment of patients with SARS-CoV-2 infection, clinicians should pay close attention to the impact immune inflammatory factor release, and several effective cytokine storm blockers and therapeutic methods have been reported. In the clinical process of COVID-19 pneumonia, there is a window period between the diagnosis and the occurrence of MODS (about 5–7 days). After this window, the majority of patients tend to improve (~80 %), whereas ~20 % of the patients progress to severe pneumonia, with ~ 2 % mortality [23,24,2]. To improve the prognosis, we suggest that patients with COVID-19 pneumonia be given immunotherapy treatment at the time of diagnosis, in order to block the possibility of a subsequent cytokine storm. The early use of immunological intervention in the evaluation of patients with MODS may reduce mortality in the most severe patients (Fig. 2, position 2).

2.2.1. Neutralizing antibodies

One strategy that has received considerable attention in the face of COVID-19 is the use of convalescent plasma, also called passive antibody therapy, to treat patients with advanced disease. The treatment uses plasma from a patient who has survived COVID-19 infection to provide neutralizing antibodies against the virus; the antibodies are available and active immediately, but only for a limited time. As an example of one study, five patients critically ill with COVID-19 and on mechanical ventilation received convalescent plasma 10–22 days after being admitted to a hospital in Shenzhen, China. All patients improved; three were discharged after 50 days in hospital, while the other two patients were in stable condition. Well controlled clinical evaluation of this strategy is currently ongoing in light of such positive anecdotal responses.

Another potential treatment involves the use of anti-IL-6 monoclonal antibody (SILTUXIMAB) (Johnson & Johnson) which was used previously to treat the consequences of cytokine storm following by CAR-T cell therapy for cancer. Interleukin-6 (IL-6) has become a key point in some CRS. Originally described as B-cell differentiation factor-2 (BSF-2) and macrophage and granulocyte induction factor-2 (MGI-2), IL-6 has significant pro-inflammatory and pyrogenic properties, and given chronic overproduction in COVID-19 patients, anti-IL-6 monoclonal antibody may be beneficial in controlling cytokine release. Also IL-17 inhibitor (Secukinumab) (Novartis) was used as a specific treatment for severe patients with COVID-19 pneumonia [25] to control Th17 cell activation. An additional observation indicated that the expression levels of $CD4^+$ T and $CD8^+$ T were low, while IL-6 levels were high in patients with severe pneumonia, suggesting that T cell subsets and cytokine levels could be used as one predictor of the transition from mild to severe pneumonia [15].

2.2.2. Interferons

Pegylated and non-pegylated interferons (IFN) have been under intensive study for some time. However, in the case of HCoV infection, the results of IFN therapy were mixed, as predicted by animal and human HCoV infection models. Early application of IFN was slightly beneficial to reduce viral load and improve clinical outcome. However, delayed IFN administration was of no benefit, compared with the placebo group. Early application of IFN and ribavirin moderately improved disease severity without affecting mortality [26]. The use of Sifalimumab monoclonal antibody, produced against multiple IFN subtypes (MedImmune) has not been examined clinically but could hold promise in situations of constitutive IFN production.

2.2.3. IFN-αβ inhibitors and IFN-λ

The early use of IFN had some beneficial effects in SARS-CoV-infected animal models, although the timing of IFN treatment was crucial in determining the course of disease. The use of IFN-αβ receptor inhibitors or antagonists could be considered as an approach to avoid excessive inflammatory reactions in late stage severe HCoV infection [27]. Since SARS-CoV and MERS-CoV infect mainly airway epithelial cells and IFN-λ stimulates antiviral gene expression in these cells without over-stimulating the immune system, IFN-λ might be a option in the therapy of HCoV infection.

2.2.4. Inhibition of oxidized phospholipids

Oxidized phospholipids (OxPL) have been demonstrated to promote acute lung injury by increasing the production of cytokines/chemokines from lung macrophages via TLR4-TRIF signaling in influenza A virus (IAV)-infected mice [28]. In a recent study, therapeutic administration of the TLR4 antagonist Eritoran protected mice from lethal IAV infection by decreasing the levels of OxPL and inflammatory cytokines/chemokines [29]. Because pathogenic human coronaviruses can cause acute lung injury and promote the production of OxPL in the lungs, the strategies of OxPL suppression by using Eritoran (BOC Sciences) or other similar compounds may have value in controlling HCoV induced inflammation.

2.2.5. Sphingosine-1-phosphate receptor 1 agonist therapy

Signal transduction by the sphingosine-1-phosphate receptor 1 (S1P1) in mouse endothelial cells infected with influenza A virus has been shown to contribute to the pathogenesis of inflammation responses [30]. Targeted S1P1 antagonism inhibited the recruitment of inflammatory cells, limited pro-inflammatory cytokine/chemokine release, and reduced mortality and morbidity induced by influenza A virus [31]. S1P1 antagonism may be considered a potential therapy in HCoV-infected individuals to limit cytokine responses.

2.2.6. Inhibitors of monocyte recruitment and function

Studies in animal models have borne out claims that IMMs paly

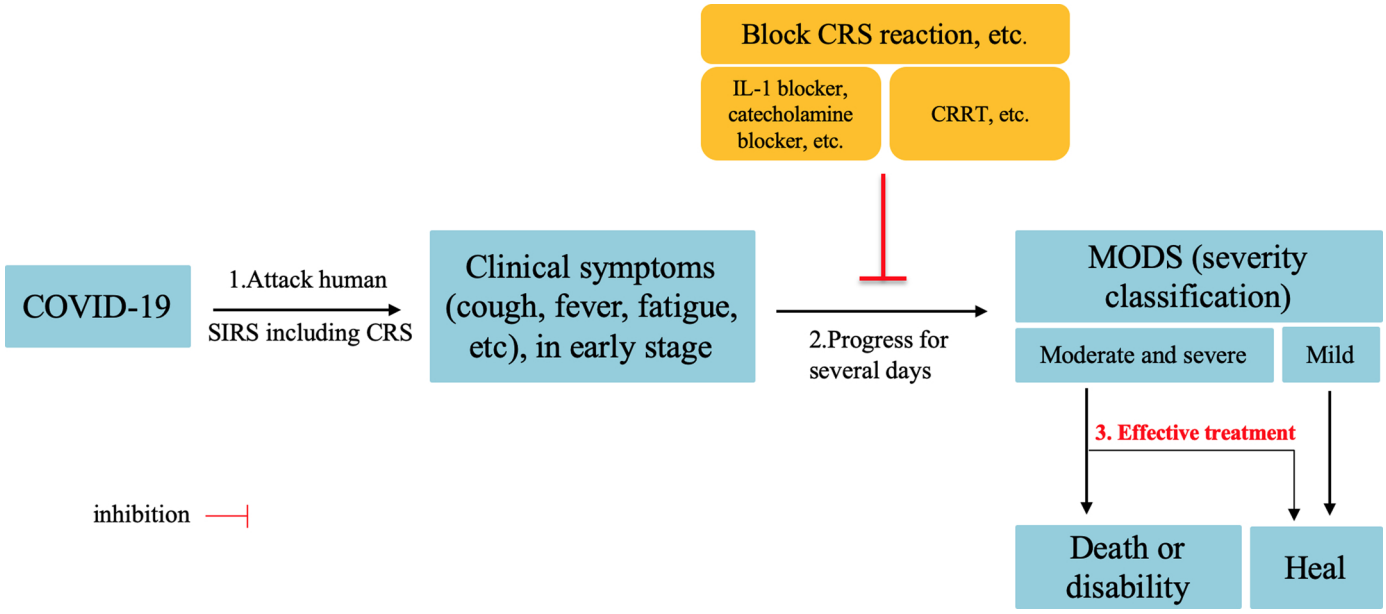

Fig. 2. A summary of the process of onset SARS-CoV2 pathogenesis with potential treatment options against the virus-induced cytokine storm.

pathogenic roles in the process of fatal HCoV infections. In the murine cardiac inflammation model, the systemic administration of optimized lipid nanoparticles including CCR2-silencing small interfering RNA (siRNA) can effectively degrade CCR2 mRNA and destroy the IMM recruitment into the inflammatory site, thus improving the outcome of the disease [32]. Because HCoVs are positive single strand RNA viruses and TLR7 agonist R837 (a synthetic single-chain RNA analog) has been shown to stimulate IMMs causing exuberant inflammatory responses, the IMM specific TLR-7 signal may promote excessive inflammatory responses caused by HCoV infection. Therefore, a TLR7 antagonist targeted approach to alleviate inflammation could be useful [33].

2.2.7. Continuous renal replacement therapy

Continuous renal replacement therapy (CRRT) may benefit severely ill patients by removing potentially harmful components and maintaining haemodynamic and metabolic status. In addition to the conventional aim of maintaining renal function, CRRT can be used to regulate the immune response of patients with sepsis, with the goal to regulate circulating levels of inflammatory cytokine mediators, as shown in studies demonstrating removal of inflammatory mediators containing cytokines and complement (TNFα, IL-1β, IL-6, IL-8, complement factors C3a, C5a, and D) by CRRT [35]. At present, there is a need for well-designed clinical trial to evaluate the efficacy of such a treatment regimen.

3. Conclusion

After COVID-19 infection, some patients develop systemic inflammatory response syndrome (SIRS) and MODS characterized by the uncontrolled release of inflammatory mediators, giving rise to a cytokine storm that contributes to increased mortality in ARDS. In summary, further experimentation is required to understand the changes in the immune response of patients with COVID-19 infection and the mechanisms of abnormal cytokine expression in COVID-19 pneumonia. Accurate prediction and targeted intervention during the course of COVID-19 pneumonia will be essential to improve patient survival (Fig. 2).

Conflict of interest

There are no financial or other interests with regard to the paper that represent a conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.04.002.

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