COVID-19 Treatment

Subjects: Pathology

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The novel coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has engulfed the world, affecting more than 180 countries. As a result, there has been considerable economic distress globally and a significant loss of life. Sadly, the vulnerable and immunocompromised in our societies seem to be more susceptible to severe COVID-19 complications. Notably, there are several significant risk factors for severe COVID-19 infection. These include the presence of poor nutritional status and pre-existing noncommunicable diseases (NCDs) such as diabetes mellitus, chronic lung diseases, cardiovascular diseases (CVD), obesity, and various other diseases that render the patient immunocompromised. These diseases are characterized by systemic inflammation, which may be a common feature of these NCDs, affecting patient outcomes against COVID-19. As a result, various antiviral treatments and anti-inflammatory agents are under investigation for their potential therapeutic value. The section presented below originates from the following article [1].

Keywords: COVID-19 ; SARS-CoV-2 ; Inflammation ; Hydroxychloroquine ; ACE Inhibition ; anti-inflammatory ; cytokines

1. Introduction

The novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is characterized by severe acute inflammation in severe cases [1].

SARS-CoV-2 is an enveloped positive-sense RNA virus that typically affects the respiratory system, whereby the main known route of transmission occurs due to the spread of droplets generated when an infected person sneezes or coughs or through other mucus environments, including saliva or discharge from the nose[2]. SARS-CoV-2 gains entry to the cell via the angiotensin-converting enzyme 2 (ACE2) receptor[3][4][5][6][7][8][9][10][11], whereby it predominantly infects the lower respiratory tract, binding to ACE2 on alveolar epithelial cells[12]. Upon binding, there is a subsequent response of the immune system via inflammation-related manifestations and recruitment of antigen-presenting cells[9][10][11]. COVID-19 infection can manifest as an asymptomatic infection, or patients can present with a mild upper respiratory tract illness that may include a cough, chills, fever, fatigue, and shortness of breath[13]. In severe cases, the most common complications are sepsis, acute respiratory distress syndrome (ARDS), heart failure, and septic shock. However, severe viral pneumonia with respiratory failure can potentially lead to death[14]. Multiple organ dysfunction is likely attributable to uncontrolled acute inflammation and cytokine storm release[9][10][11][15][16][17]. As our knowledge of the disease is evolving, it is clear that other symptoms are being identified, including chilblains[18], sudden anosmia or ageusia[19], and even stroke[20].

2. Current Knowledge of COVID-19 Treatment and Anti-Inflammatory Approaches

The inflammatory response plays a crucial role in the clinical manifestations of COVID-19. Post SARS-CoV-2 entry, host factors trigger an immune response against the virus, which, if uncontrolled, may result in pulmonary tissue damage, functional impairment, and reduced lung capacity, despite the pathogenic effect of the virus[9][10]. Apart from nonspecific inflammatory responses such as edema and inflammatory cell infiltration, severe exfoliation of alveolar epithelial cells, alveolar septal widening, damage to alveolar septa, and alveolar space infiltration has been detected in a distinctly organized manner[9][10]. Thus, SARS-CoV-2 infection can cause pathological changes, degeneration, infiltration, and hyperplasia[9]. Apart from respiratory failure, other common features amongst critical COVID-19 patients include a sudden decline of the patient's health status approximately two weeks after onset[10], infiltration of monocytes and macrophages into lung lesions, a decrease of lymphocytes such as natural killer (NK) cells in peripheral blood, extremely high levels of inflammatory response due to the proinflammatory cytokine storm, atrophy of the spleen and lymph nodes, along with reduced lymphocytes in lymphoid organs, hypercoagulability, thrombosis, and multiple organ damage[10][21]. These are just a selection of the clinical manifestations that occur as the medical community begins to learn more as the pandemic continues to grow.

It is therefore apparent that a viral infection-related inflammation and the subsequent cytokine storm in severe cases plays a crucial role in patient outcomes[9][10][11][15]. Furthermore, the coexistence of noncommunicable chronic diseases (NCDs) in COVID-19 patients may aggravate and intensify the inflammatory pathology and increase the risk for adverse outcomes and mortality[22]. As a result, anti-inflammatory agents are under investigation for their therapeutic value [1].

Classic first-line antiviral treatments are a potential therapeutic against COVID-19, which, when concomitant with organ function support, are very important to reduce mortality for mild and critical patients[10][23]. Antiviral therapy against SARS-CoV-2 consists of using different polymerase inhibitor drugs that are currently on the market and approved for use against other viruses; these include Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir[23]. These antiviral drugs have previously exhibited anti-inflammatory properties, either individually or combined as highly active antiviral therapies. However, the long-term use of some of these antiviral therapeutics against other persistent viral infections has been associated with inflammation-related cardiovascular side effects[24][25].

Researchers are also targeting inflammation through the investigation of immunomodulatory and anti-inflammatory therapies to reduce systemic inflammation before the onset of multi-organ dysfunction[10][26]. Therefore, biological agents targeting cytokines expression and specific cytokine antagonists, such as IL-6R monoclonal antibodies, TNF inhibitors, IL-1 antagonists, Janus kinase inhibitor (JAK) inhibitors, etc., have been considered[10]. Adopting an approach against specific cytokines entails the danger of only inhibiting one aspect of the inflammatory pathways involved. As a consequence, it may not be very effective in curbing the cytokine storm in COVID-19, as various cytokine pathways are of significant importance, and immunosuppression may actually compromise host defenses[27][28]. Furthermore, some of these specified anti-inflammatory medications, such as JAK inhibitors, may also block the production of the antiviral interferons such as the INF-a, which may have negative consequences for the immune response[10][29].

Researchers are also investigating the possible effects of antimalarial drugs such as chloroquine and hydroxychloroquine against SARS-CoV-2. These molecules are generally prescribed for autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis in patients whose disease status has not improved with other treatments. However, chloroquine and hydroxychloroquine possess a broad spectrum of antiviral effects against several viral infections, including coronaviruses such as SARS-CoV-1[10][30][23][24][31][32]. In vitro experiments in China identified chloroquine as a promising therapeutic against SARS-CoV-2[32][33], while the immunomodulatory effects of its derivative hydroxychloroquine may be more effective at targeting the cytokine storm that occurs in the late phase of critically ill COVID-19 infected patients, with less side effects[31][34].

Hydroxychloroquine interferes with lysosomal activity and autophagy and alters transcription and signaling pathways, which can result in the modulation of cytokine production[35], all of which are postulated to dampen the effects of the proinflammatory cytokine storm of severe COVID-19 patients. Furthermore, hydroxychloroquine has been reported to have better outcomes when combined with other drugs, such as antibiotics like azithromycin, or drugs used for rheumatoid arthritis, such as tocilizumab/atlizumab, in addition to the standard medical management for septic shock and ARDS[36]. Notably, some antibiotics, including azithromycin, have exhibited anti-inflammatory potency[26][37][38], while tocilizumab/atlizumab contains a humanized monoclonal antibody against the IL-6 receptor; thus, it is mainly used for reducing inflammation during autoimmune disorders[39].

Hydroxychloroquine, in combination with azithromycin, has been particularly focused upon due to the results of a French study where 26 COVID-19 patients received the combination treatment versus control groups. However, there were several issues with the study design, including its small sample size, the fact that the control groups were from different hospitals, the study was not blinded, and a myriad of other issues[40]. While the study provided an indication that hydroxychloroquine was worth further investigation, its results have been blown out of proportion in the media. Hydroxychloroquine has even been prematurely touted as a “game-changer” by President Donald Trump of the United States, who has admonished that he may even consider taking this untested drug against COVID-19[41], which is eventually did do. Some countries have allowed compassionate use of these drugs[42][43]. The promotion of hydroxychloroquine or chloroquine without substantial evidence of randomized, controlled trials is a significant safety and efficacy concern and requires further intensive investigation[44][45][46]. Currently, a study from the United States Veterans Health Administration indicated that patients administered hydroxychloroquine alone or in combination with azithromycin were no less likely to require mechanical ventilation and had higher mortality when on hydroxychloroquine alone versus the standard treatment[47]. This example demonstrates the necessity for world leaders to consult with their experts prior to promoting unproven medications against SAR-CoV-2 as a matter of public safety until further research is conducted. Since writing this review, several countries have chosen to stop using hydroxychloroquine and France has barred its use against COVID-19 [48].

Several researchers mention the relationship of anti-CVD-related drugs with COVID-19. Indeed, there is a focus on the anti-inflammatory drug colchicine, which has been previously used effectively against cardiovascular disorders[49]. Since ACE2 is implicated in COVID-19 infection, the role of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) of the ACE2 receptor and its rennin-angiotensin system, which are typically used for hypertension, has recently been evaluated[50][51][52][30] . ACEIs/ARBs perform a protective role in the cardiovascular system by also increasing the expression ACE2 in the heart[30]. However, the impact of ACEIs/ARBs on ACE2 in other organs, especially whether they could influence the expression level and activity of ACE2 in the lungs, with a subsequently higher susceptibility to SARS-CoV-2 infection, remains unknown. Thus, if ACEIs/ARBs have the capacity to upregulate the expression and activity of ACE2 in the lungs, they may play a dual role in COVID-19. On one hand, the higher level of ACE2 might increase the susceptibility of cells to SARS-CoV-2 viral host entry and propagation, whereas, on the other hand, the activation of ACE2 might ameliorate the acute lung injury induced by SARS-CoV-2[30][53][54]. Despite these concerns, the European Society of Cardiology recommends that patients continue their usual antihypertensive medications due to lack of evidence[55]. This also may have dietary implications due to the modulatory effects dietary patterns can have on hypertension but also due to the fact that some foods are associated with high levels of ACE inhibitory peptides[56]. Thus, further research is required to investigate the role of ACE2 activation, expression, and its related pathways in COVID-19.

As aforementioned, implementing an anti-inflammatory strategy is challenging, as it is not yet clear if any specific features of the immune response can be inhibited directly without compromising a patient's overall immune defense[27]. It is important to determine the optimum method to reduce inflammation. Further research is also required to gain an understanding of the temporal features of the COVID-19 inflammatory response and to determine at what stage of the infection should pharmaceutical treatments be administered. Similarly, an understanding of the dosing and sexual dimorphism in drug metabolism and disease presentation is required. Likewise, ethnicity may be a determining factor in severe COVID-19 infections that requires further investigation[57][58].

Furthermore, COVID-19 patients have higher risk for thrombotic disease states including acute coronary syndrome, venous thromboembolism such as deep vein thrombosis or pulmonary embolism, or stroke. Subjects with underlying CVD are also at higher risk for morbidity and mortality if infected [59]. Considering an increased risk of clot development can turn mild cases into more severe and life-threatening emergencies, a preventative approach targeting thrombosis should also be considered[60], particularly those that may also target inflammation[61]. However, management of anticoagulation and/or antiplatelet medications can be difficult in potentially critically ill patients. Therefore, guidance for the utilization of antithrombotic and antiplatelet therapies in patients with known or suspected COVID-19 is needed, and especially in the cardiovascular patient with COVID-19, in the face of a rapidly evolving understanding of this virus and its complications [59].

Reactive oxygen species (ROS) also play a crucial role in the inflammatory response. As such, utilizing compounds with antioxidant properties may also be considered to reduce the cytokine storm induced by the viral infection[62]. Indeed, antioxidative therapies are being considered for ameliorating cardiac injuries in critically ill COVID-19 patients[63].

Among other measures, the nutritional status of an infected patient should also be considered, as nutritional deficiencies may increase a patient's risk to developing a severe infection of COVID-19[64]. Introducing nutritional interventions should not be overlooked due to their potential for beneficial clinical outcomes[65]; in particular, consideration must be given to intensive care unit (ICU) patients[66].

Further research is ongoing to develop and investigate more treatments and antivirals that control or limit the damage caused by various symptoms of the viral infection and reduce the viral load until a vaccine is developed.

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