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COVID-19: Understanding the Physiopathology to Target the Therapy

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Abstract

SARS-COV-2 infects the host using the Angiotensin Converting Enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney and digestive tract. ACE2 receptors are also widely expressed by endothelial cells. The presence of viral inclusion bodies in endothelial cells of the glomerular capillary loops, within the intima of vessels in small bowel and large arterial vessel. They demonstrated cellular dysfunction caused by the presence of the virus itself in the endothelial cells and the accumulation of inflammatory cells in the surrounding milieu. The lung is one of the main targets in patients with COVID-19.

Keywords: COVID-19; Cytokine storm; Hydrochloroquine; Remdesivir; Tocilizumab; Lidocaine; Coronavirus

Introduction

Proposed mechanism

In the recent months, the infection with the novel Coronavirus-2 (SARS-CoV-2) lead to the ongoing COVID-19 pandemic. The virus is lethal and has caused extremely serious global concerns. There is currently an unprecedented ongoing international effort by Healthcare Systems worldwide, to overcome this pandemic. The patients affected by COVID-19 can present, as we know, with a wide range of symptoms, from being asymptomatic or with mild symptoms to suffering from hypoxemia and respiratory and multisystem organ failure. The overwhelming number of patients presenting with severe symptoms accompanied by a severe inflammatory response, has flooded the intensive care units and hospitals worldwide. SARS-COV-2 infects the host using the Angiotensin Converting Enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney and digestive tract. ACE2 receptors are also widely expressed by endothelial cells [1]. Varga et al. [2] identified the presence of viral inclusion bodies in endothelial cells of the glomerular capillary loops, within the intima of vessels in small bowel and large arterial vessel. They demonstrated cellular dysfunction caused by the presence of the virus itself in the endothelial cells and the accumulation of inflammatory cells in the surrounding milieu. The lung is one of the main targets in patients with COVID-19. It is known that hypoxemic pneumonia, Acute Respiratory Distress Syndrome (ARDS), is associated with a significant surge in cytokine release. Elevated levels of Interleukin-6 (IL-6) as well as high levels of C-Reactive Protein (CRP) have been consistently found in the serum of patients presenting with COVID-19 respiratory distress [3]. It is important to note that vascular inflammation in patients with ARDS has been shown to be associated with poor prognosis since it causes vascular hyper permeability and endothelial dysfunction of alveolar cells [4]. Moreover, in a Dutch ICU 31% of the COVID-19 patients had severe thrombotic complications, mainly in the lungs, despite the application of standard systemic thromboprophylaxis [5]. This incidence was dramatically high and comparable to the one from venous thromboembolism observed in overt disseminated intravascular coagulopathy [6]. According to these known physiopathological events, a drug which is readily available has a large therapeutic margin, does not suppress the activity of the immune system, can stabilize the endothelium, reduce the overwhelming cytokine storm and control the activation of thrombocyte and coagulation cascade would be well designed to manage the systemic effects of an ongoing SARS-COV-2 invasion.

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Chloroquine and Hydrochloroquine

The effect of Chloroquine and Hydrochloroquine in the context of COVID-19 is unclear and controversial [7]. The molecular mechanism of action of these 2 drugs has still not been fully understood. It is known that chloro- and Hydrochloroquine may inhibit the Coronavirus by changing the pH at the surface cell membrane and, thus inhibit the fusion of the virus to cell membrane. Other actions include inhibition of nucleic and replication, glycosylation of viral proteins, virus assembly, new virus particle transport and virus release [8]. Dealing with COVID-19, Yao et al. [9] published the results of antiviral assay, which showed that Hydrochloroquine was more effective at impairing viral replication compared to Chloroquine. A recent review including several small clinical trials, uncontrolled case series, and public figure endorsements was not able to show a clear benefit to administer these drugs in this context, although a potential therapeutic does exist [10]. There is also some concern for harm, particularly QTc prolongation and cardiac arrhythmias [11]. The last trial, the recovery trial, which included 1,542 patients, has been abruptly stopped because of the absence of benefits in patients hospitalized with COVID disease. It seems that these drugs may have the potential to reduce viral replication, but does not seem to provide any benefits as soon as the inflammatory storm has started. Not only clinical high-quality randomized trials are still needed, but more knowledge with basic science interaction of the virus with these drugs is mandatory to have their best use in this context. The absence of IV formulation may be a drawback for its use in ICU.

Remdesivir and Other Antiviral Drugs

Remdesivir is a nucleoside analogues drug with extensive antiviral effects and was shown to be effective to treat Ebola and Nipah virus infections in nonhuman primates [12]. It is a RNA-dependent RNA polymerase and therefore can inhibit the replication of multiple Coronavirus in respiratory epithelial cells, but cannot prevent the entrance of the virus in the cell. Remdesivir has recently shown promising properties against a wide array of RNA virus such as SARS-CoV infections both *in-vitro* cell experiments as well as in preclinical studies with mice and nonhuman primate models [13]. Remdesivir was given prophylactic in a mouse SARS model. Given 24 h after the onset of the disease, a significant lung virus titer decrease was observed with improvements on pulmonary function. However, when the drug was given 48 h later the survival rate of mice was low despite a reduction of the pulmonary virus titer [14]. Another study in a rhesus monkey model showed a complete resolution of the symptoms, when the drug was given before the virus application [15]. A recent study in a small human cohort with severe COVID-19 showed that 36 out of 53 patients (68%) had a clinical improvement [16]. Other drugs like Lopinavir/Ritonavir do not seem to be well indicated to fight COVID-19 [17]. The safety profile of Remdesivir has still not been extensively investigated, despite positive preliminary results. Experimentally it seems that this drug may be very effective prophylactic or at the very beginning of the disease, but its efficacy when the cytokine storm has started need to be further investigated. This treatment is also very expensive, which can be a drawback for a large application.

Tocilizumab

COVID-19 invasion is characterized by a major cytokine release syndrome (cytokine storm), including a great release of IL-6 [18]. IL-6 plays a central role in acute inflammation. Tocilizumab is a recombinant humanised anti-human IL-6R monoclonal antibody of the IgG1 subtype. It specifically binds soluble and membrane-bound IL-6 receptors and therefore inhibits receptor mediated-signal transduction [19]. This drug is mainly used in rheumatoid arthritis and systemic juvenile idiopathic arthritis [20]. Side-effects at therapeutic clinical concentrations are a decrease in neutrophils, platelets and an increase in transaminases and lipids [21]. A small retrospective analysis of 21 patients with severe COVID-19 showed a rapid decrease of fever and CRP with a marked improvement of the respiratory function. The number of lymphocytes returned to normal in 52% of the patients within 5 days of treatment [22]. Tocilizumab may be an effective drug in the management of COVID-19 induced cytokine storm. However, its action is specific for IL-6. The effect on the other inflammatory cytokines, especially IL-17, which is supposed to play an important role in the disease process, is unknown [23]. This drug may also depress with the immune system and the cost is extremely high, which could be a major drawback for a very large application.

Lidocaine

The clinical deterioration of SARS-CoV infection may result from a combination of direct virus induced cytopathic effects and immunopathology induced by a cytokine-storm [24]. If a controlled inflammatory response is considered beneficial, it is well acknowledged that when dysregulated, this response will be detrimental [25]. Therefore, using a drug like lidocaine, which can control the inflammatory response without suppressing the immunity, seems to be an option. It is well established that local anesthetics such as lidocaine, apart from being sodium channel blockers, demonstrate potent anti-inflammatory properties [26]. It has been shown that lidocaine and the amide local anesthetics attenuate *in-vivo* and *in-vitro* leukocyte adherence to vascular endothelium by inhibiting up regulation and expression of adhesion molecules [27,28]. Lidocaine attenuates leukocyte transmigration as well as priming and phagocytosis [29]. In addition, lidocaine attenuates the chemotaxis of the Polymorph Nuclear leukocytes (PMNs) during inflammation *in vivo* [27]. Lidocaine has been suggested to reduce infarct size [30]. Concerning the release of inflammatory mediators, it has been shown that lidocaine attenuates the concentrations of IL-1β, IL-6, IL-8, and the expression of Intercellular Adhesion Molecule-1 (ICAM-1) in activated human endothelial cells [31]. It has also been shown that lidocaine inhibits the release of prostanoids, thromboxane, leukotrienes and histamine from the mastocytes [32]. In addition, it has been demonstrated that lidocaine attenuates the inflammatory response by protecting the endothelial barrier. To elucidate a novel anti-inflammatory mechanism by which lidocaine could potentially attenuate endothelial injury in ARDS, it has been shown in human lung micro vascular endothelial cells, that lidocaine decreases significantly neutrophils adhesion and endothelial hyperpermeability [33]. Mikawa et al. investigated the effects of lidocaine (2 mg/kg as bolus, then 2 mg/kg/h) on rabbits incubated with *E. coli* [34]. An increase in paO_2, a better lung compliance and reduced resistance after the administration of lidocaine were observed. As compared to the control group, the level of pulmonary edema, the formation of hemorrhages, the alveolar septal thickening and the number of inflammatory cells in the alveolar space were reduced. In a model of acid-induced lung injury in rabbit, Nishina et al. [35] observed similar results. The same findings using the same model were noted by Takao et al. [36] after hyperoxia-related lung damage. More recent studies on animal models confirmed the beneficial use of local anesthetics on

lung injury [37]. The Srctyrosine kinase system has also been shown to be on the frontline of platelets activation [38]. Disseminated thrombi have been found during autopsies of patients died of COVID-19 infection [39]. It has been shown *in-vitro* that lidocaine is a potent inhibitor of the Src system activity and may therefore play a role in controlling this deleterious occurrence [40].

Human Studies in various surgical procedures have shown positive effects during the perioperative period regarding reduction of inflammatory compound release, enhancement of lymphocyte function and NK cells activity [41,42]. The application of lidocaine infusions on a selected group of patients with COVID-19 upon their admission to the hospital might prevent the cytokine surge, the further deterioration of their respiratory status and multi organ failure.

Conclusion

Lidocaine is cheap, readily available, can be given intravenously, has a large margin of safety, does not impair the immune system, has potent anti-inflammatory effects and can stabilize endothelial function. Whether this drug has a direct effect on the virus regarding its binding to the ACE2 receptor or its intracellular replication is unknown and would deserve *in-vitro* investigations. Therefore, lidocaine may contribute to improve the outcome of patients with COVID-19 infections and may have a role in the therapeutic armamentarium to fight this disease.

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