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A Few Steps Ahead to Select ACE2 in Pediatric COVID-19 Treatment: A Review of Literature

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Abstract

This review study aimed to examine the relationship between Coronavirus (COVID-19) and its uses in renin-angiotensin-aldosterone system (RAAS) to infect the patient using the related studies in this regard. Finally, the logical method of using the related medicine, and the benefits and harms of using these Medications will be indicated in the treatment of novel coronavirus. It is hoped that a short step will be taken in the attitude of scientists to plan further studies on the pediatric treatment of upgrading COVID-19.

Key Words: ACE2 enzyme, COVID-19, Pediatrics.

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1. Introduction

As you know, the world has been exposing to the pandemic caused by the new novel coronavirus called COVID-19 from China since December 2019 for three months (1). Over the past three months, the virus was a new challenge to almost every country since the beginning of 2020, when all scientists came in to treat the emerging and dangerous disease due to its side effects. Various medicines and methods have been suggested and tested worldwide to treat the virus and evaluate its side effects. Due to the outbreak of the virus, antiretroviral medicines have used for the previous generation of the same family, called SARS (Severe acute respiratory syndrome), such as hydroxychloroquine, nevertheless, in a review study by Sanders et al. they found that no effective treatment was available at the moment and that much more research was needed to understand the virus's function (2).

2. RAAS vs. COVID-19, Challenge, or Hope?

RAAS (Renin-Angiotensin-Aldosterone System), as a hormonal system, controls blood pressure, balances the body's electrolytes, and fluid levels (3). Inactivated and liver-releasing angiotensin is converted to angiotensin 1 by Renin secreted from kidneys and angiotensin 1 convert to angiotensin 2 in the lungs by ACE (Angiotensin Converting Enzyme) secreted from the lung surface. Angiotensin 2 has several effects, including controlling and lowering blood pressure, controlling the body's electrolyte balance, while maintaining body fluids, and activating the sympathetic system (4). Finally, the ACEII enzyme inactivates and reduces this enzyme in the body by converting angiotensin 2 to angiotensin 1-7. The ACEII is present in various tissues and organs, including the cardiopulmonary system, renal, central, and peripheral nervous systems (5), and cells of the gastric epithelium, duodenum, and rectum, as well as endothelial cells, and small intestinal enterocytes (6) (**Figure.1**). Preliminary reports suggested high blood pressure in patients with COVID-19 (8-10. Several cases were reported from China during the COVID-19 epidemic with high blood pressure; 1,099 patients, which had a prevalence of approximately 15%. However, this estimation appears to be lower than the prevalence of high blood pressure compared to other viral infections (11), and in the general population in China (12). Patients by high blood pressure who were infected by COVID-19 used ACEI (ACE Inhibitor) or ARB (Angiotensin Receptor Binding) for treatment. The severe and chronic decline in the ACEII enzyme in chronic diseases and elderly patients has been seen in studies that do not normally involve children (13). Evidence suggests that increased concentrations of ACEII receptors in lung pneumonitis in children may have a protective effect on severe clinical manifestations of SARS-COVID-19. Chen et al. found out that due to the higher incidence of ACEII genome among young people, the group was much less likely to develop and reduce diseases associated with the enzyme, and their side effects were less severe (14).

Besides, according to their analysis, both the well-known estrogen and androgen hormones, with aging, show that it regulates the expression of ACEII. On the other hand, milder disorders among children may be due to the presence of trained immunity. Trained immunity is created by innate immune cells after exposure to antigens and forms memory cells (15). The remaining memory cells in the pediatric hematopoietic system respond much faster and more strongly to the first stage of exposure to the antigen and keep the body immune to the antigen. Therefore, it can be concluded that both repeated viral and vaccine infections

among children can strengthen the innate immune system, which makes it more effective in defending against various other pathogens. Inconsistent with the previous studies, Schouten et al. (2019) strongly showed that there is no difference in the amount and activity of ACE and ACEII in different age groups, and the reason for this difference in age groups in the severity of lung disease in the face of invasive pathogens, is the high level of myeloperoxidase, interleukin 6 and 10, and p-selectin in the elderly group (16).

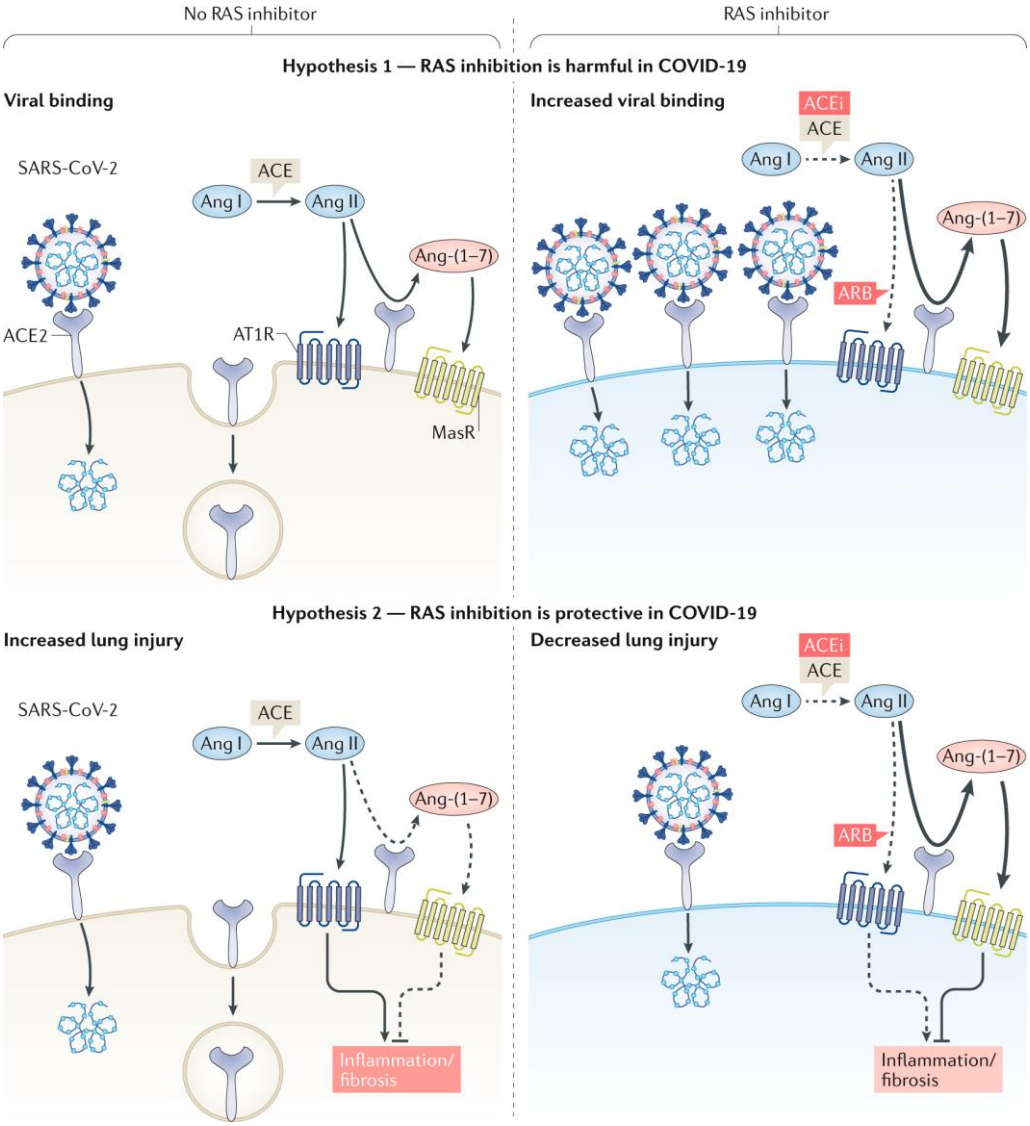

Fig. 1: Possible effects of renin–angiotensin system inhibition on COVID-19 (7).

The competing hypothetical mechanisms by which inhibition of the renin–angiotensin system (RAS) with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) might be harmful (upper panels) or protective (lower panels) in COVID-19. Hypothesis 1: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains entry into the cell by binding to angiotensin-converting enzyme 2 (ACE2; upper left panel). The addition of an ACEi or ARB could increase ACE2 abundance and thus enhance viral entry (upper right panel). Hypothesis 2: angiotensin II (Ang II) drives lung injury by activating the type 1 angiotensin receptor (AT1R), causing inflammation and fibrosis (lower left panel). Diminishing production of Ang II with an ACEi or blocking Ang II–AT1R actions with an ARB enhances the generation of Ang-(1–7) by ACE2 and activation of the Mas receptor (MasR), which attenuates inflammation and fibrosis and therefore attenuates lung injury.

3. ACE2 as the Ultimate Goal of Treatment

Zou et al. (2014), and Huang et al. (17, 18) showed that H5N1 (Influenza A), and H7N9 (the novel influenza A) influenza viruses directly caused progressive degeneration and ALI in patients through the use of ACE2 enzyme in the same year. The severity of the disease and mortality in these two viruses are directly related to the amount of angiotensin 2 due to the failure of ACEII. Similarly, in 2005, after the outbreak of SARS, Kuba et al. (19) showed that the coronavirus, like its other family member, MERS (Middle East Respiratory Syndrome), caused ALI and progressive damage through the ACEII enzyme in the lungs. In 2016, a series of in-vitro and clinical studies conducted by Gu et al. found that the RSV (Respiratory Syncytial Virus) in the same way, and through direct ACEII, caused lung injury and other clinical symptoms (20). According to the studies as mentioned above, treatment with hACEII recombinant has entered the second phase of research on humans and, in some cases, has improved patients with H5N1 (8). The same project was the subject of a study conducted by Imai et al. (2005), in which they used the ACEII enzyme to treat patients with ALI (Acute Lung Injury) following sepsis and acid aspiration (21). In addition to slowing the ALI progression, patients also improved their clinical and laboratory performance and lung function compared to patients in the control group.

4. Uncertain Effects of RAAS Inhibitors on ACE2

In 2020, after the emergence of the new member of the coronavirus family, COVID-19, it was found that the virus, besides using the ACEII enzyme to reach the target organs and its destructive effect on them, reduces the production and elimination of this enzyme (22). Moreover, this severe damage and more severe symptoms can occur probably due to the same reason, so we can hypothesize that increasing angiotensin 2 causes more and more severe damage following ALI in patients. In a study conducted by Liu et al. in a limited number of COVID-19 patients, an increase in viral load was directly related to plasma levels of angiotensin 2 and the amount of lung degradation and ALI (23). Other studies have shown that the higher the COVID-19 viral load, the lower the ACEII enzyme, and possibly the higher the angiotensin 2 (24). On the other hand, decreased production of ACEII enzymes facilitates infiltration and entry of neutrophils into lung tissue and alveoli in response to endotoxin bacteria (25), indicating further secretion in patients with secondary bacterial infection with the novel coronavirus. Therefore, according to studies and aggregation of all studies, it seems that by reducing the amount of angiotensin 2 or increasing ACEII, ALI and increasing the recovery process in patients with COVID-19 can be achieved. Since the COVID-19 uses the ACEII enzyme and enters and multiplies into the host cells, increasing ACEII in patients for treatment has acted like a double-edged sword that has yet to be studied, and the benefits have not been carried out. It is worth noting that the competition between ACEII and angiotensin 2 and the COVID-19 virus is not yet recognized, and it is not clear which one is more interested in the enzyme compared to the other users of the information available for future treatment. However, findings from an increase in angiotensin two, and its severity associated with the disease are less likely to affect treatment using this enzyme. More angiotensin 2 in the tissues, in addition to more ACE2 being occupied by this enzyme and reducing the use of the virus to enter the cells, angiotensin two itself causes more damage and increases the severity of ALI in patients. Therefore, an angiotensin two can be considered as a treatment for patients with the novel

coronavirus is an impossible assumption, which, if used, will more likely lead to more damage to the lungs and no benefit to curing the disease. It will not have and will make the patient's condition worse (**Figure.1**)

5. The balance between Benefits and Harms of RAAS inhibitor use in COVID-19 patients

Despite the lack of clear transparency in the benefits of using RAAS inhibitors in COVID-19 patients, there are potential harms and risks in other patients. Numerous underlying diseases have been reported in COVID-19 patients, the most common of which are cardiovascular (26), and hypertensive patients, who may benefit from the use of these medicines. It seems that the use of RAAS inhibitor medicines in hypertensive patients and its continuation during SARS-COVID-19 disease is much safer compared to when it is started in a stable and COVID-19 patient, at which time the possibility of acute complications and they are more dangerous and may have irreversible side effects. Therefore, physicians should be aware of the side effects of starting or continuing to take these medicines and their benefits. Finally, it is suggested that during a clinical study on treatment with RAAS inhibitors in a group of children with COVID-19 and its comparison with the control group, a specific decision must be made as soon as possible about initiating treatment or continuing or discontinuing treatment with RAAS inhibitors.

6. CONFLICT OF INTEREST: None.

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