Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 4 Issue 8 August 2020

Review Article

The Potential Double-Faced Interactions of ACE Inhibitors/Blockers with SARS-COV-2 in Cardiovascular Diseases and Diabetes Mellitus Patients Who Developed COVID 19

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Received: July 01, 2020

Published: July 18, 2020

Abstract

Coronaviruses (CoV) are a large family of viruses that cause illness that ranges from the common cold to more severe diseases. For instance, Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Ultimately, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for COVID-19, a global pandemic with disastrous ramifications for populations and healthcare systems on every side of world [1]. Since two decades, there have been outbreaks of severe, and even fatal in sometimes, resulted from human pathogenic CoVs. These CoV strains had originated in bats and were transmitted to humans via an intermediate host [1-3]. These strains displayed a stronger and quickly virulence transports from human to human. The CoVe-infection could usually produce mild symptoms, for particular individuals, responses were more severe in other cases could reach to death due to alveolar damage which finally lead to respiratory failure. During the current COVID 19 pandemic, it has been noticed that there is a number of patients who hospitalized by COVID-19 have high blood pressure as well as cardiovascular diseases (CVD). This number cannot be neglected, which could indicate to a somehow correlation between COVID 19 severity and these diseases.

Recently, in an interview with a medical journal, the U.S. government's top infectious disease expert Anthony Fauci cited a report showing similarly high rates of hypertension among COVID-19 patients who died in Italy and suggested the medicines such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) may act as an accelerant for the virus [4]. Contradictory, from animal studies, ARBs and ACEi have a potential protective effect of ARBs against lung injury in mice infected with SARS-CoV. Based on these findings and the similarities between SARS-CoV and the current SARS-CoV-2, it is thought that these drugs have the same potential protective effect against the severity of COVID 19. The question is, do ACEi/ARBs have a biphasic impact, do, is it regarded as a double-edged sword? Therefore, there is a concern that has been raised regarding whether ARBs and ACEIs would increase the morbidity and mortality of COVID-19 [5].

Keywords: ACE Inhibitors/Blockers; SARS-COV-2; Cardiovascular Diseases; Diabetes Mellitus and COVID 19

Abbreviations

CoV: Coronaviruses; MERS-CoV: Middle East Respiratory Syndrome; SARS-CoV: Severe Acute Respiratory Syndrome; CVD: As Cardiovascular Diseases; ACE: Angiotensin-Converting Enzyme; ACEi: Angiotensin-Converting Enzyme Inhibitors; ARBs: Angiotensin Receptor Blockers; ARDS: Acute Respiratory Distress Syndrome; S Protein: Spike Protein; RBM: Receptor Binding Motif; DM: Diabetes Mellitus; Ang II: Angiotensin II; RAAS: Renin-Angiotensin-Aldosterone System; TMPRSS2: Transmembrane Protease Serine 2; AT1R: Angiotensin II Type 1 Receptor

Introduction

On January 7th, 2020, the Chinese authorities promulgated that they had identified a new virus that causes cases of pneumonia called Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and responsible for a disease called COVID 19. This virus swiftly surged, and on March 11th, 2020; the World Health Organization promulgated it a pandemic. COVID-19 clinical cases ranges from asymptomatic upper respiratory infection to critically ill pneumonia correlated with acute respiratory distress syndrome (ARDS) [6]. The coronaviral genome is made up four fundamental structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein. The most significant protein which is implicated in SARS-Cov-2 into the host cell is S protein [7-9].

On April 16th 2003, following the outbreak of SARS in Asia and secondary cases somewhere else in the world, the World Health Organization (WHO) issued a press release stating that the coronavirus identified by many laboratories was the official cause of SARS-CoV. After frequent analysis of the SARS-CoV-2, S protein genome revealed that it is 75% similar to the SARS-CoV S protein [10,11]. Further, in the S protein, the analysis of the Receptor Binding Motif (RBM) illustrated that most of the amino acid remains, which are necessarily for receptor binding are preserved between SARS-CoV and SARS-CoV-2, proposed that SARS-CoV-2 strains use the same host receptor for cell entry [12]. This host receptor which implicated in SARS-CoV entering the cell is Angiotensin-Converting Enzyme 2 (ACE-2) [13] (Figure 1). Medications of angiotensin-converting enzyme inhibitors (ACEi), block ACE2 receptors, it is thought that probably protect or predispose against COVID-19 infection.

According to the analysis conducted by the Chinese Center for Disease Control and Prevention, several comorbidities, including diabetes mellitus (DM) and cardiovascular diseases, seem to be involved in COVID-19 patients with a severe course. In this analysis, 10.5% of fatal cases occurred in patients with cardiovascular disease (CVD) and 6% in patients with arterial hypertension [14]. It is thought these comorbidities contribute to subjecting those patients at a higher risk of developing a severe COVID 19. As known, most patients with CVD use ACEis or ARBs as a therapy [15]. Notably, Severe acute SARS-CoV-2 for entry into target cells uses the receptor angiotensin-converting enzyme (ACE) 2 [16]. Ferrario., *et al*. stated that both ACEis and ARBs could remarkably increase the mRNA expression of cardiac ACE2 [17]. Based on these thoughts, some hypothesis recently released that these drugs probably play a role in the severe cases of COVID-19 [18].

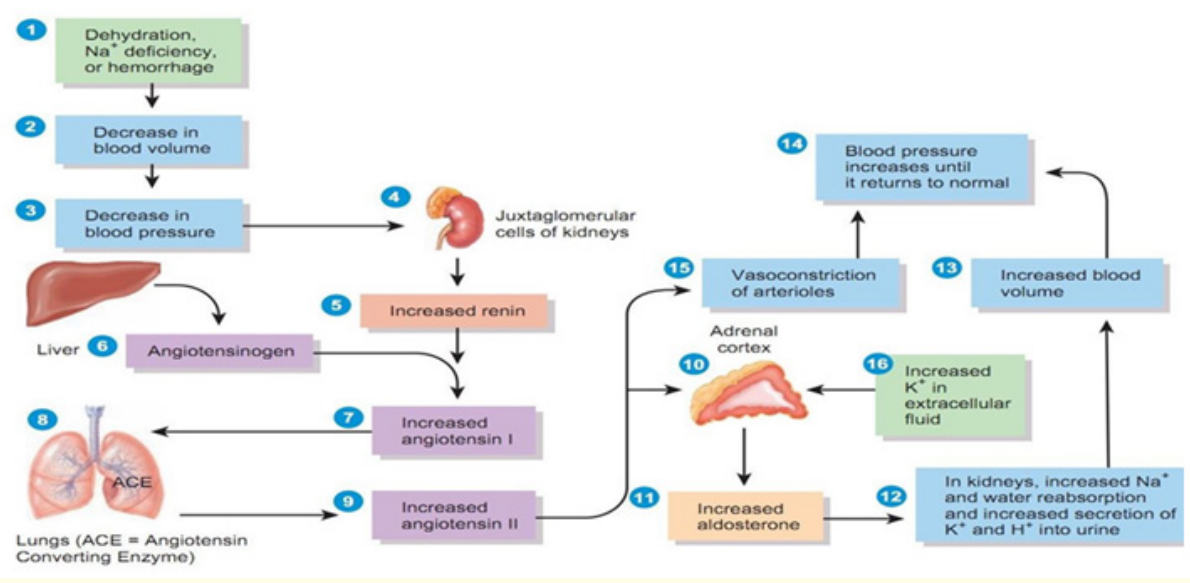

Figure 1: Renin-angiotensin-aldosterone system (RAAS).

Quoted from antranik.org

On the other hand, some studies support the position statement of the European and American Societies of Cardiology; they declare that ACEis and ARBs are safe and should be continued and prescribed according to established guidelines as there is no heretofore enough evidence on the scale of humans [19,21].

Moreover, animal data suggested a potential protective effect of ARBs against COVID-19 pneumonia because an ARB can hamper the exacerbation of acute lung injury in mice infected with SARS-CoV, which is closely related to SARS-CoV-2. Thus, which view would be valid and should take it into account, which consequently, would provide insight into COVID-19 and direct the researchers in the future about COVID 19? [2].

This conjectures about whether the safety of ACE-i/ARB treatment or their harmful effects concerning COVID-19 does not have adequate evidence to support it. In fact, there is evidence from animal studies proposed that these medications might be somehow prophylactic against serious lung complications in patients with COVID-19. Still, until now, there is no enough data in humans. The Council on Hypertension of the European Society of Cardiology wants to call attention to the lack of any evidence bolster up the harmful effect of ACE-I and ARB in the context of the pandemic COVID-19 outbreak [21].

This study is a synopsis study which summarizes the current evidence on the impact of ACEis or ARBs on severe acute respiratory illness caused by SARS CoV-2 as well as how they could have a prophylactic effect on COV-2 in order to guide clinical practices.

Methods

We have systematically searched the PubMed medical database, the World Health Organization database of COVID-19 publications, clinicaltrials.gov, and medRxiv.org from 2000 till April 2020 using terms for COVID-19, SARS virus, Middle East Respiratory Syndrome, SARAS-Cov-2, SARAS-Cov, coronavirus, hypertension, diabetes, cardiovascular disease, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors. This work has been done by regaining all the available literature in the English language, which published regarding COVID-19, that recorded the different comorbidities outcomes.

What is the relationship between Angiotensin II and ACE?

Synthesis of angiotensin II (Ang II) is the final step in renin-angiotensin System (RAS) cascade, which initially commences with altering the level of sodium/water in the blood. When renal blood flow is lower than usual; the concentration of plasma sodium is reduced; then, in the kidneys prorenin (an intracellular protein) will convert into renin which catalyzes the cleavage of angiotensinogen (in the liver) into angiotensin I [23,24]. Then, angiotensin I converted to angiotensin II by an enzyme is found in lung capillaries called the angiotensin-converting enzyme (ACE). Lung capillaries are the primary location for (ACE) [25] (Figure 2). ACE2 is one of carboxydipeptidase family. It is widely distributed in the human body such as the heart, kidney, small intestine, and lung. Lung ACE2 expression is mainly concentrated in type II alveolar cells, macrophages, bronchial, and tracheal epithelial cells [26].

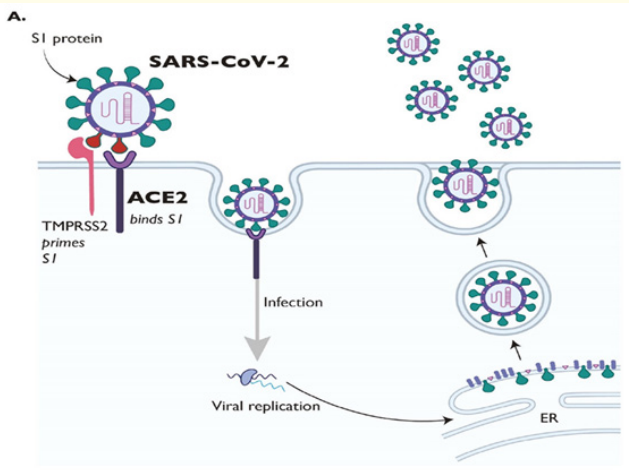

Figure 2: Shows the transmembrane spike glycoprotein (S protein) of SARS-CoV-2 when binding to cellular membrane ACE2; then attaches to the target cells of the host by cellular surface proteases priming, such as transmembrane protease serine 2 (TMPRSS2).

Quoted from The European Society for Cardiology

The angiotensin II-hemodynamic effect is stimulating the aldosterone production and systemic vasoconstriction and, then, fluid retention and increased systemic blood pressures. Therefore, ACEis/ARBs are prescribed for Cardiovascular diseases' patients. Angiotensin-converting enzyme (ACE) inhibitors assist in veins relaxing and lowering the blood pressure in arteries. ACE inhibitors prevent ACE from producing angiotensin II the substance that narrows blood vessels, causing increasing in blood pressure and inflammation as well as increasing the damage to blood vessel lin-

ings and various types of tissue injury. Here comes the crucial role of ACE2 in transforming Ang II to other molecules which in turn counteract the effects of Ang II [27].

How ACEI/ARBs medication or both could act as a double-edged sword?

In initial reports from China, in the most severe COVID-19 patients cases were the most prevalent among the older age, hypertension, diabetes mellitus, and cardiovascular disease (CVD) and patients with these comorbidities tended to have higher case fatality rates [28,29]. Besides, it has been suggested that angiotensin-converting enzyme 2 (ACE2) is a functional receptor for SARS-CoV-2 infection in those patients [30,31].

Some studies suggest a significant deleterious of Ang II, which can increase inflammation and the cell death in the alveoli which are critical for bringing oxygen into the body; these harmful effects of Ang II are stimulated by ACE 1 and can be reduced by ACE2 which in turn upregulates Ang II in the cell and prevent it from binding to AT receptor-1 and helps in converting it to Ang (1-7). Based on this suggestion, some experimental studies reported that ACEi and ARBs could increase ACE2 expressions on the cell membrane of the host. As the relationship of ACE1 and ACE2 is a "yin-yang" relationship; ACE1 urges the production of the amount of Ang II, whilst ACE2 decreases Ang II. Therefore, reducing ACE 1 amount by inhibitors or blockers; ACE2 will increase, and as a corollary, the amount of ACE 2, which is not occupied with Ag II will increase as well. Thus, SARS-CoV-2 virus binds to ACE2 and hampers ACE2 to perform its function in regulating Ang II signalling. Therefore, ACE2 action is "inhibited," removing the brakes from Ang II signalling and making more Ang II available to cause more injury to tissues. This decreased braking likely contributes to injury, especially to the lungs and heart, in COVID-19 patients [33].

Quite the opposite, some studies have another perspective that ARBs have prospective benefits in precluding and treating lung injury caused by COVID-19. By inhibiting ACE1, ACE inhibitors decrease the levels of Ang II and its ability in increasing blood pressure and injuring the tissue. ACE inhibitors are mainly prescribed for hypertension patients as well as patients with heart failure and kidney disease, hence, there is a question that has been raised, which hypothesis could be valid? [34].

Let us have a perusal look at each hypothesis in details.

Discussion

The first suggested hypothesis

The detrimental effect of ACEI/ARBs in exacerbate COVID-19 complications

Initially, this hypothesis has been raised from the resemblance, between SARS-CoV-2 with SARS-CoV; the virus which is in charge of the 2002-2003 SARS epidemic, and Middle Eastern respiratory syndrome coronavirus (MERS) [35]. Researchers extensively examined the pathophysiologic mechanisms of SARS-CoV, including the virus interaction with the lung and heart. Based on these studies, researchers go for that the ACE2 receptor, existed on alveolar epithelial cells, serves as a high-affinity receptor and co-transporter for SARS-CoV-2 for entering the lungs cells [36] (Figure 1).

A recent review published in The *Lancet Respiratory Medicine* hypothesizes that ACE2 receptor drugs usage is at a higher risk for severe COVID-19 infection. Initially, ACEI inhibits ACE then decreasing angiotensin I levels, leading to a probable negative feedback loop which in turns upregulates more ACE 2 to capable of interacting with the decreased angiotensin I level available [37]. This upregulation of ACE2 receptor results in increased binding sites for SARS-CoV-2, leading to COVID-19 infection. This is, in particular, noticed in diabetes patients and/or hypertension as they are usually taking ACEi or ARB [49]. This infection process is happening by two essential components: firstly, a transmembrane spike glycoprotein (S protein) of SARS-CoV-2 attaches to ACE2 of the cellular membrane of the target cells. Secondly, by transmembrane protease serine 2 (TMPRSS2) which in turn permits the viral fusion and cellular membranes. Finally, it enters the target cell and replicates [38] (Figure 2). Besides the binding ability of ACE2 to the SARS-CoV-2 virus; ACE2 has the ability to protect tissue from injury by alleviating the pathological effects of Ang II. However, by virus binding to ACE receptors, the available free amount of ACE2 is reduced which fundamentally responsible for Ang II-mediated injury and hinders its binding to Ang receptor-1 leading to increase susceptibility to inflammation, cell death and organ failure, especially in the heart and the lung, leading the individuals to more susceptible to severe illness from COVID-19; besides, there is an enough ACE2 is available to facilitate viral entry [34] (Figure 3).

This hypothesis has been supposed based on the findings from studies that were published in the Journal of the American Heart Association. Showing that Lisinopril one of ACE inhibitors

drugs causes a 5-fold increase in ACE2 levels and a 3-fold increase in ACE2 levels with Losartan which is an angiotensin II receptor blocker (ARB) [5,39,40].

Moreover, currently available epidemiological studies have also reported by Guan., *et al.* [41], that there is an increased prevalence of cardiovascular disease (CVD), including hypertension, among patients who developed a severe subtype of COVID-19 [41,42]. This prevalence of heart disease was fourfold more than between patients who developed the combined primary endpoint of admission to an intensive care unit, mechanical ventilation, or death, relative to patients with less severe outcomes. Further, Other studies noticed [42,43] that evaluated COVID-19-which correlated to cardiac injury has a high prevalence of hypertension (59.8 - 63.5%), coronary heart disease (29.3-32.7%), cardiomyopathy (15.4%) and chronic heart failure (14.6%) between COVID-19 patients with cardiac injury, which is separately associated with mortality with COVID-19.

The second suggested hypothesis

The beneficial effect of ACEi/ARBs in mitigating COVID-19 complications

Conversely to the first hypothesis, there are some investigators have posed another hypothesis of ACEi and/or ARBs. This hypothesis states that ACEi or ARB usage probably has a beneficial effect on COVID-19 infection prevention. For instance, a study has been provided by Li., *et al.* [49] suggested that ACEI inhibition of ACE may help in provoking negative feedback. With ACEi/ARBs given a lacking level of angiotensin II, upregulating ACE2 receptors and decreasing overall inflammation which as a corollary reduces the lung injury among CVD or Hypertension patients who developed COVID 19. ACE2 has a crucial role in degrading angiotensin II to release angiotensin 1-7, which stimulates the mas oncogene receptor which in turn negatively regulates a variety of angiotensin II actions mediated by angiotensin II type 1 receptor (AT1R). Therefore, it is thought that in hypertension, cardiac hypertrophy, heart failure, and other CVDs, ACE2/angiotensin 1-7/mas receptor axis has reversal effects against the excessively activated ACE/angiotensin II/AT1R axis [44].

Another explanation has been reported by Sun., *et al.* [45] that ACEi usage impairs the ACE/angiotensin II/angiotensin-1 receptor pathway. Therefore, impairing the integrity of the ACE2/angiotensin 1-7/MAS (MAS-related G protein-coupled receptor). This pathway disturbance of the ACE2/angiotensin 1-7/MAS could decrease the production of ACE2, which is regarded as a doorway for entering SARS-CoV-2 to the cell. Consequently, the chance of binding S-protein of SARS-CoV-2 with ACE2 receptors reduced. Recently, a retrospective study has been published in National Institutes of Health based on Yang., *et al*. Findings [46] reported that COVID-19 patients with underlying hypertension taking ACE inhibitors/ARBs had a much lower proportion of critical disease (9.3% vs 22.9%; p = 0.061) and a lower mortality rate (4.7% vs 13.3%; p = 0.283) than their hypertensive counterparts not receiving an ACE inhibitor/ARB. Moreover, patients taking ACE inhibitors/ARBs had remarkably levels of C-reactive protein and procalcitonin were lower than patients who were not receiving an ACE inhibitor/ARB, indicating a potential anti-inflammatory function in COVID-19.

Based on animal studies, RAAS inactivated animal models display relief in severe acute pneumonia symptoms and respiratory failure, through mechanisms of vasoconstriction [45]. Therefore, there is a hypothesis that the modulation of the RAS, especially by ACE2 and angiotensin II, is highlighted as a potential therapeutic target for COVID-19 as there is a genetic proof that ACE2 is a crucial SARS-CoV receptor in mice studies. SARS-CoV infections and the Spike protein of the SARS-CoV decrease ACE2 expression and the injection of SARS-CoV Spike into mice worsens acute lung failure. Therefore, it is thought that it can be languished by blocking the renin-angiotensin pathway. These results provide an explanation of why SARS-CoV infections cause severe and often lethal lung failure and suggest a rational therapy for SARS and probably other respiratory disease viruses by blocking the renin-angiotensin pathway whether by ACEis/ARBs. From the findings in some animal studies which suggested the beneficial net effects of ARB in SARS-CoV-infected acute lung injury mice. Currently, a multicenter, double-blinded placebo-controlled, randomized trials (RCTs) are being operated to scrutinize the effects of Losartan on mortality and hospital admission in COVID-19 patients requiring hospital admission (NCT04312009) and not requiring hospital admission (NCT04311177), respectively [50].

Finally, given the contradictory hypotheses (Shown in figure 3), rapidly evolving of the disease nature, and social media-related hysteria, several cardiology associations (HFSA/ACC/AHA and ESC Hypertension Council) declared an official statement regarding the continuation of ACEi and ARB for COVID-19 patients. The associations highly recommend for patients who are taking either of medication of ACEI/ARB to continue the treatment with these drugs until asserted any evidence against them [47].

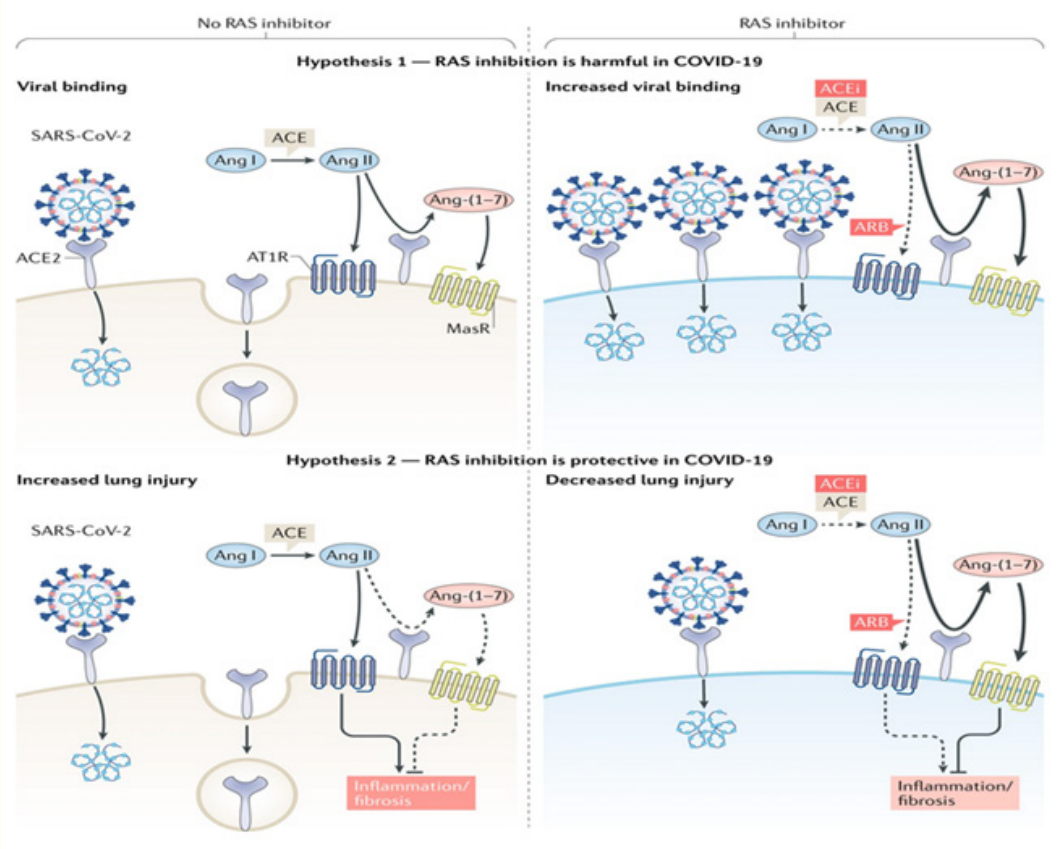

Figure 3: The two contradictory hypothetical mechanisms by which inhibition (RAS) with (ACEi) or (ARB) might be detrimental (upper charts) or prophylactic (lower charts) in COVID-19 [51].

Hypothesis 1	SARS-CoV-2 enters into the cell by binding to angiotensin-converting enzyme 2 (ACE2; upper left chart). The insertion of an ACEIs or ARBs could raise ACE2 expressions and thus increase viral entry (upper right chart).
Hypothesis 2	Ang II provokes lung injury by stimulating the type 1 angiotensin receptor (AT1R), leading to inflammation and fibrosis (lower left chart). Therefore, diminishing production of Ang II with an ACEIs or blocking Ang II-AT1R actions with an ARBs augments the production of Ang-(1-7) by ACE2 and stimulation of the Mas receptor (Mas-R), which languishes inflammation, fibrosis, and consequently lung injury.

Conclusion

These paradoxically hypotheses perhaps have appeared based on the outcomes of experimental studies, especially those of severe acute respiratory syndrome coronavirus (SARS-CoV) as at present the direct clinical data on COVID-19 are lacking; therefore, we cannot rule out a final conclusion if that long-term intake of ACEis and/or ARBs may facilitate SARS-CoV-2 entry and virus replication or intake of ACEis and/or ARBs, when infected, is beneficial concerning the pulmonary outcome. Notably, we are dealing here with a double-edged sword. That relies on the disease phase: ACE2 expression increase could potentially increase the complications in patients who developed COVID 19, and ACEi/ARB usage would be an addressable risk factor. At stark contradict, once infected, down-regulation of ACE2 may be the hallmark of COVID-19 progression.

Hence, upregulation by using renin-angiotensin system hindrance and ACE2 substitution in the acute respiratory syndrome phase may have a beneficial effect. Therefore, cardiovascular diseases and their therapies, by affecting ACE2 levels, may play a vital role concerning the infectious and outcome of COVID-19. Whether treatment or disease-induced upregulation of ACE2 influences the course of COVID-19 urgently needs to be determined. Because of at present, no clinical studies have being to confirm that ARBs and ACEis reinforce predisposition to the infection, whether they worsen or ameliorate all-cause and cardiovascular outcomes in COVID-19 patients as well as SARS patients. Thus, the hypothesis implying the concern would not be easily extrapolated to humans, especially to COVID-19 patients.

Future Suggestions

Since then, researchers predilection is to associate of CVD with the severity of COVID-19. Notwithstanding, construing such a correlation should be done with caution since many factors hamper the validity of such an association should be taken into account before reach such conclusion whether ACEis or ARBs are harmful or beneficial. Firstly, till now, most available studies which have been generated are from China. Therefore the generalizability of such a correlation to the worldwide population is confined and unwarranted to be feasible and applicable for the other communities.

Secondly, patients with CVD are probably to encounter severe morbidity from COVID 19 because they have reduced circulatory reserve, which required for the cardiovascular system.

Thirdly, since the available studies have reported that elderly patients with COVID-19 prone to develop a severe course of the disease as well as cardiac injury, noteworthy, the prevalence of CVD is increased with age. Therefore, age here may act as a confounding factor which may cause misleading results and create a false correlation between the severity of COVID 19 in CVD patients and the disease itself or even ACEi or ARBs drugs.

The risk of random imbalance of the covariates in large randomized controlled trials (RCT) is mostly negligible. However, with smaller studies, it may be substantial. Thus, to create reliable results, an assessment and adjustment for any possible confounders could be found and share in COVID 19 complications is an essential requirement in order to reduce a biased assessment of the treatment comparison. Therefore, Future studies with age-stratified analysis or any suspected confounders could shed light on such associations with the severity of COVID-19 infection.

Fourthly, Although the reduction in the odds of death and odds of risk of developing severe disease; this is not only reassuring regarding the safety of ACEi/ARB in patients with COVID-19 but also indicate towards the critical need for an adequately powered RCT for confirming these benefits with also taking into account all possible confounders.

Currently, several trials, COVID-19 patients who already were taking ACEi/ARB drugs are being randomized to continue or to stop them. In several other trials, investigators are examining whether ARBs can be used as an actual treatment for COVID-19, with infected patients being randomized to ARB or placebo groups.

Here some of the clinical trials on progress

1. ClinicalTrials.gov identifier: NCT04338009
    - Elimination or prolongation of ACE inhibitors and ARB in coronavirus disease 2019 (REPLACECOVID).
2. ClinicalTrials.gov identifier: NCT04353596
    - Stopping ACE-inhibitors in COVID-19 (ACEI-COVID).
3. ClinicalTrials.gov identifier: NCT04318418
    - ACE inhibitors, angiotensin II Type-I receptor blockers and severity of COVID-19 (CODIV-ACE).
4. ClinicalTrials.gov identifier: NCT04287686
    - Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19.
5. ClinicalTrials.gov identifier: NCT04330300
    - Coronavirus (COVID-19) ACEi/ARB investigation (CORONACION).

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