

Use of Renin-Angiotensin System Inhibitors in Hypertensive Patients in COVID-19 Era: A Review

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Abstract

The presentation of COVID-19, caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2), has largely been asymptomatic or mild in youngsters and the pediatric age group. The elderly population, however, have been at a much higher risk of severe disease with grave complications and even death. Furthermore, obesity, cardiovascular ailments and diabetes mellitus have also been implicated in severe disease outcomes. It has been found that a dysregulation of the renin-angiotensin system (RAS) plays a key role in the initiation of lung damage after SARS-CoV-2 infection, and RAS inhibitors may reestablish the equilibrium between the "classic RAS" arm and its counter regulatory arm, here defined as "anti-RAS," of which ACE2 is the keystone. Till now, there has been paucity of solid evidence to either recommend or discontinue usage of ACEI/ARB medications in hypertensive patients in the midst of menace posed by COVID-19. Hence, we tried to summarize and simplify the myths and facts known so far regarding the subject matter to find out a possibilities and feasibilities regarding the use of ACEI/ARB in hypertensives patients who have also contracted COVID-19 and the their role in influencing progression of the disease to severe forms or death.

Keywords: Angiotensin-Converting Enzyme Inhibitors; Hypertension; Angiotensin Receptor Blockers; Covid-19

Introduction

During the past one-year COVID-19 has posed the world with a new challenge. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been the causative virus. It has largely been asymptomatic or presented with mild form of symptoms in youngsters and pediatric age group. On the other hand, elderly age population has been at much higher risk of catching severe disease with grave complications and even death [1-3]. Apart from age factor, obesity, cardiovascular ailments and diabetes mellitus have also been implicated in severe disease outcomes.

High prevalence of hypertension has been found also in patients who died of Middle East Respiratory Syndrome (MERS)-CoV or influenza viruses infections [2]. There have been controversies regarding usage of angiotensin-converting enzyme inhibitors (ACEI) and

angiotensin II type 1 receptor blockers (ARB) and theoretical risk of increased patients' vulnerability to SARS-CoV-2 infection that might lead to risk for developing severe disease associated with utilization of these medications [4,5]. However, concrete evidence is not available to prove this theory. Hence, major international scientific societies and pharmaceutical groups have clarified these assumptions and have come with more logical answers. As a matter of fact, a dysregulation of the renin-angiotensin system (RAS) plays a crucial role in the commencement of lung damage after SARS-CoV-2 infection, and RAS inhibitors may reinstate the equilibrium between the "classic RAS" arm and its counter regulatory arm, here defined as "anti-RAS," of which ACE2 is the keystone. These two pathways and the possible role of a "pathophysiological" drug therapy based on RAS inhibitors, aiming at restoring equilibrium and avoiding severe lung damage and death in COVID-19, have been much thought out in past one year.

Methods

We did search on PubMed, Medline database publications using: COVID-19, Angiotensin-converting enzyme inhibitors, hypertension, Angiotensin receptor blockers, Covid-19.

The publications included were special communications, reviews, books and research studies regarding the subject matter including COVID related recent literature and few past relevant literature.

Discussions and Review of Literature

Brief summary of renin angiotensin system (RAS)

The renin angiotensin system (RAS) has a key role in homeostatic balance of cardiovascular system and renal systems alike. This results in regulating fluid volume and blood pressure, however it exerts effects on other tissues, such as lungs, where it affects the microvasculature and mesenchymal cells. Blocking the RAS pathway or its modulation, constitutes a therapeutic target of hypertension and its resultant cardiovascular sequelae (ischemic heart disease or heart failure) [6].

The classic renin angiotensin system (RAS) results in generation of angiotensin (Ang) II. Renin, a protease released by the kidneys cleaves angiotensinogen (produced in liver and adipose tissue) [7], to form Ang I. This Ang I is hydrolyzed by endothelial ACE, resulting in formation of an octapeptide Ang II. ACE is found richly in microvasculature of lungs. This is the reason why, pulmonary vasculature has the capability to swiftly convert Ang I to Ang II. It should be noted, this ability of the lung plays a crucial role in overproduction of Ang II in conditions where there are enhanced levels of Ang I (obesity) [7]. This biologically potent peptide binds Ang II type 1 and type 2 receptors (AT₁R and AT₂R, respectively). The AT₁R interaction results in vasoconstriction (note it causes vascular damage if excessively activated) [8]. Additionally, Ang II activates aldosterone secretion, encouraging sodium reabsorption and increased blood pressure.

Roles of ACE2

Angiotensin-converting enzyme 2 (ACE2) is an enzyme that is attached to the cell membranes in tissue cells in the lungs, arteries, heart, kidney, and intestines. ACE2 lowers blood pressure by catalyzing the hydrolysis of angiotensin 2 (a vasoconstrictor peptide) into angiotensin 1. ACE2 counters the activity of the related angiotensin-converting enzyme (ACE) by lowering the amount of angiotensin-II and increasing Ang, making it a promising drug target for treating cardiovascular diseases [8,9]. ACE2 is profusely present on the cell surface of alveolar type II epithelial cells (type II pneumocytes), lying in close vicinity to pulmonary capillaries and is responsible for the making of alveolar surfactant. Various well-conducted studies in animal models and humans have led to strong hypothesis that a diminished ACE2 activity may lead to unopposed activity of Ang II-AT₁R axis, leading to progression of microvascular damage and cardiovascular disease. On the contrary, enhanced ACE2 activity may have protective role against microvascular damage owing to its antihypertrophic, antifibrotic, and anti-inflammatory properties [6-9].

Renin angiotensin system pathway, virus and lung damage

The coronaviruses implicated in severe acute respiratory syndromes, such as SARS-CoV-2, can frequently lead to interstitial pneumonia. This damage is expeditiously linked with the involvement of both capillaries and lung interstitium. Alveolar epithelial injury is the initial and critical step towards development of interstitial pneumonia in humans, especially in the context of SARS coronaviruses involvement. As the inflammatory cascade leads to damaging effects, extensive fibrosis due to secondary hyper stimulation of local fibroblasts can occur, which is thought to be driven by the dysregulation of the local RAS (Renin Angiotensin System) pathways has been found to exert a key role [10].

Imbalance between classic RAS and anti-RAS in context of COVID-19

Imbalance between the classic RAS and ACE2-driven anti-RAS arms presumably foster and expedite lung injury. The ACE-Ang II-AT₁R pathway, mainly when improperly activated, or when there is ACE2 downregulation, results in pulmonary vasoconstriction and microvascular damage leading to enhanced vascular permeability. All this results in leaky pulmonary microvessels and damaged alveoli which are filled with plasma proteins. Moreover, secondary production of inflammatory cytokines, expedited apoptosis in alveolar epithelial cells, and furthering of mesenchymal cell growth and extracellular matrix synthesis-all resulting in lung fibrosis have been manifested [11]. Utilization of various angiotensin receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACE-I), have shown reduction in lung injury in animal models of ARDS [12].

Clinical studies and outcomes

Several retrospective studies regarding the COVID-19 stated that renin angiotensin system (RAS) inhibitors certainly do not pose patients with a higher risk of SARS-CoV-2 infection [1,13]. They were also of the view that treating subjects with ACE-I/ARB has no effect on duration and outcomes in terms of severity of symptoms of COVID-19 [13-16]. In one study over 1000 Chinese hypertensive patients it was revealed that there was a notably reduced risk of death in those patients who were taking ACE-I/ARB as compared to other anti-hypertensive medications [19-20]. On the other hand there were also some studies that found no correlation between COVID-19 death rates and ACE-I/ARB medications [12,18,19]. In a recent meta-analysis it was depicted that subjects taking ACE-I/ARB medications were at 43% lower risk of COVID-19 related mortality as compared to those who did not take ACE-I/ARB [17,18]. Studies have revealed that elder age patients taking ACE-I/ARB therapy had lower risk of death, possibly due to cardiovascular protection and a higher resistance in the face of acute illness during hospitalization [21]. Similar association can explain theoretically use of ACE-I/ARB therapy in COVID-19 patients. Thus, it is evident from the literature collected so far that subjects taking ACE-I and ARB for cardiovascular ailments should follow compliance with their prescribed medications even in the face of the COVID-19 pandemic [8,9].

Obesity, RAS pathway and COVID-19

As mentioned earlier, obesity is considered as one of the major risk factors for contracting severe COVID-19 course that may lead to death even in younger patients without comorbidities [22]. Obese patients have a higher risk of critical care admission and need of invasive mechanical ventilation [23,24]. Obesity is a risk factor for coronary heart disease, heart failure and chronic kidney disease [25,26]. The phenomenon of renin angiotensin system (RAS) dysregulation in obese patients is an established fact. Moreover, adipose tissue has role in upregulating RAS activity not only locally but also systemically [27]. All this leads to obesity-related hypertension [28].

Other than obesity, the male gender has been linked with an unfavorable COVID-19 course and a much greater demand for intensive care, when compared with the female gender [29,30]. In one study more than eighty percent of the COVID-19 patients shifted to intensive care units were males [31-33]. This might be explained by the fact that obese women have more subcutaneous than proinflammatory visceral adipose tissue, and adipocytes are smaller, more lipogenic and insulin sensitive compared to obese males [32-36].

Lessons learnt about role of ACE-I and ARB medications in COVID-19 era

Based on the given information in literature related to COVID 19 so far, ACE-I and ARB medications should be continued as they are mainstay treatment not only for hypertension but also for heart failure management. The balance between RAS pathways in the lung is probably of cardinal importance in the genesis and promotion of acute lung injury, however it is still not a completely understood phenomenon as it is quite a complex process, and as such more studies related to humans are required in the future. There should still be a cautious and judicious approach and one should avoid suppositions on the a negative connection between renin angiotensin system (RAS) blockers and COVID-19. We cannot fully justify these correlations based on present limited knowledge in this regard. In summary, hypertensive patients, having cardiovascular diseases such as heart failure, should continue compliance with these drugs. However, the utilization of ACE-I or ARB with a primary aim of COVID-19 prevention or reduction of disease severity is still debatable despite some encouraging observational findings in recent literature. Hence, in patients having cardiovascular diseases, renin angiotensin system (RAS) blockers may be beneficial in current pandemic but a pragmatic and cautious attitude is required regarding their usage for modulation of clinical course in COVID-19.

Conclusion

In last year of the COVID-19 challenge there have been numerous trials to modulate the course of COVID-19. Many drugs have been tried including antimalarial drugs, low-molecular-weight heparin, monoclonal antibodies against many different interleukins to counter the cytokine "storm" and the renin angiotensin system (RAS) blockers. However, more evidence based human studies are required for discovering more effective therapies for COVID-19.

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