Protective role of ACE inhibitors and ARBs in hypertensive patients suffering from COVID-19

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Abstract

There is a renewed interest in the Renin-angiotensin system (RAS) as the coronavirus SARS-CoV2 enters the human body through the host ACE2 receptor. The infection is associated with down regulation of ACE2 leading to the imbalance in the RAS. We provided mechanistic insight on immunopathology of COVID-19 with respect to innate immune activation and ensuing adaptive immune response resulting in production of viral antigen-specific antibodies. The mini-review tries to drive home the anti-inflammatory role of ACEI/ARBs as an attractive treatment option in hypertensive or heart failure patients suffering from COVID19. The hypothesis is based on the available evidence of favorable immuno-mechanistic and clinical outcome data. The review tinkers with the immuno-mechanistic pathway with a probable role type I IFN response in case of SARS-CoV2, which is not yet clear. The review interconnected the role of principal players involved in RAS such as Angiotensin-converting enzyme (ACE), ACE2, decapeptide angiotensin I (ANG I), octapeptide angiotensin II (ANG II), heptapeptide angiotensin-(1–7), nonapeptide angiotensin-(1–9), ACE inhibitors (ACEI), AT1R blockers (ARBs) with respect to cardiovascular physiology and pathology.

Introduction

The recent Coronavirus Disease (COVID-19) pandemic that had emerged during the last week of December 2019 in Wuhan, China and spread quickly among 210 countries with more than 2.5 million affected with a mortality of approximately 3·7% (WHO et al.,2020). COVID-19 is classified in three segments according to the clinical features; mild, moderate and severe. The data from around the world suggests that patients with specific co-morbidities like hypertension, diabetes, COPD, cardiovascular disease or kidney problems are mostly affected and have poor clinical outcomes. It can be stated that the patients with multiple complications are worst affected (Guan et al., 2020).

There is a renewed interest in the Renin-angiotensin system (RAS) amidst the ongoing pandemic of SARS-CoV2 infections or the Coronavirus Disease-19 (COVID-19). The novel coronavirus (SARS-CoV2) enters the human body through interaction of the viral Spike protein with the host ACE2 receptor, which is associated with down regulation of ACE2. On the contrary, present data have shown that hypertensive patients treated with (ACE inhibitors) ACEI/ARB (Angiotensin II receptor blockers) have elevated expression of ACE2 (Focosi et al., 2020; Ferreario et al., 2005; Furuhashi et al., 2015). Thus questions arise on whether the use of ACEI or ARBs in the hypertensive patients or patients with other comorbidities has any impact in treating COVID-19? or should the COVID-19 infected individuals continue taking these drugs, because discontinuation of these drugs may be associated with worsening of the hypertensive co-morbidity.

RAS has primarily regulatory role in cardiovascular physiology and pathology (Kuba et al., 2006). Angiotensinogen, the renin substrate, is hydrolyzed by renin to form decapeptide angiotensin I (ANG I, Figure

1). Angiotensin-converting enzyme (ACE) is responsible for converting ANG I to octapeptide angiotensin II (ANG II), which binds to angiotensin II receptor 1 (AT1R) and causes multiple biological functions such as vasoconstriction and vascular remodeling. Inhibition of ACE through ACE blockers results in partial inhibition of the formation of ANG II. ACE2, a homologue of ACE, hydrolyzes a single amino acid residue from ANG I to form angiotensin-(1–9) (WHO et al., 2020) and also can convert ANG II to vasodilator heptapeptide angiotensin-(1–7) through elimination of single residue phenylalanine. ACE2 and ACE jointly regulates vasodilator and vasoconstrictor functions to maintain the homeostasis of blood pressure. Both ACE and ACE2 are mainly found in lung, kidney, heart, pancreas and blood vessel tissue. Studies have shown that ACE2 protects from lung injury and reduce the risk of pneumonia (Imai et al., 2005; Henry et al., 2018).ACE inhibitors (ACEI, such as captopril, lisinopril, enalapril etc) or AT1R blockers (ARB, such as valsartan, losartan, telmisartan, olmesartan etc.) exhibits beneficial effect for the treatment of hypertension.

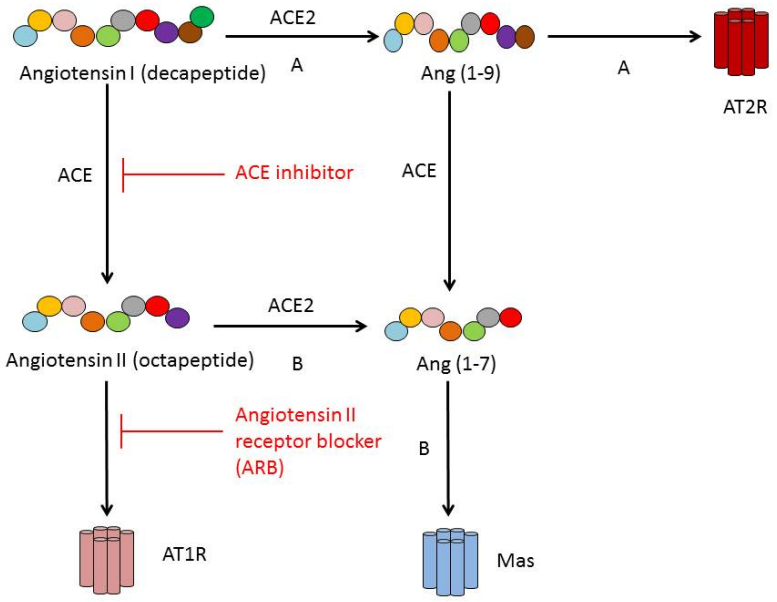

Figure 1: Renin Angiotensin system (ACEI and ARB inhibitor and proposed pathway)

ANG II and COVID-19.

Hitherto accumulated evidences suggest that upon infected with SARS-CoV-2, the ACE2 is downregulated and as a result the ANG II level goes up in a feed-back mechanism to form Ang (1-7) and Ang (1-9) is disrupted (Vaduganathan et al., 2020). Previous studies have shown that elevated ANG II level promotes inflammation and is associated with lung injury and positively regulating the cytokine production by the activation of AT1R (Kuba et al., 2006; Wang et al., 2012). Angiotensin II can induce oxidative stress through production of reactive oxygen species (ROS) via the nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase causing oxidative stress (Guzik et al., 2007). It has been shown that a number of COVID-19 patients in the high risk group suffer from severe lung injury associated with increase in plasma ANG II level (Liu et al., 2020a).

Immunopathology of COVID-19.

Upon infection of the receptor-bearing host cells, viz. type 2 lung epithelial cells, nasal epithelial cells, gut enterocytes etc., the virus is expected to induce a type I interferon (IFN) response. The type I IFN response from the infected epithelial cells are assumed to be due to cytosolic RNA sensors like RIG-I. Nucleic

acid-driven endosomal Toll-like receptor (TLR) activation in plasmacytoid dendritic cells (pDCs) and type I IFN induction has been shown to play central pathogenetic role in several systemic autoimmune diseases as well as in different components of metabolic disorders (Ganguly et al., 2018). Whether RNA-recognizing toll-like receptors, viz. TLR7 and TLR8, present primarily in plasmacytoid and conventional dendritic cells respectively, are also involved in the type I IFN response in case of SARS-CoV2 infection is not yet clear. But one report suggests considerable muting of type I IFN induction from the lung epithelial cells in response to SARS-CoV2 (Blanco-Melo et al., 2020). Apart from the viral RNA, danger signals released by stressed or dying host cells should also play a role in the innate immune activation. The ensuing adaptive immune response, following the innate immune activation, is primarily driven by the viral-antigen-specific T cells, which are presented with viral antigens by dendritic cells and macrophages. While SARS-CoV2-specific CD8+ cytotoxic T cells will be directed to kill the infected host cells to prevent virus replication to continue unabated, the CD4+ helper T cells will provide help to SARS-CoV2-specific B cells in mounting a humoral response , producing viral antigen-specific antibodies. In chronic viral infections, CD8+ T cells have been shown enter a stage of exhaustion. The recent data suggest that both CD4+ and CD8+ T cells in severe cases with COVID-19 are significantly below the normal levels, although the mechanism underlying this is far from clear. Evidences suggest that the severe COVID-19 patients experience a hyperimmune response due to high levels of proinflammatory cytokines such as MCP1, IL1-β, MIP1- α, IL-2R, IL-7, IL-8, IL-9, IL-10, IFNγ and TNFα production, dubbed the much talked about 'cytokine storm', which lead to inadvertent host tissue damage, and multi-organ involvements leading to untoward outcomes (Mehta et al., 2020; Li et al., 2020a).

Insights from Clinical Trial

At present many clinical trials are listed in the WHO's website and clinicaltrials.gov. which are in progress around the world (table 1). One of such study conducted in nine hospitals in Hubei province of China. which recruited total of 3611 patients, showed ACEI/ARB receiving patients had lower risk of COVID-19 mortality than non-ACEI/ARB (Zhang et al., 2020). The incidence of septic shock was also lower in ACEI/ARB group than non-ACEI/ARB group of patients. Another study, done at King's College Hospital and Princess Royal University Hospital, London, UK, recruited total of 205 patients with 51·2% hypertensive patients, 30·2% diabetic patients and 14·6% patients with ischemic heart disease or heart failure, and has shown reduced risk of rapidly deteriorating COVID-19 in the ACE inhibitor-treated patients (Bean et al., 2020).

In yet another study, done at Shenzhen Third People's Hospital, China, a total of 417 patients was recruited (Meng et al., 2020). Among them, 17 patients were categorized in the ACEI/ARB group and 25 patients in the non-ACEI/ARB group. The median number of days from the onset of symptoms to hospital admission was 3.0 in the ACEI/ARB group and 2.0 in the non-ACEI/ARB group. Moreover, ACEI/ARB group of patients had lower IL-6 expression than non-ACEI/ARB group, significantly lower peak viral load during hospitalization and higher CD8+ T cells. Another similar study, from Hubei Provincial Hospital of Traditional Chinese Medicine, China, recruited 462 COVID-19 patients in which 126 (27.2%) patients were hypertensive and 125 were normotensive patients (Yang et al., 2020). Hypertensive patients on ACEI/ARB had a much lower death rate than those on non-ARBs/ACEIs medications. Patients with ACEI/ARB medication had lower concentration of CRP and procalcitonin than non-ACEI/ARB medication, pointing to possible anti-inflammatory effects. In a multicentric study done at Shenzhen Third People's hospital (Shenzhen, China), Renmin Hospital of Wuhan University (Wuhan, China) and Fifth Medical Center of People's Liberation Army General Hospital (Beijing, China), the data showed, among the elderly (age>65) COVID-19 patients with hypertensive co-morbidity, the risk of severe COVID-19 was significantly lowered with ARB administration (Liu et al., 2020b).

More of such studies are still ongoing around the world, which definitely will provide further insights in days to come. These clinical studies have certain limitations such as low numbers of patients were recruited death of patients during medication and are yet to be published post-peer-review. Nevertheless, all these studies have suggested that the usage of ACEI and ARBs was associated with better prognosis in hypertensive patient suffering from COVID-19.

Table 1. Data from clinical trials that are listed in the WHO's website

Analysis by	Place of study	Total no. of patients	ACEI/ARB group divisions	Outcomes
Zhang et al.[16]	Nine Hospitals in Hubei Province of China	Recruited total of 3611 patients; Among which 3430 patients were selected comprising 1128 were hypertensive and 2302 were normotensive (Hypertensive group had comorbidities like diabetes 21.3%, coronary heart disease 11.6 %, chronic renal disease 3.1%)	In the hypertensive group, 188 patients are classified as ACEI/ARB group 940 patients are classified as non-ACEI/ARB group.	Statistical analysis showed, ACEI/ARB receiving patients had low risk of COVID-19 mortality than non-ACEI/ARB. (Mixed effect Cox Model: adjusted HR, 0.42; 95% CI, 0.19-0.92; P =0.03; Propensity score matched analysis+ mixed effect Cox model: adjusted HR, 0.37; 95% CI, 0.15-0.89; P = 0.03; Subgroup propensity score-matched analysis: adjusted HR, 0.30; 95% CI, 0.12-0.70; P = 0.01) Incidence of septic shock was 3.2% in ACEI/ARB group than 8.0 % in non-ACEI/ARB group Disseminated intravascular coagulation (DIC) was 0.0 % in ACEI/ARB group than 2.3 % in non-ACEI/ARB group

Analysis by	Place of study	Total no. of patients	ACEI/ARB group divisions	Outcomes
Bean et al.[17]	King's College Hospital and Princess Royal University Hospital, London, UK	The cohort study recruited total of 205 patients (51.2% hypertensive, 30.2% diabetic and 14.6% ischemic heart disease or heart failure)	37 patients on ACEI and 168 patients on non-ACEI 9 patients on ARB and 196 patients on non-ARB	Statistical analysis (NLP: Natural language processing; informatics tools followed by logistic regression applying Firth's correction) showed ACE inhibitor reduced risk of rapidly deteriorating COVID-19 (OR, 0.29; 95% CI, 0.10-0.75; $P < 0.01$ in patients with diabetes mellitus, ischemic heart disease, heart failure)
Meng et al.[18]	Shenzhen Third People's Hospital, China	The study recruited total of 417 patients in which 51 (12.23 %) were hypertensive. Among which 42 patients met the criteria	Among 42 patients; 17 patients were categorized in ACEI/ARB group 25 patients were non-ACEI/ARB group.	The median number of days from the onset of symptoms to hospital admission was 3.0 in the ACEI/ARB group and 2.0 in the non-ACEI/ARB group. ACEI/ARB group of patients had lower IL-6 expression (<20pg/mL) than non-ACEI/ARB group (>20 pg/mL). The peak viral load during hospitalization in the ACEI/ARB group was significantly lower than that in the non-ACEI/ARB group and CD3+ /CD8+ T cells in the ACEI/ARB group was higher than of non-ACEI/ARB group

Analysis by	Place of study	Total no. of patients	ACEI/ARB group divisions	Outcomes
Yang et al. [19]	Hubei Provincial Hospital of Traditional Chinese Medicine, China	Recruited total of 462 patients. (126 patients (27.2%) had pre-existing hypertension with 30.2% having diabetes, 18.3% having cardiopathy and 125 (27.1%) were normotensive patients	Among 126 hypertensive group; 43 patients were sub categorized in ACEI/ARB group 83 patients were non-ACEI/ARB group	Hypertensive patients on ACEI/ARB had a much lower proportion of critical patients (9.3% vs 22.9%), and a lower death rate (4.7% vs 13.3%) than those on non-ARBs/ACEIs medications Hypertensive patients on ACEI/ARB had a much lower proportion of critical patients (9.3% vs 22.9%), and a lower death rate (4.7% vs 13.3%) than those on non-ARBs/ACEIs medications

Analysis by	Place of study	Total no. of patients	ACEI/ARB group divisions	Outcomes
Liu et al.[20]	1. Shenzhen Third People's hospital (Shenzhen, China) 2. Renmin Hospital of Wuhan University (Wuhan, China) 3. Fifth Medical Center of People's Liberation Army General Hospital (Beijing, China)	Recruited total of 557 patients. (Among 511 patients, 78 patients had hypertension comorbidity); Additional 46 patients were recruited with age >65 yrs. with premedication history of anti-hypertensive drugs	78 patients were categorized as six sub groups (ACEI, ARB, CCB, BB, thiazide and none); 40 patients were categorized as COVID-19 Mild and 38 patients were categorized as COVID-19 Severe Among 46 patients; 18 were categorized as mild and 28 were categorized as severe. Meta-analysis was performed with 70346 ARB patients associated with pneumonia	78 patients shows no statistical significance in disease severity among six sub groups The risk of 28 patients (COVID-19-severe) was significantly lowered in ARB medication in comparison to patients who took no drugs (OR=0*343, 95% CI 0*128-0*916, p=0*025). ARBs were found to be associated with a declined mortality rate for pneumonia (OR=0*55, 95% CI; 0*44-0*69, p<0*01)

Protective role of ACE Inhibitor and ARBs.

ACE2 negatively regulates RAS and counterbalances the effect of ACE. From the previous study, it is known that compared to other classes of antihypertensive drugs, treatment with ACE inhibitors or ARBs leads to significant increase in CD8+ T cell counts in peripheral blood. Additionally, during hospitalization the peak viral load is significantly lower compared to non-ACEI/ARB-treated group (Zhang et al., 2020). Also, both ACEI and ARBs have shown to reduce inflammation by upregulating TGF-β as well as by increasing regulatory T cells (Sepheri et al., 2016; Platten et al., 2009). Previous biological findings have also shown that ACE inhibitors play anti-inflammatory effect by reducing mRNA expression of multiple pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, TNF-α, interferon, and MCP-1, as well as aortic wall IL-8 and MCP-1, thereby reducing vascular inflammation (Kim et al., 2014). ACE inhibitor viz. captopril plays a protective role by reducing the expression of intercellular adhesion molecule-1 in the lung tissue and in the circulating endothelial cells in the blood, block the NF-kB activation and recovery of the fibrinolytic disturbance in lung tissue (He et al., 2007). ARBs viz. losartan treatment has shown significant reduction in pro-inflammatory cytokine (TNF-α, IL-6, and IL-1β production) and improves lung injury (Shen et al., 2009; Li et al., 2015b). Retrospective studies in humans showed that ACEIs/ARBs can reduce the severity of pneumonia (Caldeira et al., 2012; Mortensen et al., 2012). As ACEIs partially block the formation of ANG II, the low level of ANG II has a favorable effect due to low level of proinflammatory cytokines. In turn, pathway A becomes predominant causing increased activity of ACE2 generating Ang (1-9), which ameliorates pulmonary hypertension, improves pulmonary vascular remodeling and has an anti-inflammatory effect (Figure 1, Pathway A) (Cha et al., 2018; Li et al., 2017). Ang(1-9) also plays a protective role by inhibiting infiltration of inflammatory cells and decreasing the level of cytokines in plasma via AT2R receptor, which in turn induces protein tyrosine phosphatase (PTP), IkB (NF-kB inhibitor) and ATF2 transcription factor phosphorylation, as well as JNK, p38MAPK, ERK1/2, and STAT3 dephosphorylation, all of which

have roles in ameliorating pulmonary, cardiovascular and renal inflammation (Cha et al., 2018; Gonzalez et al., 2018).

Other than blocking AT1R, the major protective mechanisms of ARBs also include reduction in pulmonary edema and vascular permeability. ARBs can cause downregulation of proinflammatory cytokines and NFκB pathway with reduction of pro-inflammatory cytokines, chemokines and reactive oxygen species (Saavedra et al., 2020). ARBs can prevent binding of ANG II to the AT1R, thus escalating ACE2 activity; which in turn produces Ang(1-7) and counterbalances the inflammatory activity of ANG II. (Figure 1, Pathway B). Ang (1-7) also has effects, similar to Ang (1-9), in protecting against the inflammatory response mediated by Mas receptor axis in various disease including asthma, pancreatic disease, cardiovascular disease (Santuchi et al., 2019; Yu et al., 2018; Magalhaes et al., 2018; Rodrigues et al., 2017) .Particularly some evidences proved that Ang (1-7) has anti-inflammatory role in mitigating pulmonary disease. Meng et al. reported that ACE-2/angiotensin-(1-7)/Mas axis protects against bleomycin (BLM)-induced pulmonary fibrosis via inhibition of MAP kinase and NF-kB pathway (Meng et al., 2014). Wu et al. also reported protective role by ACE2/ANG (1-7) in bleomycin treated rats (Wu et al., 2014). In a COPD murine model Zhang et al. showed Ang(1-7) protects against pulmonary inflammation and fibrosis (Zhang et al., 2018). Treatment with ARB viz losartan or Ang (1-7) reduced lung inflammation and improved lung function in LPS induced Acute respiratory distress syndrome (ARDS) models in rats (Wösten-van Asperen et al., 2011).It is evident that there are cross-talks between the receptor and peptides which in combination give an anti-inflammatory response and drive vascular remodeling in pulmonary disease.

Unresolved issues

There are also few unresolved issues regarding RAS–COVID-19 interactions. Studies documenting upregulation of ACE2 genetic activity or plasma levels with ACEI/ARB have been predominantly done in animal models. Campbell et al failed to document any increase in Ang (1-9) levels after intravenous ACEI therapy in heart failure patients thus questioning the concept of increased ACE2 activity. A protective role of Ang (1-7) and ACE2 in maintenance of hypertension with prolonged therapy with Captopril is reported. Initially based on such paradoxical reports it was speculated that as hypertensive patients treated with ARBs have elevated expression of ACE2, thus may be more susceptible to COVID-19 infection (Fang et al., 2020). As a preventive measure, a suggestion for withdrawal of ARBs were also made (Fang et al., 2020). But, measurement of plasma and urinary ACE2 levels showed mixed result with most of the studies showed no difference among the patient groups taking ACEI/ARB in various clinical subsets like atrial fibrillation, heart failure and hypertension (Sriram et al., 2020). It has also been suggested that ACE2 can have regulated ectodomain shedding (Jia et al., 2009), thus questioning the very concept of measurement of plasma ACE2 level as the marker of membrane bound SARS-CoV2 ACE2 receptor. Similarly the concept of ACE2 depletion by SARS-CoV2 leading to increased pro-inflammatory Ang II causing lung injury has been shown to reverse with recombinant ACE2 in mouse models (Essig et al., 2020).

CONCLUSION

The anti-inflammatory role of ACEI/ARB offers a very attractive treatment option in hypertensive or heart failure patients at risk or suffering from COVID-19. However it would not be prudent to rationalize clinical usage solely based on mechanistic hypothesis without gathering robust evidence from comprehensive clinical trials. Currently, none of the practice guidelines in cardiology around the globe favors ad-hoc discontinuation of ACEI/ARB in a patient at risk of COVID. On the other hand there is also no compelling data, currently, to recommend introduction of ACEI/ARB into the therapy regimen of COVID-19 patient. However, taking view of the available evidence of favorable immuno-mechanistic and clinical outcome data, continuation of ACEI/ARB in patients of hypertension and heart failure seems to be a more prudent approach, even though they are at risk of or suffering from COVID-19.

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