Commentary

Theoretical Assessment of Therapeutic Effects of Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors on COVID-19

Coronavirus disease 2019 (COVID-19) has a wide spectrum of clinical presentations and the potential to cause damage to multiple organs. Its main target organ is the respiratory system such that even a low level of pulmonary involvement can rapidly lead to acute respiratory distress syndrome in some patients. Decreased lung compliance and hypoxia might cause death due to massive alveolar damage.[1] Extensive pulmonary and systemic inflammation are the key components of this pathological process.[1] Emerging evidence indicates that the renin-angiotensin-aldosterone system (RAAS) is strongly involved in the initiation and propagation of inflammatory responses.[2] Clinical and experimental evidence supporting RAAS involvement in triggering local and systemic inflammatory responses include angiotensin II-induced synthesis of pro-inflammatory cytokines and chemokines, activation of nuclear factor kappa-B, induction of pulmonary epithelial cell apoptosis, and stimulation of fibrotic response by upregulating transforming growth factor-α (TGF-α) expression.[2, 3]

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are among the most prescribed cardiovascular drugs. Their desirable therapeutic efficacy in hypertension and heart failure has been well established. Animal-based studies have indicated that administration of ACEIs or ARBs is associated with an increase in angiotensin-converting enzyme 2 (ACE2) expression.[4] Considering the importance of ACE2, as the target point for COVID-19, there are concerns about the adverse effects of ACEIs/ARBs. However, experimental and/or clinical findings have not corroborated these concerns.

Before the COVID-19 pandemic, several studies confirmed the therapeutic benefits of ACEIs/ARBs on respiratory infections.[5, 6] The findings of some recent studies point to the protective role ACEIs/ARBs may serve against COVID-19-associated respiratory dysfunction.[7, 8] A prospective cohort study using routinely collected data from 8.3 million people showed that administration of ACEIs/ARBs is associated with reduced risks of COVID-19 without a significant increase in the risk of requiring intensive care.[9] Another retrospective cohort study using data from 4,480 patients with COVID-19 also showed that prior use of ACEIs/ARBs was not significantly associated with COVID-19 diagnosis nor with mortality among patients diagnosed with the disease.[10] The same results were obtained in a case-population study by de Abajo and colleagues[11] as well as a population-based case-control study by Mancia and colleagues.[12] Overall, emerging evidence supports the beneficial rather than deleterious effects of ACEIs/ARBs on COVID-19. However, experimental/clinical studies on pharmacological differences between the effects of ACEIs versus ARBs on COVID-19 are scarce. Theoretically, several reasons support superior beneficial effects and desirable pharmacological outcomes of ARBs compared to ACEIs. In this report, we aimed to explore various theoretical aspects of the effect of these RAAS inhibitors on COVID-19.

As shown in figure 1A,[13] ACEIs block the formation of angiotensin II (Ang II) by inhibiting ACE, but do not affect its formation via other ACE-independent pathways such as chymase.[14] An increase in plasma renin concentration, induced by inactivation of a negative feedback loop,[15] leads to the production of Ang II from other pathways, which preferentially activate AT1R followed by undesirable activation of RAAS. ACE2 is not blocked by conventional ACEIs.[13] However, during the administration of ACEIs, escaped Ang II also converts into Ang (1-7) via unaffected ACE2 enzyme that directly stimulates Mas receptors (MasR). Since the conversion of Ang (1-9) into Ang (1-7) is mediated by classic ACE, it seems that the ACEIs reduce net Ang (1-7) generation more than ARBs.[16] On the other hand, despite the expected pharmacological effects, some reports indicate that aldosterone secretion cannot be completely blocked during ACEIs therapy; a phenomenon known as aldosterone escape.[17] As reported in a previous study, this could be theoretically important due to aldosterone-induced ACE2 downregulation.[18] The most common adverse effect of ACEIs is dry cough, a complication induced by increased concentration of protrusive agents like bradykinin due to ACE inhibition.[19] Emerging evidence reinforces the role of kinins in the pathophysiology of respiratory diseases. Bradykinin-induced bronchospasm is mediated directly by bronchial smooth muscle contraction or indirectly by stimulating the inflammatory process.[20] Theoretically, it seems that accumulation of bradykinin does not favor the therapeutic effects of ACEIs on

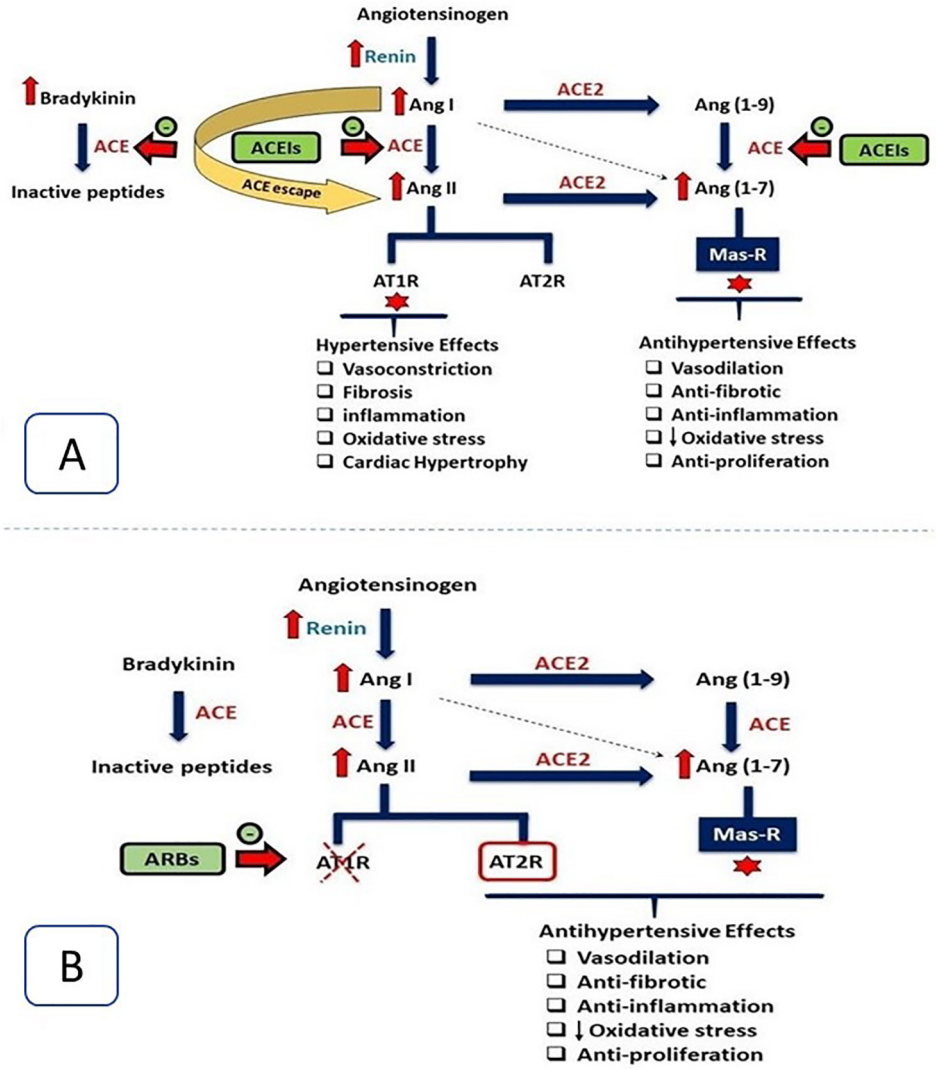

Figure 1: Schematic diagram shows the components of renin-angiotensin-aldosterone system (RAAS) and the effects of RAAS inhibitors. (A) Arrows represent the effects of angiotensin converting enzyme inhibitors (ACEIs) on RAAS components. (B) Arrows represent the effects of angiotensin II receptor blockers (ARBs) on several target points. Ang I: Angiotensin I; Ang II: Angiotensin II; Ang (1-9): Angiotensin (1-9); Ang (1-7): Angiotensin (1-7); ACE: Angiotensin converting enzyme; AT1R: Angiotensin type 1 receptor; AT2R: Angiotensin type 2 receptor; Mas-R: Mas receptor

COVID-19-induced respiratory problems. Therefore, ACEI-induced accumulation of bradykinin could be a putative mechanism, which can intensify COVID-19-induced respiratory distress. Activation of AT1R is responsible for several physiological/pathological processes such as aldosterone secretion, tubular sodium reabsorption, blood pressure elevation, induction of fibrosis, and generation of free reactive radicals.[13] ARBs block RAAS by inhibiting Ang II-mediated AT1R activation, thus effectively inhibiting the above-mentioned mechanisms. AT1R activation is also mediated through Ang II-independent pathways by conformational changes such as mechanical stress;[13] the situation that occurs during ventilator-induced respiratory distress by COVID-19. In this acute condition, activation of the counter-regulatory arm of AT2R could be life-saving.

Similar to ACEIs, ARBs also stimulate renin secretion by inhibiting Ang II negative feedback. Despite the elevation of Ang II level, blockade of AT1R by ARBs leads to the stimulation of AT2R whereby its activation effectively counteracts the pathophysiological effects of AT1R. AT2R activation is the main therapeutic advantage of ARBs over ACEIs. A higher level of Ang II also has a high potential of conversion into a higher level of protectant peptide of Ang (1-7), and consequently activation of MasR (figure 1B). ARBs activate Ang II/AT2R as well as Ang (1-7)/MasR, pathways involved in protective processes such as anti-inflammatory response, anti-fibrosis, and antihypertensive effect.[13] Secretion of aldosterone from the adrenal cortex is mediated through AT1R activation.[21] However, not all ARBs are successful in inhibiting aldosterone secretion. Aldosterone escape by administrating ARBs is dependent

on the structure.[22] Although aldosterone secretion continues during losartan and irbesartan treatment, it is more efficiently blocked with valsartan and candesartan. Aldosterone production via adrenocortical AT1R is mediated by two independent signaling pathways: the production of diacylglycerol/inositol trisphosphate and β-arrestin-1. Effective blockade of both pathways is needed to completely inhibit aldosterone production. While losartan is ineffective in inhibiting the β-arrestin-1 pathway of aldosterone production, valsartan and candesartan are the most potent β-arrestin-1 inhibitors in both in vitro and in vivo studies.[23, 24] Considering the role of aldosterone on the expression of ACE2, this could be another advantage of the therapeutic effect of ARBs, especially the aldosterone blocker types, over ACEIs on COVID-19. Unlike ACEIs, ARBs do not stimulate bradykinin accumulation. In theory, besides the lower risk of adverse effects, ARBs are not involved in bradykinin-induced respiratory distress; an acute complication of COVID-19.

Some studies have compared the anti-inflammatory properties of ACEIs and ARBs in different medical conditions. As reported by Lai and colleagues, ARBs were associated with a lower risk of severe exacerbations, pneumonia, and mortality in COPD patients compared to ACEIs.[25] This could be explained theoretically by the activation of Ang II/AT2R as well as MasR and consequently amelioration of the inflammation. In addition, bradykinin-mediated pulmonary edema induced by ACEIs is not beneficial for extensive inflammation and acute cytokine storm involved in COVID-19.[26]

Considering both the theoretical aspects and previous clinical and experimental results, attention should be paid to some important differences between the therapeutic effects of ARBs and ACEIs, especially on COVID-19-associated acute respiratory syndrome. Theoretical justifications are in favor of using ARBs over ACEIs in the case of COVID-19. Considering distinctive pharmacodynamic differences among ARBs, it seems that aldosterone blockers (e.g., candesartan and valsartan) have the preferred therapeutic benefit. This hypothesis requires further clarifications through preclinical and clinical studies.

Conflict of Interest: None declared.

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