ABSTRACT

Overactivity of the renin–angiotensin–aldosterone system (RAAS) is a consistent feature of COVID-19 as indicated by high concentrations of angiotensin II (Ang II) in lungs and other tissues. Virus-induced downregulation of angiotensin-converting enzyme-2 (ACE2) explains the raised Ang II levels. Available evidence points to the crucial role of Ang II in the pathogenesis of coronavirus disease. The proinflammatory, immune stimulant, and procoagulant effects exhibited by the peptide at high tissue levels explain lung injury, a characteristic feature of severe COVID-19.

Angiotensin II (Ang II) inhibitors (both the angiotensin-converting enzyme inhibitors (ACEIs) and the angiotensin receptor blockers (ARBs)) constitute the logical therapy for established COVID-19 infection. While ACEIs help to lower Ang II levels in the tissues, ARBs antagonize the effects of the peptide on the target tissues. Of the two, ARBs offer a better choice because of the minimal adverse effects of dry cough and angioedema. The effectiveness of Ang II inhibitors in COVID-19 is well supported by their protective effect against lung injury in animals induced by the virus spike protein as well as the clinical improvement of shortened hospital stay and reduced mortality in observational studies in humans.

A unique feature of these agents is that mutations of the coronavirus 2 (CoV-2) would have little impact on their effectiveness since they do not interfere with the host cell entry of the virus or its replication. Expectedly, the agents might retain their usefulness against variant strains, including "ο" and its subvariants. The overall safety of Ang II inhibitors has been well established beyond doubt since they have been in use for years in the management of cardiovascular (CV) diseases, diabetes mellitus, and chronic kidney disease (CKD).

Regular use of ARBs in all patients who are COVID-19 positive and symptomatic (mild, moderate, or severe) offers a good option worth serious consideration.

MECHANISM OF ACTION OF ANG II

The active moiety of the RAAS exerts all its effects, both physiological and pathological, through the activation of angiotensin II type 1 (AT-1) receptors.

ANGIOTENSIN II (ANG II)

Inhibitors of Ang II [both the angiotensin-converting enzyme inhibitors (ACEIs) and the angiotensin receptor blockers (ARBs)] constitute the logical and the most specific therapy for established COVID-19 infection. While ACEIs help to lower Ang II levels (Fig. 1) in the tissues, ARBs antagonize the effects of the peptide at high tissue levels explaining raised Ang II levels.

ANGIOTENSIN-II PLAYS A PATHOLOGICAL ROLE

Besides the conventional effects of vasoconstriction and aldosterone release, Ang II is known to exert proinflammatory and procoagulant effects at high levels found in disease states. The peptide also causes immune stimulation, endothelial dysfunction, and increased oxidative stress. Increasing evidence points to a crucial role of Ang II in the pathogenesis of coronavirus disease. Damage to the lungs leading to pulmonary edema and acute respiratory distress syndrome (ARDS) are characteristic features of severe infection (see below).

ANGIOTENSIN-CONVERTING ENZYME-2 (ACE2) IS THE CRUCIAL LINK

The ACE2 constitutes the crucial link between the SARS-Cov-2 virus and the host RAAS. The molecule appears to play a dual role. While it is a negative regulator of the RAAS in the host by degrading Ang II, it facilitates virus entry into the host cells by serving as the receptor for the virus spike protein. Regulation of Ang II levels—in normal conditions, tissue Ang II levels are regulated by two enzymes, ACE and ACE2, the former catalyzing its formation and the latter its degradation.
of the peptide at the tissue level. Of the two, ARBs offer a better choice because of the minimal adverse effects of dry cough and angioedema.

Sun et al., Gurwitz, and Hanff et al. had earlier expressed support for the use of RAAS inhibitors in COVID-19-associated pneumonia.

**COVID-19—Infectivity and Pathogenesis**

**Infectivity**

**Virus Entry into Host Cells**

The entry process involves the following steps:

1. Binding of spike protein S of the virus to the ectodomain of the ACE2 receptor (ACE2-R) removal of the ectodomain and its release into the circulation (ACE2 shedding)
2. Fusion of viral envelope with the host cell membrane
3. Internalization of the virus-receptor complex
4. Release of viral RNA into the host cell cytosol and degradation of ACE2-R (Fig. 2).

**Down-regulation of ACE2 and Enhanced Ang II Levels**

Internalization with subsequent degradation results in a decrease in the number of receptors on the cell surface. The host cell thus loses one receptor molecule with the entry of each virus particle. This is the most crucial aspect of the coronavirus infection and has been corroborated by all the studies.

The ACE2 down-regulation leads to an increase in tissue levels of Ang II since ACE2 is also the enzyme for Ang II degradation.

**Pathogenesis of Lung Injury**

**High ACE2 expression in Lungs**

Lungs constitute the prime target for coronavirus. ACE2-R is expressed in abundance in the lungs, especially in the epithelial cells of alveoli (pneumocytes type II) and endothelial cells of alveolar capillaries. Direct exposure to the external environment and the large surface area of these cells explain the high vulnerability of lung tissue. This also indicates the main route of virus entry.

**Angiotensin II Plays a Crucial Role**

The Ang II levels are significantly raised in the lung and other tissues in patients infected with COVID-19. Studies using various animal models of lung injury have demonstrated severe inflammatory lesions in the lungs, which appeared to be mediated by Ang II. In a landmark study, Kuba et al. demonstrated that the isolated spike protein of the coronavirus caused down-regulation of ACE2 with a concomitant increase in Ang II in the lungs and precipitation of severe inflammatory lesions and that Ang II inhibitors attenuated these lesions.

**Progressive Diffuse Alveolar Damage**

Elevated levels of Ang II in COVID-19 cause all-round depletion of pneumocytes, together with damage to capillary endothelium. Thickening of the alveolar-capillary membrane decreases surfactant production, and the formation of fibrin exudates causes a decrease in the elasticity of the lungs and impaired gas exchange. The resultant alveolar damage manifests as pneumonia, ARDS, and respiratory failure.

**Beneficial Effects of ARBs in COVID-19**

Studies using animal models and cell lines on Vero cells of monkeys indicate that Ang II inhibitors exert a protective effect on lungs from severe forms of injury induced by CoV-2. Retrospective/observational studies in humans corroborate this point.

**Animal Studies**

Kuba et al. showed that blockade of AT-1 receptors by losartan attenuates pulmonary edema and lung damage in mice induced by injection of Spike-Fc protein of SARS-CoV. Interestingly, ARBs exhibited the same protective effects in animals against lung injury induced by exposure to other stimuli, including oleic acid and lipopolysaccharide. Moreover, the severity of lung injury induced by influenza H7N9 virus was markedly reduced by the blockade of angiotensin receptors, indicating that activation of the RAAS is crucial in all forms of lung injury.

**Human studies (Observational Studies in COVID-19-infected Patients)**

In this regard, four studies have revealed significant improvement in clinical outcomes with the use of Ang II inhibitors. The study subjects (716 in all) were patients with hypertension already on Ang II inhibitor therapy and hospitalized for COVID-19. The most recent ongoing clinical trial, in its interim report, shows that telmisartan, in addition, shortened hospital stays.

Improvement in the clinical outcomes has been shown by either a decrease in the severity of clinical manifestations, a reduction in lymphocyte count and inflammatory markers, or a reduction in 28-day all-cause mortality.

**Beneficial Effects on Comorbidities**

Hypertension, cardiovascular (CV) conditions, diabetes mellitus, and chronic kidney disease (CKD) constitute important comorbidities for COVID-19 and are well known to contribute to the severity of the latter.

The ARBs and ACEIs have established benefits in protecting the myocardium and kidney; they reduce mortality in CV disease while ensuring system stability and also delay disease progression in CKD and diabetic nephropathy. Abrupt withdrawal of these drugs in these patients is certain to adversely affect the preexisting comorbidities and enhance the risk of clinical decompensation. As Vaduganathan et al. have stressed, RAAS inhibitors should be continued in patients in otherwise stable conditions when they get infected with COVID-19.

**Special Advantages over Antiviral Agents**

As it stands today, Ang II inhibitors (ARBs and ACEIs) offer the most specific form of therapy in the clinical management of the disease in COVID-19-infected patients since they act to interfere with disease progression by lowering tissue levels of Ang II, the peptide responsible for organ damage. Moreover, mutations of the CoV-2 would have little impact on the effectiveness of these drugs since they do.
not interfere with viral replication. This factor could be applicable to the latest variants, “6” and “ο.”

**Safety Profile of ARBs**

**Overall Safety: Excellent**

Ang II inhibitors have been in use for years in the management of CV diseases, diabetes mellitus, and CKD, and their overall safety has been well established beyond doubt. No serious adverse effects have been reported so far. Common problems include dry cough, angioedema, hypotension (with the ACEI group), and hyperkalemia.

**Safety in COVID-19 Patients: Concern does Exist, but Misplaced**

Many healthcare providers appear to harbor serious concern about the potential for enhanced severity of the disease and mortality following the use of Ang II inhibitors.

**Position Statement of Scientific Societies**

Settling the uncertainty in this regard, scientific societies have come out with statements allaying such apprehensions. In a joint statement released in March 2020, the American College of Cardiology, American Heart Association, and the Heart Failure Society of America advised clinicians against discontinuing the use of Ang II inhibitors in COVID-19 patients. The position also got the support of other academic bodies, including the International Society of Hypertension, European Society of Hypertension, European Society of Cardiology, Canadian CV Society, Canadian Heart Failure Society, and International Society of Hypertension. This has certainly helped to provide some reassurance to healthcare providers. Most clinicians, however, remain confused since the opinions expressed by the societies are quite guarded and with a certain degree of caution, the only exception being that of the Council on Hypertension of the European Society of Cardiology.

**The Scientific Brief Issued by WHO**

The note, released in May 2020, summarizes the most recent evidence on the impact of ACEIs or ARBs on severe acute respiratory illness due to SARS-CoV-2. A rapid review of 14 studies was carried out using Ovid Medline and the Cochrane Database as well as the WHO database of COVID-19 publications. The review concluded that ACEI or ARB use was not found to be associated with increased severity of COVID-19 illness.

**Studies in Human Subjects on Safety**

**Published Studies Have Provided Evidence for the Safety of ARBs/ACEIs in COVID-19 Patients: Retrospective Studies**

The subjects were mostly patients with hypertension (a handful having cardiac problems) who were hospitalized for COVID-19, with a majority of them on RAAS inhibitors or other antihypertensives on admission. The study involved a total of 362 patients, 163 on Ang II inhibitors therapy.

Population-based studies covered a very large number of COVID-19 patients drawn from different geographical areas, including Denmark, Italy, Spain, South Korea, and the city of New York. Each study worked with the official Administration Registries of the population concerned. Taken together, the five studies pertain to 5,686 patients drawn from five different communities. These patients were already on ACEI/ARB therapy at the time of hospitalization with COVID-19.

The results of these studies provide convincing evidence that ACEI/ARB therapy does not enhance susceptibility to or increase the severity of COVID-19. The 30-day mortality rate also did not differ significantly from those not receiving ACEI/ARB therapy.

**Concluding Remarks**

As Curfman observes in his editorial in JAMA, these studies on such large patient samples should lay to rest concerns about the use of these drugs in patients with or at risk of COVID-19.

**Current Status: Ang II Inhibitors Do Not Find a Place in COVID-19 Therapy: Why?**

It is quite surprising that neither ARBs nor ACEIs have been officially approved for use in COVID-19 management, irrespective of all the plus points, including effectiveness, safety, and a sound basis for their use. Uncertainty also continues to exist as to whether individuals on these drugs could continue with them or should stop their use once they become infected with the SARS-CoV-2.

The answer to the question appears to be the presumed risk of worsening the disease condition and enhancing mortality. The argument runs on the following lines:

- The ACE2 molecule constitutes the gateway for the host cell entry of coronavirus. Ang II inhibitors could arguably promote virus entry through overexpression (upregulation) of the ACE2 and increase the viral load in tissues. The enhanced viral load could increase the severity of the disease and mortality. This is more so that many patients with comorbid conditions would be on therapy with Ang II inhibitors. Generally, these assumptions are sufficient to raise serious apprehension about their use in patients infected with COVID-19. However, a detailed analysis of available facts disputes such an argument.

**Angiotensin-converting Enzyme-2 Receptor (ACE2-R) Overexpression (Upregulation)**

Overexpression of receptors as such is a well-established state of an enhanced number of the receptors and is intended to maintain routine tissue function in the face of an adverse situation. This usually occurs in the absence of an endogenous ligand or with the use of a receptor antagonist.

The points to be considered in this regard are:

- Does ACE2 overexpression occur with the use of Ang II inhibitors?
- Could this phenomenon enhance virus entry?

**Angiotensin-converting Enzyme-2 (ACE2) Overexpression and ARB/ACE Use**

The idea of upregulation of ACE2 arose from a few studies in mouse/rat and had caught undue attention from scientists and clinicians. However, neither is this concept logical nor is it supported by concrete evidence. It remains mere speculation. Many scientists concur that “ACE2 upregulation is a possibility, but not the real fact,” evading a clear-cut position. According to Danser et al., current data are not sufficient to conclude that RAAS inhibitors facilitate virus entry into cells by ACE2 overexpression. Whereas Perrotta et al. consider as highly hypothetical the issue of increased receptor availability in the lungs from exposure to RAAS inhibitors.

**A Critical Analysis of Available Data on ACE2 Expression**

A point that is beyond dispute is that the binding of the virus molecule leads to a decrease in the receptor number downregulation. The receptor molecule gets lost from the cell surface due to internalization and lysosomal degradation (see viral entry). The fear of enhanced ACE2 expression by Ang II inhibitors is thus unconvincing.
Studies on Humans

The study by Milne et al. involved the estimation of levels of both ACE2 and ACE genes from lung tissue. More than 1,000 samples were obtained from the Human Lung Tissue Expression Quantitative Trait Loci Study. Whereas ACE1 use decreased the expression of both ACE2 and ACE genes, ARBs were devoid of any effect on the expression of any of them. Increased risk of COVID-19, if any, is thus not related to upregulation of ACE2. This study is exceptional in that it recorded ACE2 levels in tissues (lungs). A few other studies performed on patients with comorbidities such as CV conditions, CKD, or diabetes mellitus monitored soluble ACE2 levels in plasma or urine samples. Here again, there is no indication of any overexpression of ACE2 protein by ARBs or ACEIs. It is to be noted, however, that levels of soluble ACE2 are not true markers of RAAS activity.

Studies on Animals

Data are confusing, even though a majority of studies in animals rule out overexpression of ACE2 following administration of ARBs. Four studies relate to ACE2 expression in lung tissue in response to different stimuli, including SARS-CoV Spike protein, whereas a few other studies involved cardiac and renal tissues. In these studies on animals, basal levels of ACE2 were lower than normal due to exposure to the applied stimuli or others, and these levels had been restored to normal by ARBs. This obviously could mean only an apparent overexpression since ACE2 levels in control animals remained largely unchanged. Of course, as mentioned earlier, three studies by Ferrario et al., Ishiyama et al., and Karam et al. did demonstrate upregulation with the use of ACEIs/ARBs, which had triggered confusion and apprehension concerning their safety.

Data from animal studies may not corroborate fully with the effects of ARBs on Ang II inhibitors in humans. All the studies on animals mentioned above were conducted in rodents (rats/mice). Significant variations in ACE2 molecules have been reported among human and animal species and in animals themselves. ACE2 of human/rhesus monkeys exhibited the highest, while that of the rat/mouse showed the lowest receptor activity. Overexpression and Enhanced Virus Entry

Even if increased expression of ACE2 does occur, this need not enhance virus entry into the host cell cytoplasm. Cellular access requires additional downstream steps, such as virus S-protein priming, internalization, etc., that are unlikely to be affected by ARBs or ACEIs.

Conclusion

Therapeutic options are very limited in patients infected with COVID-19. Currently, antivirals such as remdesivir, systemic dexamethasone, and therapeutic antibodies, including tocilizumab and bebetolovimab are the drugs approved for the treatment of COVID-19-infected persons.

Remdesivir acts by interfering with viral replication inside the host cell. WHO recommends the use of remdesivir in patients in the early stage of the disease and who require minimal supplemental oxygen. The organization advises against initiating monotherapy with the drug in those who require mechanical ventilation. In fact, evidence for its effectiveness in COVID-19 is still unconvincing. Corticosteroids, as well as antibiotics, act by suppressing the inflammatory damage to the lung tissue. Dexamethasone is recommended specifically for use in hospitalized persons on mechanical ventilation. Tocilizumab is an add-on agent in patients not responding satisfactorily to dexamethasone.

The action of ARBs resembles that of steroids and tocilizumab in blocking the proinflammatory and immune-stimulant effects of cytokines in coronavirus disease, though the molecular mechanism might be different.

A detailed perusal of the literature and in-depth analysis of studies reveal that Ang II inhibitors, both receptor blockers and ACEIs, constitute useful therapeutic agents in COVID-19. These agents are the most specific for COVID-19 management since they target the Ang II peptide involved in tissue damage. Their effectiveness is well supported by clinical improvement, shortened hospital stay in human studies, and protection effect against lung injury in animals induced by virus spike protein. The safe use of these medicines in COVID-19-infected individuals has been established in many retrospective and epidemiological studies. ARBs are being used on a regular basis in hypertension, heart failure, diabetes mellitus type II, and CKD, and this reflects their excellent record of safety. Since these disease states also constitute important comorbidities associated with COVID-19, ARBs can be continued without hesitation in COVID-19-infected patients. ARBs are easily available, cheap, and orally effective. In contrast, remdesivir and therapeutic antibodies are immensely costly and need to be injected. Thus, there are compelling reasons for advocating routine use of ARBs in all patients who are COVID-19 positive and symptomatic (mild, moderate, or severe).

Angiotensin receptor blockers (ARBs) score over ACEIs as first-line agents considering the minimal frequency of common adverse effects of dry cough, angioedema, and hypotension.

The author contends that Emergency Use Authorization could very well be granted for the use of ARBs in the management of COVID-19, a situation of global emergency.

References

COVID-19 Therapeutics


