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Angiotensin receptor blockers and COVID-19

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**ABSTRACT**
Angiotensin Receptor Blockers (ARBs) exhibit major pleiotropic protecting effects beyond their antihypertensive properties, including reduction of inflammation. ARBs directly protect the lung from the severe acute respiratory syndrome as a result of viral infections, including those from coronavirus. The protective effect of ACE2 is enhanced by ARB administration. For these reasons ARB therapy must be continued for patients affected by hypertension, diabetes and renal disease, comorbidities of the current COVID-19 pandemic. Controlled clinical studies should be conducted to determine whether ARBs may be included as additional therapy for COVID-19 patients.

Dear Editor,

Since recent publications [1,2] that have extended to social media, have questioned the therapeutic use of Angiotensin Receptor Blockers (ARBs) for the treatment of cardiovascular, kidney and metabolic disorders that may become comorbid with COVID-19, it is important to summarize the reasons why ongoing ARB treatment for these diseases may not be discontinued, and must be maintained during the development of this disease.

Angiotensin AT1 receptors (AT1R) stimulation is the major mechanism driving not only the circulatory but also the local Renin-Angiotensin Systems (RAS) [3–5], involved in the regulation of multiple functions in most organs including the lung. Increased RAS activity with enhanced AT1R stimulation is a major injury factor affecting the brain, the cardiovascular and renal function, lipid and glucose metabolism, the immune system, and more to the point, inflammatory lung disease [3].

ARBs, that effectively block AT1R and were initially developed to treat hypertension, exhibit unique pleiotropic protecting effects beyond their antihypertensive properties [3–5]. ARBs directly reduce inflammation, organ fibrosis and endothelial injury, protect mitochondrial function, maintain insulin sensitivity and energy metabolism, protect lipid metabolism and normalize the coagulation cascade, properties considered to benefit patients with acute critical disorders [3–5] (Table 1). For these reasons, ARBs are successfully used not only as first line antihypertensives but also for the treatment of diabetes, kidney disease, congestive heart failure and cerebrovascular disease.

A major beneficial effect of ARBs is their capacity to reduce inflammation and endothelial and epithelial dysfunction in many organs. ARBs directly protect the lung endothelial barrier integrity of the lung disrupted by acute injury including that produced by many viruses [5]. There is substantial clinical evidence of direct effects of ARB treatment, thus protecting the lung from severe injury associated to pneumonia, sepsis and influenza [5]. Mortality was reduced in patients who were treated with ARBs for cardiovascular disorders and later hospitalized for pneumonia [5]. Cerebral malaria also presents with endothelial dysfunction, enhanced proinflammatory cytokine production and enhanced coagulation and complement activation, and in a rodent model, addition of ARBs to the therapeutic arsenal was reported to reduce mortality [5]. In addition, it appears that treatment with ARBs dramatically reduced mortality during the Ebola outbreak in Africa, although these reports have not been fully validated [5].

Fang and colleagues [1] and Diaz [2] hypothesized that patients treated with ARBs may be at a higher risk of developing severe and fatal complications when infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, responsible for COVID-19). They recommend, as a preventive measure, to withdraw ARBs from the therapeutic arsenal to treat ongoing cardiovascular, kidney and metabolic disorders, possible COVID-19 comorbidities. These authors base their recommendation on the demonstration that ARB administration increases expression of ACE2, a receptor for SARS CoV and CoV2. The authors hypothesize that increased expression of the receptor would enhance viral uptake. Although without scientific evidence, the authors predict that ARBs may also enhance viral uptake and facilitate infection with SARS-CoV-2 [1,2].

Diaz [2] supports his recommendation on the basis of the analysis of 1099 Chinese patients infected with SARS-CoV-2, reporting more severe outcome, including death, in patients suffering from cardiovascular and kidney disorders and diabetes, that “most likely” were treated with ARBs. However, analysis of this report [2,6] revealed that the study did not address the use of ARBs in these patients. Data for previous ARB use in patients later infected with SARS-CoV-2, compared with frequency of ARB use in the general population suffering from cardiovascular disorders is not currently available.

Furthermore, the argument that children may be protected from COVID-19 because they develop cross-protective antibodies from infections with the common cold alpha coronavirus [2] has no scientific basis, since this association has never been demonstrated. The statement that children may be protected from SARS-CoV-2 infection because their ACE2 is reduced with respect to that of the elderly is erroneous; ACE2 protein and enzymatic activity decline postnatally [3]. More importantly, in the elderly there is lower ACE2 expression and enhanced Angiotensin II proinflammatory effects [6]. This information supports the hypothesis of a protective effect of ARBs in older children.
Proposed protective mechanisms of ARB administration in COVID-19 patients.

| Mechanism                                                                 | Description                                                                 |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Enhanced ACE2/Ang1–7/Mas activity                                         | Increased activity of mesoderm-derived mesenchymal stem cells (MSCs) involved in the repair of injured lung |
| Antihypertensive effects                                                  | Maintenance of insulin sensitivity and energy metabolism                     |
| Macrophage M2 polarization and decreased macrophage infiltration         | Reduces pro-inflammatory cytokines and chemokines, reactive oxygen species (ROS), inflammatory macrophage infiltration |
| Downregulation of pro-inflammatory kinase cascades and NFκB pathway      | Reduces pro-inflammatory cytokines and chemokines, reactive oxygen species (ROS), inflammatory macrophage infiltration |
| Overall and effective AT1R blockade                                       | Reduces pro-fibrotic Transforming Growth Factor Beta (TGF-β) reduction |
| Reduction of lung edema and vascular permeability                        | Enhanced activity of mesoderm-derived mesenchymal stem cells (MSCs) involved in the repair of injured lung |
| Decreased apoptosis, pulmonary edema and pulmonary fibrosis              | Enhanced activity of mesoderm-derived mesenchymal stem cells (MSCs) involved in the repair of injured lung |
| Reduction of pro-fibrotic Transforming Growth Factor Beta (TGF-β)         | Enhanced activity of mesoderm-derived mesenchymal stem cells (MSCs) involved in the repair of injured lung |
| Inhibition of the coagulation cascade                                     | Enhanced activity of mesoderm-derived mesenchymal stem cells (MSCs) involved in the repair of injured lung |
| Maintenance of insulin sensitivity and energy metabolism                  | Enhanced activity of mesoderm-derived mesenchymal stem cells (MSCs) involved in the repair of injured lung |

The Table includes but is not limited to major protective mechanisms in severe acute respiratory syndrome confirmed for ARB administration.

Individuals, at risk of COVID-19 [6]

Feng and colleagues [1] are correct when they point out that ARB treatment increases ACE2 in possible COVID-19 comorbidities such as hypertension and diabetes [1]. However, the speculation that such treatment enhances infection with this virus [1] is without scientific evidence. The suggestion to replace ARB therapy with alternative antihypertensive medications does not take into consideration that such alternatives, like the use of calcium channel blockers [1] lack the major pleiotropic beneficial characteristics of ARBs.

The argument that the ARB-dependent ACE2 upregulation may directly enhance SARS-CoV-2 infections [1,2] ignores the complexity of ACE2 function and metabolic regulation with its apparently inconsistent and paradoxical findings, including findings of multiple ACE2 substrates beyond Angiotensin II and SARS-CoV-2. ACE2 is not only a receptor for SARS-CoV-2, but also inhibits the Angiotensin cascade contributing to control excessive AT1R activity.

Substantial preclinical and clinical data supports the proposal that ACE2 upregulation is beneficial in several disorders [3]. There are many reports demonstrating that ACE2 may ameliorate acute lung injury as a result of reduced AT1R activation and beyond effects on blood pressure [3]. ACE2 has emerged as a potent physiologically negative regulator of the RAS, and the imbalanced activity of ACE/ACE2 systemically and/or locally has been proposed to be an important contributor in many disease pathogeneses including inflammatory lung disease [3,5].

In addition, and indirectly, by upregulating ACE2, ARBs enhance the ACE2/Ang1–7/Mas axis, a major protective system reduced in the elderly [6] that balances Ang II and AT1R overstimulation reducing inflammation in association with down-regulation of several kinase signaling pathways [3] (Table 1).

In agreement with the Position Statement of the ESC Council on Hypertension on ACE Inhibitors and Angiotensin Receptor Blockers [7] and with a previous report [4], we think that there is no scientific evidence to support replacing ARBs in subjects suffering from COVID-19 comorbidities and not yet infected with SARS-CoV-2. Removing ARBs from their therapeutic arsenal will enhance Ang II/AT1R receptor activity and potentially worsen lung inflammation and associated comorbidities after SARS-CoV-2 infection. Although ARBs are very well tolerated in the elderly [3–5], administration of any drug, including ARBs, to COVID-19 patients must continue to be carefully monitored.

It is imperative that data analysis be performed to determine: a) whether or not continuation of ongoing ARB treatment of comorbidity disorders improves the outcome and reduces mortality in COVID-19 patients; b) if improving the outcome and reducing mortality for this disease is confirmed, whether addition of ARBs to the therapeutic arsenal for COVID-19 in patients suffering from comorbid disorders and not previously medicated with these compounds further improves the outcome of this disease; and c) should these conditions be met, expanding treatment with ARBs to patients suffering from cardiovascular and metabolic disorders susceptible to ARB therapy but not medicated with these compounds and exposed to SARS-CoV-2 may further protect these patients from the tragic consequences of COVID-19.

Declaration of Competing Interest

The author has no conflict of interest to declare with respect to this manuscript.

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