COVID-19: Acing the Treatment

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**Highlights of the Study**

- ACE-2 is the functional receptor of SARS-Cov-2 virus and is linked to the dysregulated inflammatory conditions that cause acute lung injuries.
- Blocking the ACE-Ang II-AT1R coupling with pharmacotherapeutics may be beneficial.
- Angiotensin converting enzyme inhibitor and angiotensin receptor blocker therapeutics are both ubiquitous and may confer a survival benefit in COVID-19 infections in both naïve and non-naïve populations.

**Keywords**

Angiotensin converting enzyme inhibitors · Angiotensin II receptor blockers · COVID-19 · Novel treatments · Renin-angiotensin-aldosterone system

**Abstract**

Angiotensin converting enzyme 2 is the functional receptor that the SARS-CoV-2 virus requires to enter cells and cause dysregulated inflammatory conditions that contribute towards acute lung injuries. The renin-angiotensin-aldosterone system with its physiological surveillance and regulation system can be implicated in both harm and therapeutic benefit. The initial observational studies suggesting the discontinuation of angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been firmly rebutted by international societies. On the contrary, these therapeutics may confer a survival benefit in COVID-19 infections. Understanding the biological plausibility of this pathway alongside the emerging therapeutic evidence may yield new modes of treatment. Such developments appear fundamentally important in the battle against the inevitable emergence of new variants and their potential to drive future waves of COVID-19 pandemics.

**Introduction**

COVID-19, attributed to the SARS-CoV-2 virus, has caused hundreds of millions of infections worldwide, with total worldwide deaths approaching 6.5 million at the time of writing [1]. As new mutated variants emerge, our vaccination and treatment strategies must evolve. The renin-angiotensin-aldosterone system (RAAS) has been implicated in the pathophysiology of this multisystem disease, with angiotensin converting enzyme 2 (ACE2) identified as the functional receptor that SARS-CoV-2 requires to enter cells and cause both pulmonary and other major organ infections [2].

At 40 million users worldwide, angiotensin converting enzyme inhibitors (ACE-i) and angiotensin receptor...
blockers (ARBs) are among the most common prescriptions across almost all healthcare systems most frequently prescribed for hypertension. In the initial stages of the COVID-19 pandemic, a combination of small underpowered observational studies coupled with the disproportionate representation of cardiovascular comorbid patients developing severe COVID-19 infection led to ACE-i and ARBs being tenuously linked with more serious infections [3]. However, as evidence has evolved, both the World Health Organization (WHO) [4] and the European Society of Cardiologists (ESC) [5] have released statements questioning this paucity of evidence and highlighting the wider harms from knee-jerk discontinuation of these medications. In light of large meta-analysis data, a definite survival benefit for patients on ACE-i and a probable survival benefit with ARBs has emerged [6]. Here, we discuss this biological plausibility further.

**Fig. 1.** Positive cellular benefits of the RAAS outnumbering the negative, and how blocking the ACE-Ang II-AT1R coupling may be beneficial. Figure 1 shows the positive cellular benefits of the RAAS outnumbering the negative and how blocking the ACE-Ang II-AT1R coupling may be beneficial. ACE2 usually sits across the cell membrane, but in COVID-19 disease, it is sequestered into the cell rendering it unable to catalyse Ang 1-9 and Ang 1-7 production.
The RAAS is a fundamental hormonal pathway that confers a primitive survival mechanism in vertebrates [7]. It provides a physiological surveillance and regulation system that is vital during organ dysfunction, moderating circulating volume, blood biochemistry, and wider electrolyte balance. SARS-CoV-2 targets the very heart of this fundamental homeostatic mechanism.

Angiotensin II (Ang II) is the biologically active mediator of the RAAS. When bound to the Angiotensin receptor 1 (AT1R), it not only mediates renal and haemodynamic effects such as vasoconstriction and aldosterone synthesis, causing sodium retention, but can also increase pulmonary vascular permeability, which under certain dysregulated inflammatory conditions may contribute to an acute lung injury. By inducing genes coding for proinflammatory molecules, it mediates organ-damaging intracellular oxidative stress via mitochondrial dysfunction [8].

ACE-2 has been identified as the functional receptor for SARS-CoV-2 pulmonary infection [9]. When bound to SARS-CoV-2, ACE-2 is taken into the cell, downregulating its physiological action and driving the balance between ACE and ACE-2 in favour of ACE (Fig. 1). This would be expected to increase Ang II production and reduce its degradation. Through this imbalance in the RAAS, it is likely SARS-CoV-2 effects harm through proinflammatory mechanisms. Both ACE-i and ARBs have been shown to reduce both Ang II production and degrade existing active enzyme into vasodilatory peptides [10]. ACE-2 is a key counter regulator in the RAAS which degrades both Ang I to Ang (1-9) and Ang II to Ang (1-7) which oppose the actions stimulated by the Ang II/AT1R complex. The ACE-2/Ang (1-7)/Mas receptor activation is thought to be lung protective [11].

Pharmacological chronic inhibition of ACE decreases Ang II expression and upregulates Ang (1-7) levels through the action of the endopeptidase neprolysin. AT1R blockade also increases Ang (1-7) levels by diverting Ang II to the protective AT2 receptor pathway which mediates vasodilatation and opposes the action of the AT1R receptor.

These in vivo observations have been supported by a cluster of observational trials. An early retrospective multicentre study by Zhang et al. [6] examined the association of hypertension with COVID-19 infection in 1,128 patients [5]. They demonstrated a lower risk of mortality in those patients who received ACE-i or ARB therapy compared with those who did not (95% CI: 0.15–0.89, p = 0.03), although the former sample size was small (n = 174). Semenzato et al. [12] retrospectively analysed a much larger cohort of almost 2 million patients with uncomplicated hypertension taking either ACE-i, ARBs or calcium channel blockers. Using a French National Health Insurance database, they analysed chronically hypertensive patients who developed COVID-19. The ACE-i/ARB combined cohort was found to have a lower risk of hospitalization and a lower risk of intubation and/or death compared to the calcium channel blocker group (hazard ratio for hospitalization, 0.74 [95% CI: 0.65–0.83] and 0.84 [0.76–0.93], respectively). This large study was able to exclude confounding chronic cardiorespiratory, renal and metabolic comorbidities [12].

Duarte et al. [13], in a small RCT in Argentina, analysed the therapeutic effect of high dose telmisartan started in ACE-i/ARB naïve patients hospitalized due to COVID-19 as a targeted anti-inflammatory treatment. Unfortunately, the study was terminated early due to a sharp reduction in enrolment, leading to low recruitment numbers (n = 80 and 78 in the control and treatment arms, respectively). They reported statistically significant secondary endpoints of lowered mortality and reduced time to discharge with no adverse effects.

While the effect of ACE-i and ARBs remains uncertain, further ongoing trials may provide a clearer answer to the harm versus benefit conundrum. For instance, one research collaboration is investigating paired trials using losartan as a treatment in RAAS inhibitor naïve patients in both hospitalized and community-treated groups [14]. The STAR-COVID trial will provide more evidence regarding the safety of telmisartan in respiratory failure secondary to COVID-19 [15]. Early data suggest ACE-i therapy to be more effective than ARB; however, the research spotlight is currently illuminating the latter rather than the former. More trials are needed investigating the role of ACE-i and ARBs in COVID-19 as these therapies are not without risks, despite the clear benefit of those already stabilized on these medications.

From being treated with extreme caution, emerging ACE-i and ARBs evidence may be swinging the pendulum in the opposite direction with a clear signal of benefit in COVID-19 infection. Rather than discontinuing these medications in patients who contract COVID-19, the WHO and ESC recommend they should be continued in stable patients. However, they may also provide a valuable adjunctive treatment for patients with COVID-19 who are not previously ACE-i and ARB exposed. We await the results of ongoing high-quality prospective trials to inform our practice further, which should include ACE-i initialization in de novo COVID-19 patients. The global effect of mass vaccination will not be seen in the
short term and it seems likely we will be living with COVID-19 for the foreseeable future. The increasing frequency of identification of new variant strains appears inevitable alongside the escalating probability of further pandemic waves. Thus, understanding which treatments confer survival benefit is arguably crucial in the months and years ahead.

**Statement of Ethics**

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. No subjects were involved in this short report.

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**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Jez Hunter: analysis, interpretation of data and studies, initial and subsequent drafting, final draft, proofing, and corresponding author. Puskar Bura: analysis and interpretation, drafting of original manuscript, and final approval of the version to be published. Richard King: analysis and interpretation of data, figure graphic design, and final approval of version to be published. George Thomson: original concept, design of work, critical revision of paper, and final approval of version to be published.