Renin-angiotensin-aldosterone system inhibitors impact on COVID-19 mortality: What's next for

ACE2?

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As clinicians and researchers look to identify optimal treatments for COVID-19 and prevent its spreading, they have focused on 2 questions; 1) What risk factors lead to increased susceptibility of SARS-CoV-2 infection? and 2) What factors predict worse prognosis and increased severity of COVID-19? The answer to these questions can enlighten our ability to provide prophylactic interventions to limit transmissions of SARS-CoV-2 as governances look to reopen society and effectively treat patients that have contracted SARS-CoV-2 to limit their progression to acute respiratory distress syndrome that has been a hallmark of SARS-CoV-2 infection in the lung.

Hypertension has been shown to be associated with COVID-19 and its severity in a number of early demographic studies of COVID-19[1,2]. It remains unclear if this association is due to the pathogenesis of hypertension or confounded by an associated co-morbidity or medication. In this setting, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), medications commonly used to treat hypertension amongst other disease such as diabetes mellitus and heart failure have also been associated with COVID-19 and its severity. ACEi and ARBs have garnered particular interest given previous studies demonstrating its regulation of the carboxymonopeptidase enzyme, angiotensin converting enzyme 2 (ACE2), which has been shown to facilitate SARS-CoV-2 entry into human cells[3,4]. ACE2 expression is seen throughout the body including the respiratory tract, heart, kidney, endothelium, and intestines. Studies in rats have shown upregulation of ACE2 in cardiac[5,6] and renal tissues[6,7] with ACEi and/or ARB therapy, with mixed results in humans[8,9]. Recent data evaluating gene expression in human lung samples suggest that ACEis lower ACE2 expression further clouding our understanding[10]. Though ACE2 facilitates SARS-CoV-2 entry into human cells, it also serves a protective role in the setting of lung injury through its effect on generating angiotensin 1-7 from angiotensin II and counterbalancing effects of angiotensin II signaling[11]. This leads to the question; "Is ACE2 expression a risk factor for susceptibility to SARS-CoV-2 infection and/or protective in limiting COVID-19 severity?

In this current issue of *Clinical Infectious Disease*, Jung et al. utilized a nationwide Korean database to evaluate the impact of outpatient ACEi and ARB use noted as renin-angiotensin aldosterone system inhibitors (RAASi) on in-hospital mortality for COVID-19 positive patients. They identified 5,179 COVDI-19 positive patients of which 38% required hospitalization. The impact of outpatient RAASi on incidence of hospitalization or the incidence of a positive COVID-19 test in relation to RAASi use was not evaluated in this study. However, a previous study from New York City[12] looked at susceptibility of contracting SARS-CoV-2 infection in the setting of RAASi use and found no increase risk of infection suggesting RAASi regulation of ACE2 expression does not impact risk of contracting COVID-19.

Jung et al. evaluated in-hospital mortality and found mortality rates of 9% in RAASi users and 3% in non-RAASi users but this difference was not present after adjustment for confounders. Given hypertension is noted to be associated with COVID-19 severity and mortality, Jung et al. did a subgroup analysis of hypertensive patients and found in-hospital mortality in this group to be 9% amongst RAASi users and 13% amongst non-RAASi users demonstrating the influence of hypertension and its pathogenesis. A large cohort in Spain evaluating hospital admission with COVID-19 found no impact of RAASi use but upon sub-group analysis found diabetic patients had a lower rate of hospital admission when on RAASi suggesting certain sub-groups could gain benefit from RAASi in setting of COVID-19[13].

The authors noted most of the RAASi use in their study was from ARB with minimal use of ACEi in Korea limiting the extension of the findings to ACEi use. A recent, multinational, retrospective study identified outpatient ACEi use as protective for in-hospital COVID-19 mortality[14] though other

studies have not confirmed the same finding. As a number of different retrospective analysis evaluating the effect of RAASi use on COVID-19 severity have been recently published, it is important to identify the distinguishing characteristics. The authors are able to control for in-hospital medication exposures and particular interventions including vasopressor use and mechanical ventilation which has yet to be done in other studies. The authors also note that their study is the only retrospective analysis looking at outpatient RAASi use impacting COVID-19 mortality in a predominantly Asian population, which is relevant given noted variation in ACE2 expression amongst different ethnicities. There has been significant racial disparity in COVID-19 infection and mortality[15], ACE2 biology could be a piece of the puzzle.

Despite initial concern RAASi could be harmful in COVID-19, uncovering the potential protective effects of RAASi on viral lung injury that are independent of the regulation of ACE2 expression and the lack of clinical evidence led many hypertension and cardiology societies to encourage clinicians to continued RAASi for clinical indications[16]. As mounting retrospective evidence suggests that RAASi use does not impact COVID-19 infection incidence or severity, a better understanding of the regulation of the RAAS system in the lungs could shed light on timing and mechanism of effective RAAS targeting therapies in COVID-19.

The role of RAAS in the pathogenesis of acute lung injury appears to center around signaling through Angiotensin II type 1 receptors (AT1R). Previous work has shown that knockout and small molecule inhibition of AT1R mitigates acid-induced lung injury[11]. A key enzyme regulated by AT1R is a disintegrin and metalloproteinase 17 (ADAM17)[17], which is known to cleave membrane bound ACE2 and release of soluble ACE2 (sACE2) lead to unopposed angiotensin II. ADAM17 can additionally cleave membrane bound tumor necrosis factor alpha (TNF-α) and interleukin-6 receptor

(IL-6R) releasing them into the plasma and stimulating a pro-inflammatory milieu[18]; a hallmark of SARS-CoV-2 pathogenesis in the lung. The inflammatory cytokines can additionally affect the kallikrein-kinin system by increasing bradykinin B1 and B2 receptors that decrease vascular permeability allowing for inflammatory cell migration and increase pulmonary edema. Of note, ACE2 processes des-Arg^9-bradykinin[19] which is a ligand for B1 receptors, while ACE process bradykinin, a ligand for B2 receptors ,and thus modulation of ACE2 and ACE activity can control potentially adverse responses to SARS-CoV-2 infection.

An understanding of the interaction of signaling cascades involving innate immunity and vascular physiology with ACE2 has been hampered by lack of quantitative measurement of ACE2 levels in humans. A recent study evaluated sACE2 levels in heart failure patients and found significantly higher sACE2 levels in men. They found no effect of ACEi or ARBs on sACE2 level in their index cohort but found lower sACE2 levels with both class of medications in their validation cohort[20]. This highlights the importance of understanding soluble versus tissue bound ACE2 expression as there is high spatial specificity for ACE2 regulation of the different pathways impacting SARS-CoV-2 pathogenesis.

Jung et al. found no association of RAASi use and in-hospital mortality in COVID-19 patients in this retrospective analysis and point to the need for prospective, randomized trials to evaluate the impact of RAASi on COVID-19 outcomes. Table 1 outlines current trials which look to ask two important questions; 1) Should RAASi be continued during hospitalization in COVID-19 patient? and 2) Can RAASi improve outcomes in COVID-19 patients not previously on RAASi? As we await the results of these trials, we should continue to better understand the pathophysiology of SARS-CoV-2 infection. A mouse model over-expressing human ACE2 that recapitulates the pulmonary pathology

of SARS-CoV-2 infection in humans[3] was recently published and could serve as a tool to deconstruct the complex interactions between RAAS, inflammation, and vascular biology to provide insight into novel therapeutic approaches.

Potential conflicts:

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Table 1: Prospective, Randomized Trials evaluating the Renin-Angiotensin-Aldosterone System Inhibitors on COVID-19 outcomes.

Trial #	Name	Estimated Enrollment	Start Date	Previous ACEi/ARB Use	Other Medications Investigated (excluding anti-hypertensives)	Primary Outcome
NCT04340557	COVID-ARB	200	3/27/20	No	None	Mechanical ventilation
NCT04330300	CORONACION	2414	3/30/20	Yes	None	Death, mechanical ventilation, or non-invasive ventilation hospitalization
NCT04338009	REPLACECOVID	152	3/31/20	Yes	None	Composite rank score based on time of death, number of days on mechanical ventilation, ECMO, renal replacement therapy, vasopressor/inotropic therapy, and mSOFA score
NCT04343001	CRASH-19	10000	4/1/20	No	Aspirin, Simvastatin	Death
NCT04364893	BRACE-CORONA	500	4/6/20	Yes	None	Days alive out of hospital at 30 days
NCT04328012	COVIDMED	4000	4/6/20	No	Lopinavir/Ritonavir, Hydroxychloroquine	NIAID COVID-19 ordinal severity scale
NCT04329195	ACORES-2	554	4/9/20	Yes	None	Time to two point improvement on 7 point ordinal clinical severity scale
NCT04311177	SURG-2020-28683	580	4/9/20	No	None	Hospital admission
NCT04312009	SURG-2020-28675	200	4/13/20	No	None	Estimated ratio partial pressure of oxygen to inspired oxygen (P/F) adjusted for PEEP at 7 days
NCT04353596	ACEI-COVID	208	4/15/20	Yes	None	SOFA score or composite of ICU admission, mechanical ventilation or death
NCT04335786	PRAETORIAN-COVID	651	4/17/20	No	None	ICU admission, mechanical ventilation, or death
NCT04351581	RASCOVID-19	215	5/8/20	Yes	None	Days alive out of hospital at 14 days