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Editorial

Halting Progression to Acute Respiratory Distress Syndrome in COVID-19 using Angiotensin Converting Enzyme II Receptor Antagonists

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INTRODUCTION

The global COVID19 outbreak has reached pandemic levels with catastrophic consequences. A key health challenge has been absence of evidenced treatment options and of course an approved vaccine. Late disease manifests with severe pneumonia associated with Acute Respiratory Distress Syndrome (ARDS). Extracorporeal ventilation support ultimately becomes necessary, even when many countries especially within Africa are under equipped. Here, we argue that basing on the infection biology of the SARS-CoV2, where by target cell attachment and entry is mediated *via* Angiotensin Converting Enzyme type II (ACE2) Receptors (AAR) on Alveolar Epithelia, Existing ACE2 receptor antagonists presently approved for treating hypertension and left heart failure can be repurposed as a prophylactic treatment for COVID19 associated ARDS among patients with no prior history of longstanding drug-use. Despite earlier warning against the sustainance of ACE inhibitors (ACEi) and ARR, a recent observational cohort study involving 564 patients revealed benefits towards halting progression to ARDS. Management of the issuing hypotension might be a more amenable 'side-effect' relative to the requirement for ventilation.

Severe Acute Respiratory Syndrome Coronavirus 2019 (SARS-CoV2) is the cause of the 2019 coronavirus disease (COVID19) global pandemic [1]. Coronaviruses (CoVs) are enveloped, positive-stranded RNA viruses with a nucleocapsid [2]. SARS-CoV2 belongs to the beta category (betaCOV) of the Orthorcoronavirinae subfamily of the family *Coronaviridae* [2,3]. In genetic terms, Chan et al. have proven that the genome of SARS-CoV2 has 82% nucleotide identity with that of human SARS-CoV-1 [4].

A major and fatal outcome of human infection with SARS-CoV2, is a severe pneumonia associated with ARD [5]. Patients developing COVID19 associated ARD will require Extracorporeal Membrane Oxygenation (ECMO) or simply ventilation, to survive [6]. As a result, High Dependency Units (HDU) and Intensive Care Units (ICUs) of major hospitals of the worst hit countries like Italy have become overwhelmed [7]. Most important though, is that most nations of sub- Saharan Africa is only emerging, lack the adequate numbers of ventilators. In Uganda which remains an island with no apparent case, a key innovative strategy has been, how to halt COVID19 associated ARD.

The initial and yet critical step in the pathogenesis of COVID19 disease is the targeted attachment and entry of SARS-COV-2 into alveolar epithelia [8]. Recent studies have shown that the Spike (S) glycoprotein of SARS-CoV1 and SARS-CoV2 mediate viral entry into a similar spectrum of cell lines [8-10]. Specifically, the Surface unit (S1) of the Spike (S) protein of SARS-CoV2 engages the Angiotensin-Converting Enzyme 2 (ACE2) as the entry receptor and then uses the host serine protease TMPRSS2 for S priming, allowing fusion of viral and cellular membranes and viral entry into the cell [8]. Like SARS-CoV-1, SARS-CoV-2 employs the same host-cell ACE2 as the receptor for cell entry. The host cell serine protease TMPRSS2 primes the S protein of SARS-CoV-2 for entry. The serine protease inhibitor camostat mesylate, available in Japan to treat chronic pancreatitis and reflux esophagitis, inhibits TMPRSS2 and partially blocks SARS-CoV-2 infection of lung epithelial cells. Antibodies against S1 from convalescent sera of SARS patients inhibited SARS-CoV-2 from infecting cultured cells [8].

Against this background, our team has proposed an investigator initiated investigational trial protocol for off label ACE2 receptor antagonists. There are presently many pharmacologically licensed and approved ACE2 receptor antagonists (i.e the tetrazoles Losartan, candesartan, and azilsartan) for the treatment of hypertension with left heart failure. Theoretically, blocking the ACE2 receptors should primarily halt SARS-COV-2 attachment and entry into alveolar epithelia (prophylaxis). This effect, could secondarily abort the entire infectious process offering a cure (therapeutic). A history of long standing use of ACE2 receptor antagonists might and has been evidenced to elicit a refractory (by negative feedback) over expression of ACE2 receptor messenger RNA and protein thereby worsening the progression to ARDS among these patients. A recent retrospective, observational cohort study involving 564 patients with confirmed COVID-19, hypertension was an independent risk factor for progression to severe pneumonia irrespective of age and those on Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) therapy were less likely to develop severe COVID-19 pneumonia . The use of ACE2 receptor antagonists among drug-naive COVID19 persons could have a prophylactic effect in halting the progression from mild diseases to severe disease with ARDS, as it was shown for those with hypertension.

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Hypertensive patients on ACEI or ARB were observed to be protected from severe pneumonia in COVID-19 and hence these therapies should not be ceased unless there is a strong indication or further epidemiological evidence. ACEI and ARR work by inhibiting viral attachment to the receptors in the lung epithelia. Moreover, the same could have antiviral effect with prospects of cure if combined with other drugs to create a combinational therapy. A major fall back, will be the need to carefully manage the issuing ACE2 receptor antagonist induced hypotension. Arguably, the same might be a more amenable side-effect relative to the requirement for ventilation.

Details of proposed trial of ACE2 receptor antagonists to halt COVID19 ARD+

Design: Phase 2a, b Clinical trial.

Site: Mulago national super specialized hospital Intensive Care Units (ICUs)

Participants: 40-80 consenting adult male and females admitted for COVID19 treatment with impending ARD.

Interventions: Participants will be randomized to either 3 arms of ACE2 receptor antagonists (Losartan, Olmestan and Valsartan, n=10-20 each, 30 to 60 overall) or a standard care available.

Measurable outcomes: The primary measurable outcome will be event of ARD. A secondary outcome measure will be recovery (or death).

Specifically, we plan to undertake an independent Phase 2a, b clinical trial of ACE2 receptor antagonists as a prophylactic treatment against acute respiratory distress caused by SARS- COV2. The Makerere University Clinical Trials Unit (MakCTU) and Uganda Ministry of Health National Task Force (NTF) will be the major sponsors and technical implementers of the trial.

CONCLUSION

In conclusion, the existing ACE2 receptor antagonists presently approved for treating hypertension and left heart failure can and should be re-purposed as a prophylactic treatment for COVID19 associated ARDS among persons with no existing history of longstanding drug-use. Management of the issuing hypotension is a more amenable 'side-effect' relative to the requirement for ventilation.

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