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

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INTRODUCTION

The global COVID-19 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]. Coronavirus (CoV) are enveloped, positive-stranded RNA viruses with a nucleocapsid [2]. SARS-CoV2 belongs to the beta category (betaCoV) of the Orthocoronavirinae 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-V1 [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.
Hypertensive patients on ACEI or ARB were observed to be protected from severe pneumonia in COVID19 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, 30to 60overall) or 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 repurposed 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.

**REFERENCES**

8. Hoffmann M. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020.