Use of ARB Drugs to Decrease Morbidity and Mortality Related To COVID-19 Infection

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Abstract*: Corona Viruses belong to a large family . They are enveloped, positive-sense, single-stranded RNA viruses. Corona Viruses have wide range of hosts and can infect many birds and mammals like bats, civet cats , humans. COVID-19 can cause respiratory tract infections such as the common cold, pneumonitis,ARDS. Study of the receptor binding motif (RBM) in the S protein reveals maximum of the amino acid residues essential for receptor binding were same between SARS-Corona Virus and SARS-Corona Virus-2, suggesting that the 2 Corona Virus strains use the same host receptor for cell entry. The entry receptor utilized by SARS-Corona Virus is Angiotensin-Converting Enzyme 2 (ACE-2). The major substrate for ACE-2 is Angiotensin II.[20] ACE-2 degrades Angiotensin II to generate Angiotensin 1-7, thereby, negatively regulating RAS. On the basis of genome sequence similarities of the RBM between SARS-Corona Virus-2 and SARS-Corona Virus, research say that SARS-Corona Virus-2 also utilizes ACE-2 as a cellular entry receptor. Based on above literature and observation it seems that Corona Virus has a receptor called ACE – 2 which is also involved in the Renin-angiotensin system to lower down the blood pressure. If the angiotensin II receptor blockers are used to block the angiotensin II receptors that is AT1 the angiotensin II molecule will remain free and its level will raise which will be absorbed by the ACE – 2 receptors and hence the ACE – 2 receptors will remain engaged in catalyzing the angiotensin II molecule and will be less available to Corona virus as a receptor for endocytosis which may bring down the level of morbidity and mortality in patients. The related hypotension will be relative and not much and if more can be tackled with I.v. ionotropes , i.v. fluids and prostaglandins. In this era of corona with so many deaths I think its better to try on these drugs as these drugs have logical literature behind it and if worked can save lives which is worth.*
Key Words: *COVID-19, SARS, ARB, AT1*
Methods to search literature: Google search Engine

I. Introduction

As we know the living things being evolved on earth through some nonliving things like elements like carbon , nitrogen, oxygen , hydrogen to form water then aminoacids and the first one to evolve were viruses on earth and then the eukaryotes who eventually developed into big animals and creatures. Since those times there had been genetic linkages amongst the viruses and other creatures which led to existence of host agent and vectors for certain viral, bacteria and parasitic borne diseases. Accordingly there had been relationship between viral agents and host through certain receptors and molecular affinity among certain aminoacid chains.

Corona Viruses belong to a large family . They are enveloped, positive-sense, single-stranded RNA viruses. Corona Viruses have wide range of hosts and can infect many birds and mammals like bats, civet cats , humans[1]. Corona Viruses can cause mild to moderate upper and lower respiratory tract infections such as the common cold, pneumonitis etc.[2,3] In the past 20 years, there have been outbreaks of severe, and sometimes fatal, respiratory illnesses in China , Canada, middle east countries. These Corona Virus strains, which were determined to be diferrent from the common human Corona Viruss, had originated in horseshoe bats and were transmitted to humans, typically through an intermediate host like civet bats through trading of wildlife animals especially in countries like China .[1,4,5] These strains were seen to be highly virulent and the reproduction number was between 2.8 with high secondary attack rate and mortality varying between 10-60%. While infection with these Corona viruses typically produced diseases ranging from mild to severe cases depending on age and comorbid conditions like diabetes, hepatitis B infection, tuberculsosis. Death occurred due to respiratory failure as the result of alveolar damage leading to ARDS or immune mediated host cell damage of Pneumocytes while some theories say due to intense iron induced inflammation and hypoxia due to displacement of oxygen from oxy haemoglobin by viruses with formation of porphyrins .[3,4,6]
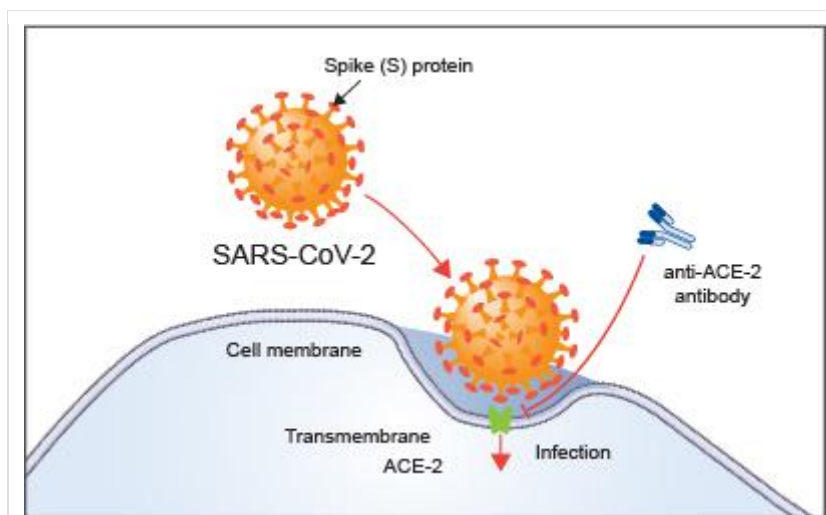
Figure 1. ACE-2 is the host cell receptor responsible for mediating infection by SARS-Corona Virus-2 and it seems treatment with anti-ACE-2 antibodies disrupts the interaction between virus and receptor.

The SARS pandemic that occurred in 2002 originated in the Guangdong Province in southern China spread rapidly through 29 countries in Southeast Asia where it resulted in 8096 confirmed cases of SARS, with 774 deaths.[7,8] Today's pandemic has surpassed these numbers. The WHO has estimated that to date, over 14,50,000 individuals in over 190 countries have been diagnosed with CORONA VIRUSID-19, with over 85,000 deaths. Scientist are behind drug trials and vaccine production in order to get hold of the pandemic. As the viruses are highly versatile and can undergo mutation in anytime more weightage is on drug creation.

II. Identification and Characterization of SARS-Corona Virus-2

A novel virus called SARS coronavirus is the etiological agent of severe acute respiratory syndrome (SARS)as studied in 2003. Corona Virus-like viruses were isolated from Himalayan palm civets found in a live-animal market in Guangdong, China in 2003. Evidence of virus infection was also detected in other animals (including a raccoon dog, *Nyctereutes procyonoides*) and in humans working at the same market. All the animal isolates retain a 29-nucleotide sequence that is not found in most human isolates. The detection of SARS corona Virus-like viruses in small, live wild mammals in a retail market indicates a route of interspecies transmission, although the natural reservoir is not known.

Y Guan et al [9] says that their findings suggest that the markets provide a venue for the animal Corona Virus-like viruses to amplify and to be transmitted to new hosts, including humans, and this is critically important from the point of view of public health.

Identifying and genome sequencing of the agent causing COVID-19 Pandemic (view SARS-Corona Virus-2 protein sequence) determined that it was a new Corona Virus that shared 88% sequence similarity with two SARS-like Corona Virus exisiting in bats.[10] Additionally, it was shown that this Corona Virus, which was termed 2019-nCorona Virus or SARS-Corona Virus-2, shared 79.5% sequence identity with SARS-Corona Virus.[5,10] The coronavirus genome has four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein.[6,7] The entry of Corona virus is made easy by the S protein. It consists of a short intracellular part, a transmembrane binder, and a large ectodomain that has a receptor binding S1 subunit and a membrane-fusing S2 subunit.[11] after doing Sequence analysis of the SARS-Corona Virus-2 S protein genome with SARS Corona Virus it revealed that it was only 75% identical with the SARS-Corona Virus S protein.[5,10] Also, study of the receptor binding motif (RBM) in the S protein reveals maximum of the amino acid residues essential for receptor binding were same between SARS-Corona Virus and SARS-Corona Virus-2, suggesting that the 2 Corona Virus strains use the same host receptor for cell entry.[12] The entry receptor utilized by SARS-Corona Virus is Angiotensin-Converting Enzyme 2 (ACE-2).[13]

III. ACE-2

ACE-2 is a type I transmembrane metallocarboxypeptidase with homology to ACE. Iy is an molecule which is found in the Renin-Angiotensin system (RAS).[14] It is mainly shown in vascular endothelial cells, the renal tubular epithelium, and in Leydig cells in the testes.[15,16] PCR analysis shows ACE-2 is also shown in the lung, kidney, and gastrointestinal tract, tissues expressed to harbor SARS-Corona Virus.[17-19] The major substrate

for ACE-2 is Angiotensin II.[20] ACE-2 degrades Angiotensin II to generate Angiotensin 1-7, thereby, negatively regulating RAS.[15,20] Its been considered that ACE-2 also plays important role in cardiovascular protection.[15]

ACE-2 is an Entry Receptor for SARS-Corona Virus-2

On the basis of genome sequence similarities of the RBM between SARS-Corona Virus-2 and SARS-Corona Virus, many independent study groups had researched about if SARS-Corona Virus-2 also utilizes ACE-2 as a cellular entry receptor. Zhou et al. showed that SARS-Corona Virus-2 could use ACE-2 from humans, Chinese horseshoe bars, civet cats, and pigs to gain entry into ACE-2-expressing HeLa cells.[5] similar findings for human and bat ACE-2 was also reported by Hoffmann et al.[21] Additionally, Hoffmann et al. also says that treating Vero-E6 cells, a monkey kidney cell line known to permit SARS-Corona Virus replication, with an Anti-ACE-2 Antibody (R&D Systems, Catalog # AF933) blocked entry of VSV pseudotypes expressing the SARS-Corona Virus-2 S protein.[21]
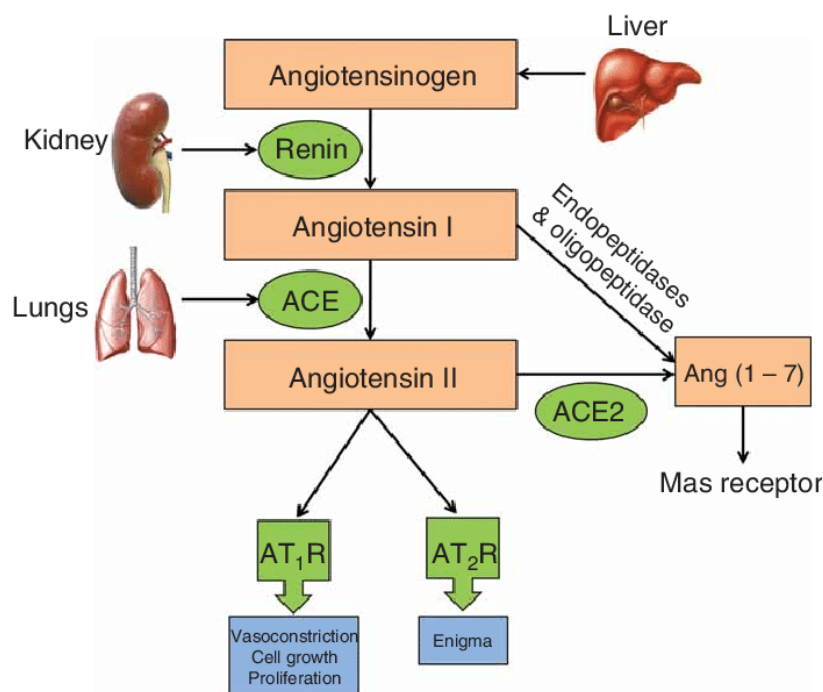

Figure no. 2 Renin Angiotensin System

IV. Renin–angiotensin system (RAS)-

The **renin–angiotensin system** (**RAS**), or **renin–angiotensin–aldosterone system** (**RAAS**), is a hormone system that maintains blood pressure and fluid and electrolyte balance, as well as systemic vascular volume.[22,23]

On decreased renal blood flow, juxtaglomerular cells in the kidneys converts the precursor prorenin (already present in the blood) into renin and releases it directly into circulation.In the liver plasma renin then causes the conversion of angiotensinogen to angiotensin I.[24] Angiotensin I is subsequently converted to angiotensin II by the angiotensin-converting enzyme (ACE) found on the surface of vascular endothelial cells, predominantly those of the lungs.[25] Angiotensin II is a potent vasoconstrictive peptide. Angiotensin II constricts the blood vessels thereby increasing blood pressure.[26] Angiotensin II also causes the secretion of the hormone aldosterone[26] from the adrenal cortex. Aldosterone causes the renal tubules to raise the reabsorption of sodium and water into the blood and at the same time causing the excretion of potassium. This raises the volume of extracellular fluid in the body, which also raises blood pressure.

If the RAS is unusually active, blood pressure will be very high. Different kinds of drugs can alter the action of RAS at different places. The blood pressure , heart failure and kidney failure and certain diabetes complications cam be controlled mainly by these drugs which can alter or control unusual functioning of RAS.[26][26] Angiotensin I is formed by Renin after activation of Renin Angiotensin system after cleavage of aniotensinogen which is secreted by liver which is further cleaved to angiotensin II in the lung capillaries.

Angiotensin II is called as a stress hormone as it activates mainly AT1 Receptor and hence drugs which alter or blocks its this action that is ARB drugs are used in stress related disorders..[27]

V. Angiotensin II receptor blockers (ARBs) -

Formally angiotensin II type 1 (AT1) receptor antagonists,[28] also known as angiotensin receptor blocker,[29][30] angiotensin II receptor antagonists, or AT_1 receptor antagonists, are a group of pharmaceuticals that bind to and inhibit the angiotensin II type 1 receptor (AT1). Angiotensin receptor blocker block the arteriolar contraction and sodium retention effects of renin–angiotensin system.[30] Angiotensin receptor blocker are mainly used in the treatment of hypertension (high blood pressure), diabetic nephropathy (kidney damage due to diabetes) and congestive heart failure. They selectively block the activation of AT_1 receptors, preventing the binding of angiotensin II compared to ACE inhibitors.[31] ARBs and the similar-attributed ACE inhibitors are both indicated as the first-line antihypertensives in patients developing hypertension along with left-sided heart failure.[32] However, ARBs appear to produce less adverse effects compared to ACE inhibitors.[32]

The angiotensin II blocker substances are AT_1-receptor antagonists; that is, they block the activation of angiotensin II AT_1 receptors. AT_1 receptors are found in smooth muscle cells of vessels, cortical cells of the adrenal gland, and adrenergic nerve synapses. Blockage of AT_1 receptors directly causes vasodilation, reduces secretion of vasopressin, and reduces production and secretion of aldosterone, among other actions. The combined effect reduces blood pressure.

Pressor inhibition

Pressor inhibition at trough level - this relates to the degree of blockade or inhibition of the blood pressure-raising ("pressor") effect of angiotensin II. However, pressor inhibition is not a measure of blood pressure-lowering (BP) efficacy per se. The rates as listed in the U.S. Food and Drug Administration (FDA) Package Inserts (PIs) for inhibition of this effect at the 24th hour for the ARBs are as follows: (all doses listed in PI are included)

- Valsartan 80 mg 30%
- Telmisartan 80 mg 40%
- Losartan 100 mg 25–40%
- Irbesartan 150 mg 40%
- Irbesartan 300 mg 60%
- Azilsartan 32 mg 60%
- Olmesartan 20 mg 61%
- Olmesartan 40 mg 74%

VI. Discussion

Drug repurposing is a kind of science in which a drug being used for a certain disease condition is logically sensed and tried to use on other diseases.

Its being also called as drug rediscovering, repositioning, reapplying. [33]. The drug researching time also can be shortened by using the existing pharmacodynamic and toxocologic data. [34]. For example ,thalidomide is a drug which has undergone repurposing and reapplication. The drug being used for controlling nausea in pregnancy came out to cause destructive side effects of congenital birth defects and hence was almost banned. After few years its role in treating the inflammation in erythema nodosum leprosum was discovered and is being also tried in treatment of multiple myeloma. [34, 35]

Marhiah et al [36] also supporting the idea of drug repurposing did a detail study about drug Tamoxifen and explained how a estrogen receptor antagonist being used in breast cancer had broad spectrum role in treating as antibacterial, anti viral , anti fungal and anti parasitic . its action is mainly through receptor blockade activity.

David et al[37] did a thorough study on Ebola patients in west Africa at Sierra Leone and summarized that that inexpensive generic agents that counteract endothelial dysfunction could be used to treat Ebola patients. David et al says that says that clinical trials at many places came to conclusion about statins and ARB drugs that they are effective in treating pneumonia patients through its broad acting pathways The drugs were primarily used for treating hypertension and heart disease. Eventually, scientists came to know that they also had broad anti-inflammatory and immunomodulatory (pleiotropic) activities that affected, inflammatory and anti-inflammatory cytokines and chemokines, the complement cascade, coagulation factors, oxidative stress, macrophage and T cell polarization, late mediators of inflammation [e.g., high mobility group box 1 (HMGB1), specialized pro-resolving mediators of inflammation (e.g., lipoxins, resolvins), mitochondrial biogenesis and energy metabolism. Thus it seems that there are variety of ways through which ARB drugs ultimately cause decreased inflammation.Overall Reports from Sierra Leone say that treatment with both drugs atorvastatin and irbesartan reduced morbidity and mortality. Both the drugs are safe and less price and they are effective in management of Ebola and it gives a hint that both these drugs can also be used in management of certain other infectious diseases.

Mortensen et al in 2012 [38] says that they conducted a retrospective cohort study using Department of Veterans Affairs data of patients aged ≥ 65 years hospitalized with pneumonia and says that Statins, ACE inhibitors and ARBs, are associated with improved pneumonia-related outcomes

Perry et al[39] in 2010 did a study on maraviroc and says that as a component of antiretroviral combination therapy regimens, is an important option for use in treatment-experienced adults with CCR5-tropic HIV-1 infection. Maraviroc acts by blocking the CCR5 co-receptors. Similarly, quinoline is a privileged scaffold that comprises the backbone for agents such as quinine (antimalarial), camptothecin (anticancer), and broxyquinoline (antiseptic) [40]. Shaheen et al [41] in 2004 did a study on HIV and its entry into host cells and says that with CD4, HIV-1 requires a chemokine receptor, CCR5 or CXCR4, as an entry co-receptor, and differential co-receptor selectivity is an important determinant of viral diversity and pathogenesis. CCR5 and CXCR4 blockers have been the focus of much research and are now entering clinical trials. Thus it supports that treatment with receptor blocking mechanism of infectious agent is a good alternative for treating infectious diseases.

Di Raimando et al[42] in 2012 did a study for mechanism of action of ARB drugs and his results obtained by trials accomplished using ARBs seem to be more univocal to confirm, although to great extent, these is an anti-inflammatory effect of drugs blocking AT1 receptor.

Ansumana et al. did a study on 581 patients at Hastings Ebola Treatment Centre [43]. All patients were treated with intravenous fluids and oral rehydration solution. The case fatality rate was 47.7% during the period from 20 September 2014 to 13 October 2014, but it declined to 23.4% during the period from 5 November 2014 to 7 December 2014. The authors could not explain this 51% decrease in mortality. Interestingly, reports from 34 Military Hospital and the Port Loko Government Hospital in November suggested that atorvastatin and irbesartan treatment was associated with improved survival, and some patients at the Hastings Center were also given the same treatment during November (O.M.R., unpublished observation). Ansumana et al. did not acknowledge this in their report [43]. Perhaps atorvastatin and irbesartan treatment of some of these patients helps explain the decrease in the Ebola case fatality rate observed at the Hastings Center.

From the above studies we can hypothesize that ARB drugs can be helpful for bringing down the morbidity and mortality by COVID-19 infection. For any infectious disease agent to cause disease most important is to get itself entered into the host which occurs through certain receptors or chemokines which facilitate its entry in to the respective epithelial or endothelial cells and from where its further action starts to cause disease in the host. This period is covered under the incubation period. If the entry of agent into the host is hampered it can cause a milder version of the disease that is reduced morbidity and the worse part mortality should go significantly down. ARB drugs , ACE inhibitors and Statins are being tried in various trials to know its effect in infectious diseases. Amongst them ARB drugs are seeming logically and hypothetically perfect as per literature to help in COVID-19 infection treatment.

Based on above literature and observation it seems that Corona Virus has a receptor called ACE – 2 which is also involved in the Renin-angiotensin system to lower down the blood pressure. If the angiotensin II receptor blockers are used to block the angiotensin II receptors that is AT1 the angiotensin II molecule will remain free and its level will raise which will be absorbed by the ACE – 2 receptors and hence the ACE – 2 receptors will remain engaged in catalyzing the angiotensin II molecule and will be less available to Corona virus as a receptor for endocytosis which may bring down the level of morbidity and mortality in patients. The related hypotension will be relative and not much and if more can be tackled with I.v. ionotropes , i.v. fluids and prostaglandins. In this era of corona with so many deaths I think its better to try on these drugs as these drugs have logical literature behind it and if worked can save lives which is worth.

We suggest that prospective cohort and randomized controlled trials are needed to examine potential mechanisms of action and acute initiation of these drugs at the time of presentation with these infections is beneficial.

VII. Conclusion

It can be hypothesized that ARB drugs can be effectively used in the treatment of COVID-19 to bring down morbidity and mortality.

Key Words : COVID-19, SARS, ARB, AT1

Methods to search literature: Google search Eng

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