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Role of Zidovudine and Candesartan in the Novel SARS-CoV-2 Treatment Trials; Theoretical Study

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ABSTRACT

The coronavirus disease 19 (COVID-19) is a highly communicable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which aroused in Wuhan, China and stretch around the humankind. Genomic analysis exposed that SARS-CoV-2 is phylogenetically associated to severe acute respiratory syndrome-like (SARS-like) bat viruses, hence bats could be the possible primary reservoir. The intermediate obtains of beginning and relocation to humans is not known, however, the rapid human to human transfer has been confirmed commonly. There is no approved antiviral medicine or vaccine ready to be used against COVID-19. However, there are a few broad-spectrum antiviral drugs have been estimated against COVID-19 in the current clinical trials, resulted in clinical recovery. In the current review, we summarize the possibility to use Zidovudine as antiviral drug and Candesartan as Angiotensin II Receptor Blocker (ARB) on the basis that Zidovudine works as RNA reverse transcriptase inhibitor (RTI), in addition to Candesartan which act as ARB, the receptors that bind to the spike protein (S-protein) present in the surface of coronavirus.

Keywords: Coronavirus; Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2); COVID-19; Reverse Transcriptase Inhibitors (RTI); Angiotensin II Receptor Blocker (ARB); Candesartan; Zidovudine.

Introduction

COVID-19 belongs to the Coronaviridae family. it represents spike protein on the outer surface of the virus. The virus contains a single-stranded RNA as a nucleic material (Fig. 1). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality. The World Health Organization (WHO) has decided to consider COVID-19 a pandemic.

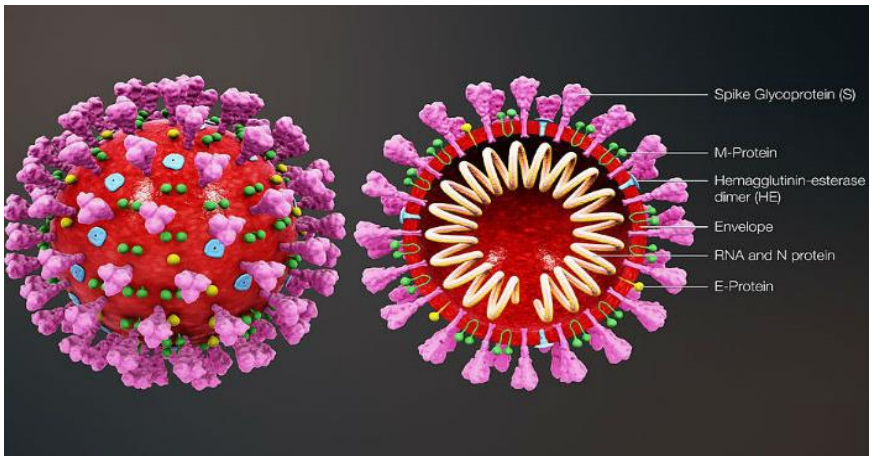

Fig. 1: Structure of COVID-19

https://www.thepharmaletter.com/article/china-s-scientists-unite-in-covid-19-fight

SARS-CoV-2 owns a structure with spike protein and expresses polyproteins, nucleoproteins, and membrane proteins, such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins [1], [2]. The spike protein of SARS-CoV-2 embraces a 3-D structure in the Receptor Binding Domain (RBD) region to keep the van der Waals forces [3]. The 394-glutamine residue in the RBD region of SARS-CoV-2 is recognized by the critical lysine 31 residue on the human ACE2 receptor [4]. The full mechanism of pathogenicity of SARS-CoV-2, from attachment to replication is mentioned in (Fig. 2).

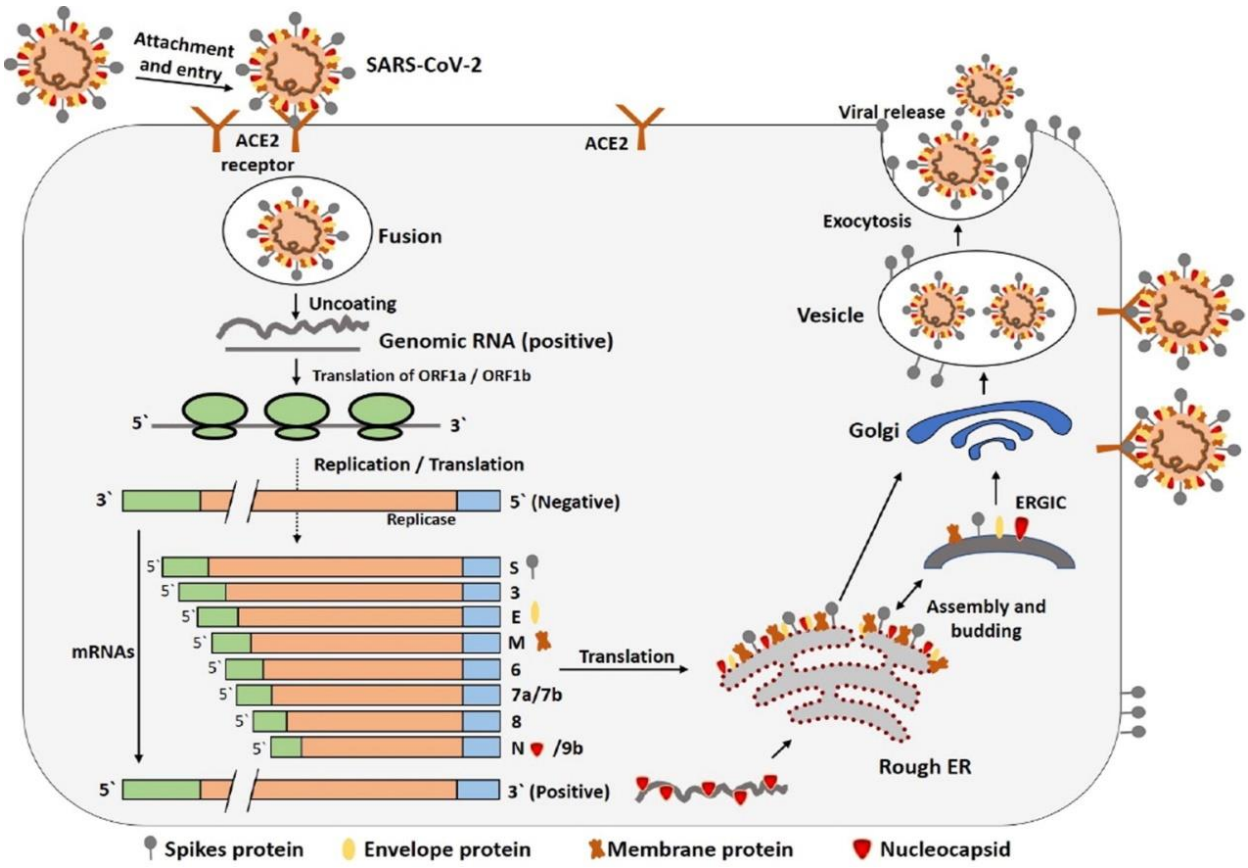

Fig. 2: The life cycle of the SARS-CoV-2 in host cells; its life cycle starts when S protein already binds to the cell receptor ACE2. After receptor binding, the conformation alternates in the S protein simplify viral envelope fusion with the cell membrane via the endosomal pathway. Thereafter SARS-CoV-2 liberates RNA into the host cell. Then RNA is translated into viral replicase polyproteins (pp1a and 1ab), after that they are cleaved into small products by the viral proteinases. The polymerase produces a series of sub genomic mRNAs by way of discontinuous transcription and later translated into applicable viral proteins. Viral proteins and genome RNA are later assembled into virions in the ER and Golgi after which transported via vesicles and released out of the cell. ER, endoplasmic reticulum; ACE2, angiotensin-converting enzyme 2; ERGIC, ER–Golgi intermediate compartment.

Zidovudine (ZDV), also known as azidothymidine (AZT), is an antiretroviral medication used to prevent and treat HIV/AIDS [5]. AZT is a thymidine analogue. AZT inhibit HIV's reverse transcriptase enzyme selectively, the enzyme used by the virus to produce a DNA copy from its positive sense single stranded RNA. Reverse transcription is essential for production of HIV's double-stranded DNA, which would be finally integrated into the genetic material of the infected cell [6], [7], [8].

AZT is converted into the effective 5'-triphosphate form by cellular enzymes. Studies have shown that the specific factor in the inhibitory effect is the termination of HIV's forming DNA chains [9]. The entire mode of action of Zidovudine is well mentioned in (Fig. 3).

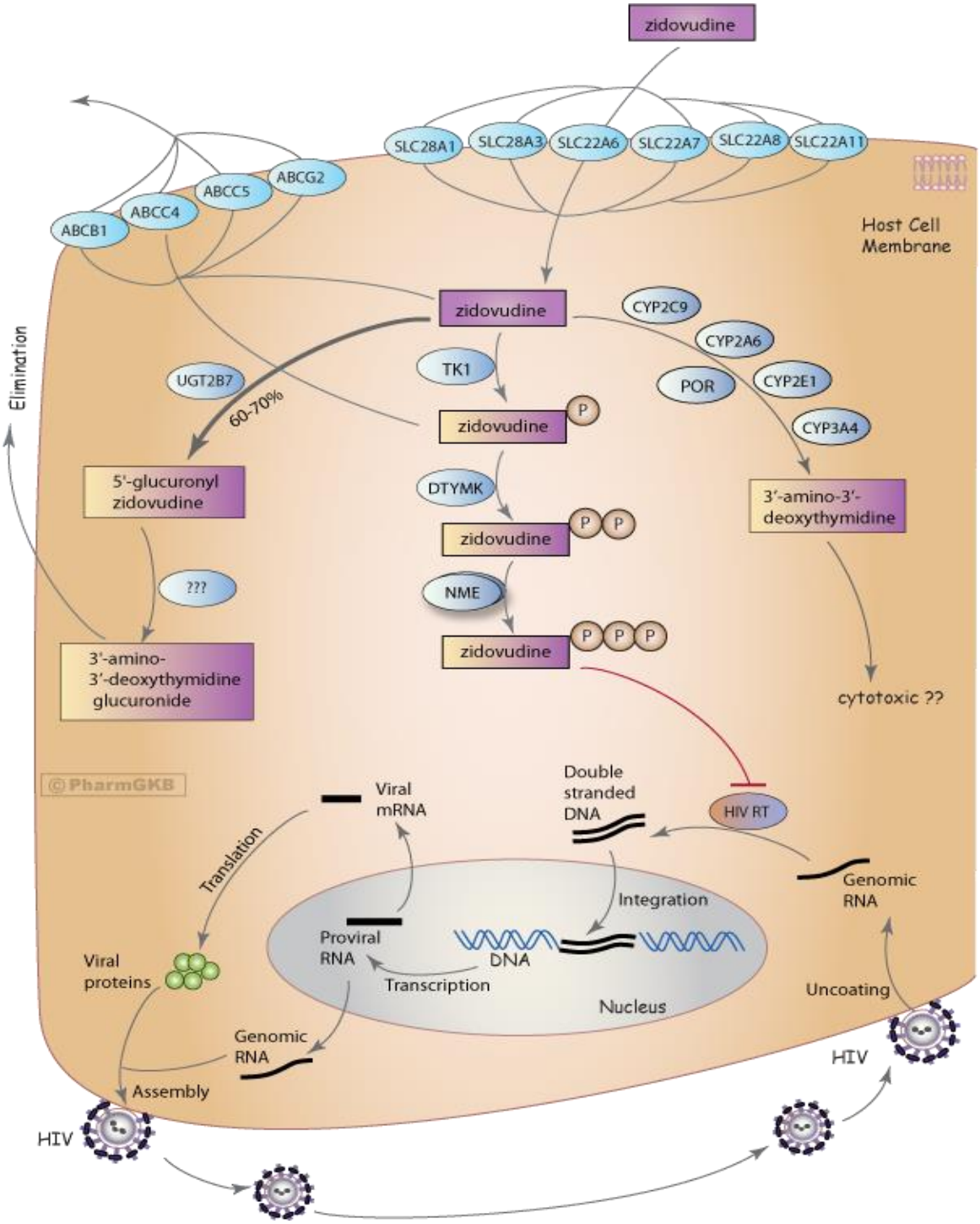

Fig. 3: Mode of action of Zidovudine in the host cell as reverse transcriptase inhibitor.

https://www.pharmgkb.org/page/pathwayLegend

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COVID-19 mode of action in both transcription and replication, and using RTIs resembles that of HIV, thus theoretically Zidovudine may be used as a trial drug in inhibition of COVID-19 transcription and replication pathway.

Candesartan is a selective AT1 subtype angiotensin II receptor antagonist (ARB) and Angiotensin II Converting Enzyme (ACE2). Candesartan medication prescribed for the treatment of hypertension in adults and in children 1 to < 17 years of age, to lower blood pressure after dose adjusting. It is AT_1-receptor antagonist; that is, it blocks the activation of angiotensin II AT_1 receptors. Blockage of AT_1 receptors directly reduces secretion of vasopressin, and reduces blood pressure. The entire mode of action of Candesartan is well mentioned in (Fig. 4).

COVID-19 begins invading into the body by binding to the host cell receptors, the same action which resemble candesartan via the same pathway of Angiotensin II, thus Candesartan may inhibit this pathway, furthermore candesartan will act as ARB leading to interference with S-protein at the site of binding.

Fig. 4: Mode of action of Candesartan as ARB and ACE2 blocker.

Discussion

The study demonstrates a correlation between the activity of both Angiotensin II Receptor Blockers and Reverse Transcriptase Inhibitors towards the binding sites and RNA replication of coronavirus 2 respectively. These data support our expectations and hypotheses, also explain the significance of using these medications with little or absence of unexpected results such as side effects or contraindications may related to Zidovudine or Candesartan, as the dosage can be adjusted in children, elderly and during pregnancy, and lactation. Also, mild hypotension that may be results due to anti-hypertensive effect of Candesartan can be monitored after adjusting its dose. The safety of these medications supports our explanations and making an argument for our position.

Conclusion

Since Zidovudine inhibits RNA Reverse Transcriptase Enzyme so it may prevent COVID-19 transcription and replication pathways. On the other hand, Candesartan which is ACE2 blocker and has ARB activity, it may prevent binding of spike protein of the virus with ACE2 receptors, therefore it can prevent the entrance of the virus inside the host cell. We suggest using of the two medicines for achieving synergy against the virus attacks. Using them as a trial drugs for treatment may be necessary in this critical time after revision by experts and primary care physicians in order to correct any identified inaccuracies or shortcomings and to ensure that the given data is relevant and concise to clinicians.

Competing Interests

The author declared that no conflict of interest exists in the publication of this article.

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