A Summary of Potential Treatments for COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is an emerging, rapidly evolving situation. The pandemic has infected over 1 million population and caused more than 60 thousand deaths. As of April 2020, no treatment has been documented as effective for COVID-19. Clinical trials and laboratory experiments are being conducted as a global effort to find out the cure. This essay summarises three prospective medication of COVID-19 by documenting their previous indication, known mechanism of action, and discussing the possibility of repurposing the treatment for COVID-19.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] is a novel coronavirus, first identified in December 2019 in Wuhan, China. SARS-CoV-2 is known to cause the acute human respiratory illness, named coronavirus disease 2019 (COVID-19) [2]. Typical symptoms of COVID-19 patients include fever (88%), dry cough (68%), fatigue (38%), and sputum production (33%) [3]. In some, the disease could rapidly progress into pneumonia, multi-organ failure, and other deadly complications. As of 4 April 2020, more than 1 million cases have been reported worldwide, with over 60 thousand deaths and rising [4]. No effective cure for COVID-19 has been identified to date. However, primary evidence is being gathered of existing drugs having potentially relieved symptoms in some COVID-19 cases. In March, the World Health Organization (WHO) launched the "Solidarity" clinical trial as a global effort of assessing the effectiveness of multiple treatments against COVID-19.

This essay is a summary of three prospective COVID-19 treatments as of April 2020. The list of candidate treatments includes Remdesivir, Lopinavir/ritonavir, and Chloroquine. Basic virology and the infectious pathway of SARS-CoV-2 is introduced. Each of the candidate treatments is discussed with the drug's known mechanism of action, laboratory and clinical results regarding SARS-CoV-2 as well as possible action mechanisms against SARS-CoV-2.

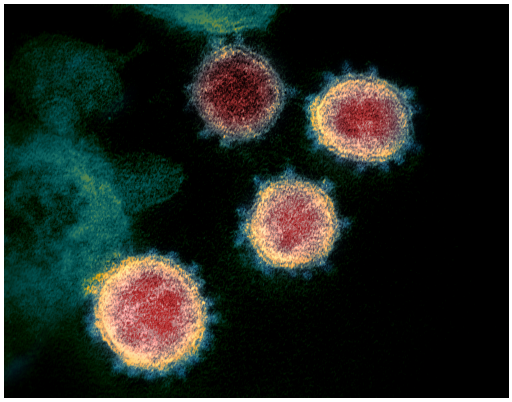

Figure 1. Transmission electron microscope image of SARS-CoV-2 virions.

2. Virology of SARS-CoV-2

The structure of a SARS-CoV-2 virion resembles a typical coronavirus with four structural proteins - the S (spike), E (envelope), M (membrane) proteins together forming the viral envelope, and the N (nucleocapsid) protein responsible for holding the RNA genome [5]. CryoEM images have suggested that the S protein is the critical structure that allows fusion with the cell membrane [6]. Studies have further suggested that SARS-CoV-2 utilizes the angiotensin converting enzyme 2 (ACE2) of human cells as the receptor of cell entry [7, 8]. This explains the SARS-CoV-2's extensive damage to the lungs, where ACE2 is most abundantly expressed.

SARS-CoV-2 is a positive-sense single-stranded RNA (ssRNA) virus. Once entered a human cell, the virus uses its genome directly as mRNA for translation of proteins. These include structural proteins of the virus, as well as the RNA-dependent RNA polymerase (RdRP), an enzyme normally absent in the human cell. RdRP then transcripts the positive-sense ssRNA into negative-sense ssRNA, which is later transcripted back to positive-sense ssRNA. These positive-sense ssRNA could either be packed with the structural proteins to form new virions or serve as mRNA for new rounds of translation.

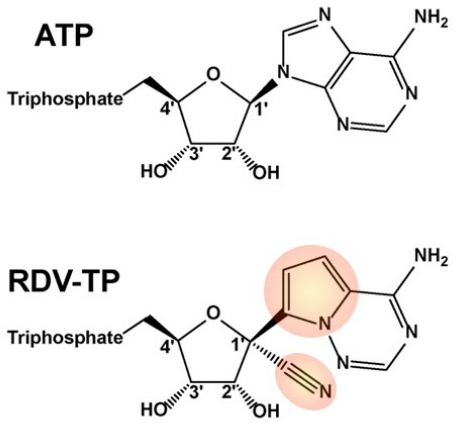

Figure 2. Similar molecular structures of Remdesivir-TP and ATP.

3. Potential Treatments

This section summarizes three potential treatments for COVID-19 as of April 2020. Each medication's previous indication is introduced with the known mechanism of action. Clinical and laboratory results of the medication in COVID-19 are presented. Possible action mechanism against COVID-19 is conjectured.

3.1. Remdesivir

Remdesivir is an anti-viral drug originally developed as a treatment for Ebola virus disease (EVD). In January 2020, the first COVID-19 patient in the United States was administered Remdesivir as compassionate drug use. The patient's condition improved dramatically on the second day and he was later discharged from the hospital [9].

The active form of Remdesivir is known as GS-441524 - an adenosine nucleotide analog. GS-441524 is known to interrupt RNA synthesis in Ebola virus (EBOV)-infected cells by forming the triphosphate Remdesivir-TP (RDV-TP), which competes for incorporation with adenosine triphosphate (ATP) and thus inhibits the EBOV RdRP activity [10].

SARS-CoV-2 (and many other coronaviruses) shares a similar RdRP-driven RNA replication scheme with EBOV. Animal studies for Middle East respiratory syndrome (MERS-CoV) [11] and severe acute respiratory syndrome (SARS) have yielded positive results, suggesting the potential effectiveness of Remdesivir as a COVID-19 treatment. The replication of SARS-CoV-2 might be hindered if RDV-TP could also be incorporated into the mRNA of SARS-CoV-2. This possibility has been confirmed by a recent in vitro experiment [12]. Multiple clinical trials are currently being conducted to validate Remdesivir's in vivo effectiveness. Preliminary results are expected in May.

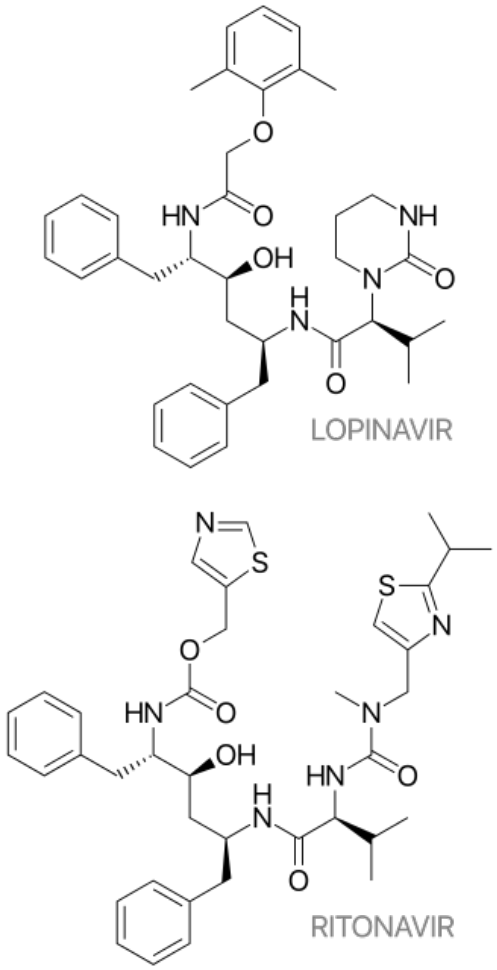

Figure 3. Molecular structures of Lopinavir and Ritonavir.

3.2. Lopinavir/ritonavir

Lopinavir/ritonavir is a first-line combination therapy for HIV/AIDS. Both Lopinavir and Ritonavir are HIV-1 protease inhibitors (Ritonavir used to delay the breakdown of Lopinavir) - enzymes that interfere with the replication of HIV by binding to HIV-1 protease. This binding behavior results in stagnant proteolysis of protein precursors essential for assembling new HIV virions, and thus hinders the HIV replication cycle.

A study in 2004 found that Lopinavir/ritonavir had been much effective among SARS-CoV-1 infected patients [13]. In vitro and in vivo animal studies have also demonstrated the effectiveness of a combination of Lopinavir/ritonavir and Interferon beta-1b against MERS-CoV [14]. With COVID-19, hopes were that Lopinavir/ritonavir could as well hinders the replication cycle of SARS-CoV-2. Results from relevant research have been mixed. It is worth

mentioning that a most recent clinical trial has found no therapeutic benefits of Lopinavir/ritonavir beyond standard care [15]. One explanation could be that that some of the protein intermediates and/or the corresponding protease in SARS-CoV-2's replication cycle has mutated (from that of SARS-CoV-1 and MERS-CoV), and Lopinavir/ritonavir might have limited inhibitory power to the new protease.

3.3. Chloroquine

Chloroquine (and Hydrochloroquine) is used primarily as an antimalarial drug. The antimalarial effect of chloroquine is believed to be associated with the diffusion of chloroquine into the food vacuole of malarial parasite cells. The malarial parasites inside the red blood cells digest hemoglobin (Hb) in a lysosome-like organelle called food vacuole. One of the degradants, heme, is highly toxic and could lyse membrane. The parasite cell detoxifies the heme into non-toxic hemozoin(Hz) crystal via a process called biocrystallization [16]. As chloroquine diffuses into the food vacuole, it is protonated by the acidic environment and becomes CQ^{2+}, which inhibits the crystallization process presumably by binding to heme [16]. The resulting heme-chloroquine complex remains highly toxic [16]. Continued digestion of Hb creates a large concentration of heme-chloroquine complex, which eventually lysis the parasite cell.

Chloroquine also has antiviral effects. Studies have found that viruses than enter host cells through endocytic pathway requires low endosomal PH to trigger the viral fusion proteins [17]. Chloroquine as a lysosomotropic weak base can increase late endosomal PH and thus impair cell entry of these viruses via pH-dependent pathways [18]. However, as SARS-CoV-2 enters the cell by fusion with the cell membrane as supposed to the endosomal membrane, the entry is most likely PH-independent and only requires binding to the receptor. Chloroquine might be effective in COVID-19 due to another antiviral mechanism - In the cell, Chloroquine acts as a zinc ionophore that binds with extracellular Zn^{2+} [19]. The excessive presence of Zn^{2+} in the host cell has been found to inhibit RdRP activity and interfere replication of coronaviruses [20].

4. Discussion

Urgent and rapidly evolving as the COVID-19 situation is, it is crucial that effective medication is found as quickly as possible before the pandemic caused much damage. Under this presumption, repurposing of the existing drugs might be the optimal thing to do. In this essay, we discussed the possibility of repurposing three existing medication as COVID-19 treatments: Remdesivir as a potential inhibitor of SARS-CoV-2 RdRP by RDV-TP incorporation into the viral mRNA; Lopinavir/ritonavir as a possible protease inhibitor to block essential protein synthesis in the

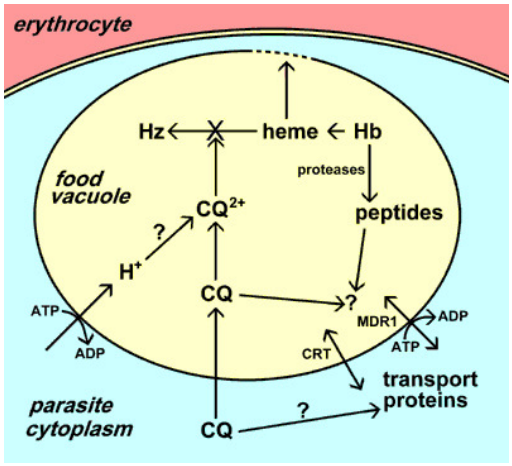

Figure 4. Chloroquine's interference with heme-hemozoin(Hz) conversion in the food vacuole of the parasite cell results in an accumulation of poisonous heme and eventual cytolysis.

replication cycle of SARS-CoV-2; and Chloroquine (Hydrochloroquine) which might inhibit SARS-CoV RdRP activity and viral replication as a zinc ionophore. The theoretical possibility of repurposing existing drugs is based upon the similarity in the structure and replication mechanism of SARS-CoV-2 and other viruses like SARS-CoV-1 and MERS-CoV. This reminds us that experience and knowledge of old viruses could serve as our weapon against the novel enemy. Many more existing drugs could be the targets of future research.

However, it should also be stressed that we must not confuse theoretical analysis with experimental data and patient response. Theory alone would not be enough to defeat the virus. Any new treatment and therapy must undergo evidence-based experimentation and cautious evaluation of benefits and risks before mass application. Moreover, the virology of SARS-CoV-2 must also be extensively studied in the future. For instance, the exact structure of the viral spike and how it connects with the mechanism of cell entry is still unclear. With that type of knowledge, we might be able to design drug molecules that selectively bind to the viral spike, alter its structure so as to compromise the efficiency of viral entry.

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