Slowing Covid-19 Infection Using "Off-Label" Drugs

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Abstract
The novel coronavirus, COVID-19, is now a deadly pandemic for which a definitive cure is yet to exist. SARS-CoV-2, like all viruses, follows similar steps of virus replication including attachment, penetration, uncoating, replication, assembly and release. By targeting each step with a specific drug, maybe we can halt the virus propagation, if not, then, at least buy time till we get the cure. Here we proposed few specific drugs to each step of virus replication.

Keywords: *Covid-19 Infection, "Off-Label" Drugs*

Introduction

Covid19 or SARS-CoV-2, of the Coronavirus family, has over the last two years quarantined the whole world. Its origin is debatable, neither does the virus has a previously used virus backbone to call it a manipulated virus nor is it identical to the bat/pangolin beta coronaviruses, which make it a pure product of natural selection. SARS-CoV-2 has a genomic sequence comprising of around 28 000 bases The outer surface of the virus is covered with spike proteins that contain receptor binding domain (RBD), which is the most variable part of the virus. The virus entry port in human host cell is via high affinity binding to human receptor ACE-2. Multiple tissues in the body contain these trans-membrane proteins, ACE2, to which the virus can interact thereafter producing multiple symptoms and organ damage. Once inside the host cell, viral mRNA replication starts thereby increasing viral load leading to viremia that will cause infected person to exhibit symptoms of Covid-19. With number of newly infected cases and death rate escalating daily, this pandemic finds a comfortable place among the deadliest pandemic experienced in history. To cure it, if possible, we need to understand its pathogenesis at different stages of viral replication cycle. Main stages of viral replication are attachment, penetration, uncoating, replication, assembly and release. In this paper, we briefly overlook the critical steps of the virus replication cycle and proposed drugs specific to each step.

STEP1 ATTACHEMENT

The surface of the virus has spikes proteins (S) which are essential for attachment to ACE-2 receptors on the surface of human host cells, mainly lining the mucosal surface of the respiratory tract. TMPRSS-2 is a trans-membrane protein at the surface of host cell whose importance is to activate the ACE-2 receptor by glycosylation. On the other side, the S proteins are activated by proteolysis. Once activated, there are conformational changes which allow for S-ACE-2 interaction. This forms the basis of attachment of the virus to human host cell. Drugs at this stage are aimed at preventing this S-ACE-2 interaction.

1. ACEi/ARB, Decoy ACE2

The spike (S) glycoprotein of SARS-Cov-2 binds to human receptor ACE2 which then involuntarily serve as main entry point of the virus into cells. ACEi, ARB or ACEi/ARB combination have been proposed to block SARS-Cov-2 entry in cell. Will decreasing level of ACE2 receptor in cells help to fight the infection or worsen infection by receptors up-regulation? A study has shown promising results in hospital where inpatient treatment including ACEi/ARB was associated with lower risk of all cause of mortality as compared to ACEi/ARB non-users. Decoy ACE2 receptors (hrsACE2) could be a promising alternative in preventing COVID19 infection[1]. As its name implies, hrsACE2 acts as a decoy attracting the virus to attach to it rather than infecting human cells and in so doing, it protects the human body from organ damage due to SARS-Cov-2.

2. CAMOSTAT

Camostat mesylate, a serine protease inhibitor, is the ideal inhibitor to the trans-membrane protease serine 2. Previous used for treatment of chronic pancreatitis and postoperative reflux esophagitis, the drug has lately been clinically proven to partially block Covid-19 virus infection through its inhibition of TMPRSS2, which almost halt the binding of S spikes to ACE-2 receptors. This drug is the ideal candidate for this attachment step.

STEP2 PENETRATION AND REPLICATION

After S- ACE-2 interaction, the virus enters the human cell and forms an endosome which has an acidic environment essential for its survival. The genetic material of the virus, in form of mRNA, is then released within the host cell and this mRNA starts multiplying. A protein called RNA dependent RNA polymerase, RdRP, is important for this replication. The three main functions of RdRP are firstly the formation of messenger RNAs, secondly increasing number of RNA polymerase copies and thirdly to enter the cell nucleus. Drug at this stage are aimed at either preventing the entry of virus in the cell or preventing the replication of mRNA in the cell.

1. Hydroxychloroquine

Hydrochloroquinine, (HCQ), has since this 2020 pandemic been the game changer drug in controlling Covid19 related infection. It works by altering the pH of lysosomes in antigen-Presenting cell thereby modifying a series of immunological pathways that results in decrease inflammatory process. HCQ blocks virus infection by altering the endosomal pH required for virus/cell fusion and also interfere with glycosylation of cellular receptors of SARS-Cov-2 and is therefore a promising silver bullet to this pandemic. HCQ has been used alone or in combination with Azithromycin (AZI) as the first line treatment option while simultaneously ongoing clinical trials were being performed to confirm its efficacy. One study, with a dose regimen of 600mg HCQ+ 5oomg AZI daily for 10 days, showed a fall in viral load of infected patient by 6^{th} treatment day and thereafter prioritized the use of HCQ+AZI combination.

2. Umifenovir

Umifenovir, brand name Arbidol, is a known antiviral medication used for treatment of influenza in Russia and China. Umifenovir is a direct-acting antiviral drug, possessing virucidal properties and also targeting multiple stages of virus life cycle. Therefore the drug efficacy is thought to be due to its dual activity. Though not FDA approved for Covid-19 treatment, the drug has shown promising results in controlled trials when used in combination with HCQ[2].

3. Remdesivir

Remdesivir is an adenosine analogue that incorporates into virus RNA chains and causes premature termination in viral mRNA chains, a property which makes Remdesivir a promising antiviral drug to prevent progression of COVID-19 infection. It prevents the enzyme RdRP to add more RNA subunits to new RNA strands. A small investigational treatment group received an initial dose of 200mg followed by daily dose of 100mg over 10 days treatment and should this proved effective when compared to placebo group and reproducible in larger study groups then Remdesivir may have a definite approval to be used worldwide to fight COVID infection.

STEP 3 REPLICATION AND ASSEMBLY

Newly formed mRNA travel to the host nucleus and enters it, under assistance of a transport protein called IMPORTIN. Once in the nucleus, the mRNA exerts its actions; firstly it inhibits the nucleus ability to divide to form new cells and secondly it hijacks the protein synthesis ability of the nucleus to produce only viral protein. The mRNA action in nucleus also suppresses the ability of the cell to signal any invasion thereby affecting the

body immune response. Once new viral cells are formed, the cells burst and release the new virus in the blood stream to infect other cells and organ distally. Here we aimed for drugs to prevent the mRNA to make copies of itself and/or prevent its entry in host cell nucleus.

1. **Importin inhibitor- Ivermectin**

Ivermectin is a semi-synthetic derivative of avermectin family that is used to treat parasites and pests. In body of parasites, ivermectin works by binding to some specific ivermectin-sensitive ions channels on cells surface, causing influx of Cl- ions across cell menbrane and this results in hyperpolarization leading to muscle paralysis. How an anti-parasitic drug gained overnight recognition? Well, Credit goes to a team, from Melbourne's Monash University, led by Dr Kylie Wagstaff. The scientists found that in culture, one single dose of ivermectin potentially eradicated all viral mRNA with 48 hours.

STEP 4 RELEASE, BODY RESPONSE AND CYTOKINE STORM

The new viruses travel in the blood stream to infect new host cells. The human body response depends on the host immune system status, viral infectivity and viral loads. People with lower immune system and/or associated comorbidities are more susceptible and have worst prognosis. At molecular level, there is an overproduction of pro-inflammatory cytokines leading to a cytokine storm induced by virus. These pro inflammatory cytokines lead to ARDS, multi-organ damage and death. Targeting cytokines during management could improve survival rates of affected patients.

1. **Anti VEGF-Avastin**

Avastin (Becacizumab) is an anti VEGF (vascular Endothelial Growth Factor) drug that is used primarily for treatment of cancers (colon, rectal, lung and kidney) and for specific eye disease (macular edema). VEGF, a potent vascular permeability inducer, is higher in concentration in patient infected with COVID19 than normal person. This increased vascular permeability leads to pulmonary edema that caused pulmonary edema(PE), acute lung injury(ALI) and acute respiratory distress syndrome(ARDS), all contributing to death of critically ill patients. Avastin can be used to reduce the vascular permeability, thereby reducing risk of ALI, PE,and ARDS. Few data show, Avastin has been used in some treatment center with positive results. Hence avastin may be regarded as a key therapeutic drug in milder to severe cases prone to ALI, PE and ARDS.

2. **Convalescent plasma**

Plasmapheresis is a technic where blood from a person flow through a needle, catheter to a machine which separates the blood into its major component, cells and plasma, retaining required component and returning the rest back to the person circulation. Antibodies present in convalescent plasma of a donor can then be transfused to a patient who lacks these protective antibodies and therefore the later can gain some immunity against the offending organism. This is a passive immunity. In context of SARS-Cov-2, a COVID19 survivor blood plasma contains antibodies to SARS-Cov-2 making him a potential donor and a critically ill COVID19 patient would lack these protective antibodies is a potential recipient. Once a donor fulfills some donor eligibility protocols, he can donate blood and the separated convalescent plasma collected can then be transfused to other COVID19 patients. A small study showed the efficacy of treating critically ill COVID19 patients with therapeutic plasma exchange. This technic has provided satisfying results in hospital in many countries.

3. **EXO CD24**

This new drug, under phase 1 trial, has been developed in Israel and has shown promising results. The drug has been used to help patients with moderate immune response to overcome or prevent deadly cytokine storm. In a

study, 29 out of 30 patients with moderate to severe cases of COVID 19 were treated with EXO CD24 and they quickly recovered from the disease. Credits for these findings go to Prof. Nadir Arber from Israel. The drug regulates the homeostatic proliferation of T cells and negatively regulates inflammation in the lungs to prevent ARDS and thereby it calms down the immune system and curbs the storm. Hopefully this will be the silver bullet to curing Covid-19 infected patients.

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