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Review Article

Therapeutic drug targets for COVID 19

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ABSTRACT

Covid 19, caused by Corona virus started in Wuhan, China on December 2019 and the disease has spread rapidly among 210 countries. Corona virus disease, a RNA virus infection affected millions of people and caused death in many patients. The symptoms include fever, sneezing, coughing and other respiratory symptoms. The disease can highly affect the elderly, immunocompromised and the fatality rate is increased among these people. There is no definitive treatment till now and patients are treated symptomatically. The steps involved in the pathogenesis including attachment of the virus to the host cell, replication, protease action, assembly of nucleocapsid, release by exocytosis and they are the potential targets for the drugs. There are various trials ongoing to evaluate the efficacy of antiviral drugs, chloroquine, hydroxychloroquine, convalescent plasma and monoclonal antibodies. This review gives a summary of the most important drugs and drug targets used in the management of Covid 19.

Keywords: ACE inhibitors, Convalescent plasma, Covid 19, Hydroxychloroquine, Remdesivir

INTRODUCTION

Corona virus disease (Covid 19) an infectious disease caused by severe acute respiratory corona virus (SARS-CoV-2) manifested as a series of pneumonia cases in China in December 2019. The severity ranges from asymptomatic respiratory infection to acute respiratory disease in 15% of population and fatality in 4% of population. The source of infection was believed to be zoonotic in origin until the first case of human to human transmission was reported. The mode of transmission is through air droplets and the disease is highly prevalent in the elderly, immunocompromised, diabetes, and cancer patients. The incubation period range from 2-14 days and the symptoms include cough, sore throat, fever and breathlessness. SARS Covid 19 has infected around 210 countries including China, Japan, USA, South Korea Italy, Iran and the transmission is still growing.¹⁻³ WHO declared it as a pandemic on March 11, 2020 based on its high rate of transmission and its tendency to spread worldwide There is no treatment available till now though some drugs are proposed to have effect on Covid

19. The drug that are identified to be effective in Covid 19 are hydroxychloroquine, HIV protease inhibitors ritonavir/lopinavir, convalescent plasma and remdesivir.⁴ The current management of the disease include prevention of infection, supportive care, symptomatic management and mechanical ventilation in critically ill patients.⁵ This review gives a summary of the drugs effective in Covid 19.

Structure of virus, replication and pathogenesis

Corona viruses are single stranded RNA viruses with envelope. These viruses infect a wide variety of animals like bats, dogs, turkeys, horses, and birds. Six types of corona viruses are reported till now and the characteristics of the virus include rapid mutation, cross reactivity among variety of species, adaptivity to different environmental conditions. Among the six viruses only two viruses i.e. SARS-CoV and MERS (Middle East respiratory syndrome) CoV causes severe infection. The term Corona is derived from Latin word meaning Crown or halo since the virus resembles them in shape. The

single stranded RNA virus resembles 86.9% of bat corona virus and so it is suspected to have originated from bats. Corona virus has a spike like protein which is endocytosed to the cell and attaches with the cellular receptor to initiate the replication process. The spike like protein has various structural domains like RBD, fusion domain and S2 domain which are better therapeutic targets. The virus has high affinity ACE2 enzyme in the ciliated epithelial cells of the bronchus and thus prone for the lung infection.⁶ The virus is released and translated producing polyproteins which is later cleaved by the protease to form structural proteins (Table 1). These proteins are assembled together and the corona virions leaves the cell by exocytosis.⁷

Table 1: Steps involved in pathogenesis.

Step	Drugs/targets
Attachment of the virus to the ACE 2 receptor in ciliary epithelial cells	Convalescent plasma Drugs that block ACE2
Glycosylation of ACE receptor Virus endocytosed to the cell, utilize the ribosome of the host cell, replication to polyprotein	Chloroquine
Protease action of cleaving the polyprotein to replicase transcriptase complex	Lopinavir Ritonavir
Replicase-RNA dependent RNA polymerase Replication and transcription of the RNA virus	Remdesivir
Assembly of viral nucleocapsid and release by exocytosis	-
Immune reaction and cytokine storm in Covid infection	Tocilizumab IL-6 antibody

Role of convalescent plasma and antibodies in Covid 19 infection

Convalescent plasma is the plasma derived from the recovered Covid patients aged between 18-65 years after 14 days of recovery. The dose of the convalescent plasma is 3 ml/kg per dose to be administered in 2 days. The neutralizing antibodies in the plasma prevent the attachment of the spike protein to the target cells thus reducing further viral replication. The plasma also has an immunomodulatory effect in controlling the exaggerated release of cytokines and activated complement system.⁸ The convalescent plasma administered to five critically ill patients in China is found to be effective in reducing the clinical symptoms of the patients. Another 2 case series report by Duan et al and Zhang et al also confirmed that convalescent plasma has some clinical benefits when administered in 10 critically ill and 4 critically ill patients respectively.^{9,10} The advantages of the convalescent plasma in Covid includes improved clinical efficacy, limited cost, and easy method of obtaining plasma from donors. But the limitations of these include that they are

tested in smaller population which cannot be generalized, unclear inclusion criteria, poor study design, influence of confounding factors, and late treatment in critically ill patients.¹¹ The other disadvantages are transfusion related adverse effects and less evidence of the efficacy of antiviral antibodies compared to the antiviral drugs that stop viral replication.¹²

Role of antiviral drugs in Covid 19

Antiviral drugs

In vitro and animal studies on antiviral drugs: Remdesivir, a nucleotide adenosine analog was evaluated in studies involving Ebola virus infection and Middle East respiratory syndrome. The drug was tested in in vitro studies using human epithelial cell cultures in which it prevented the SARS CoV and MERS Cov replication.¹³ The combination of remdesivir and chloroquine was also proved to be efficacious in some in vitro studies.¹⁴ An antiviral NHC EIDD 2801 tested in mice infected with MERS and SARS Cov infection was proved to be efficacious in improving the pulmonary infection.¹⁵

a) Remdesivir (GS5734)

It is a nucleotide analog inhibitor which inhibits the enzyme RNA dependent RNA polymerase and RNA synthesis. The drug incorporates into the RNA and results in premature chain termination. The drug was proved to have antiviral activity against Ebola and MERS in nonhuman primates and other animal studies.^{16,17} It is given as an injection since the drug has poor oral absorption. The most common adverse effects of the drug include renal dysfunction, diarrhoea, increased level of hepatic enzymes and rashes.¹⁸

Table 2: Compassionate use of remdesivir.

Detail of the study	Result of the study
10 day course of 200 mg of Remdesivir i.v. (n=61) 8 people data not analysed. Remaining 53;22 from US, 22 from Europe /Canada, 9 from China (funded by Gilead sciences)	36 out of 53 showed clinical improvement ²³

The first Covid patient in US was administered the drug remdesivir but the patient's condition deteriorated whereas the other patient in California showed improvement with the drug.^{19,20} The drug was provided on compassionate use i.e. the FDA approval to use the drugs without clinical trials in the case of critical ill patients. The data available about the drug is limited and several trials are ongoing to evaluate the efficacy of remdesivir.²¹ From the limited studies available it is identified that the drug has moderate efficacy, and acceptable safety. The duration of the treatment and use of i.v. drug for patients with mild illness is yet unknown.²²

b) Favipiravir

A nucleoside analogue which inhibits the enzyme RNA dependent polymerase was tested in Ebola and influenza viral infections.^{24,25} The drug is better tolerated and causes adverse effects like hyperuricemia, liver dysfunction, and gastrointestinal abnormalities.²⁶

Protease inhibitors

The cleavage of the polyprotein into helicase and polymerase is mediated by two proteases like papain like protease and chymotrypsin like protease (3CLpro). The anti HIV drugs like lopinavir/ritonavir are proved to have inhibit the chymotrypsin like protease and hence considered to be a good therapeutic target. But the levels of the protease inhibitor to be used to achieve desirable drug level requires a high dose. The protease inhibitors being a substrate of CYP3A4 has severe drug-drug interactions when used in elderly patients with Covid 19 who have other comorbidities. The p glycoprotein, an efflux transporter also reduces the efficacy of the drug.

Extracellular vesicle being the biological vesicles can be extracted from the plasma of the infected Covid patients, loaded with protease inhibitor drug and reloaded in the same patient. This enhances the targeted delivery of the drug and thus prevents the drug interactions and improve the efficacy.¹⁹ Around 77 studies are listed in the clinical trials for the use of lopinavir/ritonavir in Covid 19.

Table 3: Lopinavir/Ritonavir trials.

Place of study	Treatment arm 1	Treatment arm 2	Results
China n=199 patients	Lopinavir/Ritonavir	Standard of care	Lopinavir/Ritonavir group-decreased mortality rate and ICU stay. ²⁷
China (n=55) pre-symptomatic patients	Lopinavir/Ritonavir		No admission required and all discharged. ²⁸

Role of chloroquine/hydroxychloroquine in covid 19 infection

Chloroquine a known antimalarial drug and its analog hydroxychloroquine is used in smaller randomized trials. Both chloroquine and hydroxychloroquine act by increasing the endosomal pH and thereby inhibiting the fusion of the virus and the host cell membrane. The glycosylation of ACE2 receptor is inhibited by chloroquine. In a study conducted in small number of patients in china hydroxychloroquine showed better clinical outcome compared to ritonavir/lopinavir but it is not statistically significant.²⁹ It is essential to monitor the adverse effects and QT interval for those patients who are prescribed with hydroxychloroquine.³⁰

Table 4: List of some published small randomized clinical trials with Chloroquine/Hydroxychloroquine.

Place of study	Treatment arm 1	Treatment arm 2	Results
China Non critically ill patients	Chloroquine n=10	Lopinavir/Ritonavir n=12	Chloroquine showed better clinical outcome (negative SARS-CoV2) Limitation: Chloroquine arm had young patients. ²⁹
China Patients with mild pneumonia (Total n=62)	Hydroxychloroquine 200 +Standard treatment (Oxygen, antivirals, antibacterial)	Standard treatment	In 80.6% of patients treated with hydroxychloroquine significant improvement in chest scan. ³¹
France	Hydroxychloroquine Dose thrice daily for 3 days Out of 26 in hydroxychloroquine arm 6 excluded from study 6 received both azithromycin and hydroxychloroquine The remaining 14 only hydroxychloroquine	Treatment unknown n=16	Among the patients who received HCQ 8/14 and in the combined hydroxychloroquine and Azithromycin 6/6 showed elimination of virus on Day 6. ³²
Pilot trial China n=30 (1:1 ratio)	Hydroxychloroquine 400 mg 5 days plus standard treatment	Standard treatment	13 cases in HCQ group and 14 cases in control group -negative for virus on day 7. ³³

The list of trials with chloroquine/ hydroxychloroquine is given in the Table 4. The major limitations of these trials are small sample size. In June 2020 there are 78 studies in the use of chloroquine on Covid 19 as updated in the website clinical trials.gov.

ACE inhibitors and Covid 19

There was a hypothesis that stated the patients who are on ACE inhibitors and ARB blockers has high susceptibility to Covid 19. The other hypothesis is that the drugs and

peptides target ACE2 can be potential drugs for the treatment of the infection.³⁴

The S protein in the virus acts on ACE2 receptor in the alveolar cells and in the lymphocytes of the lung for the entry. ACE is the angiotensin converting enzyme which converts angiotensin I to angiotensin II. The angiotensin II causes vasoconstriction, bronchial constriction, inflammatory, fibrotic changes in lung that leads to acute respiratory distress syndrome. One of the hypothesis is that ACE inhibitors and ARB blockers decrease levels of angiotensin II and the disease promoting effect.³⁵

ACE 2 is a homologue of ACE and it has two actions- 1) Conversion of angiotensin I to angiotensin 1-7; and 2) Conversion of angiotensin I to angiotensin 1-9.

Some research studies hypothesized that the ACE2 levels and ACE 2 gene expression is increased in patients who are on ACE inhibitors and angiotensin receptor blockers.^{36,37} So there was a question to whether continue or discontinue the ACE inhibitors. But there is structural difference between ACE and ACE2 and their active sites and so the effect of ACE inhibitors on ACE2 levels is still not clear. A study by Mehta et al also reported that there was no association between the use of ACE inhibitors and positivity of covid19.³⁸ The European society of cardiology recommends the continuation of these drugs in haemodynamically stable patients with hypertension and other cardiovascular comorbidities. Discontinuation of the drugs may be considered in haemodynamically unstable Covid 19 patients.^{39,40} Many studies also recommend that there is no need to discontinue RAAS inhibitors as the discontinuation of ACE inhibitors may not reduce much ACE2 levels and there may not be much clinical benefits.⁴¹

Monoclonal antibodies as therapeutic targets:

The serum levels of cytokines are increased in patients with Covid resulting in cytokine storm. One strategy to decrease the cytokine mediated organ damage is the use of tocilizumab, a monoclonal antibody that targets IL-6. A clinical trial conducted in China with 21 Covid patients reported recovery of all including two critically ill patients.⁴¹ The recommended dose of tocilizumab is 400 mg diluted in 100 ml of normal saline (first dose 4-8 mg/kg).⁴³

The monoclonal antibodies are also targeted against the virus s protein which mediates the attachment of the virus to the cell surface receptor.

CONCLUSION

The ongoing trials on hydroxychloroquine, lopinavir/ritonavir, remdesivir are conducted in small number of patients and they lack statistical significance. The current data from the clinical trials is limited to

provide a clear information or guideline for the treatment or prophylaxis of Covid 19.

The medications that are currently used also has adverse effects and shows unclear efficacy. Further large randomized controlled clinical studies are required to evaluate the efficacy of these drugs. The current aim in the management of Covid 19 is to prevent further human to human transmission, to reduce the mortality and impact of burden on the population.

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