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Review Article

Pharmacological Treatments for COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) was initially reported in December 2019 in China and cause an acute respiratory disease. Since then, no specific therapy or vaccine is being available for the treatment or prevention of the disease. Teams of scientists around the world are racing to develop a treatment to end the COVID-19 pandemic. Extensive clinical trial data are required to identify safe and effective treatments for COVID-19. In this review, we aim to provide an overview of antiviral drugs, their pharmacological features, and their outcome against the disease based on the available data. We have discussed their mechanism of action, doses, and adverse effects in detail. In addition, a close review of vaccines that are in the developmental state has also been discussed.

Introduction

After the identification of the first COVID-19 cases in Wuhan, China, in December 2019, the number of cases is constantly increasing [1, 2]. As of _____, more than __ million cases have been reported across the world, causing more than ____ deaths. Due to the rapid worldwide spread of the disease, the World Health Organization (WHO) has announced COVID-19 as a pandemic and worldwide threat [2]. Corona viruses are a group of single-stranded RNA viruses characterized by a crown-like spike protein on the surface. The virus belongs to the β-coronavirus which causes severe acute respiratory syndrome (SARS-CoV) [3] and Middle East Respiratory Syndrome (MERS-CoV) [4] in Guangdong, China in 2002, and Saudi Arabia in 2012, respectively. Similar to the other corona viruses, the spike protein strongly interacts with the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease, serine 2 (TMPRSS2), both located on the surface of the target cell [5, 6]. On entry, the virus particle is uncoated, and its genome enters the host cell cytoplasm initiating the replication and transcription process [6]. The formed progeny viruses are then released from the host cell by exocytosis through secretory vesicles which can easily infect other host cells [6].

Antiviral agents

The class of medications used to treat viral infections is called antiviral drugs. The antivirals that can kill a wide range of viruses are called broad-spectrum antiviral [7]. Contrasting most antibiotics, the mechanism of antivirals is to inhibit the development of the pathogens, while antibiotics work by killing the target pathogens [7]. Some of the commonly used antivirals are used in HIV, herpes viruses, hepatitis B and C, and influenza A and B diseases. In this pandemic time, several antiviral agents, most of them used for human immunodeficiency virus (HIV), hepatitis, and flu symptoms, are been used all around the world in COVID-19 patients [8-10]. Unfortunately, developing a safe and effective drug is a challenging task as the viruses use the host's cells to replicate. Therefore, the drug should target the virus without targeting the host cell. In addition, due to the viral variations and mutation, the task becomes more difficult, Table 1.

Remdesivir

Remdesivir is also known as GS-5734 and is a monophosphate prodrug that undergoes metabolism to and active C-adenosine nucleoside triphosphate analogue. In this pandemic situation, the drug showed promising potential therapy as it has shown broad-spectrum in-vitro activity against several CoVs. In SARS-CoV-2 it has shown EC50 and EC90 values of 0.77uM and 1.76 uM, respectively [11-13]. The drug was first clinically used in the Ebola pandemic [14]; however, its use has also been recommended in COVID-19 disease as well [15, 16]. The recommended dose of remdesivir is a single 200-mg loading dose, followed by a daily infusion of 100-mg drug. As the drug supply is limited, the drug is recommended for prioritizing bases and is generally provided to patients requiring supplemental oxygen. In addition, it is only recommended for patients with moderate COVID-19 infection. The drug should be administered to the patients for five days or until gets discharged from the hospital.

The drug acts by binding to the viral RNA-dependent RNA polymerase and inhibiting the viral replication through premature termination of RNA transcription. Its activity against SARS-CoV-2 has been observed in vitro [17-19]. The drug has shown gastrointestinal symptoms like nausea, vomiting, elevated prothrombin time, and elevated transaminase levels. The use of remdesivir is not recommended with strong inducers like rifampin [13]. Moreover, the use of remdesivir is also not recommended with chloroquine or hydroxychloroquine as it may decrease the antiviral activity of remdesivir. The effectiveness and safety of the drug have not been evaluated in pregnant patients and pediatric patients. Therefore, for pregnant patients, they should only be used when the potential benefit justifies the potential risk to both mother and fetus, while a clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (ClinicalTrials.gov identifier NCT04431453) [20, 21].

Chloroquine or Hydroxychloroquine

Chloroquine is an antimalarial drug generally used in areas where malaria remains sensitive to its effects. Hydroxychloroquine, an analogue of chloroquine, and is used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Generally, hydroxychloroquine is safer than chloroquine. A new study by China has reported the drug was successful to treat only 100 COVID-19 cases causing an enhanced viral clearance, improved radiologic findings, and reduced disease progression [22-24]. However, the study has not been presented or published for peer review, restricting the validation of the study. In a different open-label nonrandomized French study performed on 36 patients, shows improvement in the virologic clearance with the use of 200mg of hydroxychloroquine (by mouth in every 8 hours) compared with the control COVID-19 patients. The authors have also suggested that the combination of hydroxychloroquine and azithromycin causes in an improved viral clearance in comparison to the use to only hydroxychloroquine [25, 26]. Contrary to these results, a prospective study Chinese study performed on 30 patients shows no difference in the virologic outcomes. In this study, the patients were given 400 mg of hydroxychloroquine daily for 5 days. At day 7, no change in the virologic clearance was observed between for the hydroxychloroquine plus standard of care group and standard care group, respectively [27, 28].

According to the proposed mechanism of action both chloroquine and hydroxychloroquine increase the endosomal pH, inhibiting fusion of the SARS-CoV-2 and the host cell membranes [4]. Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor, which may interfere with binding of SARS-CoV to the cell receptor. In vitro, both chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from early endosomes to endolysosomes, which may be required for the release of the viral genome [6]. Both chloroquine and hydroxychloroquine have immunomodulatory effects. Some of the cardiac adverse effects of chloroquine and hydroxychloroquine are; QTc prolongation, Torsade de Pointes, ventricular arrhythmia, and cardiac deaths. Furthermore, hypoglycemia, rash, and nausea (divided doses may reduce nausea), retinopathy, bone marrow suppression may occur with long-term use, but this is not likely with short-term use. No dosing changes for chloroquine or hydroxychloroquine during pregnancy has been recommended by WHO. In addition, the drug has also been recommended for pediatric populations as it has already been used routinely for the treatment and prevention of malaria and rheumatologic conditions.

Hydroxychloroquine Plus Azithromycin

Chloroquine and hydroxychloroquine have been evaluated for the treatment of COVID-19 in small, randomized clinical trials, case series, and observational studies. In COVID -19 patients prolonged QTc is found when hydroxychloroquine and azithromycin are given together. Carefulness is necessary while using these drugs as both azithromycin and hydroxychloroquine has long half-lives [1]. Multiple reports demonstrate that concomitant use of hydroxychloroquine and azithromycin can prolong QTc; hydroxychloroquine plus azithromycin is linked with more cardiac arrest [5-7]. The use of this combination warrants careful monitoring.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

The WHO recommends against using lopinavir/ritonavir or other HIV protease inhibitors for the treatment of COVID-19, except in a clinical trial. The ability of HIV protease inhibitors to inhibit SARS-CoV-2 protease is doubted. During SARS-CoV-2 replication, polyproteins are cut into an RNA-dependent RNA polymerase and a helicase [1]. This cleavage is performed by two different proteases, i.e., papain-like protease (PLpro) and 3-chymotrypsin-like protease (3CLpro). The drug acts as the inhibitor of SARS-CoV 3CLpro *in vitro*; however, due to a poor selectivity index, a high concentration of drugs is required to achieve meaningful inhibition in vivo. Some of the common adverse for lopinavir/ritonavir are nausea, vomiting, diarrhea (common), QTc prolongation, and hepatotoxicity. The lopinavir/ritonavir is generally considered safe in pregnant women with HIV. Lopinavir/ritonavir is not measured safe during pregnancy as the oral solution has a high percentage of alcohol and PEG. For the treatment of HIV, this drug is approved for infants, children, and adolescents. However, information on the value of using lopinavir/ritonavir to treat COVID-19 in pediatric patients is lacking.

In an open-label RCT study of 199 patients, Cao et al. have compared the efficacy of the drug vs standard group and found no difference between the group [29]. In addition, no significant difference in viral clearance or mortality rates was observed.

Darunavir/Cobicistat or Darunavir/Ritonavir

Darunavir a useful drug for HIV/AIDS belongs to the protease inhibitor (PI) class and works by hindering HIV proteases [30]. It also hinders the 3CLpro enzyme of SARS-CoV-2 and the PLpro enzyme [30]. The darunavir/cobicistat has been found to be not effective in the treatment of COVID-19 in an unpublished randomized controlled trial in China.The drug has several common and severe side effects but it appears to be safe for baby for pregnant women [30].

Conclusions

Even before COVID-19 was declared as a pandemic, researchers all around the world are trying to find the potential treatment of the disease. Efforts are being made to study and analyze research done on previous coronavirus outbreaks, such as SARS and MERS. The harsh reality is the development of a drug or vaccine is a lengthy and expensive process. It requires multiple drug candidates, many years, and a huge amount of investment. Clinical trials on a massive scale are being performed to evaluate new and repurposed drugs as soon as possible. With these studies still in progress WHO and public health authorities across the globe have recommended the practice of non-pharmacological interventions like social distancing, hand hygiene, use of facemask. Isolation of infected patients, usage of personal protective equipment. Although, strict adherence to these measures and community lockdown practice by the local government the cases of COVID-19 are still increasing. Recent the launch of the world's first COVID-19 vaccine by Russia has shown a ray of hope. The race to find an effective treatment will have a global implication, not just for the revenues for the successful developers and manufacturer, but for the health of billions of people worldwide.

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