

A contemporary look at COVID-19 medications: available and potentially effective drugs

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Abstract. – OBJECTIVE: There have been significant changes to the management of COVID-19 in recent months, including protocols and guidelines designed to prevent, diagnose, and treat the Novel Coronavirus (COVID-19). Several management options have been suggested and have since gained popularity, though we expect additional modifications to be made, as well as more new cases in the coming months, given a lack of definitive treatment and well-controlled experiments. This review highlights the available and potential treatments, along with the challenges associated with each.

MATERIALS AND METHODS: We conducted a comprehensive overview of all peer-reviewed studies, editorial comments, and letters to the editor based on a search in PubMed, Google Scholar, Web of Science, and Scopus. The following terms were used: “COVID-19,” “SARS-CoV-2,” “drug,” “treatment,” “medication,” and “management.” All searches were done between March and May 20, 2020.

RESULTS: There are several potential medications available for COVID-19, such as Interferon α (IFN- α), Teicoplanin, Ribavirin, Galidesivir, Lopinavir/Ritonavir, Chloroquine phosphate, Arbidol, Velpatasvir, Favipiravir, Ledipasvir, Remdesivir, Sofosbuvir, Darunavir, Qingfei Paidu Decoction (QPD), and Imatinib. However, we do not have a definitive and specific treatment yet.

CONCLUSIONS: We are expecting to have more cases in the coming weeks/months. Therefore, further research is needed to characterize the disease behavior, to find the absolute drug, and to refine the treatment.

Key Words:

COVID-19, SARS-CoV-2, Drugs, Management.

Introduction

The virus SARS-CoV-2 appeared in China in December 2019 and then spread rapidly

around the world. As of July 10, 2020, there have been more than 12 million confirmed cases of COVID-19, and almost 550,000 deaths have been reported worldwide¹. The number of cases and deaths inside mainland China has remained far less than those from outside the country, and new cases and deaths dramatically decreased at the site of origination¹. Scientists are competing globally to identify drugs to treat COVID-19². Some drugs have been quickly investigated in research trials and have shown primary efficacy against SARS-CoV-2. Others have been included in several guidelines such as the Chinese Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia, issued by the National Health Commission for COVID-19 treatment³. A research study between several Chinese institutes found 30 drugs with potential antiviral activity against COVID-19, and many scientists are exploring drugs that could potentially combat COVID-19^{3,4}. However, there are no specific verified antivirals for SARS-CoV-2 at this moment, and the efficacy and safety of these potential drugs need further confirmation in further preclinical and clinical trials. In this manuscript, we present and summarize these treatments and then discuss the challenges associated with each.

Materials and Methods

We conducted a comprehensive overview of all peer-reviewed studies, editorial comments, and letters to the editor based on a search in PubMed, Google Scholar, Web of Science, and Scopus. Many articles were assessed based on the abstract or the authors' comments. Google translation was used to translate any language, and we are espe-

cially expecting to find several articles in Chinese. The following terms were used: “COVID-19,” “SARS-CoV-2,” “drug,” “treatment,” “medication,” and “management.” All searches were done between March and May 20, 2020.

Arbidol (Umifenovir)

Arbidol is a potent Russian-made broad-spectrum antiviral that can be used to treat the influenza virus and is well-known throughout Russia and China⁵. It has shown an inhibition mechanism in the hepatitis C virus (HCV) (Table I)⁵. Arbidol involves a block of virus-mediated fusion with a target membrane which prevents the virus’ entry into target cells. One study has showed that arbidol can efficiently inhibit COVID-19 infection at a concentration of 10-30 μM ⁶. In a mul-

ticenter clinical trial in February 2020, patients with COVID-19 randomly received either favipiravir or arbidol⁶. The results did not support any efficacy of arbidol against SARS-CoV-2, as they revealed that the seven-day clinical recovery rate was lower among the arbidol group compared with the favipiravir group (55.86% and 71.43%, respectively) ($p = 0.0199$). The time to reduce fever and cough relief with favipiravir treatment was considerably shorter than arbidol (both $p < 0.001$)⁶. Arbidol is orally taken at a dose of 200 mg three times daily for a maximum of ten days⁷.

Chloroquine Phosphate

Chloroquine is a drug widely used to prevent and treat malaria and is one of the autoimmune disease drugs that emerged as a potential

Table I. List of potential COVID-19 medications.

Drug name	Main use
Arbidol	Antiviral potent broad-spectrum, used to treat influenza virus and hepatitis C virus.
Chloroquine phosphate	Antimalaria and potential broad-spectrum antiviral, widely used to prevent and to treat malaria and autoimmune diseases and in some cases of amebiasis, rheumatoid arthritis, and lupus erythematosus.
Darunavir	Antiretroviral drug used to treat and prevent HIV/AIDS, and as prevention after a needlestick injury.
Favipiravir	Antiviral approved for treatment of novel influenza.
Galidesivir	Antiviral used to treat hepatitis C, and potential treatment for filovirus infections such as Ebola virus and Marburg virus, as well as paramyxoviruses, togaviruses, bunyaviruses, and arenaviruses.
Imatinib	Anticancer drug used to treat certain types of cancer.
Interferon α (IFN- α)	Antiviral activities and treatment of hepatitis.
Ledipasvir	Antiviral drug for the treatment of hepatitis C, used with sofosbuvir as a fixed-dose combination tablet for genotype 1 hepatitis.
Lopinavir/Ritonavir (L/R)	Antiviral generally used for human immunodeficiency virus (HIV). It can be used for prevention after a needlestick injury.
Qingfei Paidu Decoction (QPD)	Chinese traditional medicine used to improve the lung system.
Remdesivir	Antiviral broad-spectrum drug used for the treatment of Ebola and Marburg virus infections.
Ribavirin	Broad-spectrum antiviral used to treat human respiratory syncytial virus infection, hepatitis C, and viral hemorrhagic fevers such as Lassa fever, Crimean-Congo hemorrhagic fever, and Hantavirus infection.
Sofosbuvir	Antiviral used to treat chronic hepatitis C. It is only advised as a combination therapy with ribavirin, peginterferon-alfa, simeprevir, ledipasvir, daclatasvir, or velpatasvir.
Teicoplanin	Antibiotic (Gram-positive bacteria) used as prophylaxis and treatment of methicillin-resistant Staphylococcus aureus and Enterococcus faecalis.
Tocilizumab	Immunosuppressive drug for the treatment of rheumatoid arthritis and systemic juvenileidiopathic arthritis.
Velpatasvir	Antiviral which is combined with sofosbuvir in all six major genotypes of hepatitis C infection.

broad-spectrum antiviral in 2006⁸. It is used in some cases of amebiasis, rheumatoid arthritis, and lupus erythematosus (Table I)⁸. It is also being used experimentally to treat COVID-19, because it can block SARS-CoV-2 infection by elevating endosomal pH and interfering with the glycosylation of cellular receptors⁹⁻¹¹. It has immunomodulatory effects through cytokine production that activate innate and adaptive immune responses for patients with COVID-19. It has demonstrated its effectiveness at low micromolar concentrations, half-maximal effective concentration (EC₅₀) of 1.13 μ M, and a half-cytotoxic concentration (CC₅₀) greater than 100 μ M¹¹. More (and lower) CC₅₀ values can be found in the proliferation of seven cell lines, and hydroxychloroquine had less toxicity compared with chloroquine¹². The recommended dose to treat COVID-19 based on the Chinese guideline is 500 mg (300 mg for chloroquine) orally twice daily for a maximum of ten days⁷. A Korean physician with familiarity in treating SARS-CoV-2 does not recommend this drug for use in healthy, young patients with mild symptoms and no underlying comorbid conditions¹³. It is only recommended in older patients or for those with underlying conditions and severe symptoms. If chloroquine is unavailable, researchers recommend considering the use of hydroxychloroquine (400 mg by mouth once daily)¹³.

Darunavir

This antiretroviral drug has been used to treat and prevent HIV/AIDS, which is a second-generation of an HIV-1 protease inhibitor, and it helped as prevention after a needle stick injury (Table I)^{14,15}. The drug is usually combined with low doses of ritonavir or cobicistat in order to improve darunavir levels^{14,15}. It is taken by mouth once or twice daily^{14,15} and could have efficacy in treating COVID-19. On February 4, 2020, investigators found that darunavir inhibited SARS-CoV-2 viral replication at a concentration of 300 μ M *in vitro*⁷. This inhibition improved 280-fold when compared to the untreated group⁷. However, darunavir failed to block SARS-CoV-2 in another *in vitro* study as well¹⁶.

Favipiravir

Favipiravir has been used as a medication for novel influenza in China since February 15, 2020, because it has faster viral clearance and a faster cure rate than lopinavir/ritonavir (L/R)^{6,17}. The drug is currently involved in several ongoing

COVID-19 clinic trials. Favipiravir is a promising antiviral drug in the treatment of the influenza virus and is capable of inhibiting the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses^{18,19}. It has shown activity against enteroviruses, rift valley fever virus, West Nile virus, yellow fever virus, and foot-and-mouth disease (Table I). Favipiravir is a nucleobase analogue which is transformed into its ribofuranosyl triphosphate form by host cell enzymes. The favipiravir ribofuranosyl triphosphate will be recognized by and will inhibit the RNA-dependent RNA polymerase^{20,21}. In a clinical trial begun at a hospital in Shenzhen, China, favipiravir had greater potent antiviral activity and lower adverse effects than that of L/R^{6,17}.

Galidesivir

Galidesivir is an antiviral adenosine analog drug used to treat hepatitis C (Table I)²². However, it has also shown potential effect for the treatment of filovirus infections such as Marburg and Ebola viruses. Additionally, it can treat paramyxoviruses, togaviruses, bunyaviruses, and arenaviruses²³. Galidesivir is one of several drugs being investigated for COVID-19 because it has shown broad-spectrum activity against a wide variety of pathogens, including SARS CoV-2²⁴. The mechanism of the drug is a nucleoside RNA polymerase inhibitor that interrupts the process of viral replication²⁴ when it binds to the catalytic center of the virus RNA-dependent RNA polymerase (RdRp)²⁵.

Imatinib

Imatinib is a kinase inhibitor and type II transmembrane serine protease (TMSPSS2) which is used to treat certain types of cancer (Table I)²⁶. Hoffmann et al²⁷ showed that SARS-CoV-2 uses the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) and the cellular protease TMPRSS2 in order to get inside the targeted cells. This drug works by inhibiting the fusion of virions with the endosomal membrane²⁷.

Interferon α (IFN- α)

IFN- α is a glycoprotein characterized by stable and broad-spectrum antiviral activities (Table I)²⁸. It is one of the early host defense mechanisms against invading pathogens and is usually used to treat hepatitis B and C²⁹. It has been investigated to possibly inhibit SARS-CoV reproduction *in vitro*, and IFN- β was superior against SARS-CoV when compared to IFN- α ³⁰.

Moreover, IFN- α has synergistic effects when used with ribavirin, IFN- β with ribavirin, or IFN- γ ³⁰. Based on the Chinese Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia, which have been revised several times since first being issued on January 15, 2020³, they recommended using IFN- α as a vapor inhalation at a dose of 5 million U or an equivalent dose for adults, two times/day, for a maximum of 10 days. It is necessary to use 2 ml of sterile water for injections as well. The use of interferon was not recommended as a first-line treatment based on a study by a group of Korean physicians who treated COVID-19 cases, due to the risk of adverse side effects^{10,13}.

Ledipasvir

Ledipasvir is a drug used for the treatment of hepatitis C, and is used with sofosbuvir as a combination tablet for hepatitis C (Table I)³¹⁻³⁴. The combination drug has a direct antiviral effect that interferes with the replication of hepatitis C and can be used to treat patients with genotypes 1a or 1b without pegylated interferon (PEG-interferon) or ribavirin. A recent study found that the combination of velpatasvir/sofosbuvir or ledipasvir/sofosbuvir could be very effective against SARS-CoV-2 viral enzymes using virtual screening^{35,36}.

Lopinavir/Ritonavir (L/R)

Distributed under the product name Kaletra, this drug is a combination of lopinavir and a low dose of ritonavir³⁷. The drug is commonly used for the treatment of human immunodeficiency virus (HIV) among patients over 14 years of age³⁷. It can be used for prevention after a needle stick injury (Table I)³⁸. Chu et al³⁹ reported that L/R has anti-SARS-CoV activity in laboratory and clinical studies. The recommended dosage of L/R is 400 mg/100 mg for adults, twice daily^{7,40}. A recent randomized clinical trial involved hospitalized patients with confirmed COVID-19 infection⁴⁰. They randomized either to L/R (400 mg and 100 mg, respectively) twice a day for 14 days, compared with a standard of care without any treatment. They found no benefit to using L/R treatment beyond the standard of care⁴⁰. However, L/R has shown to be a viable option when used as a combination therapy with interferon beta-1b and ribavirin⁴¹.

Qingfei Paidu Decoction (QPD)

QPD is a traditional Chinese medicine. When used among the 701 confirmed cases, 130 pa-

tients were healed, while clinical symptoms disappeared in 51 cases and improved among 268, and 212 cases of stable symptoms without any complications^{4,42-44}. The cure rate of QPD is over 90%. The target organ location of SARS-CoV-2 is the lung, and QPD can inhibit the replication of the virus by acting on multiple ribosomal proteins^{4,42-44}. However, no specific isolated molecule yet published will help us to understand how it may treat/prevent SARS-CoV-2.

Remdesivir

Remdesivir is a novel nucleoside analog and a broad-spectrum antiviral drug used for the treatment of Ebola and Marburg viral infections (Table I)²². It is a potential drug to be used for the treatment of SARS-CoV-2, with animal experiments showing that remdesivir could efficiently decrease the viral load in mice, recover lung function, and reduce pathological respiratory damage⁴⁵. Wang et al¹¹ reported that remdesivir potently inhibits COVID-19 at low micromolar concentrations. The drug can inhibit virus infection due to a half-cytotoxic concentration and high selectivity index¹¹. Holshue et al⁴⁶ reported that a treatment using intravenous remdesivir that was begun on day seven yielded promising results in the management of the first case of SARS-CoV-2 in the United States⁴⁶. In a multicenter clinical trial in China^{47,48}, patients were randomly selected to receive routine treatment, or an initial dose of 200 mg of remdesivir and a subsequent dose of 100mg, for nine consecutive days via intravenous infusion, in addition to routine treatment. The trial is ongoing and is expected to be finished by mid-2020^{47,48}. The results have proven controversial so far. In a randomized multicentre clinical trial, no clinical benefits of using remdesivir were found⁴⁹. However, the first patient with SARS-CoV-2 was treated successfully with remdesivir⁴⁶.

Ribavirin

Ribavirin is a nucleoside analog with a broad spectrum of antiviral effects⁵⁰. The drug is used to treat human respiratory syncytial virus infections, hepatitis C, and viral hemorrhagic fevers such as Lassa fever, Crimean-Congo hemorrhagic fever, and Hantavirus infection (Table I)^{50,51}. It has a more significant effect when combined with L/R and Interferon α or interferon beta-1b^{7,41}. In a study involving severe acute respiratory syndrome (SARS) patients, they were either treated with ribavirin as a monotherapy (111 patients) or

a combined therapy (41 patients). The researchers found that the combined treatment had a lower acute respiratory distress syndrome (ARDS) and resulted in fewer deaths³⁹. The recommended method of use in treating COVID-19 is 500 mg via intravenous infusion, two to three times daily, in combination with IFN- α or L/R, for a maximum of ten days⁷. The use of ribavirin was not recommended as a first-line treatment as Interferons, due to the same reason as that of Interferon α ^{10,13}.

Sofosbuvir

Sofosbuvir is a direct-acting antiviral medication used to treat chronic hepatitis C^{31,52}. The drug is only advised for use in combination with ribavirin, peginterferon-alfa, simeprevir, ledipasvir, daclatasvir, or velpatasvir (Table I)^{32-34,36}. Data using the SARS-CoV-2 RdRp model revealed the tight binding of sofosbuvir and ribavirin to the coronavirus RdRp, suggesting the potential efficacy of both medications in SARS-CoV-2 management⁵².

Teicoplanin

Teicoplanin is an antibiotic used in the prophylaxis and treatment of several severe Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis* (Table I)⁵³. The mechanism of action is to inhibit bacterial cell wall synthesis⁵³. The drug has been suggested recently as an alternative medication for the treatment of SARS-CoV-2. According to Zhou et al⁵⁴, Teicoplanin works on the initial coronavirus life cycle by inhibiting cathepsin L, thereby inhibiting the release of the viral RNA and stopping the virus replication cycle⁵⁴. Another experiment found that the half-maximal inhibitory concentration (IC₅₀) of SARS-CoV-2 *in vitro* was 1.66 μ M, which is much less than the concentration reached in human blood (8.78 μ M for a daily dose of 400 mg)⁵⁵. However, additional randomized clinical studies are needed in order to confirm these results.

Tocilizumab

Tocilizumab is an immunosuppressive drug for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis^{56,57}. The drug may help in severe COVID-19 cases, although it is not an antiviral molecule. This happened due to the secretion of large amounts of interleukin 6, which activate the inflammatory response⁵⁸.

Velpatasvir

Velpatasvir is an antiviral nonstructural protein 5A (NS5A) inhibitor used with sofosbuvir in all six major genotypes of hepatitis C infection (Table I)³⁵. A recent study³⁵ prepared a three-dimensional model of the COVID-19 3C-like protease. The researchers conducted a virtual screening and proposed 16 potential drugs. Among these, ledipasvir or velpatasvir were the most attractive therapeutics to treat SARS-CoV-2, with insignificant side effects, mostly just reports of fatigue and headache³⁵.

Conclusions

There are several potential medications available for COVID-19. However, we do not yet have a definitive and specific treatment. We are expecting to have more cases in the coming weeks/months. Therefore, further research is needed to characterize the disease behavior and ultimately find the absolute drug and refine the treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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