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A Review for Current Treatment Strategies and the Role of Antiviral Medication as Potential Therapeutic Interventions for Coronavirus Disease 2019 (COVID-19) Outbreak

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Review Article

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ABSTRACT

The Coronavirus disease 2019 (COVID-19) is an infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that leads to pneumonia; it was first identified in China in late 2019. This is a new coronaviruses strain that has not been previously identified or studied in humans. The common symptoms are cough and fever, similar to other respiratory tract infection. Early infected patients are difficult to detect, and the disease is rapidly spreading worldwide. Currently, there are no specific therapies or vaccines that are effective in treating or preventing this disease.

INTRODUCTION

This review article summarizes and combines information gathered from international sources, including the United States and China, on the novel coronavirus (CoV), SARS-CoV-2, and examines potential treatments for COVID-19 disease.

The COVID-19 infection caused by novel corona virus SARS-CoV-2 has rapidly spread from China to over 110 countries over the last several months (as reported by the World Health Organization [WHO] on March 11, 2020. The first confirmed case was reported in December 2019. More than 110,000 people have been confirmed to be infected by SARS-CoV-2, and more than 4,200 deaths have been reported all over the world as of March 11, 2020. As a result, WHO has declared the outbreak of COVID-19 is the first pandemic cause by coronavirus.

Both The Center for Disease Control and Prevention (CDC) and WHO confirmed that COVID-19 infection has the capacity to spread from person to person; this is primarily believed to occur when people are in close contact with one another or when touching a surface that is contaminated by the virus and then touching the mouth, nose, or eyes [1-5]. An epidemiology report from the Chinese Center for Disease Control and Prevention indicates that 86.6% of confirmed patients are between 30 to 79 years old, 80.9% of cases are considered mild cases, and the overall fatality rate is 2.3% [6]. Furthermore, 23.2% of confirmed cases have at least one underlying medical comorbidity, such as hypertension, diabetes, chronic heart disease, chronic obstructive pulmonary disease, or cancer, and these patients accounted for 37.6% of severe cases [6,7]. In addition to patients with underlying medical comorbidities, other high-risk populations include older individuals and immunocompromised patients.

LITERATURE REVIEW

Viral Classification and Drug Targets

The SARS-CoV-2 is a coronavirus which is an enveloped, positive sense, single-stranded RNA virus. Corona viruses are a large family of viruses that can cause infection in both animals and [7-9] humans. Human corona viruses were first identified in the mid-1960s. Common human corona viruses, including types (HCoVs) -229E, -NL63, -OC43, and -HKU1, can cause upper and lower respiratory tract infection [10,11]. Two human coronavirus infections, Severe Acute Respiratory [9] Syndrome (SARS) and Middle East

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Respiratory Syndrome (MERS), emerged in 2003 and 2012 causing worldwide pandemics that resulted in over one thousand deaths. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses recognized SARS-CoV-2 as a sister to SARS-CoV of the species severe acute respiratory syndrome-related corona virus [10]. Interestingly, bats and rodents are the most common hosts of corona viruses in nature, and when the genome sequences among different coronavirus are compared, SARS-CoV-2 shares 88% identity with two bat-derived SARS-like corona viruses and 96% identity with Bat-CoVRaTG1312-14.

The SARS-CoV-2 genome sequences obtained from patients with COVID-19 share 79.6% sequence identity to SARS-CoV15. The WH-human genome, a representative of the SARS-CoV-2 found in ORFia and spike gene (S-protein), shared a better sequence homology toward the genomes SARSCoV_Tor216. The S protein of coronaviruses has two function domains. The S1 domain is responsible for receptor binding, and the S2 domain is responsible for cell membrane fusion. Similar to SARS-CoV, SARS-CoV-2 uses the receptor binding domain of the surface S protein to engage angiotensin-converting enzyme 2 (ACE2) **(Figure 1)** [12-18]. Importantly ACE2 plays a critical role in enabling SARS-CoV-2 to fuse with cellular membranes, and, as a result, lung cells with ACE2 expression may act as target cells and are susceptible to SARS-CoV-2 infection [19]. It is postulated that infection with SARS-CoV-2 primarily causes pulmonary, and sometimes gastrointestinal symptoms, because ACE2 predominates in the lungs and the gastrointestinal tract.

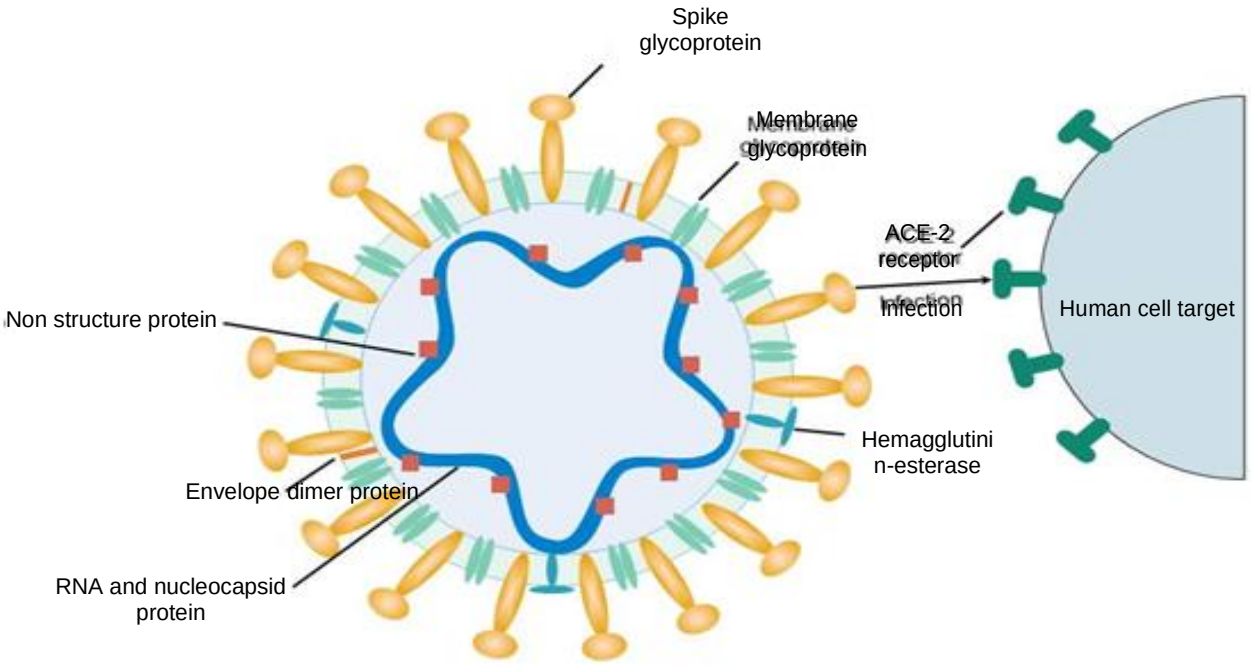

Figure 1. Coronavirus structure and target cells with ACE2 expressing structure proteins on the viral structure include: spike glycoprotein, membrane glycoprotein, hemagglutinin - esterase dimer and envelope protein. Non structure protein is bound on the single strand RNA inside of the coronavirus.

Both SARS-CoV and SARS-CoV-2 share key genomic elements which can be used to design the drug targets [19,20]. The SARS-CoV-2 genome encodes for both non-structural proteins (such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase [RdRp]) **(Figure 1)**, which are involved in viral transcription and replication, and surface structural proteins (such as spike glycoprotein) **(Figure 1)**, which are involved in the viral cell receptor interaction. These structural proteins and non-structural proteins are potential drug target for COVID-19 treatments. Another potential drug target is the RNA genome. Short interfering RNA (siRNA) molecules interfere with the specific genes by degrading mRNA after transcription and preventing translation [21]. However, current technology cannot support siRNA medication use in a large infected population [22,23]. Among existing broad-spectrum antiviral, protease inhibitors, nucleoside analogues that target RdRp, and several other small-molecule agents may be considered as potential antiviral options for COVID-1924.

Finally, although significant research is underway, there is no vaccine currently available to preventSARS-CoV-2 infection. Consequently, it is essential to examine antivirals that are currently available or already in the research pipeline for the treatment of other viruses as 6 potential therapeutic strategies This article reviews the antiviral medications currently used in the COVID-19 treatments worldwide (especially China and United States) and other potential therapeutic strategies.

Clinical Presentation and Diagnosis

The most common symptom of COVID-19 infection is cough and fever. Other early symptoms include myalgia, fatigue,sputum

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production, shortness of breath, arthralgia, sore throat, headache, chills, nausea, vomiting, nasal congestion, and diarrhea. Almost 80% of patients infected develop pneumonia. Chest imaging of patients with COVID-19 found at least half of patients have ground glass opacities and bilateral lung involvement [24,25]. Leukopenia, leukocytosis, and lymphopenia are also common. In more severe cases, patients may have additional abnormal lab values, such as D-dimer (in ICU patients), creatine, ALT, AST, and proinflammatory cytokines. Serious complications, such as acute respiratory distress syndrome (ARDS) and cytokine release syndrome (CRS), can develop in the severe cases.

Although the early symptoms are often similar to influenza, COVID-19 has multiple characteristics that differentiate it from influenza. First, the overall mortality rate for influenza is about 0.28% [26], whereas the mortality rate for COVID-19 is 10 times greater at 2.3% [7]. Likewise, the incubation period for influenza is about 2 days before symptoms occur and the reproductive number (RO) is about 2 to 327, whereas the median incubation period for COVID-19 is 3 days (with arrange of 0 to 14 days), and the RO value is estimated to be between 2.24 and 3.5828. Moreover, when patients are infected with SARS-CoV-2, recovery usually takes at least 72 weeks, which is significantly longer than the typical 1 week course of influenza. These statistics are concerning because as the number of confirmed patients exceeds epidemic thresholds, health care resources, particularly in emergency departments and intensive care units, will likely become overburdened.

There are 2 standard diagnostic tests recommend by WHO -- (1) real time reverse-transcription–polymerase chain-reaction (RT-PCR) and whole genome sequencing [4]. For these tests, CDC recommends collection of 3 specimen types: lower respiratory, upper respiratory, and serum specimens [27-29]. Multiple rapid nucleic test kits for the SARS-CoV-2were available in China in the end of January, and these kits can detect the virus within 15 to 30 minutes [30,31]. Lab Corp is currently working with CDC and FDA to develop and release a test kit in United States [32]. Unfortunately, there are several case reports of patients with false negative results on RT-PCR testing when initially tested for the disease [33-35]. There are multiple reasons that a false negative RT-PCR result can occur: the virus may still be in the incubation period, insufficient cellular material for detection (insufficient sample or lack of a quality sample), and improper extraction of nucleic acid from clinical materials [33]. There is evidence to suggest that using chest imaging results to screen patients with clinical and epidemiologic features of COVID-19 can be a useful tool to diagnose COVID-19 infection when RT-PCR testing is negative [34,35].

Current Clinical Treatment Strategies and Antivirals

Table 1 lists potential therapeutic strategies and clinical recommendations provided by CDC, 8 WHO, and National Health Commission (NHC) of China interim guideline [25,36]. Depending on the patient's symptoms, the physician will provide the most appropriate treatment for the patient. **Table 2** lists medications that may have antiviral function for SARS-CoV-2 currently used in COVID-19 treatment.

Table 1. Therapeutic strategies and clinical recommendations from CDC, WHO, and NHCa interim guideline [4,28-39].

Therapeutic Strategy	Interim Guideline and Clinical Recommendation
Supportive care	For all patients, monitoring vital signs and oxygen saturation, SpO_2 < 90%, provide fluid support, maintain water and electrolyte balance and homeostasis, routinely measuring blood, urine, C-reactive protein and other blood biochemical indexes when necessary.
Potential Antivirals	Protease inhibitors
	Nucleoside analogues
	Fusion inhibitor
Host-targeted agents	Long acting interferon
	Small-molecule agents
Antibacterial	Avoid use broad spectrum antibacterial unless evidence for bacterial infection.
Respiratory support	High flow O_2 therapy Noninvasive ventilation Mechanical ventilation
Convalescent blood products	Blood or plasma from a patient who have recovered from COVID-19 and develop humoral immunity against SARS-CoV-2.
Immune therapy	Corticosteroids should be avoided unless indicated for other reason. Immunoglobulin such as tocilizumab can be use is severe cases when indicated for CRSb.
Traditional Chinese medicine	Based on the patient symptoms, different traditional Chinese medicine are used for the COVID-19 prevention and treatment. There is no evidence to support any of them is effective for the disease.
Life saving techniques	ECMOc CRRT CBP
Note: CDC=Centers for Disease Control and Prevention, WHO=World Health Organization, NHC=National Health Commission, CRS=Cytokine Release Syndrome, ECMO=Extracorporeal Membrane Oxygenation, CRRT=Continue Renal Replacement Therapies, CBP=Continuous Blood Purification.	

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Table 2. Antiviral medications used in COVID-19 infection from interim guideline and clinical trials.

Drug Class	Medication
Protease inhibitors	Lopinavir Ritonavir
	Darunavir
Nucleoside analogues	Favipiravir
	Remdesivir
	Ribavirin
Fusion inhibitor	Umifenovir
Long acting interferon	Interferon alfa (INF α)
Small-molecule agents	Chloroquine
	Hydroxychloroquine

Protease inhibitors are commonly used in human immunodeficiency virus (HIV) and hepatitis C virus (HCV) treatment. These agents bind to the viral protease activity site and inhibit the cleavage of viral Gag-Pol polyprotein precursors into individual functional proteins to cause infection. Protease inhibitors are metabolized by cytochrome P450 (CYP) and are also inhibitors of CYP3A4. As a result, there are numerous drug interactions with other CYP450substrates, inhibitors, and inducers. Patients started on protease inhibitors need to be monitored closely for drug dosing and potential interactions.

Lopinavir/ritonavir (Kaletra®) is an older protease inhibitor with potential for COVID-19 treatment. Although the dose can vary, 400mg/100mg two times a day is often typical. With lopinavir/ritonavir, the recommend treatment duration for COVID-19 is less than 10 days. The pediatric dose is weight based, but it is not recommended for patients less than 15 kg or younger than 2 years old. Clinicians should be cautious about prescribing lopinavir/ritonavir to a woman who is pregnant or breast-feeding. The HIV guidelines indicate that there is low placental transfer to the fetus and no evidence of human teratogenicity, but the oral solution product contains 42% alcohol and 15% propylene and is not recommend for use in pregnancy (other dosage forms do not contain these products) [37]. Common adverse effects include 9 hypersensitivity, QTc or PR-interval prolongation; increase the risk of myocardial infarction, and hepatotoxicity.

In 2003, lopinavir/ritonavir was used for the SARS outbreak. A study examining lopinavir/ritonavir as an initial treatment for SARS found that it reduced the overall death rate by 2.3% [38,39]. A second study reported fewer episodes of acute respiratory distress syndrome (ARDS) or death (2.4%) compared with historical controls who had not received lopinavir/ritonavir (28.8%). In one MERS treatment guideline, a combination regimen of type 1 interferon + ribavirin + lopinavir/ritonavir is recommended for antiviral therapy [40]. In a retrospective study analyzing the effects of this antiviral treatment regimen in 44 patients with MERS, the 14-day survival rate of the treatment group (70%) was significantly higher than that of the control group (29%) [40]. This medication is recommended by the 7 (th) edition National Health Commission (NHC) of People's Republic of China diagnosis and treatment plan of pneumonia caused by novel coronavirus25. A randomized, controlled, open label clinical trial conduct 199 hospitalized moderate Covid-19 patients assigned in lopinavir/ritonavir group and standard care group observe no benefit in lopinavir/ritonavir group [41]. More studies are needed for combination therapy and severe illness patient.

Darunavir/ cobicistat (Prezcobix) is another FDA-approved protease inhibitor for HIV. It is typically dosed at 800 mg/150 mg one time per day, and common adverse effects include hepatotoxicity, gastrointestinal distress, immune reconstitution syndrome, and headache. It may also cause low blood glucose in patients with diabetes. On February, a Chinese researcher 10 report in the news that darunavir can inhibit SARS-CoV-2 infection *in vitro* [42]. More studies are needed to confirm that darunavir may have a potential therapeutic effect for COVID-19 treatment.

Nucleoside analogues are commonly used to treat hepatitis B virus (HBV), HCV, HIV and other respiratory viruses. These drugs resemble naturally occurring nucleosides and can causing pre-mature termination of RNA/DNA replication. In COVID-19 treatment, a potential mechanism for nucleoside analogues involves competing for a binding site that incorporates with adenosine triphosphate (ATP), preventing virus RNA-dependent RNA polymerase (RbRp) binding with ATP, resulting in viral RNA synthesis inhibition [43].

Ribavirin (Moderiba®) is an FDA-approved medication used for HCV. It is also used off-label for respiratory syncytial virus infection in immune compromised patients and for viral hemorrhagic fever. The guideline-recommended dose of COVID-19 is 500mg 2 to 3 times a day for 10-14 days. Pediatric dosing is weight-based. Because the drug has significant teratogenic effects reported in animal studies and patient case reports (with both male and female use), patients of both sexes are advised to avoid pregnancy for 6 months after exposure. Ribavirin also has a black box warning for haemolytic anemia and should not be used with other drugs that adversely affect red blood cells. Ribavirin use with certain antivirals for HIV increases the risk of mitochondrial toxicity, which can lead to pancreatitis, lactic acidosis, or hepatic decompensation.

Review articles mention ribavirin use in SARS-CoV infection, but there is no convincing evidence the ribavirin led to recovery, and 4 studies showed possible harm. In MERS treatment, 39ribavirin is recommended as a combination regimen with type 1

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interferon and lopinavir/ritonavir. The combination of ribavirin and interferon-α or lopinavir/ritonavir is recommended by the 7 (th) edition NHC of People's Republic of China diagnosis and treatment plan of pneumonia caused by novel coronavirus.

Remdesivir, also known as GS-57 [44], is an investigational nucleotide analog in development by Gilead. Remdesivir has broad-spectrum antiviral activity and the first clinical trial evaluated the clinical therapeutic effect on Ebola virus disease (EVD). This clinical trial failed to demonstrate that remdesivir can reduce the mortality of EVD [45]. Side effect of remdesivir is non-specific when used for short treatment periods, and more safety data are needed.

Remdesivir can inhibit SARS-CoV and MERS-CoV replication in cultured cells, mice, and nonhuman primate (NHP) models [46-48]. In the latest study for MERS-CoV in mice, remdesivir demonstrated greater improvement in pulmonary function and more substantial reduction in lung viral loads than the combination of lopinavir/ritonavir and interferon, which only slightly reduced viral loads [48]. Remdesivir also effectively inhibits the SARS-CoV-2both *in vivo* (EC 50=0.77 μM in Vero E6 cell) and *in vitro* (EC90=1.76 μM, in Vero E6 cell) [49]. The first COVID-19 patient identified in the United States had significant improvement after the use remdesivir50. Both China and United States are beginning randomized, double-blind, placebo-controlled clinical 12 trials to test the effectiveness of remdesivir as a potential treatment for hospitalized adult patients diagnosed with COVID-19.

Favipiravir, also known as T705 (Avigan®), is a broad spectrum anti-viral medication that was approved in Japan in 2014 for influenza [50,51]. In addition to influenza, there are multiple clinical trials examining efficacy of favipiravir in Ebola. The results from JIKI trail, a non-randomized trial [14] of patients with EVD, suggest that favipiravir mono therapy needs further study in patients with a medium to high viremia, but the drug should not be used in patients with very high viremia [52]. There is a case report indicating that favipiravir can cause nausea [53]. The broad anti-viral mechanism has prompted scientists to suspect that favipiravir has potential therapeutic effect on SARS-CoV-2. A recent study found that favipiravir has activity against SARS-CoV-2 *in vivo* (EC50=61.88 μM in Vero E6 cells). There is a clinical trial investigating favipiravir in COVID-19 patients that started in February 2020 [54]. However, currently, there is still no *in vitro* or patient data available for favipiravir.

Pegylated interferon alfa-2a and-2b (INF-α) is approved for the treatment of HBV, HCV, and certain types of cancer. Another multi center, randomized, double-blind trial for hand foot and mouth disease (HFMD) indicated that INF-α2b is safe and efficient for HFMD treatment. The drug is typically used in combination with other medications, such as ribavirin [55]. Administration of INF-αvia nebulizer is most common in children with upper respiratory infection but this administration method has been used in adults. The COVID-19 Interim guideline suggest that 50,000,000 units INF-α in 2 ml sterile water nebulized two times a day could be used to stimulate innate antiviral responses in patients infected with SARS-CoV-2. Because INF-αbinds to a specific receptor on the cell membrane to initiate intracellular activity, it can inhibit cellular growth, alter the state of cellular differentiation, alter cell surface antigen expression, and increase phagocytic activity of macrophages for target cells [56,57]. The adverse effects of INF-α include fatal neuropsychiatric, autoimmune, ischemic, and infectious disorders, which are highlighted in the black box warning for INF-α. Other common side effect includes bone marrow suppression, flu-like symptoms, and gastrointestinal toxicity.

The combination of interferon and ribavirin inhibits SARS-CoV in animal and human cell line [58], but no evidence has shown effectiveness in the treatment of SARS patients. In patients with severe MERS-CoV infection, ribavirin and interferon alfa therapy is associated with significantly improved survival at 14 days, but not at 28 day. Interferon combination therapy is recommended for antiviral therapy in MERS patient. In the current interim guideline, nebulized interferon is considered a therapeutic option in combination with other antiviral treatments to increase the treatment effectiveness.

Chloroquine is commonly used in malaria. Hydroxychloroquine is a less toxic metabolite of chloroquine, which is also used to treat autoimmune disease such as rheumatoid arthritis and systemic lupus erythematosus. The dose used for malaria treatment is 500 mg two times a day for 5-10 days. If a patient's GFR is less than 10ml/min, a 50% dose adjustment is recommended. The pediatric dose is 16.6 mg/kg, with a maximum of 1000 mg, divided in two doses per day. Chloroquine is recommended for the treatment of pregnant women with uncomplicated malaria. Adverse effects that require monitoring include auditory damage, retinal damage, hepatic impairment, and cardiac toxicity. Also, common drug interactions with drugs such as antacids and cimetidine may reduce absorption of chloroquine, whereas concomitant administration with cyclosporine can increase cyclosporin levels.

The mechanism of action of chloroquine is unique. Chloroquine is employed most often as an anti-malarial and autoimmune disease drug, but it also has potential broad-spectrum antiviral activities. Chloroquine increases the pH in the virus, disrupting several enzymes and decreasing the intercellular concentration of iron, which leads to inhibition of viral replication. In a recent study, chloroquine potently inhibited SARS-CoV-2 activity *in vivo* (EC50=1.13 μM in Vero E6 cells) and *in vitro* (EC90=6.90 μM in Vero E6 cells). Chloroquine also contains anti-inflammatory properties through inhibition of cytokine production and release by T cells, including IL1, 2, 6 or 18, TNFα, and IFNγ [49,59]. The unique anti-viral and anti-inflammatory activities of chloroquine demonstrate that this agent has promise as a potential COVID-19 treatment. An open label non-randomized clinical trial involving 42 patients indicate a significant virological clearance after 6 days treatment in hydrochloroquine group (77%, p=0.001) compare to control group (12.5%, p=0.001) [60].

Umifenovir (also known as Arbidol®) is a broad-spectrum antiviral medication developed in Russia and used for prophylaxis and treatment of influenza and other acute respiratory infections in Russia and China. Other viruses that may be responsive to

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umifenovir *in vivo* and *in vitro* include HCV [61], SARS-CoV [62], Ebola virus [63] and Zika virus [64]. Umifenovir functions as a fusion inhibitor, preventing viral fusion protein transition to an activated conformation, inhibiting viral entry to the cell membrane (target cell), thereby protecting the cell from infection [65]. On February 4, 2020, one Chinese epidemiologist stated that umifenovir has the potential properties to inhibit SARS-CoV-2 replication *in vitro*. There is one retrospective cohort study suggesting that umifenovir could accelerate and enhance the process of viral clearance, shortening the conversion time to stable by 2 days for patients with mild disease [66]. However, this research has not been peer-reviewed and current level of evidence is not enough to support umifenovir for clinical use in COVID-19 treatment and further randomized controlled trials are needed. **Table 3** summarizes current evidence for all antiviral medications used in the clinic.

Table 3. Antiviral medication treatment dose, mechanism of action, major side effect and dug efficacy *in vivo*, *in vitro* and in human study for SARS, MERS and COVID-19.

Drug	Dose	MOA	Major side effect	SARS/MERS	COVID-19
Lopinavir/ritonavir	400 mg/100 mg b.i.d for max 10 days	binds to the viral protease activity site and inhibits viral replication	hypersensitivity, QTc or PR-interval prolongation, increase the risk of myocardial infarction risk, hepatotoxicity	Reduce mortality and increase the survival rate in both SARS and MERS treatment	Recommended by 7 (th) edition NHC interim guideline, A randomized clinical trial indicate no difference compare to stander care group
Darunavir/cobicistat	800/150 mg qd for at max 10 days		hepatotoxicity, gastrointestinal problem, immune reconstitution syndrome, headache	Non-specific	Effective *in vitro* study but evidence not strong enough
Ribavirin	500 mg b.i.d to t.i.d for max 10 days	prevent virus RNA-dependent RNA polymerase (RbRp) binds with ATP leads to pre-mature termination of RNA replication	hemolytic anemia	Show possible harm for SARS patient, use in the combination regimen for MERS treatment	7 (th) edition NHC interim guideline recommend combine with Interferon-α or lopinavir/ritonavir
Remdesivir	200mg loading dose follow by 100 mg qd for max 10 days		Nonspecific in short term	Inhibit SARS-CoV and MERS-CoVb *in vivo* and vitro	Effectively inhibit the SARS-CoV-2c *in vivo* and vitro study
Favipiravir	1600 mg b.i.d loading dose follow by 600 mg b.i.d for max 10 days		Nonspecific in short term	Non-specific	Effectively inhibit the SARS-CoV-2 *in vivo*
Interferon alfa 2a and 2b	50,000,000 units in 2 ml sterile water, nebulization b.i.d	Bind to a specific receptor on the cell membrane, inhibit cellular growth, alters the state of cellular differentiation, alters cell surface antigen expression, increases phagocytic activity of macrophages	Neuropsychiatric, autoimmune, ischemic, infectious disorders	Effective for SARS-CoV *in vitro* but not effective for SARS patients, use as a combination regimen in MERS treatment	7 (th) edition NHC interim guideline recommend combine with ribavirin or lopinavir/ritonavir
Chloroquine/ Hydroxychloroquine	>50 kg: 500 mg b.i.d for 7 days <50 kg: 500 mg b.i.d on day 1-2, 500 mg qd on day 3-7	Inhibiting pH-dependent steps of the replication	Auditory damage, retinal damage, hepatic impairment, cardio toxicity	Non-specific	Potently blocked SARS-CoV-2 virus infection *in vitro*, An non-randomized clinical trial indicate virological clearance for hydrochloroquine group is 77% compare to 12.5% in control group
Umifenovir	200 mg t.i.d for max 10 days	Prevents viral fusion protein to transition to an activated conformation, inhibit viral entry to the cell membrane	Nonspecific in short term	Non-specific	One retrospective cohort study report that umifenovir shortened the conversion time to stable by 2 days for patients with mild disease

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Note: SARS=Severe Acute Respiratory Syndrome, MERS=Middle East Respiratory Syndrome, COVID-19=Coronavirus Disease 2019, SARS-CoV=Severe Acute Respiratory Syndrome-Related Coronavirus, MERS-CoV=Middle East Respiratory Syndrome-Related Coronavirus, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2.

Currently, there are no antiviral medications approved by the FDA for the treatment of COVID-19 or other coronaviruses. The antiviral medications discussed in this review could be considered on a case-by-case basis as off-label therapy for patients with COVID-19. Another potential treatment strategy for this disease, beyond antivirals, is convalescent blood products, which are blood or plasma from a patient who has recovered from COVID-19 and developed humoral immunity against the SARS-CoV-2.

With no specific therapies approved for the treatment of COVID-19, excellent supportive care is critical for all patients to optimize outcomes and prevent complications. For patients with mild disease, supportive care alone, usually as an outpatient, is generally sufficient. This includes avoiding the use of broad spectrum antibacterial unless there is evidence for bacterial infection or sepsis. In more severe cases, additional supportive interventions may be necessary. For patients with SpO_2 90%, effective oxygen therapy should be given immediately. Physicians can initiate high flow O_2 therapy, non-invasive ventilation, or mechanical ventilation depending on a patient's condition. Importantly, corticosteroids should be avoided in patient with viral pneumonia unless patient develops other complications. Several systematic reviews of corticosteroids administered to patients with SARS and influenza-induced pneumonia demonstrated that corticosteroid use increased mortality and prolonged viral shedding in infected patients [67,68]. The finding is not conclusive, and we need more evidence to support or reject corticosteroid used in COVID-19 treatment. In severe COVID-19 cases, patients may develop CRS as a fatal complication. Immunoglobulin is the recommended treatment for CRS to prevent organ damage. Other life-saving techniques that can be used in severe cases include extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapies (CRRT), and continuous blood purification (CBP). Traditional Chinese medicine is also recommended by NHC interim guideline for prevention and treatment; however, there is no evidence to support that any of these traditional medicines are effective for COVID-19. More studies are needed.

Minimizing the chances of exposure to SARS-CoV-2 for healthcare workers and other patients is also essential. All patients with suspected COVID-19 should be isolated in an airborne infection isolation room. Current CDC recommendations include the use of Standard Precautions, Contact Precautions, and Airborne Precautions with N95 or higher-level respirator, eye protection, gloves, and a gown when caring for confirmed COVID-19 patients [69]. As of March 9, 2020, there were 129 clinical trials listed in clinical trials related to COVID-19 and SARS-CoV-2. This number increases to 355 when clinical trials registered with the Chinese Clinical Trial Registry are 17 included. Moreover, there are 3 clinical trials listed in clinicaltrials.gov related to aSARS-CoV-2 vaccine. The first volunteer was recruited on March5, 2020 [70]. Chinese scientists believe that a SARS-CoV-2 vaccine could be ready for emergency use in April 2020 [71]. However, it is likely that the global community still has a long path ahead to find an effective vaccine and treatment for SARS-CoV-2 and COVID-19 infection.

DISCUSSION

The COVID-19 outbreak caused by SARS-CoV-2 represents a formidable challenge to the global community. However, there is hope for potential therapeutic interventions in the antiviral agents presented in this review. Currently, there is no FDA-approved medication or vaccine for SARS-CoV-2 infection and potential therapy recommendations are based on the interim guidelines, experience with SARS and MERS, and limited clinical information. Clinicians must employ their best judgment when selecting treatments for patients, but *in vitro* and *in vivo* studies suggest potential therapeutic activity for existing antiviral drugs, particularly for remdesivir, favipiravir, and chloroquine. Randomized clinical trials in humans are necessary to support and confirm the therapeutic options for COVID-19 at this time. This review is one attempt at sharing the latest knowledge about the optimal care for patients with COVID-19 with the international medical community.

Intensive randomized clinical trials for existing medications and experimental medications are needed to confirm their therapeutic effect for COVID-19 infection.

CONCLUSION

This review summarizes the current understanding of COVID-19, including the molecular characteristics and potential drug targets for SARS-CoV-2. Evidence-based therapeutic strategies and antiviral medications that could potentially be used in COVID-19 treatment are also described. Three agents, remdesivir, favipiravir, and chloroquine, have some efficacy data against SARS-CoV-2 *in vivo* or *in vitro*. However, this evidence is not conclusive enough to support any specific antiviral recommendations and more clinical evidence is needed.

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