

Current Status of Treatment Options, Clinical Trials, and Vaccine Development for SARS-CoV-2 Infection

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Abstract

The severe acute respiratory syndrome virus (SARS-CoV-2), a novel coronavirus first discovered in Wuhan, China in December 2019 causes the Coronavirus Disease 19 (COVID-19), which presents with a wide range of clinical symptoms from mild or moderate to severe and critical illnesses. With the continuing transmission of the virus worldwide and the rapidly evolving situation globally, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic in March. Currently, there is no proven specific treatment for this potentially deadly disease beyond supportive care. However, a massive effort has been put globally into the investigation of medications and other interventional measures to fight COVID-19. Convalescent plasma therapy from recovered patients has recently drawn considerable interest. Several alternative medical treatments, although evidence of their efficacy still lacking, have also gained popularity, especially in countries with such traditions such as India and China. Rapid repurposing of drugs for COVID-19 has revealed a few promising candidate antiviral agents, but further research, especially high quality randomized controlled trials, will be needed to prove their efficacy and safety in the clinical use to treat COVID-19. Vaccine development has been the imperative task in the battle against SARS-CoV-2. While clinical trials have been launched for several candidate vaccines, research on COVID-19 vaccines is still at an early stage. So far, optimized supportive care remains the best practice against COVID-19.

Keywords: COVID-19, SARS-CoV-2, Supportive Care, Clinical Trials, Vaccine

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INTRODUCTION

The Severe acute respiratory syndrome virus (SARS-CoV-2), initially named as 2019 novel coronavirus (2019-nCoV), is a novel strain of zoonotic coronavirus that was first discovered in Wuhan, China, where a cluster of pneumonia cases was first reported in December 2019¹. The disease caused by SARS-CoV-2, later designated the Coronavirus Disease 2019 (COVID-19), rapidly evolved into an epidemic in China, and shortly after, a pandemic throughout the world. As of May 10, short of 5 months after it was first reported, over 4 million of COVID-19 cases have been confirmed in 187 countries worldwide with the death toll reaching nearly 280,000².

Although the understanding of the transmission of SARS-CoV-2 is still incomplete, current evidence suggests the virus is primarily transmitted person-to-person through respiratory droplets or close contact³. Although SARS-CoV-2 causes only mild, flu-like symptoms in the majority of cases, severe illness can occur in as high as 14 percent of patients contracted with this virus⁴. As of May 10, in 4,038,747 confirmed cases, 279,468 (6.9%) patients eventually died of the disease². As the U.S. Food and Drug Administration (FDA) has not approved any medications or other therapeutics for COVID-19, the mainstay of clinical management is symptomatic treatment and supportive care. However, there has been a massive global effort in finding the potential treatment options, including pharmaceutical or other interventional measures, for COVID-19 and in designing the vaccinations to protect against SARS-CoV-2. To date, more than 600 interventional studies and clinical trials have been launched worldwide, and multiple candidate vaccines have entered different stages of clinical trials⁵. Here we review the current status of treatment options, clinical trials, and vaccine development for SARS-CoV-2 infection.

Current Treatment Options

COVID-19 presents with widely various severity of symptoms that range from very mild to severe. In around 80% of the cases, SARS-CoV-2 causes only mild illnesses that do not require inpatient treatment. However, around 14% of the patients infected develop severe illnesses, and in roughly 5% of confirmed COVID-19 cases, patients require critical care⁴. A couple of risk

factors for developing severe illnesses or escalating to intensive care have been identified, including older age and multiple underlying comorbidities⁶. Fever, cough, fatigue, and shortness of breath or difficulty breathing are among the most common symptoms of COVID-19⁷. Symptomatic treatments, such as antipyretics, respiratory therapy, and oxygen supplementation, have been the mainstay in the current clinical management. Although there has been hypothesis that the use of non-steroidal anti-inflammatory drugs (NSAIDs) could aggravate COVID-19 symptoms⁸, there is no clinical evidence connecting the use of NSAIDs with worsening symptoms of COVID-19. In patients with sustained hypoxemia refractory to supplemental oxygen therapy, other modalities, including high flow nasal cannula, non-invasive or invasive positive pressure ventilation, and in extreme cases, extracorporeal membrane oxygenation (ECMO), can be used to maintain oxygenation⁹. While most common symptoms are respiratory, as many as 31.9 % of the patients with COVID-19 present with gastrointestinal symptoms, including nausea, vomiting, and diarrhea¹⁰. In such patients, it is crucial to pay attention to maintaining adequate nutrition and hydration.

Although there is no strong scientific evidence that any alternative medicine can prevent or cure COVID-19, in countries with a deep culture or tradition of alternative remedies such as India and China, several alternative medicines have gained popularity for helping with either prevention or treatment of COVID-19¹¹. However, the WHO has advised against alternative approaches including traditional herbal remedies for the treatment of COVID-19 and there are reported adverse effects of the alternative medicines that make them unsafe to consume¹². With more and more people having fully recovered from COVID-19, convalescent plasma containing neutralizing antibodies is being investigated as a potential treatment. There have been several preliminary studies regarding its safety and effectiveness that have shown promising results, although further investigation is still necessary¹³⁻¹⁵.

Clinical trials for antiviral drugs

The COVID-19 pandemic has elicited an unprecedented enthusiasm for clinical trial research with the hope of investigating the safety and efficacy of various candidate antiviral agents.

As of May 10, more than 600 clinical trials have been registered internationally⁵. While most of the candidate antiviral agents are repurposed from targeting other pathogens, a few drugs have shown

to be promising in published randomized clinical trial studies. Here we present a brief summary of such antiviral agents under investigation (table 1).

Table 1. Potential COVID-19 drugs under investigation

Medication Name	Classification	Possible Mechanism of Action against SARS-CoV-2	Most Advanced Stage in Clinical Trials
Remdesivir	Nucleoside/nucleotide analog	Incorporate into viral RNA and inhibit normal viral replication.	Phase 3
Favipiravir	Nucleoside/nucleotide analog	Incorporate into viral RNA and inhibit normal viral replication.	Phase 4
Lopinavir/ ritonavir	Protease inhibitors	May inhibit the enzyme 3-chymotrypsin-like protease, thus disrupt replication and release of the virus.	Phase 4
Ribavirin & interferon	Ribavirin: Nucleoside/nucleotide analog Interferon: cytokine	Ribavirin: incorporate into viral RNA and inhibit normal viral replication. Interferon: activate the transcription of interferon-stimulated genes whose product proteins exert antiviral activities through diverse mechanisms.	Phase 2 (as a combination)
Tocilizumab	Humanized monoclonal antibody	Reduce the cytokine storm by blocking Interferon-6 receptors	Phase 4
Chloroquine and hydroxy-chloroquine	Antimalarials and amebicides	Increase lysosomal pH and interfere with viral release	Phase 4
Ivermectin	Anthelmintic	Unknown, possibly through inhibiting IMP α / β 1-mediated nuclear import of viral proteins	Phase 2

Remdesivir

Remdesivir (GS-5734), an adenine analog that can incorporate into viral RNA and inhibit normal viral replication is by far the most promising drug and has gained attention from both the scientific world and the general public. Initially designed during the Ebola outbreak, remdesivir was shown to be safe for use in human subjects even though its efficacy against Ebola virus needed further investigation¹⁶. There have been a few studies that showed the antiviral activity of remdesivir in vivo and in vitro against SARS-CoV and MERS-CoV¹⁷, the exact two other coronaviruses that have caused severe respiratory illness outbreaks in the 21st century. Remdesivir has also shown antiviral activity against SARS-CoV-2 in vitro (Vero cells) in a study¹⁸, making it furthermore

a promising candidate that gained great research interest. Several clinical trials have been initiated to test for the efficacy and safety of remdesivir in fighting against SARS-CoV-2. On April 29, 2020, the National Institute of Allergy and Infectious Diseases (NIAID) announced that remdesivir has shown to be effective in shortening the time to recovery by 4 days (from 15 days to 11 days) in people with severe illness from COVID-19¹⁹. On May 1, 2020, the FDA issued an emergency use authorization for remdesivir to be used for the treatment of suspected or confirmed COVID-19 cases in both adults and children hospitalized with severe disease²⁰. Of note, another study in China, however, showed evidence that remdesivir was not effective in treating COVID-19²¹. Although there is contradicting data regarding the effectiveness

of remdesivir against SARS-CoV-19, with its approval for clinical treatment in more and more countries and regions, more clinical research data is expected to emerge for further investigation of the therapeutic efficacy and safety of remdesivir in patients with SARS-CoV-2 infection.

Favipiravir

Favipiravir (T-705) is another nucleoside/nucleotide analog that has been shown to be effective against several viruses, including influenza virus and Ebola virus^{22,23}. After undergoing phosphoribosylation intracellularly, favipiravir resumes its active form that resembles guanine and thus inhibits the normal viral replication²². Several clinical studies have been approved for its use in COVID-19 patients. In a study on 80 patients, the drug was found to reduce viral clearance time compared to lopinavir/ritonavir²⁴, although the evidence is less persuasive as the study is not randomized double-blinded or placebo-controlled. Favipiravir was recently approved by the Drug Controller General of India to be evaluated for the treatment of COVID-19, and several studies have already been initiated in China, Japan, the United Kingdom, and the U.S.

Lopinavir/ritonavir

Commonly used in combination to treat HIV infection, lopinavir and ritonavir are protease inhibitors that have shown potential for the treatment of COVID-19. Although there has been no evidence from randomized trials of their efficacy against SARS-CoV or MERS-CoV, in-vitro and in-vivo antiviral activities have been observed in a couple of studies against a variety of RNA viruses including influenza viruses, arenaviruses, and flaviviruses²⁵. This drug combination has been undergoing investigation in multiple clinical trials, but the preliminary results have not been as promising. In a recently published study on hospitalized adult patients with severe COVID-19, no benefit was observed with the use of lopinavir/ritonavir compared with standard supportive care, and there was also no difference in time to viral clearance between the two groups²⁶. Although the combination of lopinavir/ritonavir has been widely used in HIV infection and proven to be relatively safe, further investigations, especially randomized controlled trials will be needed for evaluation of the efficacy of the drug combination in COVID-19 patients.

Ribavirin and interferon

Ribavirin is another guanine analog widely used for the treatment of hepatitis C virus infection, while interferon, secreted by the virus-infected cells, has been observed to have broad-spectrum antiviral activities^{27,28}. In a recent study comparing the triple combination of ribavirin, interferon, and lopinavir/ritonavir and lopinavir/ritonavir alone, early administration of the triple antiviral therapy was observed to be safe and superior in helping with the symptoms and shortening the viral clearance time in patients with mild to moderate COVID-19²⁸. The use of type 1 interferons alone has also been investigated as a potential treatment against COVID-19.

Tocilizumab

Cytokine storm, a process involving the release of large quantities of proinflammatory cytokines including interleukin-6 (IL-6), IL-1, IL-12, tumor necrosis factor- α (TNF- α) among others, were observed in severe cases of the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), and has also been reported to play an important role in causing acute respiratory distress syndrome (ARDS) in patients with COVID-19²⁹. Tocilizumab, an IL-6 receptor blocker can inhibit the signal transduction pathway of IL-6, a key player in the cytokine storm. Several studies worldwide have shown that tocilizumab appears to be an effective treatment in patients with severe COVID-19, demonstrating its ability to decrease inflammatory markers, reduce the need for respiratory support and improve mortality³⁰⁻³². A promising biologic, tocilizumab has been approved by the FDA for a phase 3 clinical trial for COVID-19.

Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are commonly used for the treatment of malaria and several autoimmune conditions³³. Both drugs have also been reported to have antiviral effects by increasing lysosomal pH and therefore interfering with the process of releasing the viruses, which requires a low pH³⁴. After a study done by Chinese researchers claimed to have observed inhibitory effects of chloroquine on SARS-CoV-2³⁵, there have been increasing interest in investigating their efficacy and safety in COVID-19 patients. Currently, they have been approved by multiple countries for the experimental treatment of

COVID-19. However, more recent studies failed to show benefits associated with their use in COVID-19 patients^{36,37}. Moreover, as both drugs have well documented side effects, including cardiac conduction disturbances, their safety has raised great concern and the FDA has issued cautions against the use of either drug outside of clinical trials or the hospital setting for COVID-19 due to the risk of heart rhythm problems³⁸. Larger randomized controlled trials will be needed not only to investigate the efficacy but the safety of the use of chloroquine or hydroxychloroquine as a treatment for COVID-19.

Ivermectin

Ivermectin is a widely used broad-spectrum medication to treat a variety of parasite infections in both humans and some animals. This antiparasitic drug has been studied as an antiviral agent *in vitro* and was found to be a broad antiviral agent against a variety of viruses, especially RNA viruses including dengue virus, yellow fever virus and chikungunya virus^{39,40}. However, in a phase 3 trial, it failed to show any benefit against dengue virus clinically⁴¹. Like other drugs under investigation to be repurposed to treat COVID-19, ivermectin has also been a candidate drug with promising results against SARS-CoV-2 *in vitro*, demonstrating its ability to inhibit SARS-CoV-2 in Vero-hSLAM cells in one study⁴². Although in the phase 3 study regarding its use against dengue virus mentioned above, ivermectin was observed to be safe, further investigation is warranted to evaluate its safety and efficacy against SARS-CoV-2 in humans. As of May 10, FDA has not approved the use of ivermectin for the prevention or treatment of COVID-19 and has issued a warning against the use of ivermectin intended for animals as a treatment for COVID-19 in humans on April 10, 2020.

Vaccine development

With the rapid transmission of SARS-CoV-2, developing a vaccine to prevent COVID-19 has become the best hope for putting an end to this pandemic and an imperative task globally. A regularly updated landscape document has been prepared by the WHO for the status of vaccine development globally⁴³. As of May 15, 8 candidate vaccines have entered the clinical evaluation phase, while additional 110 candidate vaccines are

undergoing pre-clinical evaluations with more still in the exploratory stage⁴³.

Multiple strategies have been applied to the development of SARS-CoV-2 vaccines. A classic approach is to develop a whole virus vaccine, inactive or live-attenuated, with the advantage of eliciting strong immune responses due to its inherent immunogenicity. Several companies and research groups are focusing on a whole virus vaccine, and 3 inactivated vaccine candidates have entered phase 1/2 trials⁴³. Subunit vaccines represent another classic approach to developing SARS-CoV-2 vaccines. This approach focusses on eliciting an immune response against the spike protein, a molecule playing an important role in virus entry by recognizing various host receptors, including ACE2⁴⁴. While no subunit vaccines have been tested in clinical trials, several are under pre-clinical investigations.

The genome of SARS-CoV-2 has been mapped and made public in January 2020. The use of nucleic acid-based vaccines (DNA or RNA), a novel strategy as an alternative to whole virus or subunit vaccines, has gained a lot of attention in the current pandemic. Simple to generate and easy to administer, nucleic acids work as great vectors for the desired genes that, after entering the host cells, can be transcribed and translated into polypeptide products recognizable by the host immune system⁴⁵. A DNA vaccine developed by Inovio Pharmaceuticals is under phase 1 clinical trial; two RNA vaccines, designed by Moderna/NIAID and BioNTech/Fusun Pharma/Pfizer separately, have also entered different stages of clinical trials⁴³.

CONCLUSIONS

In this article, we presented a brief overview of the clinical practice in treating COVID-19, the clinical trials for new pharmaceutical options, as well as the current status of vaccine development for SARS-CoV-2.

Although there has been no proven specific prevention or treatment for COVID-19, a few medications, mostly repurposed from their original use in treating other illnesses, have shown to be promising candidates (table 1). Compassionate use of such drugs is under strict supervision by health professionals in the hospital

setting. However, the general public with limited health literacy can easily misinterpret information regarding the preliminary results of the clinical trials, and attempts to self-medicate with unapproved medications under no proper medical supervision have been reported worldwide. Such behaviors could lead to potentially devastating consequences, including hospitalization, and even death in some cases. A few medications with well documented, potentially life-threatening side effects, like chloroquine and hydroxychloroquine, are at a higher risk of being used for self-medication in the COVID-19 pandemic as they can be easily obtained without a prescription from a physician and are relatively cheap. As a result, several warnings against the use of several medications, including chloroquine, hydroxychloroquine, and ivermectin, out of healthcare settings or without the supervision of healthcare professionals, had to be issued by the FDA. Moreover, the desperate hunt of COVID-19 medications of the public has resulted in stockpiling of several medications, including hydroxychloroquine and azithromycin, causing drug shortages at a national level and posing a potential threat to patients in need of the medications for their approved use (e.g. hydroxychloroquine for treating autoimmune conditions). Therefore, it remains a great task to

develop strategic plans to combat misinformation surrounding COVID-19 and educate the public to follow the accurate, official public health guidance on national and international scales as well as in local communities.

The rapid development of vaccines against SARS-CoV-2 is a global imperative and has drawn great attention from the public. Hundreds of vaccines are under development in the pre-clinical or exploratory stages, and as of May 15, 8 vaccines are undergoing clinical trials⁴³ (table 2). The research in vaccine development for COVID-19 is still in the early stages. With many candidates for COVID-19 vaccine are being investigated at an unprecedented “pandemic speed,” it will be critical for all parties involved to adhere to a rigorous scientific methodology and safety monitoring protocol.

So far, the mainstay of treatment for COVID-19 is still supportive care and optimized symptomatic treatment, and the capacity for SARS-CoV-2 testing is still limited. As there are no specific treatment and widespread testing, prevention is the key to controlling the pandemic. Proper social distancing, good personal hygiene, self-isolation or quarantine have been proven to be crucial in slowing down the spread of SARS-CoV-2 infection.

Table 2. Candidate vaccine currently under clinical evaluation

Classification	Current Stage of Clinical Trial (As of May 15)	Developer
Inactivated	Phase 1/2	Beijing Institute of Biological Products/Sinopharm
Inactivated	Phase 1/2	Sinovac
Inactivated	Phase 1/2	Wuhan Institute of Biological Products/Sinopharm
RNA	Phase 2	Moderna/NIAID
RNA	Phase 1/2	BioNTech/Fosun Pharma/Pfizer
DNA	Phase 1	Inovio Pharmaceuticals
Non-replicating viral vector	Phase 2, phase 1	CanSino Biological Inc./Beijing Institute of Biotechnology
Non-replicating viral vector	Phase 1	University of Oxford

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AUTHORS' CONTRIBUTION

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

AVAILABILITY OF DATA

Not applicable.

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