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Review

Promising Investigational Therapeutic Drugs for the Treatment of COVID-19: A Review

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Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2), the strain of coronavirus that has caused the COVID-19 pandemic, emerged from Wuhan, China, in December 2019. The pandemic has raised significant social, psychological and economic concerns in addition to direct medical issues. The novelty of the virus presents unprecedented challenges for healthcare systems around the world to identify effective drugs for prevention and treatment. Currently, there are no proven vaccines or therapeutic agents against the virus. While current therapies include supportive care such as the use of supplemental oxygen and mechanical ventilatory support, a pressing demand for effective treatment of COVID-19 still exists. One approach has been to repurpose existing drugs to inhibit the virus' propagation. Many of these drugs inhibit the viral replication process through interference with enzymes such as RNA-dependent RNA polymerase (RdRp) or inhibit viral particles from entering the cell. Initial research and clinical trials on repurposed drugs have yielded some encouraging results. This review aims to provide an updated summary and analysis of the most plausible repurposed investigational therapeutic drugs and preliminary clinical trial results for the treatment of COVID-19 patients.

INTRODUCTION

COVID-19 is caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). As of 13th June 2020, the World Health Organization (WHO) has reported over 7.6 million cases of COVID-19 and 428,000 deaths worldwide (World Health Organization, 2020). The virus can be transmitted by patients with or without symptoms. This transmission and the lack of a specific treatment or vaccine makes the control of the disease outbreak a challenging task (Rothe et al., 2020). Without an efficacious licensed vaccine, control of the pandemic relies on self-isolation to prevent close contact with other people alongside basic measures, such as hand washing. Quarantine is effective, but causes major disruptions such as the pause of global economies (Wilder-Smith et al., 2020). Therefore, the development of a safe and effective treatment against COVID-19 is an urgent public health priority.

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Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020 (Li et al., 2020). Transmission occurs primarily via respiratory droplets from coughs and sneezes within a range of about 1.8 m (6 ft) (Centers for Disease Control, 2020; Kuo, 2020). Indirect contact via contaminated surfaces is another possible cause of infection (Edwards, 2020). Preliminary research indicates that the virus may remain viable on plastic (e.g., polypropylene) and stainless steel (AISI 304) for up to three days, but does not survive on cardboard for more than one day or on copper for more than four hours (van Doremalen et al., 2020). The virus has been shown to be inactivated by soap through destabilization of its lipid bilayer (Yong, 2020). Viral RNA has also been found in stool samples and semen from infected individuals, although there has not been any confirmed report of the virus spreading from feces to a person (Holshue et al., 2020).

SARS-CoV-2 belongs to the broad family of viruses known as coronaviruses. It is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. Each SARS-CoV-2 virion is 50–200 nm in diameter (Huang et al., 2020). Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope (Nextstrain, 2020). The spike protein, which has been imaged at the atomic level using cryogenic electron microscopy, is the protein responsible for allowing the virus to attach to and fuse with the membrane of a host cell (Wu et al., 2020; Wrapp et al., 2020). Specifically, its S1 subunit catalyzes attachment, the S2 subunit fusion (Mandelbaum, 2020). Protein modeling experiments on the spike protein of the virus soon suggest that SARS-CoV-2 has sufficient affinity to the human recep-

tor angiotensin converting enzyme 2 (ACE2) to use them as a mechanism of cell entry. Studies have shown that SARS-CoV-2 has a higher affinity to human ACE2 than the original SARS virus strain (Lu et al., 2020). SARS-CoV-2 may also use basigin (BSG), a metalloproteinase inducer, to assist in cell entry (Wrapp et al., 2020). Initial spike protein priming by transmembrane protease, serine 2 (TMPRSS2), another human protein, is essential for entry of SARS-CoV-2 (Hoffman et al., 2020). After a SARS-CoV-2 virion attaches to a target cell, TMPRSS2 cuts open the spike protein of the virus, exposing a fusion peptide in the S2 subunit, and the host receptor ACE2. After fusion, an endosome forms around the virion, separating it from the rest of the host cell. The virion escapes when the pH of the endosome drops or when cathepsin, a host cysteine protease, cleaves it (Zhang et al., 2020). The virion then releases RNA into the cell and forces the cell to produce and disseminate copies of the virus, which infect more cells (Wang. et al., 2020).

SARS-CoV-2 produces at least three virulence factors that promote shedding of new virions from host cells and inhibit immune response (Wu et al., 2020). Whether they include downregulation of ACE2, as seen in similar coronaviruses, remains under investigation as of May 2020 (Zhang et al., 2020).

Although the scientific community is currently empty-handed in terms of treatment, the availability of the virus RNA genome sequence (GenBank ID: MN908947.3) is a valuable starting point for the identification of effective treatments. At present, a lot of research efforts have been invested to develop treatments around the world. This review will summarize the most popular developed drugs, currently showing antiviral pharmacotherapeutics prescribed in the treatment of COVID-19 patients.

Current Therapeutics Drugs in Treating COVID-19

Remdesivir

Remdesivir is an investigational phosphoramidate prodrug of a nucleotide analog (adenosine C-nucleoside) with broad-spectrum antiviral activity. Remdesivir's active metabolite interferes with viral RNA dependent RNA polymerase (RdRp) resulting in delayed chain termination. The CN group terminates viral transcription after the addition of three nucleotides, greatly slowing the rate of replication. The double carbon bond allows the metabolite to avoid being clipped out by the viral exoribonuclease (ExoN) enzyme. It was synthesized and developed by Gilead Sciences in 2017 initially for treatment of Ebola and Marburg viral infections but did not demonstrate clinical efficacy. However, remdesivir has demonstrated *in vitro* and *in vivo* activity in animal models against the viral pathogens MERS and SARS, which are also coronaviruses and are structurally similar to COVID-19 (De Wit et al., 2020). The limited preclinical data on remdesivir in MERS and SARS indicate that remdesivir may have potential activity against COVID-19 (Eastman et al., 2020). Because of its indicated efficacy *in vitro* and *in vivo* against not only SARS and MERS, but also zoonotic coronaviruses, HCoV-OC43, and HCoV-229E, remdesivir provides potential for a possible treatment for SARS-CoV-2A. A preliminary clinical trial report from *The New England Journal of Medicine* provides promising data on remdesivir's ability to shorten recovery time for adults hospitalized with COVID-19 (Beigel et al., 2020). Recovery for the remdesivir group was 11 days compared to 15 days for the placebo group. However, a prior, smaller study of 237 patients with severe COVID-19 conducted in Wuhan, China and published in *The Lancet Journal* suggests remdesivir was not associated with statistically significant clinical benefits (Wang et al., 2020). In addition, a further Phase III clinical trial is evaluating the efficacy and safety of remedisivir in 1,600 patients with COVID-19; this study ended in May 2020. Multiple other trials including the World Health Organization Solidarity Trial, Gilead SIMPLE study in patients with severe disease (NCT04292899), Gilead SIMPLE study in patients with moderate disease (NCT04292730), and Inserm DisCoVeRy trial are ongoing (NCT04315948) (National Library of Medicine, NCT04292899; National Library of Medicine, NCT04292730; National Library of Medicine, NCT04315948). Gilead is working in collaboration with Roche to evaluate the safety and efficacy of remdesivir in combination with tocilizumab, an anti-inflammatory drug, compared to remdesivir plus a placebo in patients with severe COVID-19 pneumonia. The Phase 3, double-blind, placebo-controlled trial called *REMDACTA Trial,* is expected to begin enrolling in June, with a target of approximately 450 patients globally. Results from a preclinical study indicated that, *in vitro*, the association of remdesivir/chloroquine could be highly effective in controlling the SARS-CoV-2 infection (Wang et al., 2020). Gilead Sciences has announced that the Health Sciences Authority of Singapore has granted conditional approval of remdesivir as a treatment for COVID-19 ("Singapore approves Gilead's remdesivir," 2020). The approval is based on clinical data from the US National Institute of Allergy and Infectious Diseases' global Phase 3 trial and Gilead's Phase III SIMPLE trial in patients with severe manifestations of COVID-19. Notably, remedisivir is not currently FDA-approved and must be obtained via compassionate use, expanded access, or enrollment in a clinical trial. Nevertheless, these initial results provide optimism towards a remdesivir-based treatment for COVID-19 patients.

Chloroquine and Hydroxychloroquine

Hydroxychloroquine (Plaquenil) and chloroquine are two medications that have recently been making headlines as possible treatments for COVID-19. Hydroxychloroquine and chloroquine are oral pills originally used to prevent or treat malaria. Hydroxychloroquine is also approved for long-term use in rheumatoid arthritis and lupus (Liu et al., 2020). Chlo-

roquine and Hydroxychloroquine, both anti-malarial drugs, are also being investigated as potential treatment for COVID-19 patients. Chloroquine raises the pH of endosomes and lysosomes, inhibiting endocytosis. This alkalization results in decreased endosomal and lysosomal function (Liu et al., 2020). Chloroquine can also induce the uptake of zinc into the cytosol of the cell, which is capable of inhibiting RNA-dependent RNA polymerase and ultimately halting the replication of coronavirus in the host cell. In addition, a recent study showed that, in the presence of chloroquine (or its more active derivative, hydroxychloroquine (CLQ-OH)), the viral S protein is no longer able to bind gangliosides, ultimately inhibiting the virus' ability to enter the cell (Fantini et al., 2020). However, the drugs' efficacy in the treatment of COVID-19 in humans remains controversial as most preliminary studies have been *in vitro*. Some trials, such as *Chloroquine for the 2019 novel coronavirus SARS-CoV-2* published in *The International Journal of Antimicrobial Agents* suggest significant reduction of the viral carriage after six days of treatment and much lower average carrying duration compared to patients receiving other treatment (Colson et al., 2020). However, many recent large-scale studies indicate little to no benefit from the drugs. A retrospective study conducted in France yielded similar outcomes between patients receiving hydroxychloroquine and not receiving the drug (Maheévas et al., 2020). An additional large observational study in New York saw in-hospital mortality rates among patients given and not given hydroxychloroquine was not significantly different (Rosenberg et al., 2020). The use of hydroxychloroquine as a preventative drug has been controversial as well. While notable figures such as Donald Trump encourage the drug for preventative measures, recent studies show little to no benefit from taking hydroxychloroquine after exposure. A double-blind randomized, placebo-controlled trial of hydroxychloroquine showed it did not prevent illness compatible with COVID-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure (Boulware et al., 2020). The FDA has cautioned against the use of the drug outside of hospital settings after reports of "serious heart rhythm problems" (Lovelace, 2020). Overall, while researchers are hopeful hydroxychloroquine acts as a prophylactic and treatment for COVID-19, emerging studies are showing mixed results (Saey, 2020).

Lopinavir and Ritonavir

Lopinavir and Ritonavir, often used together to treat HIV, stand as potential candidates for the treatment of COVID-19. Lopinavir is a protease inhibitor with high specificity for HIV-1 protease. Lopinavir is marketed and administered exclusively in combination with ritonavir. This combination was first marketed by Abbott under the brand name Kaletra in 2000 (KALETRA (lopinavir and ritonavir) Label, n.d.). Due to lopinavir's poor oral bioavailability and extensive biotransformation, it is co-formulated with ritonavir to enhance its exposure. Ritonavir is a potent inhibitor of the enzymes that are responsible for lopinavir metabolism, and its co-administration "boosts" lopinavir exposure and improves antiviral activity. The enzyme 3-chymotrypsin-like protease (3CLpro) plays a crucial role in processing the viral RNA. As lopinavir is a protease inhibitor, it may inhibit the action of 3CLpro, thereby disrupting the process of viral replication and release from host cells. Recent evidence suggests that lopinavir has antiviral activity against SARS-CoV-2 *in vitro*. However, coronavirus proteases, including 3CLpro, do not contain a C2-symmetric pocket, which is the target of HIV protease inhibitors, leading some to question the potential potency of HIV protease inhibitors in treating COVID-19. (Dorward and Gbinigie, 2020). Clinical trials for lopinavir and ritonavir in the treatment of COVID-19 are ongoing, although most are not promising (Lim et al., 2020). A trial of 200 patients with severe COVID-19, published in *The New England Journal of Medicine* observed no benefit was with lopinavir and ritonavir treatment beyond standard care (Cao et al., 2020). A phase II clinical trial in *The Lancet Journal* combined interferon beta-1b, lopinavir, ritonavir, and ribavirin in the treatment of hospitalized patients with COVID-19. The trial found triple antiviral therapy with interferon beta-1b, lopinavir, ritonavir, and ribavirin was safe and superior to lopinavir and ritonavir alone in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19 (Hung et al., 2020) In summary, lopinavir and ritonavir are protease inhibitors that may be investigated further as a treatment for COVID-19 patients.

Ribavirin

Ribavirin, an antiviral medication used to treat respiratory syncytial virus (RSV) infection, hepatitis C virus (HCV) infections and some viral hemorrhagic fevers, holds the potential to significantly impact the treatment of nCoV infections. (Khalili et al., 2020). Ribavirin is a guanosine analog that interferes with the replication of RNA and DNA viruses and makes it a candidate for treatment of COVID-19. However, the antiviral activity of ribavirin is not limited to interference with polymerases. The structure of ribavirin also interferes with RNA capping, which relies on guanosine triphosphate to prevent RNA degradation. Moreover, to further promote the destabilization of viral RNA, ribavirin inhibits natural guanosine generation by directly inhibiting inosine monophosphate dehydrogenase, a key step in the metabolic pathway that converts guanine to guanosine. Ribavirin's multimodal antiviral properties may limit viral replication, reducing the patient's viral load, subsequent pathological tissue damage, and the risk of transmission (Arabi et al., 2020). There is no knowledge regarding the dosage required to experience each of the unique mechanisms of action of ribavirin, and it is also not known whether the relative threshold for the activity will vary among different patient populations and clinical contexts (Khalili et al., 2020). The challenges in the

evaluation of ribavirin efficacy from 2003 during SARS and the 2013 MERS outbreaks led to a summary evaluation of its utility as controversial in the treatment of COVID-19 patients. A clinical trial with a triple combination of interferon beta-1b, lopinavir and ritonavir, and ribavirin in the treatment of hospitalized patients with COVID-19 has been published in *The Lancet Journal*. The trial found the triple combination may rapidly suppress the amount of virus in a patient's body, relieve symptoms, and reduce the risk to healthcare workers by reducing the duration and quantity of viral shedding (when the virus is detectable and potentially transmissible) (Hung et al., 2020). The inconclusive efficacy data with ribavirin for other nCoVs and its substantial toxicity suggest that it has limited value for treatment of COVID-19. If used, combination therapy likely provides the best chance for clinical efficacy.

Favipiravir

Favipiravir, previously known as T-705, is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate. The active agent inhibits the RNA polymerase, halting viral replication. Most of favipiravir's preclinical data are derived from its influenza and Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses (Furuta et al., 2017). Favipiravir is an antiviral medication used to treat influenza in Japan and China. The US Food and Drug Administration (FDA) recently granted favipiravir, from Appili Therapeutics to proceed with an expanded phase 2 clinical trial into the US (National Library of Medicine, NCT04448119). A purine nucleoside analogue, favipiravir acts as a competitive inhibitor of RNA-dependent RNA polymerase. Favipiravir was identified to have activity *in vitro* against SARS-CoV-2, albeit requiring a high concentration compared with chloroquine or remdesivir (EC50 = 61.88 μM). (Coomes and Haghbayan, 2020). A study examining the effects of favipiravir versus lopinavir and ritonavir (for the treatment of COVID-19 found that favipiravir showed better therapeutic responses on COVID-19 in terms of disease progression and viral clearance (Cai et al., 2020). However, a comparative clinical trial found that favipiravir did not significantly improve the clinically recovery rate at Day 7. Favipiravir significantly improved the latency to relief for fever and cough (Chen et al., 2020). Multiple other trials are still ongoing.

DISCUSSION

COVID-19 demands a rapid, systematic response in research efforts towards finding an efficient treatment. Repurposing existing drugs exists as an avenue to approaching an effective treatment for COVID-19. Many of these drugs inhibit the viral replication process through interference with enzymes such as RNA dependent RNA polymerase (RdRp) or inhibit viral particles from entering the cell. This review provided a summary and analysis of the most plausible therapeutic drugs being investigated as well as preliminary clinical trial results. Studies and clinical trials regarding use of remdesivir provide the most encouraging results. Early in-vitro studies regarding chloroquine and hydroxychloroquine yielded optimism, but newer studies present contrary findings. Treatment with these drugs remains controversial with a variety of clinical outcomes. Lopinavir and ritonavir, a combination used to treat HIV, inhibits 3-chymotrypsin-like protease (3Clpro), thereby disrupting the process of viral replication and release from host cells. Clinical trials of lopinavir and ritonavir in combination with interferon beta-1b and ribavirin show the combination was safe and superior to lopinavir–ritonavir alone in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19. The above-mentioned ribavirin is a guanosine analog that interferes with the replication of RNA and DNA viruses. Finally, favipiravir acts as a competitive inhibitor of RNA-dependent RNA polymerase and studies examining the effects of favipiravir versus lopinavir and ritonavir for the treatment of COVID-19 found that favipiravir showed better therapeutic responses on COVID-19 in terms of disease progression and viral clearance. This review of proposed drugs is by necessity selective. A recent comprehensive review conducted by a division of the *American Chemical Society* analyzed scientific data related to therapeutic agents and vaccines in human coronaviruses since 2003, using both published literature and patents worldwide. They reported more than 130 patents and more than 3000 potential small molecule drug candidates with potential activity against human coronaviruses (Liu et al., 2020). The same analysis identified more than 500 patents for biologic agents with activity against coronaviruses including therapeutic antibodies, cytokines, RNA therapies, and vaccines. Another preprint analysis of SARS-CoV-2–human protein-protein interaction maps identified 332 high-confidence protein-protein interactions, yielding 66 candidate druggable human proteins or host factors targeted by either existing FDA-approved or investigational drugs (Gordon et al., 2020). This large number of potential agents will hopefully yield more candidate therapeutics in the race to find effective treatments or preventive strategies against COVID-19.

Repurposed and investigational therapeutic drugs serve as a potential avenue towards finding a cure to the SARS-CoV-2 virus. There seems to be enormous political and economic will to support research and development efforts. Clinical approaches regarding repurposed therapeutic drugs present challenges and optimism towards developing a cure. Extensive research into these therapeutics remains an answer to beating the virus that has upended the world.

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