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Therapeutic Candidates for COVID-19: A Comprehensive Review of Antiviral, Immunomodulatory, and Emerging Treatments

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ABSTRACT

Background and Objectives: The coronavirus first appeared in Wuhan, China, in late November 2019, and has since spread to more than one hundred countries. COVID-19 has been declared by the World Health Organization as a Public Health Emergency of International Interest. This has been the result of a virus now having reached pandemic proportions and there not being an effective vaccine or antiviral treatment. In this article, we aim to highlight each current drug being tested for potential effectiveness on this disease.
Methodology: The research is a descriptive review conducted by a search in reputable scientific databases, including Scopus, Google Scholar, and PubMed, utilizing the phrases virus, coronavirus, COVID-19, SARS-CoV-2, and treatment. The latest expertise:given that the development and efficacy of antiviral drugs require substantial time, monotherapy for other diseases may represent the most efficient therapeutic option for a certain condition. Pharmaceuticals with broad-spectrum efficacy, including Bevacizumab, Methylprednisolone, Fingolimod, fluoxetine, Ritonavir, chloroquine Fesnate, remdesivir, and Favipiravir, are currently under investigation as prospective candidates in various clinical trials.
Conclusion: To conclude, all these drugs are potentially useful in the prevention and treatment of diseases. But none of these drugs is a cure-all, specific treatment for COVID-19. Therefore, we must continue to search for an effective drug treatment for this disease until we have a proven successful agent available. May you own for all of eternity.

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INTRODUCTION

COVID-19, caused by the SARS–coronavirus 2 (SARS-CoV-2), was first identified in late November 2019 in Wuhan, China, and has since developed into a global health emergency (1, 2). COVID-19 is declared a Public Health Emergency of international concern by the WHO With the epidemic growing into a pandemic, and no antiviral drugs or vaccinations available yet, new therapeutics strategies need to be developed (3). But after SARS in 2003 and MERS in 2012, a new member of the coronavirus family has given itself to the human population, making the challenge a different one. Like SARS-CoV, SARS-CoV-2 is activated by its interaction with the enzyme ACE (angiotensin-converting enzyme) within the host cell (4). before the lungs, SARS-CoV-2 is found across the whole body nasal tract. ACE-2 is thought to play an important role in protecting humans from lung injury and airway epithelial inflammation, but after viral infection, the protein expression of ACE-2 decreases (5). It is a beta-coronavirus, like SARS and MERS. Sequencing of the SARS-CoV-2 genome showed 96% homology with bat coronaviruses, and 79.6% homology with SARS-CoV. No approved drug or vaccine for COVID-19 is available; however, many clinical trials are underway (6). Clinical trials have used lopinavir and ritonavir.

Delivering new medicine is a long process involving years between discovery research and clinical approval (7). Some recent studies have used viral proteins to screen molecular biomarkers. The results of this work may help in selecting suitable drug candidates in laboratory and clinical settings (8). On the other hand, the use of drugs approved for specific diseases and found to be safe for human use needs to be assessed for a new disease. Such a pharmacological approach is especially beneficial in cases of life-threatening illness if there is a substitute medication or vaccine available (9). However, clinical trials still need to confirm whether the drug is safe for humans. It also is appropriate for this treatment (5). Chloroquine phosphate, previously used to treat malaria, is one of the drugs being explored for this disease's treatment (10). Method: An in silico analysis on 39 drugs performed by the researchers revealed that chloroquine phosphate has anti-COVID-19 activity. Proteasome inhibitors, including lopinavir and ritonavir (which are approved for the treatment of other viral infections), are also the subject of clinical trials (11, 12). Despite 96% homology between the M protein of SARS-CoV and SARS-CoV-2, early studies used lopinavir and ritonavir against the M protein of SARS-CoV. Understood that the sequence similarities between a potential COVID19-associated protein and the SARS-CoV M protein could be utilized to model the Mpro-2CoV-SARS-associated protein. It has been recently demonstrated that using homology-based models to screen a library of small molecules for potential COVID-19 therapeutics will be quite advantageous (13).

METHODOLOGY

This study focuses mainly on the treatment prospects for the distinct COVID-19 disease. This study is a prospective one, which has been done by searching the scientific and academic databases PubMed, Google Scholar, and Scopus with keywords virus, coronavirus, COVID-19, SARS-CoV, and treatment as well new information. It was used to obtain the newest information from the world's most respected health agencies, such as the World Health Organization and the Centers for Disease Control and Prevention.

Manifestations of disease

The main symptoms of SARS-CoV-2 infection in humans include fever, fatigue, dry cough, and dyspnea (Table 1). A significant percentage of patients with COVID-19 have deteriorated and remained in critical (14). The main consequences of this phenomenon are acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) and increased the trend of incidence of pneumonia. Another key component of the pathophysiology of ARDS/ALI is supplemental oxygenation, mechanical ventilator, or ECMO (15).

Therapeutic Approaches

One type of process uses limited chemistries and therefore produces a small variety of existing molecules as potential pharmaceuticals. The first line treatment gives antiviral agents with a high attraction to the virus (16). In Europe, interferon and ribavirin, and cyclophilin inhibitors have also been used for the treatment of coronavirus pneumonia (17). The advantage of different types of treatment such as metabolic impact, doses, side effects, and also adverse side effects have been clear (18), and proven in the treatment of viral diseases. However, these drugs have a "very high affinity for steroids," and cannot only target coronaviruses, and their side effects should be considered seriously (19). A second method makes use of existing repositories of molecular data to screen compounds that may be therapeutically interesting for coronaviruses (20). This is possible to screen for these agents, and the effect of these new therapeutic compounds can, therefore, be investigated by this method. For example, the antiretroviral agent lopinavir/ritonavir (21). A third method is to directly use genomic and pathophysiological data from multiple coronaviruses to derive new targeted therapeutics (22). In principle, however, drugs engineered in this manner will have better anti-coronavirus therapies; however, formulation research for new medicines is very likely to take many years, perhaps more than a decade. Table 1 lists several of these medications and their mechanisms of action.

Categories of pharmaceuticals suggested for the treatment of viral infections

Bevacizumab

VEGF is known to be the strongest vascular permeability enhancer. Patients with COVID-19 displayed significantly higher VEGF levels than healthy individuals (23). Hypoxia and inflammation and the deregulation of the respiratory epithelium may lead to increased levels of VEGF. VEGF has been shown to play an important role in mediating vascular permeability and pulmonary edema in the pathogenesis of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), and multiple studies have confirmed this (24). As a result, the anti-VEGF agent bevacizumab could be a potential therapeutic option for this disease. It is an FDA-approved drug for the treatment of ARDS/ALI caused by COVID-19 (25). Bevacizumab is an extended half-life humanized monoclonal antibody. And, it was approved by FDA on February 26, 2004, and is now widely used in clinical cancer it pharmacokinetics and pharmacodynamics from available (26). Consequently, bevacizumab

This medicine appears promising for treating ARDS/ALI and for reducing morbidity and mortality in severely ill patients with COVID-19 by attenuating

Table 1. Mechanism of the effectiveness of different drugs

Drug	DrugMechanism of Effectiveness	Additional Information
Remdesivir	Inhibits RNA-dependent RNA polymerase (RdRp), disrupting viral replication	Used primarily for treating COVID-19; works by incorporating into viral RNA, causing premature termination
Chloroquine/Hydroxychloroquine	Increases endosomal pH, inhibiting viral/cell fusion and glycosylation of cell receptors.	Initially used for malaria; investigated for COVID-19 treatment; potential immunomodulatory effects.
Methylprednisolone	Reduces inflammation by suppressing the immune response.	Corticosteroids used for various inflammatory and autoimmune conditions; can reduce cytokine production.
Combination of Ritonavir and Lopinavir	Ritonavir inhibits the breakdown of lopinavir, enhancing its antiviral activity against HIV.	Used in HIV treatment; ritonavir acts as a pharmacokinetic enhancer.
Favipiravir	Inhibits viral RNA-dependent RNA polymerase, preventing viral replication.	Broad-spectrum antiviral; used for influenza and investigated for COVID-19.
Fingolimod	Modulates sphingosine-1-phosphate receptors, reducing immune cell migration to the central nervous system.	Used for multiple sclerosis; prevents lymphocyte egress from lymph nodes.
Bevacizumab	Inhibits vascular endothelial growth factor (VEGF), reducing tumor blood vessel formation.	Monoclonal antibody used in cancer therapy; targets angiogenesis.

pulmonary edema (27). Phase 2 and 3 clinical trials of this drug were conducted at Shanghai University Qilu Hospital and enrolled 20 patients with severe clinical symptoms of COVID-19. These studies showed that this drug as anti-VEGF treatment can alleviate VEGF induced symptoms (28). “We use methylprednisolone, which is a type of cortisone. Methylprednisolone is used to treat a variety of inflammatory conditions including rheumatoid arthritis, lupus, psoriasis, ulcerative colitis, allergy diseases, endocrine diseases, and diseases of the skin, eyes, lungs, stomach, nervous system or blood cells (29). Prednisolone and methylprednisolone may also be used in the treatment of other viral infections, including respiratory viruses such as coronaviruses (27). Two clinical trials have been reported on the research to 80 patients with COVID-19 (24). In another study in Shanghai, 24 COVID-19 patients received the medication intravenously at a dose of 1-2 mg/kg/day for three weeks, whereas in Wuhan Respiratory Hospital, China, it was used in 50 patients. At Hongji Hospital, 40 mg/kg was given intravenously for 7 days (28).

Administration of this medicine depends on the clinical manifestations of the disease in different people, and needs to be done cautiously (30).

Fingolimod: Although immunosuppressive drugs are generally contraindicated for SAR-CoV-2 pneumonia (29), the pathological features of edema and hyaline membrane noted support consideration of appropriate immunosuppressive therapy and ventilatory assistance in patients who are developing ARDS (30). Fingolimod (720FTY) is an immunomodulatory drug commonly used in the management of scleroderma (31). Currently, research is being done to see if fingolimod could help in fighting COVID-19. Results from a Phase 2 clinical trial of this drug involving 30 patients with COVID-19 at the Venice Hospital were reported to provide good clinical outcomes in modulating the immune response of the patients (24).

Chloroquine phosphate

The virus usage and the potential of anti-viral mechanisms in getting rid of more than one subscriber limit area, starting from anti-IL-6, anti-TGF-β, and other processes so that it does not enter 4 once two times and be attractive to other medications have been an advantage (31-33). Here, this drug has recently been identified as an antiviral in the current study. It interrupts SARS-CoV-2 cellular receptor maturation during viral entry and their functionality (33). In addition, in the late stages of SARS-CoV-2 infection in Vero 6E cells, chloroquine not only has direct antiviral action but also modulates the immune system. (31), in the cumulative view, its antiviral action will be strengthened outward. Orally, chloroquine is distributed throughout the body including the lungs. Using the previously established effective concentration of 90% chloroquine in COVID-19-resistant Vero 6E cells (6.9 μM), which is at physiologically active concentrations (as in the case of plasma of rheumatoid arthritis patients receiving 500 mg (34) as the baseline. It is a 70-year-old drug that is therefore considered safe to use in COVID-19 (34). It has now been removed from worldwide clinical trials because of its negative effects. In Shanghai, the drug was given to 30 pneumonia patients as part of a phase 3 experiment. Another trial has used chloroquine as a prophylactic in 1,000 people (32). These studies showed that this drug reduced the severity of pneumonia, the frequency of symptoms, and the risk of

viral pneumonia without side effects (32).

Lopinavir plus ritonavir

A combination of two drugs used for the treatment of people with drugs under the brand name Kaletra, and is also in trials in Thailand with the flu medicine oseltamivir (Tamiflu) in a regimen for COVID-19 (35). Since these pharmaceuticals block viral proteasomes, they have limited adverse effects (36). A case report followed on 18 February 2020 claiming that an old Chinese man, who was the first patient to receive "Thailand cocktail" at a hospital in Bangkok, had completely recovered from acute pneumonia caused by the COVID-19 virus (37). However, this was tested in the 2003 SARS pandemic, and the results found that patients with first-line therapy of lopinavir/ritonavir fared better, with one patient showing a decreased viral load (38). One patient given methylprednisolone developed a respiratory tract infection (39). Therefore, and indirectly, through reducing the damage done by the immune system, both antivirals may represent a suitable dual treatment for the new coronavirus (40). In this context, a phase 4 clinical trial of this drug was performed with 400 COVID-19 patients at Tongji Hospital. A study was done in the Wuhan Jinyintu Hospital with 125 patients (24). At Wuhan Jinyintu Hospital, the dosing for 80 patients was 200 mg lopinavir and 50 mg ritonavir bi-daily. Results showed that the drug reduced the titer of the virus and improved the patients clinical outcomes (28).

Remdesivir

In culture cells and in mouse and nonhuman monkey models, remdesivir has shown an antiviral effect against RNA viruses, including 5CoV-MERS/SARS (33). Remdesivir is an in vivo viral RNA replication disruptor and is the ribonucleic acid-dependent ribonucleic acid polymerase (RdRp) inhibitor of the ebolavirus (EBV) (34). The Mabulavirus (EBV) phase is active for remdesivir according to analysis. The compound was shown to be effective against EBV infection in vivo. Remdesivir acts as a nucleotide analogue (35). Warren et al. It was shown that intravenous administration of remdesivir at a dose of 10 billion mg per kg achieved blood levels (10 μM) of the active form of the drug and conferred complete protection against SARS-CoV-2 in a non-human primate model (36). The EC50 (olive oil + simonosa glycyrrhizin) of remdesivir against COVID-19 in Vero E6 cells is 1.76 μM, suggesting this is relevant to NHP (37). The EC50 of remdesivir in the SARS-CoV-2-infected Vero E6 cells was 0.77 μM, with a selection index (SI) of 12948. Remdesivir also restricts viral infection in a human cell line (human lung cancer-7Huh cells) susceptible to COVID-19 (36).

Remdesivir is now being evaluated in China in a Phase III, double-blind, randomized, controlled clinical trial. Clinical phase 2 and 3 clinical trials are performing in patient COVID-19 in University of Nebraska and University of Chicago (38). In Phase 3 clinical studies, 452 patients with acute respiratory symptoms or mild to moderate COVID-19 have been given remdesivir as a treatment (24).

Fovavivir

Fovavivir (T-705); 3-6-fluoropyrazinecarboxamide-2-hydroxy (3-hydroxypyrazine) is an antiviral compound with specificity for RNA-dependent RNA polymerases (RdRps) of RNA viruses (39).

Favipiravir undergoes intracellular phosphorylation to become the active form of the drug. RTP-Favipiravir, an RdRp substrate (46), competes with the phosphenolphosphate end of GTP, blocking RNA polymerase activity. Because favipiravir shares an conserved catalytic domain of RdRp with multiple RNA viruses, its broad-range antiviral activity may be an advantage. Favipiravir is effective against Influenza viruses, including those resistant to antiviral drugs. The active ingredient favipiravir has proven antiviral efficacy against a variety of highly pathogenic RNA viruses, including arenaviruses, bunyaviruses, and filoviruses that cause severe hemorrhagic fever (40). The drug was used in bovine studies during the SARS-CoV-2 pandemic of 2019 (41). In a controlled trial by Chun et al. Participants in (2020) had moderate symptoms, recovered within 7 months of treatment, and the medicine reduced the incidence of severe acute respiratory syndrome (SARS-CoV-2)(42). A study in a Swiss hospital of 80 patients treated with favipiravir also showed it was better than lopinavir-ritonavir (43).

DISCUSSION

Antiviral Drug Development 7 Years Ahead of Its Time. This rapid advancement is fueled by the need for effective treatments for pandemics and other widespread threats to health (44). Many of them are actually old medicines, originally designed to treat other problems, but are now indispensable for the new problems. At present other antiviral agents are being investigated in clinical trials as potential therapy for COVID-19 (45). They include bovisumab, prednisolone methionine, fingolimod, fluoxetine, ritonavir, chloroquine phosphate, remdesivir, and favipiravir. Each of these medications has a unique mechanism of action, providing a multi-faceted approach to fighting the virus. They are critical to evaluating their efficacy, appropriate dosages, and safety for treatment of COVID-19(46).

Though we have potent treatments available to combat most forms of viral infection, the ongoing SARS-CoV-2 pandemic has highlighted that our therapeutic options for dealing with mononucleosis-inducing coronavirus infections are extremely limited

(47). The SARS outbreak in 2003 and the 2012 MERS-CoV outbreak reduced considerable research initiative, however as of now no pharmacological treatment for mononucleosis-inducing coronaviruses exists(48). The severity of this disease is a key reason why no primary coronavirus has been successfully isolated so far. While SARS-CoV-2 falls under scrutiny, new viruses might threaten in the future (49). They are a global public health problem. Thus, how to modulate the virulence of human coronaviruses is an affirmed scientific task (50). Because of limited resources for antiviral drug development and commercialization, existing therapeutics for other conditions may provide the only and fastest alternative of therapy for emerging infectious diseases. The majority of the medications in question have substantial experience, with efficacy well studied and safety well established (51).

First, they bind to the RdRp of SARS-CoV-2, thereby interfering with viral RNA production. That work indicated that TP-Remdesivir and Favipiravir bind strongly to the RdRp of SARS-CoV-2, consistent with their core antiviral mechanisms, indicating that these two drugs may be suitable for treating SARS-CoV-2-induced pneumonia (52). According to the analytical results, this study discovered for the first time that Remdesivir binds to one of human 2TMPRSS, an important protein known to mediate viral replication, which provides possibilities for further investigation (53). Subsequent investigations suggest that chloroquine phosphate has greater anti-SARS-CoV activity. This medicine is unique yet unproven. Research in bioinformatics suggest that chloroquine phosphate has interaction with b3Nsp and the E channel. However, more studies are needed to confirm this finding (2). However, this drug has also recently been withdrawn in some countries due to negative impacts. Due to adverse effects associated with the use of lopinavir and ritonavir (these drugs are ineffective and dangerous in patients with coronavirus pneumonia), molecular data were analyzed (54). Molecular data suggest that c3Nsp or channel E is the main target of ritonavir, while c3Nsp has been reported as the main target of lopinavir, although it predominantly targets helicases Nsp3c, Nsp3b, and Nrp3c (55). Some of the targets (i.e., b3Nsp, c3Nsp, and channel E) might be false-positive candidates due to poor model performance for small-molecule proteins (56). Neither lopinavir nor ritonavir affects the binding affinity of the target to important proteins such as CLpro, PLpro, and RdRp(57), as shown by bioinformatics research. While this data indicates that SARS-CoV-2 infection may not be exclusively treated with high doses of lopinavir and ritonavir alone(58).

CONCLUSION

Antiviral drugs are developing much faster than the infectious disease themselves, therefore current drugs for other diseases could potentially provide the best and fastest route to therapy against emerging infectious diseases. Currently, multiple antiviral agents such as bovisumab, prednisolone methionine, fingolimod, fluoxetine, ritonavir, chloroquine phosphate, remdesivir, and favipiravir are being investigated as potential treatment candidates in various clinical trials. Thus, the results of this study suggest that synergistic administration of these two medications may benefit the war against this disease. Before anything else it is worth stressing that these medicines are not a cure, nor a specific treatment for COVID-19, and that a search for a specific cure for this disease has to continue until one is found.

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Hossein Fazli: Conceptualization, editing and review.

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Not Applicable

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