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REVIEW

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# Therapies of Interest in Combatting COVID-19

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ABSTRACT

By the end of year 2019, the coronavirus infection originated in China and in a short span of time entangled the whole world. This rapidly expanding coronavirus 2019 (also called COVID-19, 2019-nCoV or SARS-CoV-2) infected around eight lac people and resulted in more than 38000 deaths worldwide by 1st April 2020. Elderly people, immunocompromised subjects and those with comorbidities were found to be affected more often. This review focuses on the current knowledge related to therapies of interest for tackling COVID-19 which include drugs with antiviral activity that have been regularly used in other diseases and other drugs which don't fall under antiviral category but are gaining popularity in the current situation for their possible and potential effectiveness against coronavirus. Although progress has been made in determining potential of these therapeutic alternatives, long term safety-efficacy studies of these agents in COVID-19 infected subjects are required.

**KEYWORDS:** Coronavirus, COVID-19, SARS-CoV-2

## INTRODUCTION

Coronaviruses are single-stranded, positive ribonucleic acid viruses, belonging to the family Coronaviridae that can cause disease in birds, mammals and humans.[1] In December 2019, the city of Wuhan, China, became the center of a viral outbreak that attracted great international attention. The causative agent of the disease was isolated, and it was determined to be a new coronavirus in January 2020. Following SARS-CoV (2002) and MERS-CoV (2012), this is the third coronavirus outbreak reported in the current century.[2]

This novel coronavirus 2019 has rapidly spread from China to almost every corner of the globe. Due to this illness, around eight lac people were infected and more than 38000 died worldwide by 1st April 2020 with United States being the country with the highest number of victims. It has been observed that the virus most frequently affects older adults, immunocompromised people or people with comorbidities.[2]

In this review we offer a panoramic view of the current knowledge related to the treatment and therapeutic alternatives for COVID-19, from drugs that have been regularly used in other diseases with proven antiviral activity, to drugs that have usually been used as antiparasitic or antibacterial but that, in the current situation, are again known for their possible and potential effectiveness in treating COVID-19.

Preventive administration of antibiotics should not be performed without microbiologically confirming bacterial superinfection.[4] There are not yet any licensed vaccines or therapeutic agents to treat coronavirus infection, highlighting the urgent need to develop effective vaccines or post-exposure prophylaxis to prevent future epidemics. COVID-19 resembles SARS-CoV infection in a few genetic, clinical and epidemiological characteristics. Therefore, advances in research on the treatment of this virus could help develop effective therapeutic agents.[1]

## ARBIDOL (UMIFENOVIR)

Umifenovir has been shown to have a direct antiviral effect on early viral replication of SARS-CoV in vitro.[5] Arbidol inhibits virus-mediated fusion with the target membrane, thereby blocking viral entry into the target cells.[6] This product is used as a treatment for influenza in Russia and China and has been claimed to be effective in the therapy of COVID-19 in a concentration range of 10-30 μM, in vitro. A multicenter randomized controlled trial with arbidol has been initiated in China in patients with COVID-19.[7] As per the results of a study, this drug showed a trend to improve patient discharge rate and reduce mortality in a small cohort of patients with COVID-19.[6]

## REMDESIVIR

Remdesivir is a prophylactic analogue of adenosine which could interfere with NSP 12 polymerase, in

vitro.[8]

It has been recognized as an antiviral agent with a promising potential against a wide range of RNA virus infections in animal/in-vitro studies. Furthermore, it is in stage of clinical development for the treatment of Ebola virus infection.[9] It was used to treat the first COVID-19 patient in USA and resulted in a reduced viral load in nasopharyngeal and oropharyngeal samples, and the patient's clinical condition improved.[10,11] Phase III clinical trials have also been conducted for evaluating the use of intravenous remdesivir in patients with COVID -19.[12]

**LOPINAVIR/ RITONAVIR**

The protease inhibitors lopinavir and ritonavir, used in treating HIV infection, could improve the condition of patients with SARS and MERS viral infection.[8] The systematic review by Yao et al. reports that most in vitro studies have shown that lopinavir can inhibit SARS-CoV. In addition, two cohort studies of SARS-CoV patients revealed that lopinavir/ritonavir plays a critical role in clinical outcome, especially in the early stage. Treatment with lopinavir/ritonavir improved clinical outcomes in some patients with MERS-CoV and this could be an effective treatment against COVID-19 based on the previous experience against SARS and MERS.[13] In an adult patient with COVID-19 in Korea, the viral load significantly decreased after the administration of lopinavir/ritonavir.[14]

As per a published protocol for the restricted use of this association in symptomatic patients during a public health emergency, adult patients hospitalized by COVID-19 were eligible to receive this combination drug for 14 days after signing the informed consent and if useful, further evaluation by a randomized control trial design is warranted for future therapeutic use of this combination.[15]

**FAVIPIRAVIR**

This drug underwent clinical trials for evaluation of efficacy and safety in the treatment of COVID-19 with promising results.[16] Favipiravir is a new type of RNA polymerase inhibitor[17] that becomes an active phosphoribosylating form in cells and is recognized as a substrate by viral RNA polymerase, thus inhibiting the activity of RNA polymerase.[18] The preliminary result of a clinical trial indicated that favipiravir had a more potent antiviral action than lopinavir/ritonavir. No significant drug related safety signals were observed in the favipiravir treatment group which had significantly lower adverse reactions than the lopinavir/ritonavir group. Therefore, the favipiravir would have a possible antiviral action in COVID-19.[16]

**TEICOPLANIN**

The knowledge-based hit and trial of existing drugs can be a quick and effective way in identifying drugs with a known safety profile in treating an emerging disease. Teicoplanin, a glycopeptide used to treat gram-positive bacterial infections has been found to be active, in vitro, against SARS-CoV. It has joined the list of molecules that could be used as therapeutic arsenal in COVID-19 as it has demonstrated its efficacy against several viruses such as HIV, Ebola, flavivirus, influenza virus, hepatitis C virus, SARSCoV and MERS-CoV(19). This drug prevents the viral RNA release and interrupts the replication cycle of corona virus, so is placed as a potential treatment for patients with coronavirus infection.[20,21]

**CHLOROQUINE**

Chloroquine, an effective anti- malarial drug has been used for many years and has a great potential in treating COVID-19 infection. It can inhibit the pH-dependent steps of replication of various viruses with a potent effect on the infection and spread of SARS-CoV. In addition, this drug has immune-modulatory effects, which suppress the production and release of TNF-α and IL-6. Research publications have reported that this drug interferes with the glycosylation process of SARS-CoV cell receptors and also works in the entry and post-entry stages of infection in Vero E6 cells. When combined with remdesivir, has also been shown to effectively inhibit the virus in-vitro.[8] As per recent studies, it may improve the clinical outcome of patients infected with SARS-CoV-2. It is also assumed that chloroquine also interferes with the glycation of the ACE2 receptor, thus preventing the binding of the virus to target cells.[22]

As reported by Wang et al, the expression of RCT2 is increased by SARS coronavirus in lung tissue, and this may accelerate its replication as well as spread.[23] It also alters virion assembly and germination by interfering with proteolytic processing of M-protein and it could act indirectly by haltering the production of pro-inflammatory cytokines and activating antiviral CD8+ T cells.[24]

It is reported that there is preclinical evidence of

efficacy-safety for long-term clinical use in other diseases that justify clinical investigation of chloroquine use in patients with COVID-19.[24]

**HYDROXYCHLOROQUINE**

Hydroxychloroquine and chloroquine are active against malaria and have similar pharmacokinetics but differ in their toxic doses and by the presence of a hydroxyl group. The advantage of hydroxychloroquine is that it can be used in high doses for long periods with very good tolerance.[22,25] Both drugs have equivalent antiviral activity, but hydroxychloroquine has a better safety profile than chloroquine. In patients with COVID-19, these drugs may interact with lopinavir/ritonavir or azithromycin, resulting in prolongation of the QT interval. Other therapeutic agents for COVID-19 are currently being investigated, such as antivirals (oseltamivir, lopinavir/ritonavir or ribavirin), interferons and intravenous immunoglobulins that do not interfere with hydroxychloroquine.[26]

Zhou et al. propose that hydroxychloroquine, which shows an antiviral effect very similar to that of chloroquine, could serve as a better therapeutic approach. Hydroxychloroquine is likely to suppress T-cell activation, leading to inhibition of the cytokine storm and ultimately hinder the severe progression of COVID-19. In addition, it has a better safety profile and may be administered in pregnant patients.[27]

**AZITHROMYCIN**

The antibiotic azithromycin has also gained attention during this deadly outbreak. A non-randomized, open-label clinical trial was conducted to evaluate the role of azithromycin along with hydroxychloroquine in respiratory viral loads. Subjects with COVID-19 were included in the study and received study drugs and their viral loads were analyzed in nasopharyngeal swabs. Untreated patients from another center and cases who did not accept the protocol were included in the study as negative controls. The treated subjects showed a significant reduction in viral load compared to controls on 6th day after inclusion. Azithromycin added to hydroxychloroquine was significantly more effective in combatting the virus. The study showed that the combination treatment was significantly associated with viral load reduction/disappearance in patients with COVID-19.[28] This combination stands efficacious, but azithromycin is known to potentiate QT interval prolongation effect of hydroxychloroquine.

**CONCLUSION**

COVID-19 virus outbreak has handicapped the medical, financial and public health infrastructure across the globe. Current actions are focused on social distancing, hand sanitization, disinfection of surroundings and quarantine of infected subjects. An effective and safe vaccine against this pandemic might be the ultimate answer, but until such a remedy is available it is important to focus also on pharmacological therapies of interest such as described in this piece of literature. In depth research on the pathogenesis of COVID-19 might help in discovery of appropriate targets for development of specific agents against this global enemy. Healthcare researchers are working hard and significant progress in identifying therapeutic alternatives to drugs has been made, controlled studies are required to find out in detail the efficacy as well as safety profile of drugs that stand as potential candidates for the treatment of subjects with COVID-19 infection. Meanwhile, it is important to follow therapeutic regimens recommended by health authorities at individual, national and global levels.

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