# TREATMENT OF COVID-19 - A REVIEW

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***Abstract*: Infection by the SARS-CoV-2 virus, known as COVID-19 (Corona Virus Disease-19), emerged in December 2019 in China and spread rapidly all around the world infecting many peopleand has subsequently spread rapidly throughout the world, however, well-designed studies on asymptomatic or mild, or pediatric cases of COVID-19 are scarce and desperately needed to meet the clinical need. However, a trend could be observed based on current clinical evidence. Remdesivir and favipiravir may shorten the recovery time; lopinavir/ritonavir does not demonstrate treatment efficacy in severe patients. In this review, we collected information about the most widely used drugs to treat COVID-19 (coronavirus disease 2019) belonging to groups of antivirals, antibiotics, immune modulators, and anticoagulants. Some of these compounds and drugs were used directly by inpatients, so researchers have examined others in laboratory conditions. The present study provides an update on the currently applied treatment, and intends to offer helpin relation to daily care, without seeking to replace the protocols adopted in each individual center.**

***Keywords*: SARS-CoV-2, COVID-19, antiviral drugs, antibiotics, immune modulators, anticoagulants**

## INTRODUCTION

Infection due to SARS-CoV-2 virus, the so-called COVID-19 *(Corona VIrus Disease 19)*, was initially detected in China back in December 2019, [1]during which a wave of people was infected by pneumonia. Since the outbreak of severe acute respiratory syndrome coronavirus-2(SARS-CoV-2) in China toward the end of 2019, 32,110,656 cases were reported worldwide, and the virus caused 980,031 deaths, accounting for 3.05% of the infected population as of September 25, 2020 (World Health Organization, 2020). To date, no effective vaccines and promising antiviral agents for SARS-CoV-2 have been developed, and the currently available drugs are still under investigation. [2, 3] Therefore, many critically ill patients are treated with off-label antiviral drugs.[4] Many drugs used in this field have been active against the SARS virus in laboratory conditions, and some have been licensed. [5] Current strategies for pharmacotherapies are centred on three main areas: antiviral agents to prevent viral replication, immunomodulators to attenuate the dysregulated host immune response seen in severe disease, and treatments to counter the hypercoagulable state that leads to a high rate of thrombotic complications. This articles reviews the evidence for current and prospective drug candidates to treat COVID-19.[6]In this review, we presented the results of several studies on the effectiveness or ineffectiveness of these drugs. Table 1 briefly outlines the known uses of these drugs and the results of their current applications for COVID-19

**Currently Approved Antivirals for COVID-19**

## ANTIVIRAL DRUGS

### Lopinavir-Ritonavir (LPV-RTV)

LPV-RTV is a protease inhibitor used for a variety of treatments, including the initial treatment of HIV (Human Immunodeficiency Virus) infected adults.[7] One study used a combination of Chinese and Western therapies, including LPV-RTV, arbidol, and Shufeng Jiedu Capsule (SFJDC), which improved the patients significantly.[8] In another study, the interaction was investigated between LPV-RTV and oseltamivir as a neuraminidase inhibitor. As a result, these drugs were found to function more effectively when used together than when used separately.[9]

A clinical trial was conducted on 199 patients with COVID-19 divided into two groups and treated with LPV- RTV and standard treatment. The results showed that LPV- RTV treatment was associated with lower mortality, shorter stay in the intensive care unit, and fewer gastrointestinal side effects, although it did not significantly improve the treatment of the patients. This issue is related to the patient selection process because the patients were late during the infection, which caused damage to their tissues. What encourages the use of LPV-RTV for COVID-19 treatment is its availability in large quantities with approved licenses and the fact that many reports suggest it for COVID-19 treatment. In one study, COVID-19 patients treated with LPV- RTV were at increased risk of bradycardia. In the study, the heart rate dropped to less than 60 beats per minute for more than 24 hours. Bradycardia was resolved in the patients when the LPV-RTV dose was reduced or stopped. According to this result, it was reported that RTV-LPV could increase the risk of bradycardia when used in inflammatory injury conditions and during critical stages of the disease. [10]

### Remdesivir (RDV)

RDV is another antiviral drug that can change to its active form (GS-441524). It causes to obscure the RNA polymerase, and eventually, prevents its replication. RDV was developed in 2017 to treat Ebola, and has a wide spectrum of antivirus activities. In an experiment, a recombinant MERS-CoV was used to express a reporter nanoluciferase on a mouse laboratory model to measure RDV, LPV-RTV, and interferon beta antiviral activity. Interferon beta had little effect on the virus, and the performance improvement was not significant with LPV-RTV. However, treatment with RDV could improve the disease outcomes and reduce the virus proliferation in mice infected with MERS-CoV. The treatment with RDV could also reduce acute lung injury in the studied

mice. RDV has also been shown to improve pulmonary function and reduce viral load in chimeric virus-infected mice, making it a suitable candidate for COVID-19 treatment. [11]

In one study, the RDV effectiveness was evaluated in COVID-19 patients using statistical methods. The results showed that RDV was effective in patients who were not in the severe stage of the disease. In a trial in China, COVID-19 patients over the age of 18 accidentally received RDV. There was no significant difference in terms of clinical benefits between the group receiving RDV and the control group. However, a numerical decrease was observed in the recovery time of the treatment group.In a randomized trial, more than 1000 adult patients with COVID-19 were treated with RDV for 10 days. The recovery time was shorter in patients receiving RDV than in controls, and RDV was reported to be effective in shortening the recovery time in the patients.In one study, 397 COVID-19 positive patients were randomly divided into two groups receiving RDV for 5 or 10 days.[13]

**Table 1 Available Drugs for the Treatment of Patients with COVID-19**

| Groups | Drugs | Applications | Results Related to COVID-19 |
|---|---|---|---|
| **Antivirals** | Lopinavir–ritonavir (LPV-RTV) | HIV[11] | Reducing the disease symptoms in the early stage, [16-17] not accelerating the disease treatment, increasing the risk of bradycardia[12] |
| | Remdesivir (RDV) | Ebola[14] | Accelerating the patient's recovery, having no specific side effects[15] |
| | Favipiravir (FPV) | Influenza[18-19] | Accelerating the patient's recovery, having few side effects[20-21] |
| | Arbidol (ARB) | Influenza[22] | Having proper performance,[23- 24]having no specific side effects[23] |
| | Ribavirin | Lassa[25] | Having no clear benefit, having no treatment advantage, [26] having in vitro antiviral effects against SARS-CoV-2[27] |
| **Antibiotics** | Azithromycin | Many types of bacterial infections[28-29] | Having good performance in combination with HCQ, reducing mortality, having no special side effects[30-31-32] |
| **Immune modulators** | Anakinra | Inflammatory diseases[54] | Having good performance, reducing mortality, |
| **Anticoagulants** | Heparin | Coagulation problems[33] | Reducing mortality, [34] having side effects including drug resistance and heparin-induced thrombocytopenia (HIT)[35-36] |

**Favipiravir (FPV)**

FPV, in previous years and various studies, was proved to be able to inhibit different strains of influenza virus resistance to drugs such as amantadine, zanamivir, and rimantadine. The FPV function involves a variety of activities against viruses resistant to various drugs. FPV directly inhibits influenza virus transcription, and the drug inhibits the virion M2 ion channel. [18-19] A study in the Third People's Hospital of Shenzhen examined clinical results in people with COVID-19 treated with FPV and in those treated with LPV-RTV. They found that patients treated with FPV recovered faster, and the chest radiography of both groups showed more changes in the FPV group than in the LPV-RTV group. [20]

In a clinical trial with COVID-19 confirmed patients, the results showed a rapid antiviral response with FPV. Side effects observed in the patients included those previously reported in patients taking FPV. However, it is recommended to use this drug in patients with respiratory and immunological problems, only in combination with drugs that have proven effectiveness. [21]

**Arbidol (ARB)**

Umifenovir, under the brand name ARB, is used as a drug against the flu virus.[22] It can inhibit the fusion of the virus to the cell membrane.[37] ARB can have more inhibitory effects on a variety of viruses, such as RNA viruses. It can also be effective before or during a virus infection.[38] A study on the comparison between different types of drugs used to treat Lassa (LasV) and Ebola (EboV) infections showed that ARB could control of two viruses.

Treatment with arbidol and interferon alfa-2b has proven to be effective in treating patients with mild disease.[51] ARB can reduce the hospitalization duration; moreover, it has been suggested that the use of this drug in combination with adjuvant therapy can somewhat speed up treatment time. Finally, the results showed that there was insufficient evidence to support the use of this drug for recovering COVID-19 patients.[52]

**Ribavirin**

Ribavirin is also known as tribavirin is an antiviral medication is a guanosine analogue with a wide range of antiviral activities associated with the proliferation of RNA and DNA viruses.A few years ago, there was a study on the RNA- dependent RNA polymerase (RdRp) as one of the components involved in catalyzing the synthesis, transcription, and proliferation of RNA as well as the pathogenesis of the virus.[40] ribavirin treatment was evaluated. The results showed that the ribavirin therapy of the patients did not reduce the mortality rate compared with the control group.[41]

## ANTIBIOTICS

### Azithromycin

Hydroxychloroquine is a 4-aminoquinoline antimalarial drugthat has proven to have *in vitro* activity against several RNA viruses including SARS-CoV-2.. This antibiotic has shown better performance than erythromycin against gram-positive and gram- negative pathogens.[42-43] In one study, the relationship was investigated between macrolides and mortality in MERS- CoV patients. The results showed no significant relationship between macrolide treatment in the patients and reduced mortality.[44] However, the treatment of COVID- 19 patients with azithromycin cannot be avoided because the number of studies with similar results is small.Azithromycin has been used in many reports examining the effects of HCQ. In a study on 80 patients, azithromycin and HCQ were used to treat COVID-19, which significantly reduced the viral load in the patients. In the United States, a retrospective study was conducted on the history of hospitalized patients with COVID-19. Mortality was lower in the group receiving HCQ with azithromycin than in the group receiving HCQ alone. In another study, the use of HCQ with azithromycin was implicated in reducing the mortality of COVID-19 patients.

### Immune Modulators

Following the exacerbation of the disease in COVID-19 patients, complications such as worsening of cellular immune responses and increased cytokines have been reported. Researchers in China have found that there are very high levels of cytokines in the plasma of patients with COVID-19, which is interpreted as a cytokine storm or cytokine release syndrome (CRS).It means that the release of high-level cytokines cannot be controlled. This usually occurs in severe infectious diseases, when the body's immunity reaches a very high level. The high serum concentrations of cytokines, especially IL-6, were also observed in MERS-CoV infection. If CRS occurs, problems such as macrophage activation syndrome (MAS) and cytopenia may also occur.Secondary haemophagocytic lymphohistiocytosis (sHLH) can occur in hyperinflammatory conditions and can be caused by a severe viral infection that can be detected with manifestations such as cytopenia and CRS.It has been reported that a protein called angiotensin-converting enzyme (ACE2) functions as the main receptor for SARS-CoV-2 virus on the surface of many types of human cells. Following the binding of the spike-like protein of the virus to this receptor, the entry of the virus and its RNA into the cytoplasm is facilitated. The ACE2 receptor is expressed in various tissues of the body as well as in the immune system cells such as macrophages and monocytes. It can be concluded that the receptor expression increases in special immunological conditions caused by COVID-19. To improve this situation, treatments such as convalescent plasma, interleukin inhibitors, and other inflammation inhibitors, were suggested.[11]

### Anakinra

In addition to CSs, interleukin inhibitors are used to control immunological conditions caused by COVID-19, such as CRS and its complications. Patients with immune- mediated inflammatory diseases (IMID) who typically use cytokine-inhibiting drugs have been reported to be less susceptible to SARS-CoV-2-induced infection than IMID patients who do not use these drugs.[55] Most reports highlight the use of IL-6 and IL-1 inhibitors in the treatment of this disease, which will be described below.

Anakinra (Kineret®) is an IL-1 receptor antagonist (Ra) that can block its activity in the regulation of inflammatory responses. It has been reported that anakinra is effective in treating conditions such as sHLH and MAS. In one report, eight patients with COVID-19 pneumonia and complications such as sHLH were treated with anakinra. The data showed that the use of anakinra by patients with such symptoms is beneficial.[48]Further, it has been reported that anakinra reduces mortality in patients with severe COVID-19. During a course of treatment with this drug, a large percentage of COVID-19 patients improved significantly. Anakinra, like CSs, is involved in suppressing the immune system, and thus, great precautions and considerations are necessary for its administration.[11]

## ANTICOAGULANTS

In addition to the mentioned inflammatory conditions, abnormal coagulation parameters are worth considering when treating COVID-19 patients. In fact, coagulation problems occur in many of these patients, especially in the severe stages of the disease and later. The results of this study showed that abnormal coagulation outcomes and existence of disseminated intravascular coagulation (DIC) were common in deaths with NCP.[45] Infections actually disrupt the function of endothelial cells, resulting in high levels of thrombin production, inactivation of fibrinolysis, and conditions occurring with high level coagulation.[46]

### Heparin

The therapeutic effect of this drug has been previously reported on SARS patients.[47] Another study at the Tongji Hospital examined the mortality rate of 449 patients with severe COVID-19, of whom 99 used heparin..[34] However, there is evidence that taking heparin in COVID- 19 patients may lead to drug resistance and complications such as heparin-induced thrombocytopenia (HIT).[49-50]

## COVID-19 vaccine

As earlier mentioned, countless laboratories areworking towards finding a COVID-19 vaccine.Customarily, vaccine development and in particularCOVID-19 vaccine development is assuming a5-stage process. This is especially following WHO'sguidelines on clinical evaluation of vaccines which isso lengthy that it forces vaccine development totake months if not years. All this is however done ingood faith seeing that a matter as delicate as humanlives should not have any chances taken on it. Atthe moment, the World Health Organization requiresvaccine developers to follow these guidelines (WorldHealth Organization (WHO)):

- Good Manufacturing Practice (GMP) for pharmaceuticals.
- Good Manufacturing Practice (GMP) for biologicals.
- Guidelines for state establishments on quality assurance for biological products.
- Guidelines that manufacture and control WHO defined vaccines are reviewed in detail by WHO reviewing bodies.[53]
- Novavax. NVX-CoV2373. Phase 1. This vaccine has reached Phase 3 trials. ...
- Serum Institute of India. COVOVAX. Phase 1. ...
- Zydus Cadila. ZyCoV-D. Phase 1. ...
- Gamaleya. Sputnik V. Phase 1. ...
- Oxford/AstraZeneca. AZD1222. Phase 1. ...
- Serum Institute of India. Covishield (Oxford/AstraZeneca formulation) Phase 1. ...
- Bharat Biotech. Covaxin. Phase 1.

**Covaxin**

Covaxin is an inactivated vaccine which means that it is made up of killed coronaviruses, making it safe to be injected into the body.

Bharat Biotech, a 24-year-old vaccine maker with a portfolio of 16 vaccines and exports to 123 countries, used a sample of the coronavirus isolated by India's National Institute of Virology.

When administered, immune cells can still recognise the dead virus, prompting the immune system to make antibodies against the pandemic virus.

The two doses are given four weeks apart. The vaccine can be stored at 2C to 8C.

The vaccine has an efficacy rate of 81%, preliminary data from its phase 3 trial shows.

India's regulators gave the vaccine emergency approval in January while the third phase of the trial was still underway, sparking scepticism and questions from experts.

**Covishield**

The Oxford-AstraZeneca vaccine is being manufactured locally by SII.

The vaccine is made from a weakened version of a common cold virus (known as an adenovirus) from chimpanzees. It has been modified to look more like coronavirus - although it can't cause illness.

When the vaccine is injected into a patient, it prompts the immune system to start making antibodies and primes it to attack any coronavirus infection.

**How effective is Covishield?**

International clinical trials of the Oxford-AstraZeneca vaccine showed that when people were given a half dose and then a full dose, effectiveness hit 90%.

But there was not enough clear data to approve the half-dose, full-dose idea.

However, unpublished data suggests that leaving a longer gap between the first and second doses increases the overall effectiveness of the jab - in a sub-group given the vaccine this way it was found to be 70% effective after the first dose.

## CONCLUSION

The COVID-19 pandemic has challenged the world not just in the global health but also the global psychosocial and economic health. This pandemic is testing our resolve to solve challenging situation together. This review aimed to present current treatment options in combating SARS-CoV-2. Based on the many studies and by the considering of many aspects, it can be concluded that remdesivir and hydroxychloroquine with or without azithromycin are still effective treatment options for COVID-19 patients in the mild to moderate stages of the disease.We hope that researchers will discover a definitive treatment for this disease as soon as possible.

## ABBREVIATIONS

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ACE2, angiotensin-converting enzyme 2; ARB, Arbidol; CQ, chloroquine; CQP, chloroquine phosphate; CP, convalescent plasma; CPT, convalescent plasma transfusion; COVID-19, coronavirus disease 2019; EboV, Ebola virus; FPV, favipiravir; HIT, heparin-induced thrombocytopenia; LPV-RTV, Lopinavir-ritonavir;HCQ, hydroxychloroquine

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