

## DRUG REPURPOSING FOR TREATMENT OF COVID-19 PATIENTS

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**Abstract:** Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has claimed more than four million lives worldwide. Daily cases and death rates are on the rise and, unfortunately, the therapeutic vaccine or drug treatment is still nowhere to be found. Finding a cure for viruses is not easy, as vaccine and drug development may take many years of trial and error. There is, however, a way to speed up the process by repurposing the available drugs on the market. Considering that all physico-chemical properties, efficacy, and safety profiles of the drugs have been established, we believe that by repurposing drugs, it would provide a short cut in finding a cure for COVID-19. In the second opinion, we believe that a combination of drugs will also be beneficial in preventing a recurrence of infection. Thus, here we highlight several combinations of drugs that have potential to treat COVID-19.

Keywords: COVID-19, SARS-CoV-2, Kaletra, chloroquine, remdesivir.

Dear editor,

A disease with pneumonia symptoms of unknown etiology was first reported in Wuhan, China, in December 2019 (Wu & McGoogan, 2020). It was subsequently named coronavirus disease 2019 (COVID-19) after being determined as a novel zoonotic disease cause by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In just three to four months, the deadly SARS-CoV-2 has infected three million people, spreading widely and rapidly via human-to-human transmissions in more than 210 countries. COVID-19 thus became a global health problem and was declared a pandemic the World Health Organisation (WHO) on 11<sup>th</sup> March 2020 (Che Mat *et al.*, 2020).

Many health institutions and hospitals are now facing a shortfall of beds, especially in their intensive care unit (ICU), putting the healthcare system of countries at breaking point in accommodating a growing number of COVID-19 cases. And we are yet to find a therapeutic regimen for these patients. The development of new drugs for SARS-CoV-2

infection may not be a good option due to its lengthy procedure, including the time needed for pre-clinical and clinical trials. Thus, the possible and feasible alternative for COVID-19 treatment is by repurposing existing drugs. Out of the thousands of drugs available in the market, some may be therapeutically effective in treating COVID-19 patients.

COVID-19 patients will normally develop clinical symptoms like fever, dry cough, fatigue, muscle aches, flu and sore throat at the onset of infection. These symptoms may deteriorate into respiratory problems, leading to pneumonia (lung infection). COVID-19 patients are usually treated based on symptoms, which may or may not completely kill or eliminate the viruses. Therefore, the possibility of SARS-CoV-2 recurrence in discharged patients or infecting those in close contact cannot be discounted (Chen *et al.*, 2020). There are studies looking at the possibility of using drugs, such as antivirals, anti-inflammatory agents and antibiotics, to treat COVID-19 patients, and some of them are listed in Table 1.

Table 1: Repurposed drugs for COVID-19 treatment

Repurposed drug	Original treatment of disease	Mechanism of action	Case study for COVID-19	Reference
Kaletra (lopinavir/ritonavir)	Human immunodeficiency virus-1 (HIV-1)	Ritonavir inhibits the CYP3A-mediated metabolism of lopinavir to maintain plasma levels of lopinavir. Lopinavir, in turn, inhibits viral protease to prevent Gag-Pol polyprotein cleavage, which results in the development of immature, non-infectious viral particles.	A 54-year-old Korean patient with early diagnosis of pneumonia has recovered after Kaletra administration.	(Lim <i>et al.</i> , 2020)
Hydroxychloroquine	Malaria	Hydroxychloroquine inhibits terminal glycosylation of ACE2, the receptor that viruses like SARS-CoV-2 target for cell entry. It also increases the pH in endosomes to prevent the virus from utilising their activity for fusion and entry into the cell.	Isolation of SARS-CoV-2 in 19 out of 25 clinical samples from patients.	(Gautret <i>et al.</i> , 2020)
Chloroquine (phosphate)	Malaria	Similar to hydroxychloroquine.	100 COVID-19 patients with pneumonia at more than 10 hospitals in China showed recovery after being administered with chloroquine.	(Gao <i>et al.</i> , 2020)
Remdesivir	Ebola	Remdesivir is a ribonucleotide analogue that inhibits the action of viral RNA polymerase by binding to the RNA template, which leads to the termination of RNA transcription.	Positive result in cell culture – cytotoxicity assay.  The first remdesivir treatment was administered in the United States and the patient recovered.	(Holshue <i>et al.</i> , 2020; Wang <i>et al.</i> , 2020)

Favipiravir	Influenza	Favipiravir acts as a prodrug that undergoes intracellular ribosylation and phosphorylation to become active favipiravir. Active favipiravir binds and inhibits RNA-dependent RNA polymerase (RdRp) to prevent viral transcription and replication.	Ongoing clinical trials.	(DeL Rio & Malani, 2020)
Baricitinib	Rheumatoid arthritis	Baricitinib is an anti-inflammatory drug that inhibits the Janus Kinase (JAK1 and JAK2) genes to modulate their signalling pathways, thereby reducing the phosphorylation and activation of transcription (STAT) pathway.	<i>In silico</i> – bioinformatics analysis.	(Stebbing <i>et al.</i> , 2020)
Teicoplanin	Gram-positive bacteria infection	Teicoplanin inhibits peptidoglycan polymerisation, resulting in inhibition of cell wall synthesis and cell death.	<i>In vitro</i> study in cell culture.	(Baron <i>et al.</i> , 2020)
Sofosbuvir Ribavirin Galidesivir	Hepatitis C	Sofosbuvir prevents viral replication by binding to metal ions present in viral proteins and preventing further replication of viral genetic material. Ribavirin may increase the mutation frequency in the genome of several RNA viruses. Galidesivir binds to viral RNA polymerase, which results in structural changes in the viral enzyme due to altered electrostatic interactions. This results in early termination of elongated RNA strands.	<i>In silico</i> – molecular docking.	(Elfiky, 2020a)

Among the drugs, Kaletra (a combination of two anti-HIV drugs lopinavir and ritonavir) seems to have the highest potential to treat COVID-19 infection. Kaletra is taken orally and recommended for high-risk COVID-19 pneumonia groups, particularly elderly patients or those with underlying diseases (Lim *et al.*, 2020; Xu *et al.*, 2020). Kaletra is originally developed to treat adults and children with HIV but is later found to be safe for all population groups (Puthanakit, 2010). Polytherapy using a combination of several drugs is a common medical procedure, especially for treatment of HIV, tuberculosis, and malaria, to avoid relapse and disease recurrence. With the half-life ranging from two to six hours, Kaletra may potentially be administered in partner with other drugs that have a longer half-life to ensure a rapid and full elimination of SARS-CoV-2 in patients.

Theoretically, hydroxychloroquine or anti-malarial chloroquine may be a suitable partner to use in tandem with Kaletra because of its long half-life, which is around one to two months. The latter has also been shown to have apparent efficacy and acceptable safety against COVID-19 associated pneumonia cases in a clinical trial conducted in China (Gao *et al.*, 2020). However, *in vitro* results have demonstrated that hydroxychloroquine is more potent than chloroquine when combined with the antibiotic azithromycin (Gautret *et al.*, 2020; Yao *et al.*, 2020).

Other potential repurposed drug for SARS-CoV-2 is remdesivir, which is intended for Ebola patients. Remdesivir has been found to be highly effective in killing novel coronavirus in isolated cells, but its use for treating humans has yet to be approved. Nevertheless, two clinical trials for this drug are underway in China (Wang *et al.*, 2020). A combination of remdesivir and anti-inflammatory agents such as baricitinib has been suggested as the pair is able to reduce viral infectivity and replication, besides attenuating lung inflammatory responses (Stebbing *et al.*, 2020).

The antiviral favipiravir has also been tested to treat COVID-19. This drug was

originally designed for influenza and is now at the clinical trial stage for COVID-19 treatment in China. Perhaps, it may be potentially used with a longer half-life anti-bacterial, such as Teicoplanin (half-life around three to four days), which showed positive results on COVID-19 cell culture experiments (Baron *et al.*, 2020). Drug repurposing were also conducted using *in silico* approach to elucidate interactions between drugs and their effects on essential proteins of SARS-CoV-2. Results showed that sofosbuvir, ribavirin and galidesivir interacted with the coronavirus, but random clinical trials are still needed to confirm such findings (Elfiky, 2020b).

Overall, several studies have demonstrated the effectiveness of repurposed drugs as therapeutic agents for COVID-19. Drug combinations are highly recommended instead of monotherapy to achieve effective elimination of SARS-CoV-2. The pharmacokinetics parameters of drugs, such as half-life, volume of distribution, clearance, and bioavailability, need to be considered for prescription of repurposed drug due to variability in paediatric and geriatric populations, and patients with underlying diseases.

On a second note, drug interactions need to be properly evaluated too to avoid adverse effects to the patients. Factors such as glucose-6-phosphate dehydrogenase deficiency and cardiac Q-T prolongation, or any side effects caused by the repurposed drugs, should all be well considered before designing any regimen to COVID-19 patients. The battle against COVID-19 has not yet ended, so the search for its cure or any treatment options should continue.

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