



# Antiviral Therapy of COVID-19

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## Abstract

The COVID-19 pandemic required rapid response to the needs of critically ill patients, and one of the solutions was re-purposing of drugs with wide spectrum of antiviral action for treatment of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. The re-purposing characteristically started with out-of-label use in single or series of cases, to continue after the first promising results with randomised clinical trials. There are several drugs that are currently tested in ongoing clinical trials: antimalarials hydroxychloroquine and chloroquine, HIV protease inhibitors lopinavir/ritonavir, broad spectrum antivirals umifenovir (anti-influenza drug) and favipiravir, antiparasitary drug ivermectin and nucleotide analogue remdesivir. However, up to date only a few trials are completed and published, precluding definitive conclusions about efficacy and safety of these drugs. Until major clinical trials are completed, physicians who decide to use these drugs out-of-label should properly inform their patients of all potential risks and benefits and seek for their consent before administration of the drugs.

**Key words:** COVID-19; Antiviral agents; Drug repurposing; Out-of-label use; Adverse effects.

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## Introduction

Pandemic character of coronavirus disease 19 (COVID-19) and anti-epidemic measures imposed by states that affected almost any person in the world raised unprecedented interest in finding drugs that will block replication of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) causing COVID-19. Several dozens of clinical studies of different design are already published in medical journals, so numerous research groups all over the world prepared and published systematic reviews or meta-analyses in an attempt to summarise the findings and give definite recommendations about particular drugs. Most of the drugs tested for antiviral activity are repurposed, ie, they were initially developed and/or approved for other indications, and then tested in patients with COVID-19: antimalarials hydroxychloroquine (HCQ) and chloroquine

(CQ), HIV protease inhibitors lopinavir/ritonavir, broad spectrum antivirals umifenovir (anti-influenza drug) and favipiravir,<sup>1</sup> antiparasitic drug ivermectin and nucleotide analogue remdesivir.<sup>2</sup> Repurposing was a deliberately chosen strategy since there was no time to develop a completely new drug (usually it requires 7 or more years). Unfortunately, it is still far from having sufficiently efficient and safe drug to inhibit replication of SARS-CoV-2 and get it approved for antiviral treatment of COVID-19.

## Clinical trials

### Hydroxychloroquine and Chloroquine

Hydroxychloroquine and chloroquine are anti-

malarials that block entry of SARS-CoV-2 in human cells through inhibition of terminal phosphorylation of angiotensin-converting enzyme 2 (ACE2 – serving as receptor for the virus on human cells), and elevation of the pH in endosomes. These drugs were tested in four randomised controlled trials, 10 cohort studies and 9 case series. The studies failed to prove significant effect of antimalarials on all-cause mortality, the disease progression, clinical picture and virologic clearance from upper respiratory tract. On the other hand, prolongation of QTc interval over 500 ms was reported in several studies, although with different rate and unknown clinical significance.<sup>3</sup>

### Umifenovir

Umifenovir (arbidol) was used previously in China and Russia for treatment of influenza; it prevents entry of the influenza virus in human cells through binding for viral haemagglutinin. Precise mechanism of action of umifenovir on SARS-CoV-2 virus is not known, but *in vitro* experiments showed that it inhibits early phase of viral replication.<sup>4</sup> Recent systematic review has found only one randomised clinical trial and one observational study with umifenovir and COVID-19 that could pass minimum requirements for design quality. The randomised trial included only 23 patients and found decreased progression to severe disease forms and more rapid viral clearance with umifenovir, while the observational trial showed decreased mortality. However, potential for bias in these two studies was high, so definitive conclusion about efficacy of umifenovir in COVID-19 will have to wait for results of clinical studies with more appropriate design.<sup>5</sup>

### Favipiravir

Favipiravir is an RNA polymerase inhibitor, designed and developed for treatment of influenza and tested in clinical trials with patients with Ebola.<sup>6</sup> Currently, there are 17 ongoing randomised clinical trials and two completed investigating efficacy of favipiravir in patients with COVID-19. The completed trials showed that favipiravir decreased chances of the disease progression, mitigated cough and improved viral clearance, but this could be regarded just as an interim result until the rest of the studies are published.<sup>7</sup> Although review of 29 clinical studies concluded that favipiravir has favourable safety profile, it may cause significant QTc prolongation and hyperuricaemia; its teratogenicity is also a concern, but additional studies are necessary to clarify this issue.<sup>6</sup>

### Lopinavir/ Ritonavir

Combination of protease inhibitors lopinavir/ritonavir (being strong inhibitor of cytochromes, ritonavir just serves to increase plasma concentrations of lopinavir) used for the treatment of the Acquired Immune Deficiency Syndrome (AIDS) was repurposed for treatment of COVID-19 early in the course of current pandemic. Currently, there are results of two completed randomised clinical trials and 10 observational studies, which speak in favour of lopinavir/ritonavir efficacy: it reduced mortality inconsistently from study to study and reduced somewhat need for invasive mechanical ventilation and rate of respiratory complications. On the other hand, hospitalisation was not shortened with lopinavir/ritonavir and the rate of adverse events was increased.<sup>8</sup> Main problem with these clinical studies are deficiencies in design that created high potential for introducing various types of bias. The latest systematic reviews concluded that existing results of clinical studies are not sufficient to decide whether lopinavir/ritonavir has beneficial ratio of efficacy and safety in patients with COVID-19.<sup>9</sup>

### Ivermectin

Ivermectin is a drug with broad spectrum of action against parasites, mycobacteria, nematodes and a number of viruses, especially flaviviruses. It is highly lipid-soluble and remarkably well tolerated. High activity of ivermectin against SARS-CoV-2 was first noted *in vitro* and inhibition of importin  $\alpha/\beta$  receptor was proposed as its mechanism of action, resulting in decreased entrance of viral proteins to the cell nucleus.<sup>10</sup> However, although some clinical trials with ivermectin in COVID-19 patients are ongoing,<sup>11</sup> there are no published results yet, precluding any conclusion about its efficacy and safety in this particular indication.

### Remdesivir

Remdesivir is a nucleotide analogue that inhibits viral RNA polymerase, primarily designed for treatment of ebola. However, high activity against SARS-Cov-2 *in vitro* was noted in several studies and at the beginning of current pandemic it was used in some critically ill patients with COVID-19, mostly without appropriate controls.<sup>12</sup> Published case reports and case series from these early experiences found some clinical improvement in the treated patients, but it was not clear whether this was effect of the drug used or not. Only one small randomised clinical trial (n = 237) conducted in China with remdesivir in COVID-19 patients was

published until now; it did not show benefits of remdesivir. However, there are 8 ongoing large randomised clinical trials with remdesivir in COVID-19 patients, enrolling several thousands

of subjects (the largest trial has enrolled as many as 6,000 patients); the results from the ongoing trials will give definite answer about the efficacy and safety ratio of remdesivir.<sup>12</sup>

## Conclusion

This short review of the best evidence of antiviral drugs efficacy and safety against COVID-19 gives us little grounds to either recommend or reject any of them as potential therapeutic agent. Almost all of these drugs are currently tested in ongoing clinical trials and the results are awaited. In the meantime, physicians should avoid use of these drugs unless as part of clinical trials, because they may make more harm than benefit to their patients. If such use is still insisted on, the patients should be properly informed about all potential benefits and adverse effects, and the drugs should not be used until the patient signs consent to receive an out-of-label therapy.<sup>13</sup>

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## Conflict of interest

None.