

# COVID-19 pandemic: How close are we for an effective therapy?

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Coronaviruses are a type of RNA virus found in birds, mammals, and humans, causing upper-respiratory tract infections. In humans infection in the respiratory system can range from mild to lethal [1]. Six major types of viruses affecting humans are documented. Among these six members, four (HKU1, 229E, NL63, and OC43) cause cold and flu like symptoms [2], while rest two are responsible for severe acute respiratory syndrome (SARS-Coronavirus) and Middle East respiratory syndrome coronavirus (MERS-CoV) [3]. There is a high probability of coronavirus pandemic recurrence because of its zoonotic nature and the genetic variation [4]. COVID-19 is spreading quickly across the globe, but unfortunately, we have only limited specific tools for controlling and managing this ongoing epidemic. Most countries follow the same quarantine strategy, isolation, and social distancing to prevent the disease spread and care for the sick.

No SARS-CoV-2 treatment is officially endorsed, but already approved medicines are being investigated for the efficacy in various clinical trials. Nucleoside analogs, interferon, plays an immune modulatory role and commonly used drugs for malaria with antiviral activity like chloroquine/hydroxychloroquine we are using as a treatment option.

**Antiviral drugs**

The prime target for ribavirin, favipiravir, galidesivir, and remdesivir is the RNA dependent RNA polymerase (RdRp) enzyme to restrict viral RNA synthesis [5]. Favipiravir inhibits RNA-dependent RNA polymerase of influenza virus, hence an effective choice of treatment for influenza [6]. So, clinical trials are on a full swing with a combination of favipiravir and interferon- $\alpha$ 12 and a combination of novel inhibitors of the influenza RNA replication namely favipiravir and baloxavir marboxil by targeting different protein subunits of the influenza polymerase complex to determine the efficacy as a choice of treatment [7].

Although ribavirin is a well-known derivative antiviral drug approved for the treatment of hepatitis C virus (HCV) and respiratory syncytial virus (RSV), in higher doses, it causes anemia. So, its efficacy and uses for the treatment of coronavirus is questionable [8]. Remdesivir a prodrug of a nucleotide analogue, can be used to treat filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses [9, 10].

Recent studies have shown a promising result of Remdesivir administration in SARS-CoV-2 patients with a high recovery rate [11, 12]. Phase-III clinical trials have recently undergone to assess the effectiveness of remdesivir as 200 mg OD (loading dose) and 100 mg OD (maintenance doses) for nine days. [13]. lopinavir and ritonavir two well-known HIV protease inhibitors; whose activity was in the limelight during SARS and MERS outbreaks [14, 15]. Combination therapy of these two drugs, which increases drug bioavailability, probably inhibits the chymotrypsin-like protease of MERS, and SARS is currently under trial against SARS-CoV-2 [16]. Why are we attracted to this combination therapy? The answer is the wide availability, and it is manufacturable to scale, so a prime choice for the clinicians. Ample case reports and case series are published to support it. Still, a million-dollar question can be raised towards its trustworthiness.

Promising results came using a combination of Remdesivir and chloroquine in a study with infected Vero E6 cells with SARS-CoV-2. EC90 value of Remdesivir was obtained 1.76  $\mu\text{M}$  [11]. A randomized clinical trial on lopinavir–ritonavir from Wuhan, the first epicenter of COVID-19 pandemic was done early in this year [17]. Unfortunately, the trial results were disappointing and concluded with no benefit beyond standard care. The reason may be due to the study population's choice who was already in an advanced stage of infection with substantial tissue damage. Oseltamivir was administered orally, because this drug was effective during MERS-COV outbreak. In China, suspected cases of COVID-19 infection were treated with oral oseltamivir, which had success in history during the MERS-COV outbreak.

### Chloroquine and hydroxychloroquine

Chloroquine is a small molecular weight 4-aminoquinoline with antimalarial, anti-inflammatory activities. It has a strong inhibitory potential against SARS-CoV-2 (EC50 = 1.14  $\mu\text{M}$  in Vero E6 cells) [11]. Discovered in 1960, the antiviral activity of this antimalarial drug was reported against SARS, enterovirus, and Zika virus. Mechanism of action includes an increase in endosomal pH followed by blocked viral cell fusion of SARS-CoV-2 with the host cell and interference with glycosylation of angiotensin-converting enzyme receptors (ACE-2 receptors). Hence viral attachment and replication is stopped [18]. Although recent evidence of the reduced duration of the disease and diminished pneumonia symptoms was observed by administering chloroquine phosphate in SARS-CoV-2 patients [19], but FDA warned against the use of hydroxychloroquine or chloroquine for COVID-19 treatment due to the risk of heart rhythm problems [20].

### Chymotrypsin-like inhibitors

This is a serotonin antagonist was tested in humans in the 1960s, and research-documented its inhibitory action on 3CL proteinase thereby inhibition of SARS-CoV replication and shown promising results [21]. Clinical trials are ongoing worldwide; in the meantime, there are changes in the guidelines. Some of the trials still need to be passed through many hurdles, and it is not very clear how quickly we will find a suitable answer.

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### Keywords

Antiviral, chloroquine, drug, infection, SARS-CoV-2, treatment, trials, virus

### Abbreviations

Coronavirus disease (COVID-19), Severe acute respiratory syndrome (SARS-Coronavirus) Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), Middle East respiratory syndrome coronavirus (MERS-CoV)

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