



Clinical Trials of Repurposed Antivirals for SARS-CoV-2

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ABSTRACT The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has prompted the repurposing of drugs on the basis of promising *in vitro* and therapeutic results with other human coronavirus diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). These repurposed drugs have mainly included remdesivir, favipiravir, lopinavir-ritonavir, ribavirin, interferons, and hydroxychloroquine. Unfortunately, the first open-label, randomized, controlled trials are showing poor efficacy of these repurposed drugs. These results highlight the necessity of identifying and characterizing specific and potent SARS-CoV-2 antivirals.

KEYWORDS COVID-19, SARS-CoV-2, antivirals

The worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has, as of 20 May 2020, caused at least 5 million infections and 328,000 deaths (1). The virus is highly transmissible, and in addition to its death toll, coronavirus disease 2019 (COVID-19) has a high percentage of morbidity. This has necessitated social confinement, causing great economic losses. Therefore, preventive and therapeutic measures are urgently needed. To this end, from the beginning of the COVID-19 pandemic, several clinical trials have been initiated to test repurposed drugs that either were effective in inhibiting SARS-CoV-2 *in vitro* or displayed some therapeutic utility in treating other human coronavirus infections. Here, we discuss the results obtained with some of the repurposed drugs that seemed to hold the most promise of stopping COVID-19 (2).

For those who become COVID-19 symptomatic, the incubation period, i.e., the time from exposure to symptom onset, is 4 to 5 days on average (3). Current data indicate that 5 to 20% of patients with COVID-19 develop critical illness approximately 5 to 10 days after symptom onset, resulting in complications such as acute respiratory distress syndrome and other end-organ failure (4, 5). Although the antiviral host immune response is essential to eliminating invading viruses, a strong and persistent antiviral immune response might also include the massive production of inflammatory cytokines and related host tissue damage. In symptomatic COVID-19 patients, cytokine storms are a major cause of disease progression and eventual death (6). Consequently, it has been suggested that therapeutics that modulate inflammation are the most effective therapeutic strategy for treating COVID-19 (6). However, the administration of a potent and specific antiviral against SARS-CoV-2 after the onset of the first disease symptoms and prior to viral peak could actually stop or avoid the pathogenic course of COVID-19.

As exemplified by the life cycles of other pathogenic viruses, that of SARS-CoV-2 has a number of targetable stages. These include the endocytic entry of the virion into host cells, RNA replication and transcription, translation and proteolytic processing of viral proteins, virion assembly, and release of new viruses through the exocytic systems (7). Diverse host targets essential for viral replication also can be interfered with, but few successful marketed drugs against viral diseases target host cell-virus cofactors. Dis-

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rupting host cell targets is thought to be more toxic than disrupting virus-specific processes.

Chloroquine (CQ) and its hydroxyl analogue, hydroxychloroquine (HCQ), are generic antimalarial drugs also employed to treat amoebic liver abscess and rheumatic disease. The early promising results of these two drugs, displaying antiviral activity against SARS-CoV-2 at micromolar concentrations in tissue culture (8) and in some ongoing clinical trials (9), drove their repurposing as possible therapies for COVID-19. It has been hypothesized that CQ and HCQ block virus cell entry by decreasing autophagosome-lysosome fusion and inhibiting autophagic flux (10). An early open-label, nonrandomized clinical trial on 20 SARS-CoV-2-infected patients revealed that HCQ treatment was significantly associated with viral load reduction/disappearance in COVID-19 patients (9). This study also concluded that azithromycin (AZ), a widely used broad-spectrum antibiotic that also blocks autophagosome clearance in human cells, reinforced the antiviral effect of HCQ. This study promoted public interest in and widespread utilization of HCQ for treatment and prophylaxis of COVID-19. Moreover, several health authorities have recommended HCQ off-label use in the treatment of COVID-19 (11). Unfortunately, more recent studies have not identified a benefit of HCQ in COVID-19 and have even raised concerns about its safety. A retrospective analysis of data from 368 patients hospitalized with confirmed SARS-CoV-2 infection in U.S. Veterans Health Administration medical centers up to April 2020 found no evidence that the use of HCQ, either with or without AZ, reduced the risk of mechanical ventilation in patients hospitalized with COVID-19. Importantly, an association of increased overall mortality was identified in patients treated with HCQ alone (12). Another observational study of HCQ, in patients hospitalized with COVID-19 in New York City, also found that HCQ administration was not associated with either a greatly lowered or increased risk of the composite endpoint of intubation or death (13). Another French observational study of 181 patients admitted to the hospital with COVID-19 found that survival at 21 days with or without acute respiratory distress syndrome did not differ between the groups treated with HCQ versus standard care, and 8 of 84 patients receiving HCQ had the drug stopped because of electrocardiogram changes (14). A multicenter, open-label, randomized, controlled trial with mainly mild to moderate COVID-19 in 16 government-designated COVID-19 treatment centers in China also indicated that HCQ administration did not result in a significantly higher probability of negative conversion than standard of care alone in patients admitted to hospitals (15). In the safety population of this trial, adverse events were recorded in 7/80 (9%) non-HCQ-treated patients and in 21/70 (30%) HCQ recipients. The most common adverse event reported in this study in the HCQ-treated group was diarrhea, reported in 7/70 (10%) patients; 2 HCQ recipients experienced serious adverse events. The toxicity displayed by HCQ also may preclude the use of this drug as a prophylactic against SARS-CoV-2. Lastly, a randomized, double-blind, placebo-controlled trial of HCQ as postexposure prophylaxis for COVID-19 showed that after a high-risk or moderate-risk exposure, HCQ did not prevent illness or confirmed infection (16). This trial, which included 821 asymptomatic participants that received HCQ within 4 days after SARS-CoV-2 exposure, did not demonstrate a significant benefit of HCQ as postexposure prophylaxis for COVID-19.

Available, successfully marketed drugs targeting such diverse viruses as human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus, influenza virus herpes simplex virus, varicella zoster virus, and human cytomegalovirus demonstrate the utility of nucleoside/nucleotide analogues in inhibiting viral RNA/DNA polymerases and stopping virus replication and spread (17). From the beginning of the SARS-CoV-2 pandemic, the most promising antiviral for fighting COVID-19 has been remdesivir. Remdesivir is an adenosine nucleotide analogue prodrug, developed by Gilead Sciences, with broad-spectrum antiviral activity against filoviruses, paramyxoviruses, pneumoviruses, and pathogenic coronaviruses, including SARS-CoV and Middle East respiratory syndrome (MERS)-CoV (18). Initially developed to treat filoviruses, remdesivir has been shown to be safe in clinical trials against Ebola virus (19). Although nucleotide analogues may show low efficacy against coronaviruses due to the presence of the viral

exonuclease proofreading enzyme, remdesivir was found to be effective against SARS-CoV, MERS-CoV, and bat CoV strains, with tissue culture effective concentrations (EC_{50} s) in the low micromolar range (18). The specificity of remdesivir in targeting coronavirus RNA-dependent RNA polymerase (RdRp) was further demonstrated by propagating the virus in tissue culture. After 23 passages in the presence of the drug, two mutations (F276L and V553L) were identified in the SARS-CoV viral RdRp gene that conferred viral resistance to remdesivir (20). In addition to cell culture experiments, remdesivir significantly reduced lung viral loads in mouse models of SARS-CoV (18) and MERS-CoV (21). The prophylactic and therapeutic efficacy of remdesivir treatment was also tested in a nonhuman primate (rhesus macaque) model of MERS-CoV infection (22). In light of these previous results with other human coronaviruses, remdesivir was repurposed as a possibly effective COVID-19 treatment.

One of the first studies testing the efficacy of remdesivir on COVID-19 described the compassionate use of this drug in 61 patients with severe disease (23). In this cohort of hospitalized patients, clinical improvement in oxygen support status was observed in 36 of 53 patients (68%), and overall mortality was 13% over a median follow-up of 18 days. This study was criticized for its lack of a control patient group, which made it difficult to estimate the efficacy of remdesivir in this group of advanced-disease patients. A more controlled trial with remdesivir was recently published (24). In this randomized, double-blind, placebo-controlled, multicenter trial performed in China, 237 hospitalized adult patients were enrolled and randomly assigned to two 10-day treatment groups (158 to remdesivir and 79 to placebo). Although the difference was not statistically significant, patients receiving remdesivir had a faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (18 versus 23 days). Mortality at 28 days was similar between the two groups (14% versus 13%). It is important to mention that adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients, and that remdesivir was stopped early because of adverse events in 18 (12%) patients versus 4 (5%) patients who stopped placebo early. The authors of this study concluded that remdesivir was not associated with statistically significant clinical benefits; however, they also suggested that the reduction in time to clinical improvement in patients treated earlier begged confirmation in larger studies. A larger randomized, controlled clinical trial sponsored by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and others noted that remdesivir was better than placebo from the perspective of the primary endpoint, i.e., time to recovery, a metric often used in influenza trials (25). This study was carried out with 1,063 hospitalized patients with advanced COVID-19 and lung involvement in the United States and 21 European countries and Asia. Those who received a 10-day course of remdesivir had a median recovery time of 11 days, compared with 15 days in those who received placebo ($P < 0.001$). Although these results also suggested a survival benefit, with a 14-day mortality rate of 7.1% for the group receiving remdesivir versus 11.9% for the placebo group, this difference was not significant. The comprehensive data that we have so far suggest that remdesivir is a useful drug but not the one that is going to cure and stop the spread of COVID-19. Indeed, the authors of the former study recommended the combination of different antiviral agents to continue to improve COVID-19 patient outcomes. They also suggested that antiviral treatment should start before the pulmonary disease progresses to the point of requiring mechanical ventilation. However, the intravenous administration of remdesivir makes this drug difficult to prescribe following the first mild or moderate symptoms observed after the first few days of SARS-CoV-2 infection.

Favipiravir triphosphate is a purine nucleoside analogue that functions as a competitive inhibitor of RdRp (26). Favipiravir has been found to have *in vitro* antiviral activity against influenza A and B viruses as well as many other RNA viruses, including SARS-CoV-2 (26). Nevertheless, the tissue culture EC_{50} for SARS-CoV-2 is within the high micromolar range (27). This poor *in vitro* inhibitory capacity of favipiravir against SARS-CoV-2 has not prevented it being tested as an experimental treatment for COVID-19. An open-label, nonrandomized trial of 80 patients with COVID-19 in China

identified a significant reduction in the time to SARS-CoV-2 viral clearance in patients treated with favipiravir compared with historical controls treated with lopinavir-ritonavir (28). In this trial, a significant reduction in the median time to viral clearance with favipiravir compared with that for lopinavir-ritonavir ($P < 0.001$) was observed. There was also a significantly lower rate of adverse events in patients receiving favipiravir (11.4% versus 55.6%; $P < 0.01$). Again, no control patient group was included. Moreover, patients were cotreated with interferon- α 1b (IFN- α 1b) until viral clearance, which makes it difficult to estimate the antiviral activity of favipiravir. Further trials will be necessary to evaluate the efficacy of favipiravir against COVID-19.

Previous work with SARS-CoV found that lopinavir combined with ritonavir had antiviral activity in tissue culture and in infected patients (29). Lopinavir is an HIV-1 protease inhibitor used, in combination with ritonavir (another HIV-1 protease inhibitor) to increase its half-life, in HIV clinics. The combination of lopinavir and ritonavir also reduced weight loss, clinical scores, viral titers, and disease progression in marmosets infected with MERS-CoV (30). Targeting viral proteases has been essential in developing successful therapies for HIV and HCV. Most RNA viruses generate viral polyproteins that have to be processed to complete the corresponding viral cycle. To evaluate the efficacy and safety of oral lopinavir-ritonavir treatment for SARS-CoV-2 infection, a randomized, controlled, open-label clinical trial was performed in China in adult patients hospitalized with COVID-19 (31). Patients (199) were randomly assigned in a 1:1 ratio to receive either lopinavir-ritonavir for 14 days (99), in addition to standard care, or standard care alone (100). Regrettably, treatment with lopinavir-ritonavir was not associated with a difference in outcome compared with standard care. Mortality at 28 days was similar in the lopinavir-ritonavir group and the standard-care group (19.2% versus 25.0%). Similarly, the percentages of patients with detectable viral RNA at various time points were similar. Although no serious adverse events were associated with lopinavir-ritonavir treatment, gastrointestinal adverse events were more common in the treated group of patients. Overall, this study showed an absence of benefit of lopinavir-ritonavir treatment in COVID-19 patients. Other HIV-1 protease inhibitors, such as darunavir, are also being tested in SARS-CoV-2-infected patients, with no positive results reported so far (32).

A triple combination containing lopinavir-ritonavir and IFN- β 1b plus ribavirin has been explored in an open-label, randomized phase 2 trial in patients admitted to the hospital with COVID-19 (33). Here, 127 patients were recruited; 86 were randomly assigned to the combination group, and 41 were assigned to the control group (lopinavir-ritonavir alone). The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 versus 12 days; $P = 0.0010$). No differences in adverse events were reported. Assuming that lopinavir-ritonavir has poor antiviral activity, IFN-ribavirin might be responsible for the efficacy of the abovementioned triple combination. Different IFNs have been employed to combat diverse viral infections. Some success has been achieved, mainly in the treatment of HCV and in combination with ribavirin. Work in tissue culture has demonstrated that treatment with IFN- α or IFN- β at a concentration of 50 international units (IU) per milliliter reduces SARS-CoV-2 titers by 3.4 logs or over 4 logs, respectively, in Vero cells, with EC_{50} s of IFN- α and IFN- β treatment of 1.35 IU/ml and 0.76 IU/ml, respectively (34). The success of IFN as an antiviral has been obtained mainly by administering it for long periods of time in chronic viral infections (e.g., HCV). The effectivity of IFNs in short, nonchronic virus infections remains to be elucidated. In addition, it is necessary to know whether IFNs administered to SARS-CoV-2-infected patients are acting as coadjuvants in generating the cytokine storm observed in some COVID-19 patients. Notably, the ACE2 gene encoding the SARS-CoV-2 cell receptor is stimulated by IFN, suggesting that SARS-CoV-2 could exploit species-specific IFN-driven upregulation of ACE2, a tissue-protective mediator during lung injury, to enhance infection (35).

The proportion and magnitude of the COVID-19 pandemic have made necessary the repurposing of several drugs to quickly stop the morbidity, mortality, and spread of this new disease. While many clinical trials have been completed and many more are still

running, no repurposed drug has been found that could significantly impact the course of this pandemic. Remdesivir has shown the most promising results and might now be an important tool with which to try to reduce the mortality of COVID-19, but more specific and potent antivirals against SARS-CoV-2 will be necessary to curb present and/or future coronavirus pandemics. Apart from an effective vaccine, the way to stop SARS-CoV-2 in the first days of the infection, when virus transmission is greatest, is through a competent antiviral. The magnitude of the present viral pandemic requires the use of different strategies in concert, including an effective vaccine and antivirals. The crystal structures of the three likely most relevant SARS-CoV-2 targetable proteins, spike, RdRp, and main protease, have been resolved (36–38). It is not difficult to guess that first-generation SARS-CoV-2-specific antivirals have already been identified. Efforts should be made to move first-generation specific and potent antivirals to the clinic.

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