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MINI REVIEW

Potential therapeutic agents against COVID-19: What we know so far

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Abstract: The emerging outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 continues to spread all over the world. Agents or vaccines of proven efficacy to treat or prevent human coronavirus infection are in urgent need and are being investigated vigorously worldwide. This review summarizes the current evidence of potential therapeutic agents, such as lopinavir/ritonavir, remdesivir, favipiravir, chloroquine, hydroxychloroquine, interferon, ribavirin, tocilizumab, and sarilumab. More clinical trials are being conducted for further confirmation of the efficacy and safety of these agents in treating COVID-19.

Keywords: Chloroquine; COVID-19; Favipiravir; Hydroxychloroquine; Interferon; Lopinavir/ritonavir; Remdesivir; Ribavirin; Sarilumab; Severe acute respiratory syndrome coronavirus 2; Tocilizumab

1. INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread all over the world and has a significant impact on global public health and economies. According to the COVID-19 situation report published by the World Health Organization, a total of 462 684 confirmed cases and 20 834 deaths were identified globally until March 26, 2020.[1] However, there is no antiviral medication or vaccine of proven efficacy to treat or prevent human coronavirus infection, hence the crucial and urgent need to identify effective, safe, and available treatment strategy for the disease.

SARS-CoV-2 is a novel human coronavirus identified in 2019. It is an enveloped, positive-sense, single-stranded RNA beta-coronavirus and is structurally similar to SARS-CoV-1 and Middle East Respiratory Syndrome coronavirus (MERS-CoV) which were identified in the 2003 SARS and 2012 MERS outbreak, respectively.[2] Considering the threat of the COVID-19 epidemic and past experience with the treatment of SARS and MERS, many efforts in vaccine and treatment strategy development are being made vigorously. This review focuses on the potential therapeutic agents that have been reported with experience in treating SARS-CoV-2 infection.

2. POTENTIAL THERAPEUTIC AGENTS

Lopinavir/ritonavir (LPV/RTV) are antiretroviral protease inhibitors used in combination for the treatment of human immunodeficiency virus (HIV) infection since 2000. RTV is used together with LPV to increase the LPV half-life via inhibition of cytochrome P450 and acts only as its pharmacokinetic enhancer.[3] LPV acts against the viral 3-chymotrypsin-like protease and has been reported with promising results against SARS-CoV-1 and MERS-CoV.[4–6] LOTUS China trial (Lopinavir Trial for Suppression of SARS-CoV-2 in China), which is a randomized, controlled, open-label study, was initiated to investigate the efficacy and safety of oral LPV/RTV for SARS-CoV-2 infection in 199 adult patients hospitalized with severe COVID-19. Patients were randomized in a 1:1 ratio to receive either LPV/RTV (400 mg/100 mg) twice a day in addition to standard care (n = 99) or standard care alone (n = 100) for 14 days. The result showed no difference in clinical improvement between the two groups (hazard ratio = 1.24, 95% CI, 0.90 to 1.72). Mortality at 28 days was also similar in both groups (19.2% vs 25.0%, 95% CI, –17.3 to 5.7). The author concluded that no benefit was observed with LPV/RTV treatment beyond standard care in adult patients hospitalized with severe COVID-19.[7]

Remdesivir (RDV) is a novel antiviral drug developed by Gilead Sciences, originally for the treatment of Ebola virus disease and Marburg virus infections. RDV is an adenosine nucleotide analogue with broad-spectrum antiviral activity, which acts as an inhibitor of RNA-dependent RNA polymerases (RdRps).[8] RDV inhibits viral replication through premature termination of RNA transcription and has been demonstrated to improve pulmonary function and reduce lung viral loads in mice infected with MERS-CoV.[9] A recent *in vitro* study indicated that RDV potently inhibited SARS-CoV-2 (EC_{50} = 0.77 μM) in Vero E6 cells.[10] A single case report by Holshue et al described clinical improvement after RDV used to treat the first US case of COVID-19.[11] There are several randomized control trials currently being conducted to evaluate the efficacy and safety of RDV in patients with COVID-19. Two phase III trials initiated in China in February 2020, aimed to evaluate RDV in hospitalized adult patients with mild/moderate (NCT04252664) or severe (NCT04257656) COVID-19 (RDV 200 mg on day 1 and 100 mg once daily for 9 days vs placebo). Preliminary results of these trials are expected to be announced

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at the end of April 2020. Thereafter, three international phase III trials were launched in the USA and Asia, including hospitalized adult patients with COVID-19 (RDV 200 mg on day 1 and 100 mg once daily up to a 10 days course vs placebo; NCT04280705), patients with moderate COVID-19 (RDV 200 mg on day 1 and 100 mg once daily for 4 days vs RDV 200 mg on day 1 and 100 mg once daily for 9 days; NCT04292730), and patients with severe COVID-19 (RDV 200 mg on day 1 and 100 mg once daily for 4 days vs RDV 200 mg on day 1 and 100 mg once daily for 9 days; NCT04292899). Two of these trials are estimated to complete in May 2020.

Favipiravir (FPV) is a guanine analogue that selectively inhibits RdRP of RNA viruses and has been approved for the treatment of novel influenza since 2014.[12] *In vitro* study showed inhibition of SARS-CoV-2 by favipiravir (EC_{50}= 61.88 μM in Vero E6 cells).[10] Cai et al conducted an open label, controlled study to examine the effects of FPV (1600 mg twice daily on day 1 and 600 mg twice daily on days 2-14) versus LPV/RTV (400 mg/100 mg twice daily) in addition to interferon-α1b 60 mg twice daily by inhalation for the treatment of COVID-19. The preliminary results reported significant clinical differences between FPV (35 patients) and LPV/RTV (45 patients) with median viral clearance time (4 vs 11 days, $p < 0.001$) and chest image improvement rate (91.43% vs 62.22%, $p = 0.004$).[13]

Chloroquine (CQ) and hydroxychloroquine (HCQ) are aminoquinolines, which have been used to treat malaria and autoimmune diseases for over 50 years. These two drugs are weak diprotic bases and can elevate the pH of the endosome, which prevents viral fusion into the cell.[14] Recent *in vitro* studies reported CQ and HCQ against SARS-CoV-2 at a multiplicity of infection (MOI) of 0.01 with EC_{50} = 2.71 and 4.51 μM in Vero E6 cells, respectively.[15] Several clinical trials are being conducted in China to evaluate the efficacy and safety of CQ and HCQ in COVID-19, one of which revealed that chloroquine is superior to the control group in clinical improvement, promoting virus-negative conversion and shortening the disease course.[16] Meanwhile, the preliminary study in France evaluated the efficacy of HCQ in COVID-19 patients. There were two groups in this study, 26 patients received HCQ (200 mg tid for 10 days) and 16 patients received standard of care. Six HCQ group patients lost to follow up due to early cessation of treatment. Six patients in HCQ group received additional azithromycin (500 mg on day 1, 250 mg once daily for 4 days) to prevent bacterial superinfection. The result showed the virologically cured rate was significantly higher in HCQ combined with azithromycin-treated patients compared with the HCQ only group or control group (100% vs 57.1% vs 12.5%, p = 0.001).[17] Although this study demonstrated promising results, further larger trials are still needed to verify the efficacy and safety of HCQ alone or in combination with azithromycin in COVID-19. In addition, HCQ as postexposure prophylaxis/preemptive therapy for SARS-CoV-2 infection is now under evaluation in the USA (NCT04308668), using the regimen of 800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600 mg once a day for four consecutive days. The results shall be reported soon.

Interferon is a broad-spectrum antiviral agent through interaction with toll-like receptors and inhibit viral replication.[18] Interferon-alfa and beta both demonstrated an anti-SARS-CoV-1 activity *in vitro*.[19,20] Interferon-beta displayed potent activity in reducing MERS-CoV replication (EC_{50} = 1.37-17 IU/mL).[21,22] Ribavirin is a guanosine analogue with a broad-spectrum antiviral agent and used in combination with interferon for the treatment of chronic hepatitis C. Ribavirin in combination with LPV/RTV had been used to treat SARS-CoV-1 infection with lower risk of acute respiratory distress syndrome (ARDS) and death than LPV/RTV alone.[4] However, in a recent *in vitro* study, the result revealed that ribavirin required high effective concentration (EC_{50} = 109.50 μM) against SARS-CoV-2.[10] An ongoing trial evaluating the efficacy and safety of interferon-alpha used in combination with ribavirin, LPV/RTV, or ribavirin plus LPV/RTV for SARS-CoV-2 infection in China (ChiCTR2000029387) is currently being conducted.

Interleukin (IL)-6 was reported to be released considerably in SARS and MERS patients and might play a role in the pathogenesis of these diseases.[23,24] A recent report on the clinical features of COVID-19 patients also found higher plasma levels of cytokines in intensive care unit (ICU) patients.[25] Tocilizumab is a recombinant humanized monoclonal antibody which acts as IL-6 receptor antagonist and is used for the treatment of rheumatoid arthritis.[26] One study in China recruited 21 patients with severe or critical COVID-19, 75% of patients had lowered their need for oxygen supplement after receiving tocilizumab (400 mg once through IV infusion; three patients had another dose administered due to continued fever within 12 hours). Nineteen patients discharged on average 13.5 ± 3.1 days hospitalization time after the treatment with tocilizumab.[27] The US Food and Drug Administration (FDA) also approved a phase III clinical trial for evaluating tocilizumab in hospitalized patients with severe COVID-19 pneumonia (NCT04320615). Meanwhile, sarilumab, which is another IL-6 receptor antagonist, has also launched phase II/III clinical trial to evaluate its efficacy in patients with severe COVID-19 infection (NCT04315298).

In conclusion, the spread of COVID-19 is continuing at a rapid pace as confirmed cases exceed 460,000 until March 26, 2020. Measures to stop the pandemic through discovering and identifying effective treatment or prophylactic agents are crucial. To date, several agents have demonstrated with some efficacy to COVID-19 in humans, but mostly through case reports or preliminary data from clinical trials with small sample sizes. Many ongoing randomized controlled trials are currently being conducted to further confirm these results. With the joint effort of the healthcare professionals and the scientific community worldwide, new evidence for managing COVID-19 is expected to be revealed shortly. Although the potential treatment agents discussed here may provide clinical benefits, it should also be noted that each of the medications may lead to substantial side effects. Healthcare professionals should take great caution during practice.

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