

**Review Article**

Updates on the Current Antivirals Therapy for the COVID-19 Pandemic: A Mini-Review

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Abstract: *Background:* The Coronavirus disease 2019 (COVID-19) has been recognized as a global public health threat and announced as a pandemic by the World Health Organization (WHO). In the absence of vaccine development for the COVID-19, one of the most common and currently implemented ways to combat the COVID-19 is to test the currently used antivirals through vitro and vivo trials. *Objective:* This mini-review aims at reviewing the latest available evidence on the potentially effective and safe antiviral drugs that can be used for controlling the COVID-19. *Methods:* Three databases (PubMed, Google Scholar, and Cochrane) were rapidly searched from 30 March to 2nd of October 2020 on studies reporting clinical outcomes of antivirals against SARS, MERS, or COVID-19. *Findings/Conclusion:* Currently, many antivirals that have been used with previous infectious diseases, are being used to treat the COVID-19 infection. Most of the observational studies and the RCTs have provided mixed or confusing findings. Due to the lack of reliable evidence from Randomized Controlled Trials (RCTs), no effective antiviral drug proved its efficacy and safety against the COVID-19. This rapid review focuses mainly on the latest findings of the most common used antivirals, hoping to continue the next reviews once we have stronger published RCTs based evidence.

Keywords: SARS-CoV-2, Pandemic, Antiviral, Corona Virus, Clinical Trial

1. Introduction

The (COVID-19) is a respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causes pneumonia-like symptoms [1]. The first cases were reported in Wuhan, China on December 12, 2019. Since January 2020, COVID-19 has started to widely spread to other countries, and the WHO announced it as a pandemic in March 2020. According to the COVID-19 global situation report published by the WHO, until 1st October 2020, more than 33 million confirmed cases and nearly 1000 000 deaths of COVID-19 has been reported [2]. In the absence of vaccine development for the COVID-19, one of the most common and currently implemented ways to combat the COVID-19 is to test the currently used antivirals through

vitro and vivo trials as most viruses have a similar genome. Although several approved therapeutic drugs have shown antiviral activity against SARS-CoV-2 in vitro [3, 4], at present there are no antiviral therapies of proven efficacy to prevent or treat patients with human coronavirus infection. Many case-reports and observational studies have shown few numbers of antivirals to potentially be effective in improving the outcome of COVID-19 patients [5]. However, many RCTs are currently implemented to evaluate the efficacy and safety of different antiviral drugs in treating patients with COVID-19 infection, but their results have not been published yet [6]. This study aimed at reviewing the latest available evidence on the potentially effective and safe antiviral drugs that can be used for controlling the COVID-19. The authors have summarized a few and rapid latest important findings here.

2. Potential Antiviral Drugs

2.1. Remdesivir

Remdesivir is a monophosphoramidate prodrug of an adenosine C-nucleoside synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection [7]. It is a broad-spectrum antiviral agent against various RNA viruses, including the Paramyxoviridae, Pneumoviridae, Orthocoronavirinae, Filoviridae [8], and the coronaviruses MERS-CoV and SARS-CoV [9]. Remdesivir decreases the viral RNA production by interfering with the function of viral RNA-dependent RNA polymerase (RdRp) leading to premature viral termination [8]. In vitro studies, remdesivir showed a high block of COVID 19 infection at a lower range (30)[10]. In cell culture experiments with simian Vero E6 cells infected with SARS-CoV-2, remdesivir showed a good result against the SARS-CoV-2 infection at EC90 of 1.76 μM , suggesting a similar result in non-human primate models [3]. In the United States, among 12 patients confirmed with COVID-19 from January 20 to February 5, 2020, three patients were successfully treated with the investigational antiviral remdesivir [11]. Many ongoing studies are currently evaluating the efficacy and safety remdesivir in COVID-19. In a clinical trial on remdesivir effect with a compassionate-use basis of 53 patients in the USA, Europe, Canada, and Japan who were hospitalized for severe Covid-19, during a median 18 days follow up, clinical improvement was observed in 36 (68%) patients, while 7 patients died with a mortality rate of 13%[12]. Despite this result suggests an important benefit of the remdesivir in patients with severe COVID-19 infection, the absence of a control group prevents obtaining a final conclusion. A randomized, double-blind, placebo-controlled, multicenter trial in Hubei, China was conducted to investigate the effectiveness of remdesivir in 273 adults with severe COVID-19 (158 received remdesivir and 79 received placebo) [13]. The study couldn't prove any statistically significant clinical benefits of using the remdesivir compared with using the placebo. On the other hand, a randomized, double-blind, controlled trial of IV remdesivir in 1059 patients (538 received remdesivir and 521 received placebo) with Covid-19 was conducted [14]. The study revealed that using remdesivir statistically improved the recovery time and slightly decreased the mortality rate when comparing with using the placebo.

2.2. Hydroxychloroquine and Chloroquine

Chloroquine and hydroxychloroquine are aminoquinolines drugs commonly used in the treatment of malaria and some autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis [15]. The mechanism of action of chloroquine and hydroxychloroquine is targeting lysosomal membranes inhibition of polymorphonuclear chemotaxis and phagocytosis, interference with pro-inflammatory cytokine production (by monocytes and inhibition of the release of superoxide by neutrophils [15]. In vitro trials, both chloroquine and hydroxychloroquine showed antiviral effects against SARS-CoV-2 infection [16, 17]. Their

action was based on blocking of the glycosylation of cellular receptors of SARS-CoV, and thus interfering with cell-virus binding [18]. Moreover, the aminoquinolines influence the immune system through cell signaling and regulation of pro-inflammatory cytokines. Such an immunomodulatory effect suggests the benefit against COVID-19 pneumonia [15]. In vivo trials, a newly randomized open-label, randomized, controlled trial of 150 patients mainly with persistent mild to moderate COVID-19, exposure to hydroxychloroquine led to a similar negative conversion rate comparing to the current standard of care [19]. A similar finding was observed with 30 randomized control trial study using hydroxychloroquine in the treatment of patients with moderate COVID-19 infection [20]. A retrospective analysis of data from 368 patients hospitalized with confirmed SARS-CoV-2 infection in the United States found no evidence that the use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation COVID-19 patients [21]. However, the overall death was significantly higher in patients treated with hydroxychloroquine alone compared with patients treated with hydroxychloroquine/ azithromycin or with the standard care [21]. On the other hand, many reports pointed out the effective role of hydroxychloroquine and Chloroquine in treating early COVID-19 pneumonia or as post-exposure prophylaxis of healthcare professionals exposed to the infection [22]. In multicenter clinical trials conducted in China in more than 10 hospitals, the results from more than 100 patients showed that Chloroquine has obvious efficacy and acceptable safety against COVID-19 associated pneumonia [23]. A more recent systematic review and meta-analysis of randomized controlled trials revealed no benefit of hydroxychloroquine in COVID-19 patients with mild to moderate symptoms [24]. A systematic review and meta-analysis included 32943 participants surprisingly showed that hydroxychloroquine alone didn't significantly reduce the mortality in hospitalized COVID-19 patients but the combination of hydroxychloroquine and azithromycin significantly increased mortality [25].

2.3. Lopinavir-Ritonavir

Lopinavir is an antiretroviral protease inhibitor used in combination with ritonavir to treat patients with AIDS and HIV infection. Ritonavir is a potent inhibitor of the enzymes that are responsible for lopinavir metabolism, and its co-administration increases the antiviral effectiveness of lopinavir [26]. In vitro study, the analysis showed that the lopinavir inhibited the replication of the COVID 19 virus with about 50% effective concentration at 26.63 μM [27]. In various studies conducted on patients or animals reported that using the lopinavir/ritonavir was effective in clinically improving the respiratory symptoms caused by the COVID-CoV or MERS-CoV [28]. A Retrospective matched cohort study on 75 patients diagnosed with SARS and treated within the first 7-10 days of infection with lopinavir/ritonavir in addition to a standard treatment compared with a control group treated with only a standard treatment was conducted. Despite the methodological limitation of the study, the finding

revealed a relative reduction in mortality rate and incubation rate compared with the control group [29]. A randomized, controlled, open-label trial involving hospitalized 199 Chinese adult patients with confirmed COVID 19 infection who received either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone, was conducted during January and February 2020. The trial revealed that no significant difference between the therapy with Lopinavir-Ritonavir and the standard of care [30]. Furthermore, there was no variation in mortality at 28 days between the case and control group. Gastrointestinal adverse events including nausea, vomiting, and diarrhea were the most reported in lopinavir–ritonavir group than in the standard care group, but serious adverse events were mainly reported in the standard-care group [30]. A living systematic review concluded that lopinavir/ritonavir might play a role in improving outcomes (e.g. slight risk reduction of being mechanically ventilated or developing respiratory failure) in severe and critical COVID-19 cases, although the limitation of the available evidence [31].

2.4. Umifenovir (Arbidol)

Umifenovir is an antiviral drug developed in 1988 and approved by Russia and China in the treatment and prophylaxis of infections with influenza A and B viruses [32]. Its mechanism of action depends on blocking the fusion of virus-cell membrane and virus-endosome through incorporation into cell membranes and interference with the hydrogen bonding network of phospholipids [33]. In vitro models, umifenovir showed an effective role in the inhibition of SARS-CoV-1 and SARS-CoV-2 infection [34]. In a retrospective cohort study in Guangdong, China, 16 patients infected with COVID 19 received a combination of orally 200 mg umifenovir every 8 h and lopinavir (400 mg)/ritonavir (100 mg) every 12 h for 5-21 days, while a control group of 17 patients received lopinavir (400 mg)/ritonavir (100 mg) every 12 h [35]. The study concluded that in the case group, the detection of the COVID 10 by PCR test was negative in 12 (75%) of 16 patients after 7 days, compared with 6 (35%) of 17 in the control group, meanwhile, the chest CT scans were improving for 11 (69%) of 16 patients in the case group compared with 5 (29%) of 17 in the control group after 7 days. A review study of 69 cases infected with SARS-CoV-2 in Wuhan, China, revealed that umifenovir had a tendency to decrease the death rate and improve the discharge rate [36]. A retrospective analysis of 50 patients (34 received lopinavir/ritonavir and 16 received arbidol) diagnosed with COVID 9 showed that arbidol was more effective than lopinavir/ritonavir. On day 14, the viral load wasn't detected among patients received the arbidol, but the viral load was detected in 15 (44.1%) of patients received the lopinavir/ritonavir [37]. On the other hand, a study aimed at exploring the clinical effect of umifenovir combined with adjuvant therapy on 62 patients diagnosed with COVID-19 (42 cases and 20 control group) pointed out that there was no apparent difference between both group, despite the effect of umifenovir in accelerating the patient recovery and relieving

the fever faster [38]. A recent systematic review and meta-analysis included 1052 COVID-19 patients showed no evidence to support the use of umifenovir for improving COVID-19 patient-important outcomes [39].

2.5. Favipiravir (Avigan)

Favipiravir a guanosine analog and an oral anti - influenza drug that targets RNA - dependent RNA polymerase (RdRP), which converts to active phosphoribosylated form in cells and acts as an RNA polymerase inhibitor [40]. Favipiravir inhibits replication of a large number of RNA viruses, including influenza A virus, Ebola, and Lassa virus [41]. In vitro study, it has been shown that remdesivir and chloroquine are highly effective in the inhibition of COVID 19 compared to other antivirals including ribavirin, favipiravir, penciclovir, nitazoxanide, and nafamostat [3]. A prospective, randomized, controlled, open-label multicenter trial involved patients with COVID-19 (116 received favipiravir, and 120 received arbidol) was conducted. Compared with the arbidol, the study found that favipiravir didn't significantly improve the clinical recovery rate at day seven [42]. However, the favipiravir significantly showed a shorter duration of fever and cough relief time compared with the arbidol. An open-label non-randomized trial of 80 patients with COVID-19 (35 received favipiravir plus interferon and 45 received lopinavir/ritonavir plus interferon) was conducted in China. Compared with lopinavir/ritonavir, the study found that favipiravir was significantly associated with less viral clearance time, higher radiographic improvement, and less adverse events [43]. A recently rapid systematic review and meta-analysis concluded that the Favipiravir leads to significant clinical and radiological improvement in comparison to the standard of care with no significant differences on viral clearance, oxygen support requirement, and side effect [44].

2.6. Ribavirin

It is a guanosine nucleoside analog and antiviral compound. It was used to treat various viral infections, such as RSV, hepatitis C virus, bunya virus, herpes virus, adenovirus, poxvirus, and some viral hemorrhagic fevers. Ribavirin is an inhibitor of RNA synthesis by viral RdRp as well as an inhibitor of mRNA capping [45]. In vitro studies, ribavirin with high concentration works as an inhibitor of the growth of SARS-CoV or MERS-CoV [46]. Clinical trials on using the ribavirin as monotherapy with infected COVID 19 couldn't be found. A recently published multicenter, prospective, open-label, randomized trial was conducted to assess the effectiveness of the triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in treating patients with COVID-19 [47]. The case group was 86 patients who received a 14-day combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days, while the control group was 41 patients who received 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h. The

study revealed that the combination group had a significantly faster recovery time, alleviating symptoms, and shorting the hospital stay in patients with mild to moderate COVID-19 [47]. A retrospective cohort study of 115 COVID-19 patients comprised 44 patients who received intravenous ribavirin (treatment group) and 71 who did not (control group), concluded that ribavirin is not associated with improved negative conversion time for SARS-CoV-2 test and is not associated with an improved mortality rate [48].

3. Conclusion

In vitro studies, almost the aforementioned antivirals were effective against the COVID-19 infection. In vivo studies, the current findings showed that Remdesivir could be the promising antiviral drug against COVID-19. The potentially second promising drug might be the Favipiravir (Avigan) which significantly contributed to the clinical and radiological improvement. Hydroxychloroquine with azithromycin showed mixed results. Despite Lopinavir-Ritonavir and Umifenovir (Arbidol) may help in improving the clinical outcome, both aren't the drugs of choice. It can be concluded from the aforementioned findings that at the present, there is no specific antiviral against the COVID-19 infection. Most of the observational studies and the RCTs have provided mixed or confusing findings. Many of the studies had several methodological limitations in terms of study design, sample size, sampling process, and randomization style, and statistical tests. Such limitations might impede synthesizing reliable, high-quality clinical evidence about COVID-19 treatment. Meanwhile, without relying on evidence from RCTs, it would be difficult to prove the effectiveness, efficacy, or safety of the potential antiviral for the treatment of COVID-19. However, currently, there are plenty of ongoing RCTs testing the most efficacious and safe antiviral against the COVID-19. Perhaps the upcoming evidence from these trials would provide hope to alleviate the suffering of millions of patients infected with COVID-19.

Author Contributions

All authors have contributed significantly in this research work. The principal investigator (MR) collected, analyzed, interpreted the data, and wrote the first draft of the manuscript. The authors (AE, RH) remarkably contributed in reviewing and editing the manuscript. Final approval was given by all authors.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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