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Review Article

Pharmacological treatment for the Novel Coronavirus Disease 2019 (COVID-19 Infection)

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ABSTRACT

As of March 22, 2020, a total of 292,142 confirmed coronavirus disease 2019 (COVID-19) cases have been reported globally. Although there are currently no specific antiviral agents but all coronaviruses shared similar key elements of target for currently approved antiviral or new drug development. Several agents might be considered as a possible treatment based on the efficacy in SARS and MERS.

1. INTRODUCTION

In late December 2019, a series of pneumonia with unknown cause emerged in Wuhan, Hubei, China, with clinical presentation greatly resembling viral pneumonia. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of this pneumonia which then was known as coronavirus disease 2019 (COVID-19)[1]. As of March 22, 2020, a total of 292,142 confirmed cases have been reported globally. Identifying the treatment is crucial for the response to COVID-19 outbreak.

1.1. Characteristics of SARS-CoV-2

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA betacoronavirus. The genomic characterization of SARS-CoV-2 suggested that this virus belongs to the subgenus Sarbecovirus, exhibited 79% and 50% identity to severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV), respectively[2]. All coronaviruses shared similar key elements of target for currently approved antiviral or new drug development including two viral proteases (papain-like protease, 3C-like protease), non-structural protein (RNA-dependent RNA polymerase) and structural protein (such as spike glycoprotein)[3]. It is, therefore, reasonable to reconsider antiviral agents used in SARS and MERS for SARS-CoV-2. Here is a review of possible antiviral treatment.

1.2. Oseltamivir

Oseltamivir has long been used for treating influenza virus. It inhibits neuraminidase enzyme and prevents the release

of newly formed virons from the cell surface. Oseltamivir has also been used in coronavirus infection. During the emergence of MERS-CoV between 2003 and 2006 in Paris, oseltamivir in combination with effective antibiotics were considered as the empirical therapy for patients suspected with MERS[4]. Furthermore, recent report showed that almost all patients (89.9%) with confirmed SAR-CoV-2 infection in China received oseltamivir[5]. Considering *in vitro* activity, neuraminidase inhibitors, zanamivir and oseltamivir, has no *in vitro* antiviral activity against SARS-CoV even the concentration was as high as 1,000 and 10,000 μM, respectively[6]. It is likely because neuraminidase enzyme is not being used during coronavirus replication. However, anti-influenza virus might be beneficial since influenza virus infection was confirmed in about 30% in those patients[4]. Therefore, during the influenza season, oseltamivir might be considered as a part of medical treatment. Whether oseltamivir has a clinical benefit in SARS-CoV-2 should be confirmed by clinical trials (NCT04255017, NCT04261270).

1.3. Ribavirin

Ribavirin, a purine nucleoside analogue, inhibits enzymatic activity of Inosine-5'-monophosphate dehydrogenase (IMPDH), resulting in decrease intracellular guanosine triphosphate pools which then causes suppression in cellular DNA, mRNA and protein synthesis[7]. There were several studies showed antiviral activity of ribavirin against SARS-CoV and MERS-CoV. Ribavirin showed *in vitro* activity against two strains of SARS-CoV with the IC_{50} of 20±15 μg/mL (Frankfurt-1 strain) and 80±28 μg/mL (HKU39849 stain) but neither strain was completely inhibited even the concentration of ribavirin was as high as 100 μg/mL[8]. Pharmacokinetic study in human after 1000 mg of ribavirin was administered intravenously resulting in mean plasma concentration of only 25 μg/mL, suggested that plasma concentration after normal therapeutic dosing might not reach the inhibition level of SARS-CoV[9]. This finding was consistent with postmortem lung tissue sample collected from patient who died with a diagnosis of probable SARS, which still showed high viral loads ($2.7x10^4$ to $3.8x10^9$ copies/g tissue) even the use of ribavirin or steroid[10]. This suggested that ribavirin likely to have only a small beneficial effect in SARS. In addition, ribavirin has an activity against MERS-CoV *in vitro* with the IC_{50} quite high as 41.45 μg/mL, however, the IC_{50} was reduced to 12 μg/mL when combined with interferon-α2b (IFN-α2b) suggested that this combination may have benefit in MERS[11]. Ribavirin combined with IFN-α2b was then studied in the rhesus macaque model. Comparing to untreated macaque, treated macaque exhibited significantly better clinical outcomes including improved clinical parameters, better radiographic evidence of pneumonia, lower mean lung tissue viral load (0.81 log median tissue culture infectious dose ($TCID_{50}$) equivalents per gram tissue lower, P=0.0428), and reduced systemic and local pro-inflammatory markers[12]. Unfortunately, the retrospective cohort study in critically ill patients with MERS suggested that the treatment with ribavirin in combination with recombinant interferon (rIFN-α2a, rIFN-α2b, or rIFN-β1a) was not associated with 90-day mortality (adjusted odd ratio [aOR] 1.03, 95% confidence interval [95% CI] 0.73 to 1.44, P=0.87) or with more rapid MERS-CoV RNA clearance (aOR 0.65, 95% CI 0.30 to 1.44, P=0.29)[13].

Recently, *in vitro* study showed that ribavirin also has an activity against SARS-CoV-2 with the EC_{50} of 109.5 μM[14] (26.74 μg/mL), which this concentration may achieved by normal therapeutic dosing. However, the efficacy in COVID-19 patients still need to be confirmed by clinical trials (NCT 04276688, NCT04306497).

1.4. Lopinavir/ritonavir

Lopinavir/ritonavir, a boosted protease inhibitor, was initially developed for a treatment of human immunodeficiency virus (HIV) infection but it can also inhibit the SARS-CoV, 3C-like protease (3CLpro) *in vitro* (IC_{50} 50 μM)[15] resulting in termination of viral replication. An open-labelled which compared the efficacy of treatment between a combination of lopinavir/ritonavir-ribavirin and ribavirin alone in SARS patients. An adverse outcome of acute respiratory distress syndrome (ARDS) or death within 21 days was significantly decreased in the combination group (absolute risk 26.4%, 95% CI 16.8 to 36.0, P<0.001). In addition, multiple logistic regression with adjusted baseline lactate dehydrogenase (LDH) also suggested that

treatment with lopinavir/ritonavir was independently associated with better outcome (aOR 0.076, 95% CI 0.01 to 0.589, *P*=0.014). Based on these studies, lopinavir/ritonavir is appeared to be a promising agent in SARS. In terms of MERS-CoV, lopinavir can inhibit viral replication *in vitro* with the EC_{50} of 8 μM[17], which is within the range of plasma concentration achievable by normal therapeutic dosing in HIV patients (8 to 24 μM)[18]. It also improve clinical, radiological and pathological outcomes in marmosets infected with MERS-CoV compared to untreated animals[19]. A clinical study on the efficacy of lopinavir/ritonavir in combination with IFN-β1b in MERS is still on going (NCT02845843)[20].

In SARS-CoV-2, although there is lack of *in vitro* data, lopinavir/ritonavir (200/50 mg) 2 capsules twice a day can be considered as antiviral treatment base on certain benefits of lopinavir/ritonavir against SARS-CoV and MERS-CoV (weak recommendation)[21]. Recently, a randomized, controlled, open-label trial, which compared the efficacy of treatment between lopinavir/ritonavir plus standard care and standard care alone in patients with severe COVID-19 found that lopinavir/ritonavir treatment did not significantly accelerate clinical improvement (hazard ratio for clinical improvement, 1.24; 95% CI 0.90 to 1.72), reduce mortality (19.2% vs. 25.0%; difference, -5.8%; 95% CI, -17.3 to 5.7), or diminish throat viral RNA detectability compared to standard care alone[22]. Due to the several limitations of those study (eg. underpowered, not blinded), COVID-19 patients were further recruiting in clinical trials for efficacy evaluation of lopinavir/ritonavir and the results are still awaiting. (NCT04252885, NCT04261907, NCT04255017). In addition, other protease inhibitors, darunavir/cobicistat, was also evaluated for the treatment of COVID-19 in China (NCT04252274). The dosage regimen used in COVID-19 trials were lopinavir/ritonavir (200 mg/50 mg tablet) two tablets twice daily for 7-14 days or darunavir/cobicistat (800 mg/150 mg) 1 tablet once daily for 7 days.

1.5. Remdesevir (GS-5734)

Remdesevir, a nucleoside analog prodrug, can competitively incorporates with viral RNA-dependent RNA polymerase (RdRp), resulting in RNA synthesis inhibition[23]. *In vitro* data showed that remdesevir can effectively inhibit replication of both SARS-CoV (IC_{50} 0.069 μM) and MERS-CoV (IC_{50} 0.074 μM) and also improve lung viral load, clinical sign of lung disease, and respiratory function in mouse model[24]. In addition, compared to lopinavir/ritonavir, remdesevir has superior anti-MERS-CoV activity, with lower EC_{50} *in vitro* (0.09 μM vs 8.5 μM), better improvement of pulmonary function, reduced lung viral load, and reduced severe lung pathology in transgenic mouse model[25]. Data in MERS-CoV rhesus macaque model also provided additional benefits. Prophylaxis with remdesevir at 24 hours prior to inoculation completely inhibited MERS-CoV replication in lung tissue and effectively prevented clinical disease associated with MERS-CoV. Therapeutic treatment after 12 hours inoculation also reduced in clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions[26]. According to low *in vitro* inhibitory concentration (IC_{50}, EC_{50}) and vivid outcomes in animal model against both SARS-CoV and MERS-CoV, remdesivir was considered as a promising agent to be evaluated for the efficacy in SARS-CoV-2. Recent *in vitro* study showed that remdesevir efficiently inhibits SARS-CoV-2 with low EC_{50} of 0.77 μM[14] and one patient infected with SARS-CoV-2 was clinically improved after treatment with remdesevir[27]. Several clinical trials are recruiting patients to evaluate the clinical efficacy of remdesivir in COVID-19 (NCT04252664, NCT04257656) using the dosage regimen of 200 mg loading dose on the first day, following by 100 mg intravenous once-daily maintenance dose for 9 days.

1.6. Sofosbuvir

Sofosbuvir, a nucleotide analog, was originally approved for the treatment of hepatitis C virus (HCV) infection. It inhibits HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication, and acts as a chain terminator[28]. Recently, the molecular docking experiment using SARS-CoV-2 RNA dependent RNA polymerase (RdRp) model identified tight binding of sofosbuvir and ribavirin to the coronavirus RdRp[29], suggesting the possibility of using sofosbuvir and ribavirin in COVID-19 infection. However, the efficacy of this combination should be further confirmed by clinical trial.

1.7. Favipiravir (T-705)

Favipiravir, a purine nucleoside analog, was originally developed and approved for the treatment of influenza viruses in Japan. Unlike oseltamivir, favipiravir is phosphoribosylated to an active form, favipiravir ribofuranosyl-5B-triphosphate, which is then recognized as a purine nucleotide by RdRp, and inhibits its activity. Favipiravir inhibits *in vitro* replication of wide range of influenza viruses and many other RNA viruses including arenaviruses, bunyaviruses, flaviviruses, alphaviruses, paramyxoviruses, and norovirus family[30]. Favipiravir also suppressed replication of Zaire ebolavirus (EBOV) *in vitro* with IC_{50} of 67 μM and can induced rapid virus clearance, reduced biochemical parameters of disease severity, and prevented a lethal outcome in mice model[31]. Based on these data, favipiravir has been proposed to treat patients infected with EBOV. Considering SARS-CoV-2, recent study showed that favipiravir has *in vitro* antiviral activity with the EC_{50} of 61.88 μM, which was higher than one with chloroquine and remdesevir[14]. Patients hospitalized with COVID-19 are being recruited for clinical trial evaluating the efficacy of favipiravir (ChiCTR2000029600, ChiCTR2000029544, NCT 04303299, NCT04310228, NCT04273763). The dosage regimen used in COVID-19 trials were mostly based on the dosing approved for influenza treatment, for example, 1,600 mg twice daily on the first day, following by 600 mg twice daily for 6 days.

1.8. Chloroquine

Chloroquine is an antimalarial agent with additional antiviral effect. It inhibits viral infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptor of SARS-CoV. Chloroquine effectively inhibits SARS-CoV *in vitro* with the IC_{50} of 8.8 μM[32]**.** It also has an *in vitro* activity against MERS-CoV (IC_{50} of 4.1 μM)[33] and SARS-CoV-2 (EC_{50} of 1.13 μM)[14]. Chloroquine has an additional immunomodulatory activity by suppressing the production and release of tumor necrosis factor (TNF) and interleukin 6 (IL-6), which mediate the inflammatory complications of several viral diseases. In addition, hydroxychloroquine, a less toxic derivative of chloroquine, also has an *in vitro* activity against SARS-CoV-2 with the EC_{50} of 4.06 μM, which was higher when compared to chloroquine (3.81 μM)[34]. According to those *in vitro* data, chloroquine and hydroxychloroquine are being evaluated for the efficacy in COVID-19 patients (ChiCTR2000029609, ChiCTR2000029741, NCT04303299). The dosage regimen used in COVID-19 trials were chloroquine 500-1,000 mg per day for 7-10 days or hydroxychloroquine 400 mg per day for 5-10 days.

1.9. Umifenovir (Arbidol)

Umifenovir, also known as Arbidol, was approved in Russia and China for the prophylaxis and treatment of influenza A and B infection. It interacts with haemagglutinin (HA) to stabilize it against the low pH transition to its fusogenic state and consequently inhibit HA-mediated membrane fusion during influenza infection[35]. For other viruses, it intercalates into membrane lipid leading to inhibition of membrane fusion between virus particle and plasma membrane, and between virus particle and the membrane of endosome[36]. Umifenovir showed *in vitro* active against numerous DNA and RNA viruses including Lassa virus (IC_{50} of 1.42 μM) and Ebola virus (IC_{50} of 2.83 μM)[37]. Interestingly, it also exhibited *in vitro* activity against SARS[38]. Based on these data, clinical trials have been initiated to test umifenovir in patients infected with SARS-CoV-2 (NCT04260594**,** NCT04254874, NCT04255017, NCT04252885)

1.10. Interferon

Interferon (IFN) inhibit viral infection by directly interfering with viral replication by inducing both innate and adaptive immune response to infection[39]. IFN-α and IFN-β have an *in vitro* activity against SARS-CoV and MERS-CoV[6, 40]. Among IFN subtype, IFN-β showed the strongest *in vitro* inhibition against MERS-CoV with the lowest IC_{50} of 1.3 U/mL compared to other subtype (IFN-α2a, IFN-α2b, IFN-γ, and IFN-universal)[41]. Various combinations of IFN-α or IFN-β with other antivirals such as ribavirin and/or lopinavir/ritonavir have been used to treat patients with MERS. Overall, combination treatments consisting of interferons and ribavirin did not consistently

improve outcomes in MERS[13]. However, the randomized double blinded trial on the efficacy of IFN-β1b combination with lopinavir/ritonavir in MERS patients is still ongoing (NCT02845843). In addition, based on efficacy in SARS-CoV and MERS-CoV, combination of antiviral and various subtype of interferon (eg. PegIFN-α2b, IFN-α1b, IFN-β1a) were studies for the efficacy in COVID-19 patients (ChiCTR2000029387, NCT04293887, NCT04254874).

2. CONCLUSIONS

Currently, there are no specific antiviral agents for COVID-19. Several agents might be considered as a possible treatment based on the efficacy in SARS and MERS. Due to the limited data, the most likely promising agent should be remdesevir (GS-5734) due to its low inhibitory concentration and satisfied therapeutic outcomes in SARS and MERS. However, favipiravir (T-705) and chloroquine might be considered. In addition, apart from non-structural protein, spike glycoprotein-targeted and host-targeted agents is currently in development, suggested other possible options to treat COVID-19. However, the efficacy and safety of all proposed anti-SARS-CoV-2 agents should be further confirmed by clinical studies.

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