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A comprehensive analysis of possible treatment for COVID–19

Md. MonowarHossain, Md. ShahedAlam, AshikTanvirRiham, FarinAngoomMithila, SanjidaKhanam,MrinmoyMajumderandMahbubulMorshed
Department of Biochemistry and Molecular Biology, Jahangirnagar University, Bangladesh

Abstract: *The first case of 2019 novel coronavirus (COVID-19) was reported in Wuhan, Hubei Province, China and so far more than 2,53,000 infections and over 10,400 deaths have been reported. This virus could transfer during human-to-human close contacts, with a basic reproductive number as 2.2-2.6. For the outbreak of COVID-19 infection, the necessary requirement for efficient antiviral treatment is a burning issue. Chloroquine, hydroxychloroquine, chloroquine phosphate, cepharanthine, selamectin, mefloquine hydrochloride, niclosamide, losartan, olmesartan, arbidol, moxifloxacin, lopinavir, ritonavir, interferon, favipiravir, remdesivir, darunavir, intravenous antibody, traditional Chinese medicine, etc. have been used or suggested for the treatment of novel coronavirus. This study is an overview of these drugs to treat COVID-19.*

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I. Introduction

From December 2019, a novel corona virus outbreak has happened at Wuhan city in China. The situation was quite critical and became epidemic. A lot of patient was affected in a short period of time globally. The disease was spreading very rapidly. COVID-19 now a days a pandemic disease and the situation is becoming worse and worse as there is no available curative vaccine. In this review we summarized the drugs that had been used or suggested to use for the treatment of COVID-19.

Chloroquine, hydroxychloroquine and chloroquine phosphate

Chloroquine is a cheap and safe drug that has been used for more than 70 years.According to some research, there is a possible effect of antimalarial drug chloroquine in the treatment of novel coronavirus (COVID-19). Chloroquine and hydroxychloroquine are proven to have antiviral activity in vitro, including SARS coronavirus. But chloroquine has no effect on dengue affected patients. Chloroquine doesn't show any activity in vivo in case of Ebola, Nipah and Influenza virus. It has shown promising activity in case of chikungunya virus (CHIKV). Chloroquine shows immune modulation and anti-inflammatory properties in vivo.Chloroquine has shown effective result in treatment of chronic hepatitis C (HCV). The drug has no considered effect on HIV infected patients[1].

Chloroquine was used in COVID-19 treatment on the other hand hydroxychloroquine have no evidence to use in SARS-CoV-2 infection treatment but it has same mechanism of action in association with more tolerable safety profile. Vero cells infected with SARS-CoV-2 were used to determine the pharmacological activity both chloroquine and hydroxychloroquine. PBPK (Physiologically-based pharmacokinetic) models was used in lung fluid to determine the drug's safety profile.The in vitro result showed that hydroxychloroquine (EC_{50}=0.72 μM) contains better activity than chloroquine (EC_{50}=5.47 μM). Dose of hydroxychloroquine sulfate (400 mg) twice in a day followed by the dose 200 mg twice daily for 4 days is recommended.The growth inhibitory effect of chloroquine suggests the use of its analog, hydroxychloroquine, as a therapeutic agent of COVID-19 infection. By altering cell surface pH, these drugs inhibit viral fusion. The drug has other inhibitory effects such as inhibition of viral replication and assembly. The lower EC_{50} for hydroxychloroquine implies its better effect against viral replication. The higher free lung trough concentration to EC_{50} ratio (R_{LTEC}) of hydroxychloroquine indicates its better clinical efficacy. This in vitro study finds that one daily dose regimen of hydroxychloroquine for 5 days is effective and safe. Based on its auspicious antiviral and prophylactic activity hydroxychloroquine may be used as a therapeutic agent of COVID-19 infection. There is evidence that COVID-19 patients have elevated level of cytokines IL-6, IL-10 causing a cytokine storm. The immunomodulatory effect of both chloroquine and hydroxychloroquine can reduce these cytokines. The use of corticosteroid and immunosuppressants is complicative in COVID-19 patients. Hydroxychloroquine is more effective due to its antiviral and immunomodulatory effect. A low dose of hydroxychloroquine combined with an anti-inflammatory drug is effective to reduce the cytokine storm in COVID-19 patients[2].

Chloroquine phosphate is an old drug for treatment of malaria which had demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicenter clinical trials conducted in China. In the early in vitro studies, chloroquine was found to block COVID-19 infection at low-micromolar concentration. It has been quickly conducted in China to test the efficacy and safety of chloroquine or hydroxychloroquine in the treatment of COVID-19 associated pneumonia in more than 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo. The results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course. Government and regulatory authorities and organizers of clinical trials has been agreed that chloroquine phosphate has potent activity against COVID-19 and the drug is recommended for inclusion in the next version of the Guidelines for the prevention, diagnosis, and treatment of pneumonia caused by COVID-19 issued by the National Health Commission of the People's Republic of China. In future to minimize the outbreak of COVID-19, chloroquine phosphate is recommended to treat COVID-19 associated pneumonia. Positive RT-PCR test results in patients recovered from COVID-19[3].

Cepharanthine, selamectin and mefloquine hydrochloride

2019-nCoV related coronavirus model is necessary to know the pathology and treatment of COVID-19. A model was derived from Panglion (which are considered might be the possible intermediate host for COVID-19) coronavirus. Its spike protein shares a 92.2% amino acid identity with the spike protein of 2019-nCoV isolate Wuhan. This research brought two libraries of 2406 clinically approved drugs that were screened for their ability to inhibit cytopathic effects on Vero E6 cells by the spike protein of coronavirus.The spike protein of coronavirus GX_P2V uses ACE2 as the receptor for infection just like 2019-nCoV. Among this colossal collection of drugs, only three drugs - cepharanthine (CEP), selamectin and mefloquine hydrochloride exhibited complete inhibition of cytopathic effects in cell culture at 10 μmol/L. CEP demonstrated the most potent inhibition of GX_P2V infection, with a concentration for 50% of maximal effect [EC50] of 0.98 μmol/L. Based on their study the scientists also suggest that CEP can inhibit coronavirus infection at viral entry and post entry. They concluded the study by suggesting that CEP and mefloquine are likely to treat host cell pathways while selamectin might be a 2019-nCoVr specific inhibitor. It is also found thatCoV GX_P2V is nonpathogenic in humans so it can be used as an in vitro model for developing therapies against 2019-nCoV[4].

Niclosamide

Niclosamide have been widely used to treat tape worm infection in human, it is FDA approved and listed as essential medicines by WHO.Niclosamide can regulate multiple signaling pathways and biological processes including Wnt/β-catenin, mTORC1, STAT3, NF-κB, Notch,NS2B-NS3 interaction, etc. Thus indicating that niclosamine has the ability to be used as anticancer, antibacterial and antiviral agents. It was found that niclosamine inhibit SARS-CoV replication and completely abolished viral antigen synthesis at 1.56 μM conc. Niclosamide also inhibit MERS-CoV replication, enhances BECN1 and ATG14 oligomerization affecting autolysosomes of MERS-CoV infected cells.Niclosamide has proven antiviral activity against various viruses of different classes hence called broad spectrum antiviral, shows antiviral activity against viruses like Zika, Ebola, Dengue, Hepatitis C, HRVs, Chikungunya, Adenovirus and Epstein-Barr virus.Niclosamide also have some limitation like low absorption from intestine, rapid clearance, low bioavailability and poor solubility in water. But modification or conjugation with other compound may overcome these limitations[5].

Losartan and olmesartan

SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as receptor binding site for its spike protein to enter into the body. This spike protein has 72% amino acid sequence identity to that of SARS virus and also has more affinity for ACE2 than of SARS because of presence of flexible glycyl residues.If coronavirus spike protein binds to ACE2 causes downregulation of ACE2 expression which ultimately results in excessive production of angiotensin by related enzyme ACE. This resultant angiotensin causes AT1R stimulation which ultimately causes increases pulmonary vascular permeability thus mediating increased lung pathology.The use of AT1R antagonist losartan and olmesartan results in up-regulation of ACE2 expression. Therefore it seems paradoxical that up-regulation of ACE2 which is binding site for SARS-CoV-2 will give protection from SARS-CoV-2.There are some limitation of this approaches like this therapeutic approaches might exacerbate the already existing hypotensions in some SARS patients and this could be happened to COVID-19 patients also (though no data available regarding hypotension of COVID-19 patients). For assessing the feasibility of this therapeutic approach, clinical patientsrecords and data have to be analysed like analysing the outcome of patients with pre-treated (before diagnosis) AT1R blockers with patients of chronically medicated with AT1R blockers[6].

Arbidol

Arbidol is a broad-spectrum antiviral drug, which had potential antiviral effects on many other viruses, like herpes simplex virus I, zika, ebola viruses, as well as foot-and-mouth disease virus. In vitro studies also found that the reproduction of severe acute respiratory syndrome (SARS) coronavirus could be effectively inhibited by arbidol. In this retrospective cohort study, all patients with confirmed novel coronavirus pneumonia were monitored for some specific time. At first, the diagnosis and severity of illness were assessed based on the latest guidelines of COVID-19 infection enacted by national health commission of when the patients were admitted. Depending on the levels of severity in China, patients were categorized into four groups: mild, ordinary, was given to patients at a dose of 200 mg each time, and severe, and critical illness. There is no sign of pneumonia in mild cases. In this study, mild and ordinary cases were combined as mild cases, and severe and critical illness cases were combined as severe cases to simplify the analysis process. Among the total 111 patients, 49 were assigned to the empirical treatment with arbidol group and 62 were assigned to the empirical regimens group. Arbidol was given to patients at a dose of 200 mg each time, and three times a day according to the drug instructions. The empirical regimens of antiviral therapy included Interferon-α, lopinavir/ritonavir, favipiravir, rabivirin, darunavir/cobicistat.Arbidol could partially prevent symptoms exacerbation and slow the deterioration of respiratory function. Arbidol showed no effect on temperature recovery. There was no superior effect of arbidol in severe patients. These results indicated that the effect of arbidol in severe patients were not as obvious as that in mild patients.Arbidol showed relatively very few side effects. The usual side effects of arbidol are nausea, diarrhea, dizziness, and elevated serum transaminase, with bradycardia occasionally. Arbidol is clinically effective treatment for COVID-19 infection in patients with mild symptoms at admission[7].

Moxifloxacin, lopinavir, ritonavir, interferon

The patients who visited Wuhan(75) recently were affected and family cluster (45) also found because novel coronavirus pneumonia spread fast near the patient.Diabetes(10) and hypertension(15) mildly affect the virus to spread out but when the patient with these diseases contact to COVID-19 can lead to enter the ICU. Symptoms including fever(86), cough(83) and myalgia or fatigue (30) is common.All patients had pneumonia whether 27 are with dyspnea. Differences between ICU and non-ICU patients in laboratory test results vary significantly.Several drugs (moxifloxacin (85 patients), lopinavir/ritonavir(84 patients),and interferon(89 patients)) were used to treat the patient with mild symptoms but gamma globulin can improve the mild symptoms significantly.For the treatment of severe condition even at ICU methylprednisolone was used of which doses plan was developed by Wuhan Union Hospital. Antibiotics(4 patients),antiviral(5 patients),interferons and other drugs also used in this analysis.Use of methylprednisolone at earlier stage isimportant that can develop the patient condition but at later stage it can rise blood sugar.Single dose including three drugs known as moxifloxacin,interferon and lopinavir/ritonavir (3 patients) can lead to the patient at serious condition but using gamma globulin ventilation these condition was improved.Among the admitted COVID-19 affected 89 patients 16 were discharged, 2 were in deteriorate,1 died who was late to admit in the hospital and the others have stabilized[8]**.**

A 54 years old patients had the following physical conditions- height of 193 cm and weight of 96 kg (body mass index, 25.7), and had no major illness, always denied any smoking and drinking, had no respiratory symptoms,had a blood pressure of 152/93 mmHg, pulse rate of 73 beats per minute, respiratory rate of 20 breaths per minute,a body temperature of 37.0°C, no pharyngeal injection, clear lung sounds and had no haziness on chest X-ray were observed. The patient was treated with lopinavir/ritonavir 8 days after admitting the hospital in order to both the tablets together per dose (lopinavir 200 mg/ritonavir 50 mg). During treatment with this dose the symptoms were improved and the viral load was reduced. So these doses can be recommended for the treatment of COVID-19 at the early stage to a relatively high risk groups but study is neededfor further confirmation[9].

A lung cancer patient with COVID-19 infection was treated with kaletra (lopinavir/ritonavir) for pneumonia treatment and was recovered. The patient was EGFR mutant and gefinitib was used as a therapeutic agent followed by osimertinibmonotherapy. When a patient was treated with nine round of radiation for enlarged lymph nodes, some complications arose. The COVID-19 infected patient was treated with kaletra and subsequent diagnosis showed COVID-19 negative. The continuation of osimertinib during the COVID-19 treatment is possible due to the well condition of the patient. At the end of the treatment, the patient had stable cancer disease and was cured from COVID-19[10].

Favipiravir, remdesivir

A study primly mentioned the drugs that are issued by the National Health Commission (NHC) of the people republic of China for the treatment of COVID-19, which are antivirals including IFN-α, lopinavir/ritonavir, and ribavirin. Experiments over these drugs found their effectiveness in treating viral infections. As IFN-α is a broad-spectrum antiviral that is usually used to treat hepatitis, though it is reported to

inhibit SARS-CoV reproduction in vitro. A previous research finding is that lopinavir/ ritonavir has anti-SARS-CoV activity in vitro and clinical studies. On the other hand, ribavirin is a nucleoside analog with a broad-spectrum of antiviral effects. Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, thus inhibiting RNA polymerase activity while remdesivir can effectively reduce the viral load in lung tissue of mice infected with MERS CoV, improve lung function, and alleviate pathological damage to lung tissue. But the scientists concluded their study by saying that there are no finally verified antivirals specific to COVID-19 at present. The efficacy and safety of these candidate drugs in the treatment of COVID-19 need to be confirmed in further preclinical and clinical trials[11].

Oxygen, antiviral, intravenous antibody, traditional Chinese medicine

9 COVID-19 infected patients with known and unknown causes of exposure to the virus were analyzed in a study. Among them, 4 were severally ill and 5 were moderately ill. 9 patients showed different significant symptoms but among them fever was common. One patient had significantly low WBC count and absolute nutrophil count (ANC). Another patient had low absolute lymphocyte count (ALC). These abnormalities returned to normal after treatment. C-reactive protein (CRP), lactate dehydrogenase (LDH), was significantly increased in some patients. Lung lesions were significant among all nine patients and partially or completely resolved after treatment. Oxygen therapy, antiviral therapy (lopinavir and ritonavir), intravenous antibody treatment, traditional Chinese medicines(QingfeiPaiduPecoction), moxifoxacin hydrochloride were used in the treatment for those patients. The average period of treatment was 6 days[12].

Coronavirus disinfection

Various disinfection procedures and histotechnology processes are used for diagnosis of infectious samples containing COVID-19 to alleviate the risk of infection to laboratory stuff. Appropriate WHO standard precautions and laboratory biosafety guidelines from CDC should be maintained. Other coronaviruses (SARS, MERS) inactivated by disinfection procedures with 62-71% Ethanol,0.5%Sodium peroxide,0.1% Sodium hypochlorite with 1 minute. Other biocidal agents containing 0.05-2% benzalkonium chloride, 0.02% chlorohexidinedigluconateare less effective. Irradiation with UV light for 60 minutes makes viral infectivity undetectable. Infectivity of COVID-19 is inactivated by formalin and glutaraldehyde in a temperature and time dependent manner. Using Formalin incubated at 4^0C and at 37^0C room temperature infectivity can be decreased on day 1 where glutaraldehyde in 1-2 days.Several coronavirus can be noninfectious at temperatures such as 90 min 56^0C, 60 min 67^0C, 30 min 75^0C.Aerosols and Cryostat must be contained in laboratory. Formalin fixation and Paraffin embedded tissue block as Paraffin infiltrated at 60-65^0C were used for two or more hours to inactivate the novel Corona Virus 19[13].

II. Conclusion

Based on the analysis hydroxychloroquine, chloroquine phosphate, niclosamide, olmesartan, arbidol, interferon, lopinavir/ritonavir, favipiravir, remdesivir, darunavir, etc. could be used for the treatment of COVID-19.

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Conflict of interests

The authors declare no conflict of interests.

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