Review Article

CONCURRENT PHARMACOLOGICAL COVID-19 TREATMENT: A REVIEW

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ABSTRACT

The pandemic of COVID-19 is an extreme respiratory ailment brought about by human Covid (HCoV), otherwise called SARS (severe acute respiratory syndrome)- CoV-2 or novel Corona virus. COVID- 19 is an exceptionally infectious illness brought about by SARS- CoV- 2. The sickness might fluctuate from asymptomatic cases, gentle side effects to life- compromising intricacies like ARDS, multiorgan disappointment, sepsis, and demise. Specifically, older with comorbid conditions are at higher danger. The COVID-19 flare-up is as yet difficult for clinicians. The seriousness of COVID-19 has brought about a worldwide race to find the right antiviral treatment that decreases the danger of inconveniences and works on persistent result. This review emphasizes on the different aspects of COVID-19 such as the epidemiolo- gy, clinical features and preventive measures to be adopted in order to fight this pandemic.

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Introduction

Coronavirus is one of the major pathogens that primarily target the human respiratory system. The chronology of COVID-19 infections is as follows.1,2 The first cases were reported in Wuhan City, China at the end of December 2019 has caused a large global outbreak and is a major public health problem worldwide. Current evidence indicates that SARS-CoV-2 spread from wild animals illegally sold in the Huanan Seafood Wholesale Market indicating possible animal-to-human transmission, studies have increasingly demonstrated human-to-human transmission of SARS-CoV-2 through nasal droplets, direct contact, uncooked foods and excreta of conciliator animals.3,4 The pandemic 'coronavirus disease 2019' (COVID-19) is a severe respiratory illness caused by human coronavirus (HCoV), also known as SARS (severe acute respiratory syndrome)-CoV-2 or novel coronavirus which contains a single-stranded RNA genome. Phylogenetic analysis shows that SARS-CoV-2 is a new member of the Coronaviridae family but is distinct from SARS-CoV (identity of approximately 79%) and MERS-CoV (identity of approximately 50%). Notably, SARS-CoV-2 shares a high level of genetic similarity (96.3%) with the bat coronavirus RaTG13, which was obtained from

bats in Yunnan in 2013; however, bats are not the immediate source of SARS-CoV-2. By far most of patients who are basically sick with COVID-19 have qualities and co-morbidities that place them at higher danger for genuine illnesses, like more established age, hypertension, cardiovascular sickness, diabetes, constant respiratory infection, malignant growth, renal sickness, and corpulence. The common side effects of COVID-19 are fever, sore throat, weariness, hack, or dyspnea combined with ongoing openness. 4

The COVID-19 outbreak is still a major challenge for clinicians. Due to interventions and control measures from the government (shutting down public transportation and implementing a treatment strategy) and in addition to other personal protective equipment (i.e., gloves, gown, and eye protection such as a face shield or safety goggles).

A study of early transmission dynamics of COVID-19 revealed that the mean incubation period was 5.2 days (95% confidence interval [CI], 4.1-7.0), with the 95th percentile of the distribution at 12.5 days. Current diagnostic tests for coronavirus include reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification. According to current diagnostic criteria founded by the China National Health Commission, laboratory examinations, including nasopharyngeal and oropharyngeal swab tests, have become a standard assessment for diagnosis of COVID-19 infection. Classical public health measures, including isolation, quarantine, social distancing and community containment, can be used to curb the pandemic of this respiratory disease.5,6

The severity of COVID-19 has resulted in a global rush to find the right antiviral treatment that reduces the risk of complications and improves patient outcome.Currently, the Food and Drug Administration has not approved any drugs for the treatment of COVID-19. Extensive review analyses using non-randomized clinical studies and in vitro/culture studies reveal that several approved drugs including anti-viral (remdesevir), anti-retroviral (ritonavir, darunavir, lopinavir)7, anti-malarial (chloroquine, hydroxychloroquine)8, anti-protozoal (nitazoxanide, ivermectin) and immunosuppressive (tocilizumab) have been included in the latest version of the Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia issued by the National Health Commission (NHC) of the People's Republic of China for tentative treatment of COVID-19.

Clinical Features

SARS-CoV-2 contamination patients present with a wide scope of manifestations from asymptomatic cases to intense respiratory pain conditions (ARDS), septic shock, and multiorgan disappointment. In mild- to moderate cases, patients typically present with fever, hack, sore throat, disquietude, migraine, windedness, and tachypnea. In extreme cases, patients might experience the ill effects of pneumonia, intense respiratory manifestations, and septic shock. Patients with comorbidities are known to have a high case casualty rate. Laboratory findings include lymphopenia, elevated prothrombin time, lactate dehydrogenase,

creatinekinase, and C- reactive protein. Patients also showed abnormal findings suggestive of myocardial, renal, or hepatic injury. Elevated ILs and tumor necrosis factor- alpha (TNF- α) levels are usually observed in critically ill patients.9

Table No: 1: Currently Available Drugs Used For the Treatment of Covid-19

THERAPEUTIC CLASS	DRUG	MOA	DOSE	RATIONAL USE	ADVERSE EFFECT	DRUG-DRUG INTERACTION	TOXICITY
Antimalarial	**(Hydroxy)chloroquine[11]**	Interferences with terminal glycosylation of ACE2 receptor	400 mg by mouth every 12h×1d, then 200 mg by mouth every 12h×4d; alternative dosing: 400 mg by mouth daily×5dor200mg by mouth 3 times/d for 10 d. Available as: 200-mg tablets of hydroxychloroquinesulfate (salt) = 155 mg hydroxychloroquine base. Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution. Administration: Manufacturer does not recommend crushing tablets; however, some sources suggest that tablets can be crushed and dispersed with water OR compounded into an	(Hydroxy)chloroquine Antimalarial Changes the pH of the cell membrane surface and thus inhibits the fusion of the virus with the cell membrane. Inhibits nucleic acid replication, glycosylation of viral proteins, assembly of the virus, and release of the virus from the infected cell.	Cardiovascular disorders, including prolongation of QT	Digoxin, class IA and III antiarrhythmic, tricyclic antidepressants, antipsychotics CYP3A4	Common: Abdominal cramps, anorexia, diarrhea, nausea, vomiting. Major: Cardiovascular effects (including QTc prolongation), hematologic effects (including hemolysis with G6PD deficiency
Antiviral for HIV	**Lopinavir/Ritonavir(LPV/RTV)combination[12]**	HIV protease inhibitor/CYP450 inhibitor	400 mg/100 mg by mouth every 12 h for up to 14 d. Available as: lopinavir/ritonavir, 200-mg/50-mg tablets; lopinavir/ritonavir, 100-/50-mg tablets; lopinavir/ritonavir 400-mg/100-mg per 5-mL oral solution (can be given via feeding tubes compatible with ethanol and propylene glycol, contains 42% alcohol). Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution in hepatic impairment. Administration: Food restrictions: Tablets, take without regard to meals; oral solution, take with food. Do not crush tablets; oral solution not recommended with polyurethane feeding tubes 200mg	Lopinavir is a protease inhibitor used to treat HIV infection in combination with ritonavir to increase its availability	Common adverse events Gastrointestinal adverse events (nausea, vomiting and and diarrhoea)	CYP3A inhibitors, tadalafil, riociguat, vorapaxar, fusidic acid, salmeterol and rivaroxaban	Common: gastrointestinal intolerance, nausea, vomiting, diarrhea. Major: Pancreatitis, hepatotoxicity, cardiac conduction abnormalities

Antiviral for Ebola	**Remdesivir[13]**	RNA-dependent RNA polymerase inhibitor	200 mg × 1,100 mg every 24h infusion.Available as: 5-mg/mL vial (reconstituted). Dose adjustments: Kidney: Not recommended for GFR <30. No kidney/hepatic dose adjustment currently recommended but holding doses may be considered if significant toxicities occur. Administration: 30-min IV infusion	Inhibits RNA-dependent RNA polymerase, prematurely blocking RNA studies; transcription.	Hepatic adverse event	The risk of drug–drug interactions is limited by remdesivir rapid clearance	Elevated transaminases (reversible), kidney injury
Antiviral for flu and ebola	**Favipiravir[13]**	RNA-dependent RNA polymerase inhibitor	Doses vary based on indication, limited data available. Available as (not in the US): 200-mg tablet. Dose adjustments: Kidney: no dose adjustment recommended, limited data available, Hepatic: Dose adjustment considered in Child-Pugh C, increased exposures observed in Child-Pugh class A to C. Administration: Tablet can be crushed or mixed with liquid, bioavailability>95%	RNA polymerase inhibitor	Abnormal liver function test, psychiatric and gastrointestinal adverse events, increase in serum uric acid		
Antiviral for influenza viruses	**Umifenovir[10]**	S protein/ACE2, membrane fusion inhibitor	200mg every8hby mouth 7-14 d. Available as (not in the US): 50-mg and 100-mg tablets, capsules and granules. Dose adjustments: Kidney: no dose adjustment necessary. Hepatic: No specific recommendations available, caution in those with hepatic impairment. Administration: Bioavailability 40%	Blocking the penetration of the virus into cells (fusion inhibitor) immunomodulatory effect.		Metabolized by CYP3A4, monitor with strong inducers/inhibitors	Allergic reaction, gastrointestinal upset, elevated transaminses
Immunomodulatory	**Tocilizumab[10]**	IL-6R inhibitor	400 mg IV or 8mg/kg × 1-2 doses. Second dose 8-12 h after first dose if inadequate response. Available as: IV infusion injection: 80 mg/4 mL (20 mg/mL); 200 mg/10 mL (20 mg/mL); 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to IV infusion. Dose adjustments: Kidney: No dose adjustments recommended in mild or moderate kidney impairment. Not studied in patients with severe impairment. Hepatic: No dose adjustments recommended (not studied); initiate based on benefit. Administration: Infuse over 60 min, should not be infused concomitantly in the same IV line with other drugs	IL-6 receptor antagonist	Infections, headache, hypertension and increase in hepatic enzymes	Drugs metabolized by CYP3A4, 1A2 or 2C9	Common: Increase in upper respiratory tract infections (including tuberculosis), nasopharyngitis, headache, hypertension, increased AST, infusion related reactions. Major: Hematologic effects, infections, hepatotoxicity, gastrointestinal perforation, hypersensitivity reaction

SARS-CoV-2: Virology and Drug Targets10

Selected Repurposed Drugs

LOPINOVIR/RITONIVIR

In hospitalized adult patients with severe Covid-19, no benefit was observed withlopinavir–ritonavir treatment beyond standard care. Future trials in patientswithsevere illness may help to confirm or exclude the possibility of a treatment benefit.7

DPP

The use of DPP4 inhibitors, such as gliptins, in patients with COVID-19 with, or even without, type 2 diabetes, may offer a simple way to reduce the virus entry and replication into the airways and to hamper the sustained cytokine storm and inflammation within the lung in patients diagnosed with COVID-19 infection.14

UMIFENOVIR

Umifenovir was safe and associated with higher negativerate of PCR on day 14 in laboratory-confirmed COVID-19 adult patients.However, it could not significantly shorten nucleus acid negative conversiontime or hospital LOS, improve symptoms or decrease risk ofdisease progression. In conclusion, there is no evidence to support theuse of umifenovir for improving patient-important outcomes in patientswith COVID-19. 15

RAMDESIVIR

In this cohort of patients hospitalized for severe Covid-19 who were treated with Compassionate use remdesivir, clinical improvement was observed in 36 of 53 patients(68%). Measurement of efficacy will require ongoing randomized, placebocontrolledtrials of remdesivir therapy.16

TOCILIZUMAB

Treatment with tocilizumab, whether administered intravenously or subcutaneously, might reduce therisk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia.17

DEXAMETHASONE

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower28-day mortality among those who were receiving either invasive mechanical ventilationor oxygen alone at randomization but not among those receiving no respiratorysupport.18

FAVIPIRAVIR

The purpose of the review was to analyze the recent published articles about favipiravir effects in COVID-19 patients. The results suggest that favipiravircould be a suitable antiviral drug against COVID-19. The medication's mechanism of action relies on RNA chain termination and error catastrophe. However, it is clear from the review that most COVID-19 patients experience underlying cardiovascular disease and close to one-third of those hospitalized suffer from cardiac injury. Together, these studies support a possible role for high disease of favipiravir for future human interventions, as long as hospitals and clinics establish the right administrative protocols.19

CHLOROQUINE AND HYDROXYCHLOROQUINE

In vitro studies, in vivo studies, original studies, clinical trials, and consensus reports, that were conducted to evaluate the antiviral activities of chloroquine and hydroxychloroquine. Multinational, observational, real- world study of patients with COVID-19 requiring hospitalisation found

that the use of a regimen containing hydroxychloroquine or chloroquine (with or without a macrolide) was associated with no evidence of benefit, but instead was associated with an increase in the risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19.20 Although relatively safe at a therapeutic dose and for a short period of time, this drug has a narrow therapeutic index, which requires regular cardiac and therapeutic drug monitoring. Serious adverse reactions of hydroxychloroquine have already been reported in patients with COVID-19, especially when it is combined with azithromycin. The combination of hydroxychloroquine plus azithromycin (AIII), because of the potential for toxicities. The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial (AII). Given the risk of dysrhythmias, the Food and Drug Administration (FDA) cautions against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 outside of a hospital or clinical trial.21

IVERMECTIN

A new subsection was added to Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19 to address the use of ivermectin for the treatment of COVID-19. The Panel recommends against the use of ivermectin for the treatment of COVID-19, except in a clinical trial (AIII). Special Considerations in Adults and Children with Cancer patients who are receiving active treatment for cancer have a higher risk of severe complications from COVID-19 than patients without cancer. These complications include a greater risk of mortality and a greater likelihood of being admitted to the intensive care unit. This new section provides recommendations for screening certain asymptomatic cancer patients for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The Panel also emphasizes the importance of consulting a hematologist or oncologist before adjusting a patient's cancer-directed therapy. Decisions about administering cancer-directed therapies to patients with SARS-CoV-2 infection should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient's history of tolerance to the treatment.

Conclusion

COVID-19 is a pandemic, hence drug repositioning that is "old pills for new indications" is being tried worldwide. Globally, hundreds of clinical trials are ongoing to evaluate the efficacy of these old drugs in SARS-CoV-2 infection. Hence, repurposing of the drugs is an attractive and a feasible option because PK/PD profile, toxicity profile, and drug interactions are already known. This review emphasizes on the different aspects of COVID- 19 such as the epidemiology, clinical features and preventive measures to be adopted in order to fight this pandemic. The control of the outbreaks of SARS-CoV-2 is now becoming a world challenge. The development of preventive and controlling remedies along with personal precautions are urgently needed to avoid SARS-CoV-2 infection. The WHO has also planned a large global trial known as "Solidarity Trial" mainly to generate a robust clinical evidence to combat this pandemic. As there is no specific treatment till date, prevention is the only

measure to contain the infection. Even a small negligence in following the preventive measures would be very expensive for the mankind. The ICMR has given some recommendations regarding COVID-19 prevention and treatment

Conflict of Interest

Authors declare that there is no conflict of interest.

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