Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Current Medicine Research and Practice 10 (2020) 100–109

Contents lists available at ScienceDirect

Current Medicine Research and Practice

journal homepage: www.elsevier.com/locate/cmrp

Review Article

Literature-based review of the drugs used for the treatment of COVID-19

Meda Venkatasubbaiah [a, *], P. Dwarakanadha Reddy [b], Suggala V. Satyanarayana [c]

[a] Jawaharlal Nehru Technological University Anantapur (JNTUA), Ananthapuramu, Andhra Pradesh, India
[b] Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampet, Andhra Pradesh, India
[c] Department of Chemical Engineering, JNTUA College of Engineering, Ananthapuramu, Andhra Pradesh, India

ARTICLE INFO

Article history:
Received 11 April 2020
Received in revised form
26 May 2020
Accepted 29 May 2020

Keywords:
COVID-19
Coronavirus
Treatment
Hydroxychloroquine
Remdesivir

ABSTRACT

COVID-19 is primarily a respiratory disease caused by a newly discovered SARS-CoV-2 virus and identified in the city of Wuhan, China in December 2019. WHO has declared this disease as a pandemic, and warned other countries. Presently this has affected 216 countries, areas or territories worldwide, spreading of this disease is very fast in USA, Brazil, and Russia than in the country of its origin, China. Like other coronaviruses, this may develop respiratory tract infections in the patients range from mild to fatal illness like pneumonia and acute respiratory distress syndrome (ARDS). As of now, no effective drug, vaccine, or any procedure is available and experiments are underway. However, empirical therapy is being followed to manage and save the lives of the patients. There is a need for pharmacological alternatives to combat this deadly virus and its complications. Based on the previous experiences with similar coronavirus management and present preliminary data from uncontrolled studies, drugs like chloroquine, hydroxychloroquine, remdesivir, lopinavir/ritonavir, and favipiravir have been recommended by the researchers to manage COVID-19. This review had assessed the potential mechanisms, safety profile, availability and cost of these drugs. This review concludes that the drugs mentioned above are having different properties and act differently in combating the COVID-19 viruses. Instead of single drug, combination of antivirals with different mechanism of action may be more effective and at the same time their adverse events should not be underestimated.

1. Introduction

COVID-19, previously known as 2019 Novel Coronavirus (2019-nCoV) respiratory disease caused by a newly discovered coronavirus, SARS-CoV-2 virus and identified in the city of Wuhan, Hubei province, China in December 2019. World Health Organization (WHO) declared the official name as COVID-19 in February 2020.[1,2] Virus isolated from the COVID-19 patients belongs to the genus betacoronavirus, this group of viruses can cause simple/common cold to severe acute respiratory syndrome (SARS) caused by SARS-CoV was identified in 2002, and another syndrome Middle East respiratory syndrome (MERS), caused by MERS-CoV identified in 2012.[3–6] According to the report of the WHO and China Joint Mission on Coronavirus Disease 2019 (COVID-19), it is a zoonotic virus, based on the data available, bats seems to be the reservoir of COVID-19 virus.[7]

1.1. Epidemiology

On 11 March 2020, WHO declared this disease as a pandemic, based on its spread to 118,000 cases in 114 countries, and 4291 deaths on that date and warned other countries about its seriousness.[8] According to the WHO COVID-19 dashboard globally, as of 9:20am CEST, 26 May 2020, 5,370,375 confirmed cases of COVID-19, including 3,44,454 deaths, have been reported to WHO from 216 countries, areas or territories. Its spread and mortality is more in the United States of America with 16,18,757 Confirmed cases and 96,909 deaths, followed by Brazil: 3,63,211 cases and 22,666 deaths; Russian Federation: 3,53,427 cases and 3633 deaths; The United Kingdom: 2,59,563 cases and 36,793 deaths; Spain: 235,772 cases and 28,752 deaths; Italy: 229,858 cases and 32,785 deaths; Germany: 178,570 cases and 8257 deaths; Turkey:

* Corresponding author.
E-mail address: pharmachinna@gmail.com (M. Venkatasubbaiah).

https://doi.org/10.1016/j.cmrp.2020.05.013
2352-0817/

156,827 cases and 4340 deaths; France: 142,204 cases and 28,315 deaths.[9]

In India as on, 26 May 2020, 08:00 IST (GMT+5:30), 141,213 were infected, among them 60,490 were cured/discharged and 4167 were died. In India, the mostly affected states includes Maharashtra with 52,667 cases (1695 deaths) followed by Tamil Nadu 17,082 (118); Gujarat 14,460 (888); and Delhi 14,053 (276).[10]

1.2. Virus characteristics and clinical manifestations

Like other coronaviruses, these are spherical shaped containing genetic material inside and with spike proteins protruding from their surface, which helps to latch onto the human cell followed by fusion and transfer of genes to the host cell. The latest data shows that, like the virus that caused the 2002 SARS outbreak, SARS-CoV-2 spikes bind to receptors on the human cell surface called angiotensin-converting enzyme 2 (ACE2).[11] This latest virus can develop respiratory tract infections in the patients range from mild to fatal illnesses like pneumonia and acute respiratory distress syndrome (ARDS). The majority of the patients will experience mild to moderate respiratory illness and recover with supportive treatment and do not need any special care/treatment. Geriatric patients and patients with comorbidities like diabetes, cardiovascular, chronic respiratory disorders, cancer, immunodeficiency patients and other chronic disorders are more prone to develop serious pathological issues related to COVID-19.[3]

Symptoms may appear after 2–14 days (Based on MERS-CoV virus data) of infection, which includes fever, cough, shortness of breath, trouble breathing, persistent pain or pressure in the chest, new confusion or inability to arouse and bluish lips or face, COVID-19 is also associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, stroke, meningoencephalitis, impaired sense of smell or taste, anxiety, depression and sleep problems, multisystem inflammatory syndrome in children and adults is also observed in some cases.[12,13] Unfortunately, three types of extra pulmonary complications were reported by the COVID19 patients, includes liver injury as that of other corona infections (SARS and MERS) and fulminant myocarditis and acute kidney injury.[14–16]

1.3. Pharmacological agents recommended for SARS and SARS-CoV-2 management

As of now, the exact effective drug, vaccine, or any therapeutic procedure is not available and experiments are underway. However, empiric therapy is being practiced to manage and saves the life of the patient with the known antivirals, antibiotics, corticosteroids biological and traditional preparations, either alone or in combination based on the patient's condition (signs, symptoms, and severity), need and availability along with other supportive therapies. For managing any disease, early identification of the disease and assessment of associated risk factors (modifiable/nonmodifiable) is paramount, secondly, supportive care which includes curative therapy (if available), symptomatic therapy. As SARS-CoV-2 virus belongs to the SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV), prescribers are administering the drugs which have shown some promising results in managing similar viral infections.[17]

Healthcare systems of different countries have suggested few drugs based on the preliminary data obtained through uncontrolled studies:

National Health Commission of the People's Republic of China has recommended favipiravir, chloroquine phosphate, plasma transfusion therapy, remdesivir, and traditional Chinese medicine.[18]

The Indian Council of Medical Research (ICMR), New Delhi, has recommended hydroxychloroquine for empirical use for prophylactic purposes in asymptomatic healthcare workers and household contacts of laboratory confirmed patients.[19]

According to the guidelines given by the Government of India, Ministry of Health & Family Welfare, Directorate General of Health Services (Emergency Medical Relief (EMR) Division), lopinavir/ritonavir can be given only after proper informed expressed consent from the patient and ensuring all necessary monitoring measures to avoid possible serious adverse reactions.[20]

Spanish Society of Hospital Pharmacy for the management of antiviral treatment in the new coronavirus SARS-CoV-2 disease COVID-19 guidelines has recommended lopinavir/ritonavir, lopinavir/ritonavir (oral) + interferon alfa-2B and beta-1B, remdesivir, hydroxychloroquine, chloroquine, darunavir/cobicistat, tocilizumab.[21,22]

There are no US Food and Drug Administration (FDA)-approved drugs specifically for the treatment of patients with COVID-19. Centers for Disease Control and Prevention have provided information about the currently recommended drugs in the United States i.e. chloroquine, hydroxychloroquine, remdesivir, and lopinavir/ritonavir.[23]

As per the data available on 22.05.2020, in NIH US National Library of Medicine clinicalTrial.gov, 977 interventional clinical trials for COVID-19 are currently at various stages of development throughout the world, of them 11 drug intervention trials on DAS181; Hydroxychloroquine, Lopinavir/Ritonavir, Interferon Beta-1A and 1 B; Baricitinib 4 MG; methylprednisolone; Ganovo (Danoprevir)+ritonavir ± Interferon nebulization; Ribavirin, were completed, but no results were posted on the website.[24]

To date, the Emergency Use Authorization (EUA) authority of the US FDA has issued 2 therapeutic EUAs for combating this pandemic: On 28.03.2020, FDA has issued first Emergency Use Authorization (EUA) for the use of hydroxychloroquine sulfate and chloroquine sulfate in certain adolescent and adult patients hospitalized patients weigh 50 kg or more with COVID-19 when a clinical trial is not available or feasible. They also instructed that the prescribers should use the stock supplied from the Strategic National Stockpile. And on 01.05.2020, FDA issued the second EUA for remdesivir to treat severe COVID-19 in both adult and children.[25]

With this review, shreds of evidence for considering these drugs for managing COVID-19 were assessed through the evaluation of possible mechanism, safety profile, and availability with a note on the cost.

2. Pharmacological and clinical aspects of important SARS-1 and SARS-COV-2 therapeutic agents

2.1. Favipiravir

Favipiravir (T-705 or Avigan), an oral antiviral drug approved in Japan for influenza infection in 2014.[26] It has also been used for treatment of Ebola virus infection. It acts by direct inhibition of viral replication and transcription through misincorporation in nascent vRNA (viral ribonucleic acid), or by binding to conserved polymerase domains, preventing incorporation of nucleotides for vRNA replication and transcription.[27]

2.1.1. Preclinical evidence

According to the Madelain V et al[28] nonhuman primate (NHP) model study, favipiravir was found to have adaptive immune response in viral clearance, and can become a treatment option for other emerging viral diseases. Other studies have also reported that favipiravir acts by inhibiting RNA dependent RNA polymerase (RdRp) by converting into its active metabolite

(favipiravirribofuranosyl-5′-triphosphate (RTP)) in cells and is recognized as a substrate by viral RNA polymerase. As SARS-CoV-2, is an RNA virus, this drug might be one of the options for treating COVID-19.[29,30]

2.1.2. Clinical evidence

National Medical Products Administration of China has included this drug in the potential treatments for COVID-19.[18] The clinical evidence on the efficacy of this drug was observed in the clinical trial conducted by the third People's Hospital of Shenzhen in Guangdong province, where favipiravir group patients' ($n = 35$) laboratory tests shown negative for COVID 19 after 4 days of treatment, whereas other group patients took 11 days for the same.[31]

In an open-label non-randomized control study conducted by Q Cai et al, favipiravir (FPV) 1600 mg twice daily as a loading dose and 600 mg twice daily plus interferon (IFN)-α 5 million U twice daily by aerosol inhalation were administered to 35 patients with a median age of 43 (35.5–59) years. In another group lopinavir 400 mg/ritonavir 100 mg (RTV) twice daily plus IFN-α 5 million U twice daily by aerosol inhalation were given in 45 patients (median age was 49 (36–61) years). They observed a shorter viral clearance time and significant improvement in chest imaging in FPV group with few ADRs. Preliminary results of another comparative study conducted in Wuhan, China, with 120 COVID-19 patients have also supported the efficacy of favipiravir and they also stated that administration of favipiravir tablet is easier.[32,33]

2.1.3. Adverse drug reactions (ADR), cost and availability

According to the data obtained from the Uppsala Monitoring Centre (UMC)-Global adverse reactions reporting system as on 22.05.2020 only 24 ADRs were reported.[34] the cost of the drug is not found with our extensive search and the global commercial availability of this drug is very less.

2.1.4. Current clinical research

Currently, there are 17 clinical trials specific to COVID-19 are at various phases of development and researchers are expecting promising results in clearing the virus.[35]

Recently, a reputed pharmaceutical company has initiated Phase-3 clinical trials for COVID-19 in India with tablet favipiravir, and it is expecting the complete study results by August.[36]

2.2. Chloroquine (CQ)

Chloroquine is approved for the prophylaxis and treatment of malaria, to treat extraintestinal amebiasis and chloroquine is also used off label for the treatment of various rheumatic diseases, as well as treatment and prophylaxis of Zika virus.[37,38] As per the Emergency Use Authorization (EUA) of US FDA for the unapproved use of this drug in COVID-19 patients and the dosing schedule for this drug is 1 g on day one, followed by 500 mg once a day for 4–7 days based on clinical evaluation.[25]

2.2.1. Preclinical evidence

Preclinical data from various studies has confirmed the role of chloroquine in controlling the human coronavirus infection through different mechanisms, which includes; through protease inhibition in SARSCoV; inhibition of sialic acid biosynthesis; inhibition of HCoV-OC43 replication in HRT-18 cells by chloroquine in newborn mice; the activation of p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) in human coronavirus 229E infection in human epithelial lung cells; Inhibition of viral spread in cell culture through endosomal pH rise and interfering with terminal glycosylation of angiotensin-converting enzyme 2 receptor; Inhibition of the replication of SARS-CoV in Vero E6 cells.[6,39–43]

In 2020, docking study results of Wu C et al[44] predicted the possibility of combining with Nsp3b and E-channel and further and also supported the potentiality of the chloroquine to become a therapeutic option for COVID-19 infection; Zhang S et al[45] and Colson P et al[46] also stated that the alkalization of phagolysosome and slowdowns the pH-dependent viral replication, including fusion and uncoating. And they also commented as chloroquine is both a safe and economic drug than others at this current junction for both prophylactic and curative treatment of novel coronavirus infection.

2.2.2. Clinical evidence

Chloroquine phosphate tablet 500 mg 12 hourly for 10 days might have benefits in controlling the novel coronavirus pneumonia irrespective of their severity.[47] In other studies conducted on COVID-19 patients, researchers have found the superiority of chloroquine over other therapy in terms of both efficacy and safety in reducing the exacerbation of pneumonia.[46,48] With the support of this data, Chinese government recommended chloroquine along with other therapies for the prevention and treatment of COVID-19 pneumonia.[18]

2.2.3. Adverse drug reactions (ADRs), cost and availability

The American Academy of Ophthalmology stated that risk of toxicity with the usage of chloroquine/hydroxychloroquine is dose and duration dependent with the normal daily dose for less than 5 years therapy has <1% chance of retinopathy, however regular monitoring is required to prevent retinopathy.[39,49] A total of 6189 ADRs were reported to UMC, Sweden. Of which 1873 were skin and subcutaneous disorders, 1676 were gastrointestinal disorders, 1447 were nervous system disorders, and 738 were eye disorders.[34]

This drug is widely available globally in all the areas at affordable prices, the cost range of 250 mg tablets is 0.35 USD tablet is 5.42–7.85 USD, In India, it is available in a variety of formulations for all age groups i.e. drops, injection, tablet, syrup, etc., at very low cost and the cost of 10 ml drops (80 mg/ml) is 7.05 INR, 2 ml (80 mg) ampoule is 3.65 INR the cost of each 250 mg tablet is 0.50 INR to 1.0 INR and 500 mg is 1.25 INR to 2.0 INR, and Syrup (60 ml) is 11.50 INR to 15.0.INR.[50]

2.2.4. Current clinical research

Currently, a total of 67 clinical trials are underway with chloroquine for the management of COVID-19.[51]

2.3. Hydroxychloroquine (HCQ)

Hydroxychloroquine (HCQ) is an aminoquinoline. It is indicated for both the prophylaxis and treatment of uncomplicated malaria. It is also prescribed for the management of rheumatoid arthritis, chronic discoid lupus erythematosus, and systemic lupus erythematosus. In pediatric age group it is used for the management of juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus.[52,53]

The recommended dosing schedule for both prophylactic and therapeutic use in COVID-19:

- As per ICMR, the prophylactic dosing schedule of HCQ in COVID-19 is as follows[19]:
  For asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on Day 1, followed by 400 mg once weekly for the next 7 weeks; to be taken with meals.

For asymptomatic household contacts of laboratory-confirmed cases: 400 mg twice a day on day 1, followed by 400 mg once weekly for the next 3 weeks; to be taken with meals).

- The dosing schedule of HCQ as per the US FDA's EUA for hospitalized COVID-19 adults and adolescent patients who weigh ≥50 kg is 800 mg on the first day and then 400 mg daily for four to seven days, duration of total treatment is based on clinical evaluation.[25]
- Some U.S. clinicians have reported different dosing schedules: 400 mg 12 hourly on day one, then daily for 5 days; 400 mg BID on day one, then 200 mg 12th hourly for 4 days; 600 mg 12th hourly on day one, then 400 mg daily for 2–5 days.[23]

2.3.1. Preclinical evidence

Literature confirms that both the CQ and HCQ have similar properties and acts in the same way with minor changes in their dosing schedule, researchers also said that the HCQ is their first choice in treating the SARS-CoV-2 infection, as HCQ is showing less toxicity (~40%) in animals than chloroquine.[46,54]

An in-vitro study conducted by Yao X et al,[55] using SARS-CoV-2 infected Vero cells, concluded that the HCQ ($EC_{50} = 0.72$ μM) at an oral loading dose of 400 mg 12th hourly, followed by 200 mg twice daily for 4 days is better than chloroquine ($EC_{50} = 5.47$ μM) 500 mg 12th hourly for 5 days for treating SARS-CoV-2 infection, they also quoted that, the immunomodulatory effects of these two drugs can suppress the raised immune factors (cytokines IL-6 and IL-10) as an immune response to SARS-CoV-2 virus and prevents the complications.

Christophe B et al[56] studied the antiviral activity of ferroquine (FQ) derivatives, hydroxychloroquine, and chloroquine in viruses infecting vero cell cultures where they found the better inhibitory activity of hydroxychloroquine than chloroquine (CQ).

2.3.2. Clinical evidence

The revised advisory report of the Joint Monitoring Group under the Chairmanship of DGHS on the safety and efficacy of prophylactic use of Hydroxychloroquine (HCQ) in India has drawn the following conclusions from the clinical studies:

- A significant dose-response relationship was observed between the number of prophylactic doses taken and frequency of occurrence of SARSCoV-2 infection in symptomatic healthcare workers
- The probability of SARSCoV-2 infection in healthcare workers who have taken the prophylactic HCQ was less when compared to those who have not taken
- Another study conducted at AIIMS, New Delhi on prophylaxis HCQ (median 6 weeks of follow up) had reported the lower incidence of this infection in healthcare workers.

They have also assessed the safety of HCQ prophylaxis among 1323 healthcare workers and found mild adverse effects such as nausea (8.9%), abdominal pain (7.3%), vomiting (1.5%), hypoglycemia (1.7%) and cardio-vascular effects (1.9%).[57]

Recently, Magagnoli J et al[58] have conducted retrospective analysis of 368 SARSCoV-2 infection in-patients in United States, and they concluded that the use of hydroxychloroquine alone or in combination with azithromycin, has not proven the efficacy in controlling the infection, however, the mortality rate was more in patients administered with hydroxychloroquine alone. The authors have also stated the need of sufficient data to widespread use of these drugs.

Mehra MR et al[59] have analyzed the multinational registry of 96,032 of COVID-19 in-patients who were admitted during December 20, 2019 to April 14, 2020. A total of 14,888 patients were received hydroxychloroquine or/and chloroquine with or without a macrolide along with other treatments. Authors have not found the any evidence of benefit with these drugs, in-spite they noted the risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19. Results of this analysis suggested to not to use these drug regimens without clinical evidence.

2.3.3. Adverse drug reactions (ADRs), cost and availability

The risk of toxicity with the usage of HCQ is dose and duration dependent. With a normal daily dose for less than 5 years therapy has a <1% chance of retinopathy. They recommend a maximum daily dose, which can lead to this toxicity is ≤5.0 mg/kg for HCQ, but with CQ damage may occur at ≤2.3 mg/kg weight. But, the duration of the therapy may not be longer in controlling COVID-19, so there is a less possibility of developing retinopathy.[49] No significant elevation of liver enzymes and Liver injury with the HCQ is rare in normal individuals but, it may alter the metabolism of co-administered drugs.[60]

A total 23,994 ADRs were reported to UMC Sweden on HCQ, of which general disorders and administration site conditions (10,232), skin and subcutaneous tissue disorders (5802), gastrointestinal disorders (4207), musculoskeletal and connective tissue disorders (3385), nervous system disorders (2658) and eye disorders (2118) are commonly affected systems.[34]

It is available in different strengths i.e. 100 mg, 200 mg 300 mg, and 400 mg tablets, the cost of HCQ ranges from for 400 mg 10 INR to 16 INR, for 300 mg 11 INR to 14 INR, for 200 mg 5 INR to 10 INR.[61]

2.3.4. Current clinical research

To date, 201 HCQ clinical trials are being conducted with or without other treatments in different parts of the world and are at different stages of development for prophylaxis and treatment of mild, moderate, and severe SARS-CoV-2 infections. Of 201 trials, 5 were completed and expecting defined guidelines for the use of HCQ in COVID-19 patients with more scientific evidence[62]

Due to its safety profile, availability and low cost and efficacy, most of the prescribers are advising this drug in their COVID-19 patients and as prophylaxis for non-infected healthcare workers, COVID19 patients exposed people. In recent days, after the announcement of potential beneficial effects with rational use by some organizations and famous persons, the irrational purchase of the CQ and HCQ has increased enormously, this led to the shortage of these drugs for chronic inflammatory diseases. In some cases, irrational use leads to poisoning.[63,64]

2.4. Combination of HCQ with azithromycin

Philippe Gautret et al[65] have studied the efficacy of HCQ in combination with azithromycin, 22 confirmed COVID-19 patients received 600 mg of hydroxychloroquine daily and depending on their clinical presentation, azithromycin was added to the treatment. A significant reduction of the viral load was observed on day 6 when compared to controls. They concluded that hydroxychloroquine treatment had significantly reduced the viral load in COVID19 patients and its effect was synergized with azithromycin.

Researchers are investigating the efficacy of this combination in various countries with or without other drugs.[62]

2.5. Remdesivir

Remdesivir, or GS-5734, is an investigational adenosine triphosphate analog and used in the treatment for Ebola and coronavirus infections. Remdesivir shuts down viral replication by inhibiting a key viral enzyme, the RNA-dependent RNA polymerase.[66]

Based on the preclinical data and preliminary evidence on speedy recovery in clinical trials, on 1st May 2020, Food and Drug Administration (FDA) issued the EUA for its emergency use for the treatment of hospitalized COVID-19 patients.[25]

2.5.1. Preclinical evidence

Preclinical studies conducted by researchers have demonstrated the antiviral activity through various mechanisms against coronaviruses like MERS and SARS, which are structurally similar to SARS-CoV-2.

Dong L et al[29] reported that the remdesivir is a nucleoside analogue with potential and broad-spectrum antiviral activity. Wang M et al[2] concluded that remdesivir acts through incorporation into nascent viral RNA chains and results in premature termination at a stage post virus entry in RNA viruses including SARS/MERSCoV. In 2020, Timothy P S et al[67] observed a potent inhibition in MERS-CoV replication with EC_{50} of 0.09 μM, with no observable cytotoxicity up to 10 μM in primary human lung epithelial cell cultures. Tchesnokov E P et al[68] have demonstrated delayed chain termination in the Ebola virus, HIV-1, and the hepatitis B virus cell cultures. Agostini M L et al[69] has identified the efficacy of remdesivir in targeting the proofreading exoribonuclease through the incorporation of the active triphosphate into viral RNA.

Sheahan T P et al[70] said that the nucleotide pro-drug remdesivir has shown inhibitory properties against SARS-CoV and MERS-CoV replication in primary human airway epithelial cell cultures. Also, it has demonstrated the broad-spectrum anti-CoV activity in circulating contemporary human CoV in primary human lung cells. It has reduced the viral load significantly in both prophylactic and therapeutic use in a mouse model against SARS-CoV. Authors have opinioned that, this drug has a strong potential to become a therapeutic option for CoV in the future. Emmie de Wit et al[71] have reported the efficacy of prophylactic and therapeutic remdesivir (GS-5734) use in the rhesus macaque model of MERS-CoV infection.

Lo M K et al[72] have also reported the efficacy of remdesivir in a variety of viruses including coronaviruses. Elfiky A et al[73] stated that remdesivir along with other antiviral binds to the new coronavirus strain RdRp tightly rather than the polymerase. They also suggest GTP as one of the targets in inhibiting SARS-CoV-2.

According to the report by Abby Olena,[74] remdesivir mimics adenosine, one of the building blocks of any RNA virus's genome can interfere with the RNA-dependent RNA polymerase.

2.5.2. Clinical evidence

Holshue M L et al[75] have reported the first case of a 35-year-old man who was confirmed with novel COVID-19. Intravenous remdesivir was initiated from the evening of day 7, as the patient's condition was worsen and continued till the discharge day. 0n 11th day the viral loads were decreased in respiratory fluid specimens are on the 12th day, specimen tested negative for 2019-nCoV and the patient's clinical condition was improved. And no adverse events were observed in association with the remdesivir infusion. They also mentioned the need for extensive clinical investigation on the usage of remdesivir.

A news report by Suryatapa Bhattacharya[76] in the Wall Street Journal revealed that the 14 American cruise passengers in Japan who contracted the novel coronavirus were treated effectively with the antiviral drug remdesivir. International Pharmaceutical Federation and American Society of Health-System Pharmacists (ASHP) have stated the importance of remdesivir in treating COVID-19 in their treatment guidelines for COVID-19 and they also mentioned that this drug is under evaluation in different clinical trials.[77,78]

A randomized, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China on 237 COVID 19 patients, Remdesivir in a dose of 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions was given in158 patients and remaining were received placebo. They also received lopinavir–ritonavir, interferon, and corticosteroids as and when. The non statistical significant clinical improvement at a faster time was observed with remdesivir. The incidence of adverse effects was similar in two groups i.e. 66 % and 64% respectively. Remdesivir was withdrawn from 18 (12%) patients. Study findings revealed that dose regimen was well tolerated but no significant efficacy was observed in seriously ill patients. However, reduction in some clinical parameters was observed. Authors concluded the need of vigorous research with this drug is needed to confirm its benefits in larger population.[79]

2.5.3. Adverse drug reactions, cost and availability

A total of 74 ADRs were reported to UMC, Sweden of which, majority were related to the investigations (28), followed by renal and urinary disorders (14), skin and subcutaneous tissue disorders (14), infections and infestations (11), and respiratory, thoracic and mediastinal disorders (9).[34] The cost of the remdesivir 1 mg is USD 220 and 5 mg USD 550.[80] As of now, this drug is not widely available globally.

2.5.4. Current clinical research

Currently, 24 clinical trials are being conducted to know the efficacy of remdesivir in COVID-19 patients, of them 1 trial was completed. Some uncontrolled studies are showing some clinical evidence and may expect the same with these clinical trials and this may become a potential treatment option for COVID-19 patients.[81]

Though it is effective in combating COVID-19, its limited availability and high cost becomes challenge, so, governments and researchers have to take necessary actions to overcome these issues.

2.6. Lopinavir-ritonavir (Kaletra)

Lopinavir and low dose of ritonavir are antiretroviral protease inhibitors; together they work effectively in the treatment of HIV infection, in the year 2000 this combination was released by Abbott under the brand name Kaletra. The metabolism of lopinavir is inhibited by ritonavir and enhances the half-life and antiviral activity. American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines recommend ritonavir-boosted combination therapies as first-line therapy for HCV Genotype 1a/b and 4 treatment-naïve patients with or without cirrhosis.[82]

The Government of India Ministry of Health & Family Welfare Directorate General of Health Services (EMR Division) has recommended this drug combination for the clinical management of COVID − 19 in the following dosing schedule[20]:

- Lopinavir 200 mg/ritonavir/50 mg 2 tablets twice daily,
- Lopinavir400 mg/ritonavir 100mg/5 ml, 5 ml suspension twice daily, (if the patient is unable to take orally)
- The duration: for 14 days or for 7 days after becoming asymptomatic

The Spanish Society of Hospital Pharmacy has also suggested this drug in alone and in combination for the management of antiviral treatment in the new coronavirus SARS-CoV-2 disease COVID-19[21]:

- Lopinavir/ritonavir: 400/100 mg at every12 h through oral route for 14 days. And
- Lopinavir/ritonavir (oral) + interferon alfa-2B: For mild cases: 100,000–200,000 IU/kg through nebulization. For severe cases:

200,000–400,000 IU/kg two times a day for 5–7 days and beta-1B 250 mcg/48 h through subcutaneous for 14 days.

2.6.1. Preclinical evidence

Chymotrypsin-like protease (3CLpro) and a papain-like protease (PLpro) are important for the replication of SARS-CoV. These proteases are important targets for the development of antiviral drugs. In-vitro/animal studies conducted in 2020 have revealed the inability of this drug to bind to major targets like 3CLpro, PLpro, RdRp, and a comparative study between the remdesivir and lopinavir/ritonavir (LPV/RTV), and interferon-beta (IFN-b) against MERS-CoV in mice found slight reduction in viral loads and improved the pulmonary function but not reduced the viral replication or severe lung pathology.[68,69]

2.6.2. Clinical evidence

According to the case report published by Han W et al[83] this combination has shown efficacy in a 47 years old male SARSCoV-2 patient in 800/200 mg dose along with, methylprednisolone 40 mg (for 2 days only), recombinant human interferon alfa-2b 10 million IU per day, patient was recovered on the 10th day and tested negative for the virus and discharged.

In Chen Q et al[84] case series, lopinavir and ritonavir tablets (800/200 mg daily) were given to 9 patients along with other treatments based on the severity, all the patients become negative for SARS-CoV-2 (range 4–11 treatment days). The average days of hospital stay were 14.2 (range from 9 to 20) for the recovery from the lung lesions, as well as from the clinical symptoms. Fortunately, no deaths were reported during the treatment period and authors concluded that effective treatment should include the combination of traditional Chinese and western medicine.

B Cao et al[85] have conducted a randomized, controlled, open-label trial on 199 SARS-CoV-2 infected adult patients with the median age of 58 (49–68) years. Patients were randomized into two groups i.e. 99 were assigned to the lopinavir-ritonavir group (The dose of 400 mg and 100 mg, 12th hourly for 14 days.) and 100 to the standard care group. They have observed a similar reduction in the viral loads from day 1 to day 28 in both groups. Adverse events were monitored up to 28 days and found 46 ADRs in the lopinavir-ritonavir group and 49 in the standard group, gastrointestinal adverse events were more common in the lopinavir-ritonavir group, but serious adverse events were more common in the standard care group. Drug discontinuation was observed in 13 patients of the Lopinavir–ritonavir group due to these safety issues. The authors conclude that there was no difference observed in the outcomes of both groups. This suggests further evaluation to confirm the benefits of lopinavir-ritonavir.

2.6.3. Adverse drug reactions (ADRs), cost and availability

A total 10,786 ADRs reported to UMC Sweden of which, the majority were related to injury, gastrointestinal disorders (3117), followed by general disorders and administration site conditions (1913), injury, poisoning and procedural complications (1544), investigations (1483) metabolism and nutrition disorders (1267), skin and subcutaneous tissue disorders (1189), nervous system disorders (1083).[34] The cost of this drug combination is around 100–150 INR for one tablet of 400mg/200 mg composition and the availability is not much.[86]

2.6.4. Current clinical research

Presently, 64 clinical trials are underway on this combination along with other drug interventions and the majority at an initial stage of the development.[87]

Based on the effectiveness in the clinical conditions rather than preclinical studies and when compared to other anti-viral drugs' cost and availability, this drug has the possibility of becoming an effective treatment option for COVID-19.

2.7. Ribavirin (Virazole)

Ribavirin, a guanosine analogue discovered by Witkowski and coworkers in 1972, originally approved only for the treatment of severe respiratory syncytial virus (RSV) infection in children. It has a broad spectrum activity against RNA and DNA viruses and also used in the treatment of Lassa fever virus infection, influenza A and B, and other viruses. Later it was tested for hepatitis C virus infections and found effective in combination with interferon-alfa in treating chronic hepatitis c infections. It acts by incorporating into viral RNA and inhibition of its, inducing viral genome mutations, and inhibiting normal viral replication. It also inhibits the RNA dependent RNA polymerase activity.[88–90]

2.7.1. Preclinical evidence

Based on the docking study results of 2020 Wu C et al[43] this drug might be a potent SARS-PLpro inhibitor as it bound to the active site of the enzyme with low energy. An extensive review done by Vincent C C C et al[91] had reported that, ribavirin suppresses the pro-inflammatory response while augmenting viral replication in this mouse model. And it has shown activity in human Caco-2 and pig kidney cell lines but failed to show effects in Vero cells.

Ning Q et al[92] study reported the immunomodulatory effects of ribavirin i.e. inhibiting the production of IL-4 by Th2 cells, and positive effect on interferons in Th1 cells in both in-vitro and in-vivo. It also inhibits macrophage proinflammatory cytokines and Th2 cytokines while preserving Th1 cytokines.

2.7.2. Clinical evidence

Sun D et al[93] have reported the efficacy of ribavirin along with other medications in pediatric patients with lower case fatality rate than adults. In Kenneth W et al[94] study, a total of 10 severe acute respiratory syndromes (SARS) patients with an average age 52.5 ± 11.0 years were treated empirically with ribavirin (8 mg per kilogram of body weight every eight hours) or oral ribavirin (1.2 g every eight hours, in patient 4 only) and intravenous corticosteroids (hydrocortisone at a dose of 4 mg per kilogram every eight hours tapered to 200 mg every eight hours or methylprednisolone at a dose of 240–320 mg daily). Out of 10 patients, only one patient got discharged with complete recovery by the 20th day of admission. 7 patients were unwell even after 18–33 days of admission and the remaining 2 were died.

A retrospective study was conducted by Booth CM et al[95] on 144 SARS patients with the median age of 45 (34–57) years, where, ribavirin (loading dose of 2 g iv, followed by 1 g iv every 6 h for 4 days, followed by 500 mg every 8 h for 3 days) was given to 126 patients with a median of 6 (5–7 days) treatment days. By 14th day majority (74%) of the patients got recovered and discharged. But, the safety issues warns the prescribers to monitor the patients closely, around 50% were developed hemolysis and low hemoglobin. And in 18% patients, the drug was discontinued due to the toxicity. They have also reported 8 deaths.

Leong H N et al[96] have reported that out of 229 SARS cases 97 (42.4%) were received ribavirin for mean days of 5.6 at a dose of 1.2 g three times a day, in either oral or intravenous routes, 10 patients have died and anemia was observed in 24 patients. They conclude Ribavirin should be given along with other therapies like immune therapy.

In a study conducted by Peiris JSM et al,[97] 75 SARS confirmed patients were treated with 8 mg/kg intravenous ribavirin every 8 h for 14 days, along with other treatment based on the patient's condition. Improvement was seen in 46

patients, 11 were stable at, the condition of 18 patients' was worsened and 5 were died.

Arabi YM et al[98] retrospective cohort study on 349 MERS critically ill patients reported that, 144 (41.3%) patients have received ribavirin/rIFN. The median age of these 144 patients was 57.5 years, 205 patients have received other therapy. The dose of the ribavirin was as per the creatinine clearance, (if it is **>50 ml/min,** 2000 mg orally loading dose then 1200 mg every 8 hrs for 4 days, then 600 mg PO every 8 hrs for 4–6 days; **20–50 ml/min-** 2000 mg orally loading dose then 600 mg every 8 hrs for 4 days, 200 mg orally every 6 hrs for 4–6 days. And in **<20 ml/min** and hemodialysis patients- 2000 mg orally loading dose then 200 mg every 6 hrs for 4 days, then 200 mg every 12 hrs was given). The average duration of therapy was 8 days. RBV/rIFN has cleared the viral load in 28 days and another group, it was found to be in 22 days. 90-day mortality was more with RBV/rIFN (73.6% vs 61.5%). In safety profile, no difference was found between the two groups, but, RBV/rIFN group patients had received more blood transfusions, which indicate that more number of patients from this group had developed hemolysis. They concluded that RBV/rIFN therapy may not be effective than other therapy.

2.7.3. Adverse drug reactions (ADR), cost and availability

At the time writing this article a total 90,864 ADRs were reported to UMC Sweden, of which general disorders and administration site conditions are 36,378, followed by gastrointestinal disorders (22,119), infections and infestations, skin and subcutaneous tissue disorders (20,160), investigations (19,020), nervous system disorders (19,055), blood and lymphatic system disorders (17,769), psychiatric disorders (14,552), respiratory, thoracic and mediastinal disorders (10,301).[34]

Ribavirin is available as capsules, tablets, and syrup in different strengths. The cost of a single dose of 100 mg is ranging from INR 29.00–33.00, for 200 mg cost range is INR 56.00–78.00 and the cost of 30 ml syrup is INR 80.00–100.00.[99]

2.7.4. Current clinical research

As on date, only 8 clinical trials are being conducted by researchers on this drug, of them 2 were at completed stage and report of one trial concluded that the ribavirin triple antiviral therapy was safe and superior to lopinavir-ritonavir alone.[100–101]

2.8. Other drugs

Apart from these drugs, **Ivermectin** and **Nitazoxanide** have also showing the some evidences of becoming promising drugs for treating the COVID-19 patients.

Ivermectin is a broad spectrum anti parasitic. In 2012, it was approved for lice infestations. Preclinical studies recommend the ivermectin's anti SARS-CoV-2 activity in Vero-hSLAM cells where drug has reduced the viral RNA at 48 h and impede the viral replication in Bovine herpesvirus1 (BoHV-1) through the inhibition of DNA polymerase nuclear Import. Ivermectin also inhibits the entrance of DNA polymerase UL42 into the nucleus of pseudorabies virus and its proliferation.[102–105]

According to the Momekov G et al,[106] the available pharmacokinetic data of the routine doses of ivermectin may not attain the SARS-CoV-2 inhibitory concentrations and they are not justifying the empirical use of this drug in COVID-19 patients in spite of its broad spectrum anti viral activity, but they are not discouraging its use in COVID-19.

As on 26.05.2020, around 14 clinical trials are at the initial stage of development either in alone or combination with other drugs for COVID 19, among them majority are being conducted in combination with Nitazoxanide.[107]

Nitazoxanide is a first line broad spectrum antiviral drug and also used in influenza patients. Preclinical studies have reported the anti MERS-CoV and other coronaviruses. It acts by different mechanisms i.e. by inhibiting N protein expression of the virus; suppression of pro-inflammatory cytokines and interleukin-6 production; inhibition of the broad spectrum RNA and DNA viruses' replication. According to the review of Pepperrell T et al, a superior safety profile was observed with approved doses of nitazoxanide. They have also suggested further investigation to confirm the hepatorenal, cardiovascular, and teratogenicity effects. And opinioned the possibility of becoming a promising drug for COVID-19.[108–110]

3. Discussion

Scientists have developed 3 strategies in the development of drugs to combat this deadly virus, which includes:

- Testing of the existed antiviral drugs.
- Screening of chemical libraries against the targets and knowing their properties.
- Discovery and development of the new molecules requires the genomic and pathological characteristics of different coronaviruses. Though it is a promising strategy, it may take around 10 years to develop one promising molecule.

As COVID-19 is a pandemic disease with the high transmission rate, the best strategy is to the testing of marketed antivirals empirically and developing the specific molecules based on the outcomes. So, this review tried to find the properties of recommended molecules for the treatment of this pandemic, especially their mechanisms, efficacy and safety through preclinical and clinical literature in combating coronaviruses and similar viruses, cost, and availability.

Favipiravir has been recommended by the National Health Commission of the People's Republic of China against the SARS-COV-2 virus. It may acts at two stages after the virus has entered into the host cell, i.e. inhibition of RNA-dependent RNA polymerase and inhibiting the incorporation of nucleotides for vRNA replication and transcription. Some more clinical evidence on this drug is required for considering this drug the treatment of COVID-19 either in alone or in combination with other drugs, and it is not a widely available drug globally.

Both chloroquine and hydroxychloroquine may act at different stages of the virus life cycle and interferes with the viral entry through endosomal pH rise and interfering with terminal glycosylation of ACE2 receptors, translation, proteolysis, and replication. Among these two, HCQ is may be more effective than CQ. Though, the early positive clinical outcomes, less possibility of severe adverse effects, might drawn the attention of the prescribers to use these drugs empirically, but latest evidences are not supporting the use of these two drugs either in alone or combination and also with or without macrolide, especially in curing the infection. But, prophylaxis use of hydroxychloroquine in Indian healthcare workers has been producing the beneficial effects with mild adverse effects.

On 22.05.2020, Ministry of Health and Family Welfare has reported the efficacy of prophylaxis hydroxychloroquine in healthcare workers,[57] in controversial to this on 25.05.2020, in the media briefing in view of the safety concerns raised by Mehra MR et al[59] WHO has announced the temporary pause of the hydroxychloroquine arm within their solidarity trial.[111] this data indicates the variations in the responses of one drug in different population.

Another promising drug is remdesivir, which acts at more than one site of viral life cycle i.e. through incorporation into nascent

viral RNA chains and results in premature termination at a post virus entry stage. Interfere with RNA dependent polymerase and inhibits the replication and targeting the proofreading exoribonuclease and acts through the incorporation of the active triphosphate into viral RNA. And clinical evidence in around 15 patients has shown positive results with minimal or no adverse reactions and deaths. This drug has got US FDA emergency use authorization in COVID-19 patients and also recommended by more national healthcare organizations as a potential option against COVID-19.

Although the in-vitro data of lopinavir-ritonavir may not support its mechanism of action i.e. proteolysis, the clinical evidence suggests that it is an effective drug in combination with interferon as this combination has managed the more than 100 SARS patients with a moderate rate of ADR occurrence.

Ribavirin acts rather than on the replication it may show immunomodulatory actions on the virus and inhibit the macrophage proinflammatory cytokines and Th2 cytokines while preserving Th1 cytokines. Among 460 coronavirus positive patients 21% of patients had developed ADRs and 5% were died during treatment. The preclinical and clinical data is not encouraging its use especially as mono therapy and further studies are mandatory to support its utilization in COVID-19.

And it has not recommended by major national healthcare organizations and the reason may be its safety concerns.

As of now, it is early to suggest ivermectin and nitazoxanide as the available data is limited to confirm the role of these drugs in COVID-19 patients and clinical trials are at initial stage.

Apart from these drugs, some other biological, chemical and traditional drugs are also showing promising results in uncontrolled studies.

4. Conclusion

This review concludes that the drugs mentioned above are having different properties and act differently in combating the COVID-19 viruses. No drug may be superior or inferior, however, the use of single drug may not be effective enough to control this deadly virus, so use of combination of antivirals with different mechanism of action may be more effective and at the same time their adverse events should not be underestimated.

Author contribution

All authors are equally contributed in data collection, review, and preparation of this manuscript and approved the final version for the publication.

Statement of funding source

We have not received any funding from government or private or any other organizations.

Declaration of competing interest

No conflicts of interest.

Acknowledgement

We thank all our well wishers and family members for their support.

References

1. World Health Organization Coronavirus. https://www.who.int/healthtopics/coronavirus#tab=tab_1 Accessed 23 March 2020.
2. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30:269–271. https://doi.org/10.1038/s41422-020-0282-0.
3. COVID-19: Prevention & Investigational Treatments. https://www.drugs.com/condition/covid-19.html Accessed 23 March 2020.
4. Peeri Noah C, Shrestha Nistha, Rahman Md Siddikur, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Inter J of Epid*. 2020:1–10. https://doi.org/10.1093/ije/dyaa033.
5. Berger A, Preiser W. *SARS. Encyclopedia of Environmental Health*. second ed. vol. 5. 2011. https://doi.org/10.1016/B978-0-444-63951-6.00624-0.
6. Six questions and answers about the coronavirus (COVID-19) (News). https://www.wur.nl/en/Research-Results/Research-Institutes/Bioveterinary-Research/show-bvr/Six-questions-and-answers-about-the-Wuhan-coronavirus.htm. Accessed 30 March 2020.
7. Report on the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-oncoronavirus-disease-2019-(covid-19). Accessed 30 March 2020.
8. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-openingremarks-at-the-media-briefing-on-covid-19—11-march-2020 Accessed 30 March 2020.
9. Coronavirus disease (COVID-19) Situation Dashboard. https://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd Accessed 26 May 2020.
10. Epidemiology in India: https://www.mohfw.gov.in Accessed 26 May 2020.
11. National Institute of Health (NIH) Novel coronavirus structure reveals targets for vaccines and treatments. https://www.nih.gov/news-events/nih-research-matters/novelcoronavirus-structure-reveals-targets-vaccines-treatments Accessed 30 March 2020.
12. Centers for disease control and prevention. Coronavirus Disease 2019 (COVID-19) Symptoms of Coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/symptomstesting/symptoms.html Accessed 30 March 2020.
13. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html Accessed 20 May 2020.
14. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int*. 2020:1–7. https://doi.org/10.1111/liv.14435.
15. Hu Hongde, Ma Fenglian, XinWei, Yuan Fang. Coronavirus fulminantmyocarditis saved with glucocorticoid and human Immunoglobulin. *Eur Heart J*. 2020. https://doi.org/10.1093/eurheartj/ehaa190. ehaa190.
16. Acute Kidney Injury in Patients Hospitalized with COVID-19 study. https://clinicaltrials.gov/ct2/show/NCT04316299?recrs=e&cond=COVID19&draw=2&rank=2 Accessed 01 April 2020.
17. WHO: Severe Acute Respiratory Infections Treatment Centre: Practical manual to set up and manage a SARI treatment centre and a SARI screening facility in health care facilities. https://apps.who.int/iris/rest/bitstreams/1273270/retrieve Accessed 30 March 2020.
18. National Health Commission of the People's Republic of China. *Potential Treatments for COVID-19*; 2020. http://en.nhc.gov.cn/2020-03/19/c_77977.htm. Accessed March 18, 2020.
19. ICMR Recommendation for empiric use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact =8&ved=2ahUKEwjcvMqzpMToAhXEfH0KHS9tCJcQFjAAegQIAhAB&url=https%3 A%2F%2Ficmr.nic.in%2Fsites%2Fdefault%2Ffiles%2Fupload_documents%2FHCQ_Recommendation_22March_final_MM.pdf&usg=AOvVaw2x2JJ3yMp21njj9Opfir-q; Accessed 31 March 2020.
20. Government of India Ministry of Health & Family Welfare Directorate General of Health Services (EMR Division). Guidelines on Clinical Management of COVID – 19 dated 17th March 2020. https://www.aiims.edu/images/pdf/notice/Guidelines%20Clinical%20Management%20C OVID19-23-3-20.pdf Accessed 25 March 2020.
21. Spanish Society of Hospital Pharmacy (SEFH) - Hospital pharmacy procedures for the management of antiviral treatment in the new coronavirus SARS-CoV-2 disease (COVID-19). https://www.eahp.eu/sites/default/files/hospital_pharmacy_procedures_covid-19_march19th.pdf Accessed 23 March 2020.
22. EAHP: COVID-19 Resource Centre. https://www.eahp.eu/hp-practice/hospitalpharmacy/eahp-covid-19-resource-centre Accessed 23 March 2020.
23. Centers for disease control and prevention: Information for Clinicians on Therapeutic Options for COVID-19 Patients. https://www.cdc.gov/coronavirus/2019ncov/hcp/therapeutic-options.html Accessed 30 March 2020.
24. NIH US National Library of Medicine clinical trial database. https://clinicaltrials.gov/ct2/results?cond=covid&Search=Apply&recrs=e&age_v=&gndr=&type=Intr&rslt= Accessed 23 May 2020.
25. FDA Emergency Use Authorization (EUA) information and list of all current EUAs. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-andpolicy-framework/emergency-use-authorization Accessed 23 May 2020.
26. Favipiravir. https://www.drugbank.ca/drugs/DB12466 Accessed 26 March 2020.
27. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antivir Res*. 2013;100:446–454. https://doi.org/10.1016/j.antiviral.2013.09.015.

28. Madelain V, Mentré F, Baize S, et al. Modeling favipiravir antiviral efficacy against emerging viruses: from animal studies to clinical trials. *CPT Pharm Syst Pharmacol*. 2020;9:258–271. https://doi.org/10.1002/psp4.12510.
29. Dong L, Hu Shasha, Gao Jianjun. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Dis & Ther*. 2020;14:58–60.
30. Delang L, Rana Abdelnabi, Neyts Johan. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. *Antivir Res*. 2018;153:85–94. https://doi.org/10.1016/j.antiviral.2018.03.003.
31. Potential treatments for COVID-19. https://covid-19. chinadaily.com.cn/a/202003/19/WS5e72e741a3101282172806a4.html Accessed 26 March 2020.
32. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering*. 2020. https://doi.org/10.1016/j.eng.2020.03.007.
33. News: Zhejiang Hisun shows positive effect of Favipiravir on COVID-19. https://www.biospectrumasia.com/news/25/15639/zhejiang-hisun-shows-positive-effectof-favipiravir-on-covid-19.html Accessed 26 March 2020.
34. VigiAccess: Uppsala Monitoring Centre. http://www.vigiaccess.org/Accessed 02 April 2020.
35. NIH US National Library of Medicine clinical trial database. https://clinicaltrials.gov/ct2/results?cond=COVID&term=favipiravir&cntry=&state=&city=&dist= Accessed 23 May 2020.
36. News: Glenmark begins Phase-3 clinical trials on antiviral drug Favipiravir for COVID-19 patients in India. https://www.thehindu.com/news/national/glenmark-begins-phase-3-clinical-trials-on-antiviral-drug-favipiravir-for-covid-19-patients-in-india/article31563198.ece Accessed 25 May 2020.
37. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-Chloroquine. [Updated 2017 Feb 2]. https://www.ncbi.nlm.nih.gov/books/NBK548224/.
38. Li C, Zhu X, Ji X, et al. Chloroquine, a FDA-approved drug, prevents Zika virus infection and its associated congenital microcephaly in mice. *EBioMed*. 2017;24:189-94. https://doi.org/10.1016/j.ebiom.2017.09.034.
39. Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. *Lancet Inf Dis*. 2006;6:67–69. https://doi.org/10.1016/S1473-3099(06)70361-9.
40. Keyaerts E, Li S, Vijgen L, et al. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. *Antimic Agents Chemo*. 2009;53:3416–3421. https://doi.org/10.1128/AAC.01509-08.
41. Kono M, Tatsumi K, Imai AM, Saito K, Kuriyama T, Shirasawa H. Inhibition of human coronavirus 229E infection in human epithelial lung cells (L132) by chloroquine: involvement of p38 MAPK and ERK. *Antivir Res*. 2008;77:150–152. https://doi.org/10.1016/j.antiviral.2007.10.011.
42. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2:69. https://doi.org/10.1186/1743-422X-2-69.
43. Keyaerts E, Vijgen L, Maes P, Neyts J, Ranst MV. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochem Biophys Res Commun*. 2004;323:264–268. https://doi.org/10.1016/j.bbrc.2004.08.085.
44. Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Phar Sinica B*. 2020. https://doi.org/10.1016/j.apsb.2020.02.008.
45. Zhang S, Yi C, Li C, et al. Chloroquine inhibits endosomal viral RNA release and autophagy-dependent viral replication and effectively prevents maternal to fetal transmission of Zika virus. *Antivir Res*. 2019;169:104547. https://doi.org/10.1016/j.antiviral.2019.104547.
46. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020. https://doi.org/10.1016/j.ijantimicag.2020.105932.
47. Multicenter collaboration group of department of science and technology of Guangdong province and health commission of Guangdong province for chloroquine in the treatment of novel coronavirus pneumonia [Abstract only] *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;43:E019. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.0019.
48. Gao J, Tian Z, Breakthrough Yang X. Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72-73. https://doi.org/10.5582/bst.2020.01047.
49. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF, American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology*. 2016;123:1386-1394. https://doi.org/10.1016/j.ophtha.2016.01.058.
50. Cost of Chloroquine. https://www.medindia.net/drug-price/chloroquine.htm Accessed 28 March 2020.
51. NIH US National Library of Medicine clinical trial database. https://clinicaltrials.gov/ct2/results?cond=COVID&term=chloroquine&cntry=&state=&city=&dist= Accessed 23 May 2020.
52. Hydroxychloroquine. https://www.drugbank.ca/drugs/DB01611#reference-L12609 Accessed 28 March 2020.
53. Plaquenil-Hydroxychloroquine sulfate 200mg Film-coated Tablets-EMC. https://www.medicines.org.uk/emc/product/1764/smpc Accessed 28 March 2020.
54. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6. https://doi.org/10.1038/s41421-020-0156-0.
55. Yao X, Ye Fei, Zhang M, et al. In Vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Inf Dis*. 2020. https://doi.org/10.1093/cid/ciaa237.
56. Christophe B, Daher W, Chavain N, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *J Med Chem*. 2006;49:2845–2849. https://doi.org/10.1021/jm0601856.
57. Ministry of Health and Family Welfare: Latest Updates. https://www.mohfw.gov.in/pdf/RevisedadvisoryontheuseofhydroxychloroquineasprophylaxisforSARSCOVID19infection.pdf Accessed 23 May 2020.
58. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with Covid-19. *medRxiv*. 2020. https://doi.org/10.1101/2020.04.16.20065920.
59. Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *The lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)31180-6.
60. NCBI Bookshelf, Drug information on Hydroxychloroquine. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK548738/.
61. Hydroxychloroquine cost. https://www.1mg.com/search/all?name=Hydroxychloroquine&filter=true&sort=price_lo w&state=1&scroll_id=odjRRlodmFNZvpJrS2xOcypvZaqT75iETCzgmbbJMjY= Accessed 02 April 2020.
62. NIH US National Library of Medicine clinical trial database. https://clinicaltrials.gov/ct2/results?cond=COVID&term=hydroxychloroquine&cntry=&state=&city=&dist= Accessed 23.05.2020.
63. News by Christopher Rowland, on March 23, 2020, As Trump touts an unproven coronavirus treatment; supplies evaporate for patients who need those drugs. https://www.washingtonpost.com/business/2020/03/20/hospitals-doctors-are-wiping-outsupplies-an-unproven-coronavirus-treatment/Accessed 01 April 2020.
64. News by Kimberly Hickok. *Husband and Wife Poison Themselves Trying to Self-Medicate with Chloroquine*; 2020. https://www.livescience.com/coronavirus-chloroquine-self-medicationkills-man.html. Accessed March 31, 2020.
65. Gautret P, Lagier JC, Parola P, et al. *Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial*. Inter J of Antimicr Agents; 2020. https://doi.org/10.1016/j.ijantimicag.2020.105949.
66. Remdesivir. https://www.drugbank.ca/drugs/DB14761 Accessed 29 March 2020.
67. Timothy PS, Sims Amy C, Leist Sarah R, et al. Comparative therapeutic efficacy of Remdesivir and combination lopinavir, Ritonavir, and interferon beta against MERS-CoV. *Nat Commun*. 2020;11:222. https://doi.org/10.1038/s41467-019-13940-6.
68. Tchesnokov EP, Feng JY, Porter DP, Götte M. Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. *Viruses*. 2019;11:326. https://doi.org/10.3390/v11040326.
69. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio*. 2018;9. https://doi.org/10.1128/mBio.00221-18. e00221-18.
70. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med*. 2017;9, eaal3653. https://doi.org/10.1126/scitranslmed.aal3653.
71. de Wit Emmie, Feldmann F, Cronin J, et al. Prophylactic and therapeutic Remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *PNAS*. 2020;117:6771–6776. https://doi.org/10.1073/pnas.1922083117.
72. Lo MK, Jordan R, Arvey A, et al. *GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses*7. Scientific reports; 2017. https://doi.org/10.1038/srep43395.
73. Elfiky AA. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study [published online ahead of print, 2020 Mar 25]. *Life Sci*. 2020;253:117592. https://doi.org/10.1016/j.lfs.2020.117592.
74. Abby Olena report on Remdesivir Works Against Coronaviruses in the Lab: The antiviral disables RNA replication machinery in MERS and SARS viruses. Can it beat back SARS-CoV-2?. https://www.the-scientist.com/news-opinion/remdesivir-works-greatagainst-coronaviruses-in-the-lab-67298. Accessed 29 March 2020.
75. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med*. 2020;382:929-36. https://doi.org/10.1056/NEJMoa2001191.
76. News by Suryatapa Bhattacharya, The Wall Street Journal Updated March 17, 2020 10:30 am Experimental Drug Helps Some Americans Ride Out Coronavirus, NIH Doctor Says. https://www.wsj.com/articles/experimental-drug-helps-some-americans-ride-outcoronavirus-nih-doctor-says-11584094955?mod=pls_whats_news_us_business_f Accessed 29 March 2020.
77. International Pharmaceutical Federation. FIP Health Advisory COVID-19: Clinical Information And Treatment Guidelines, Updated 26 March 2020. www.fip.org/coronavirus.
78. Assessment of Evidence for COVID-19-Related Treatments: Updated 3/27/2020 https://www.ashp.org/-/media/assets/pharmacy-practice/resourcecenters/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx?

la=en&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C Accessed 01 April 2020.
79. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395:1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9.
80. Cost of Remdesivir. https://www.fiercepharma.com/pharma/gilead-ceo-pledgesaffordable-remdesivir-as-promising-covid-19-drug-expects-clinical-data Accessed 31 March 2020.
81. NIH US National Library of Medicine clinical trial database https://clinicaltrials.gov/ct2/results?cond=COVID&term=remdesivir&cntry=&state=&city=&dist= Accessed 23 May 2020.
82. Lopinavir, Ritonavir. https://www.drugbank.ca/unearth/q?utf8=%E2%9C%93&query=lopinavir%2Fritonivir&searcher=drugs Accessed 02 April 2020.
83. Han W, Quan B, Guo Y, et al. The course of clinical diagnosis and treatment of a case infected with coronavirus disease 2019. *J Med Virol*. 2020;92:461-63. https://doi.org/10.1002/jmv.25711.
84. Chen Q, Quan B, Li X, et al. A report of clinical diagnosis and treatment of nine cases of coronavirus disease. Short Communication *J Med Virol*. 2020;92:683–687. https://doi.org/10.1002/jmv.25755.
85. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19. *N Engl J Med*. 2020;382:1787-99. https://doi.org/10.1056/NEJMoa2001282.
86. *Lopinavir-Ritonavir Cost*; 2020. https://sastimedicine.com/salt-alternatives/162992634021/Lopinavir-200mg-2B-Ritonavir-50mg-Price-Dosage-Side-Effects-and-GenericAlternatives-its-cost. Accessed April 1, 2020.
87. NIH US National Library of Medicine clinical trial database. https://clinicaltrials.gov/ct2/results?cond=COVID&term=lopinavir-ritonavir&cntry=&state=&city=&dist= Accessed 23 May 2020.
88. Te HS, Randall G, Jensen DM. Mechanism of action of ribavirin in the treatment of chronic hepatitis C. *Gastroenterol Hepatol (N Y)*. 2007;3(3):218-225.
89. Compound Summary: Ribavirin. https://pubchem.ncbi.nlm.nih.gov/compound/Ribavirin Accessed 23 May 2020.
90. Ribavirin. https://www.drugbank.ca/drugs/DB00811 Accessed 23 May 2020.
91. Vincent CCC, Susanna KPL, Patrick CYW, Kwok YY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clin Micro Rev*. 2007;20:660–694. https://doi.org/10.1128/CMR.00023-07.
92. Ning Q, Brown D, Parodo J, et al. Ribavirin inhibits viral-induced macrophage production of TNG, IL-1, the procoagulant fgl2 prothrombinase and preserves Th1 cytokine production but inhibits Th2 cytokine response. *J Immunol*. 1998;60:3487–3493.
93. Sun D, Li H, Lu X, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr*. 2020. https://doi.org/10.1007/s12519-020-00354-4.
94. Kenneth WT, Pak LH, Gaik CO, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1977–1985. https://doi.org/10.1056/NEJMoa030666.
95. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater toronto area. *JAMA*. 2003;289:2801–2809. https://doi.org/10.1001/jama.289.21.JOC30885.
96. Leong HN, Ang B, Earnest A, Teoh C, Xu W, Leo YS. Investigational use of ribavirin in the treatment of severe acute respiratory syndrome, Singapore, 2003. *Trop Med Int Health*. 2004;9:923–927. https://doi.org/10.1111/j.1365-3156.2004.01281.x.
97. Peiris JSM, Chu CM, Cheng VCC, Chan KS, Hung IFN, Poon LLM. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet (London, England)*. 2003;361:1767–1772. https://doi.org/10.1016/s01406736(03)13412-5.
98. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Cli Infec Dis*. 2020;70:1837–1844. https://doi.org/10.1093/cid/ciz544.
99. *Ribavirin Cost*; 2020. https://www.1mg.com/search/all?name=Ribavirin+&st=Ribaverin%20&sl=Ribavirin&s= Ribavirin. Accessed April 1, 2020.
100. *NIH US National Library of Medicine Clinical Trial Database*; 2020. https://clinicaltrials.gov/ct2/show/NCT04276688?term=RIBAVIRIN&cond=Covid19&draw=2&rank=1. Accessed April 1, 2020.
101. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial [published online ahead of print, 2020 May 8]. *Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)31042-4. S0140-6736(20)31042-31044.
102. Ivermectin. https://www.drugbank.ca/drugs/DB00602 Accessed 25 May 2020.
103. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antivir Res*. 2020;178. https://doi.org/10.1016/j.antiviral.2020.104787.
104. Raza Sohail, Shahin Farzana, Zhai Wenjun. Ivermectin inhibits bovine herpesvirus 1 DNA polymerase nuclear import and interferes with viral replication. *Microorganisms*. 2020;8:409. https://doi.org/10.3390/microorganisms8030409.
105. Lv C, Liu W, Wang B, et al. *I*vermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo. *Antivir Res*. 2018;159:55-62. https://doi.org/10.1016/j.antiviral.2018.09.010.
106. Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. *medRxiv preprint*. 2020. https://doi.org/10.1101/2020.04.11.20061804.
107. NIH US National Library of Medicine clinical trial database. https://clinicaltrials.gov/ct2/results?cond=COVID+19&term=ivermectin&cntry=&state=&city=&dist= Accessed 26 May 2020.
108. Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. *J Infect Public Health*. 2016;9(3):227-230. https://doi.org/10.1016/j.jiph.2016.04.001.
109. Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antivir Res*. 2014;110:94-103. https://doi.org/10.1016/j.antiviral.2014.07.014.
110. Pepperrell T, Pilkington V, Owen A, Wang J, Hill AM. Review of safety and minimum pricing of nitazoxanide for potential treatment of COVID-19. *J Virus Erad*. 2020;6(2):52–60. Published 2020 Apr 30.
111. WHO Director-General's opening remarks at the media briefing on COVID-19 - 25 May 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—25-may-2020 Accessed 26 May 2020.