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Review Article

A Review on various promising antivirals for management of COVID 19 & Comparison of Regimens of Antivirals in various Treatment guidelines for Management of Covid-19 across the world

[1]Muhammed Rashid A.K, [2]Jimcy Mathew

[1]Inpatient Pharmacist, Sheikh Shakbouth Medical City (SSMC) Hospital
[2]Inpatient Pharmacist, Danat Al Emarat Hospital, Abu Dhabi, United Arab Emirates

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ABSTRACT

An acute respiratory disease, caused by a novel coronavirus SARS-CoV-2 (COVID-19) has spread from Wuhan city of China and received worldwide attention. On 30 January 2020, World Health Organization (WHO) officially declared the COVID-19 as a PANDEMIC. The emergence of SARS-CoV-2, since the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, marked the third introduction of a highly pathogenic and large-scale epidemic coronavirus into the human population in the twenty-first century. In this article, we are discussing about various promising antivirals showing potential effect in COVID 19 management worldwide.

Keywords: COVID-19 Antivirals, SARS-COV2 Antivirals, Antivirals used in management of COVID-19,Covid-19 treatment guidelines

INTRODUCTION

Several independent research groups have identified that SARS-CoV-2 belongs to β-coronavirus, with identical genome to bat coronavirus, pointing to bat as the natural host. The novel coronavirus uses the same receptor, angiotensin-converting enzyme 2 (ACE2) as that for SARS-CoV, and mainly spreads through the respiratory tract. Importantly, increasingly evidence showed sustained human-to-human transmission, along with many exported cases across the globe. The clinical symptoms of COVID-19 patients include fever, cough, fatigue and a small population of patients appeared gastrointestinal infection symptoms. The elderly and people with underlying diseases are susceptible to infection and prone to serious outcomes, which may be associated with acute respiratory distress syndrome (ARDS) and cytokine storm. Currently, there are few specific antiviral strategies, but several potent candidates of antivirals and repurposed drugs are under urgent investigation. In this review, we summarized various promising antivirals used in the treatment and management of COVID-19.[1]

Address for Correspondence: Muhammed Rashid A.K, Inpatient Pharmacist, Sheikh Shakbouth Medical City (SSMC) Hospital, Abu Dhabi, United Arab Emirates

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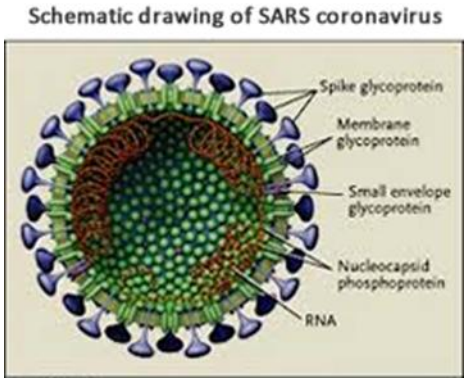
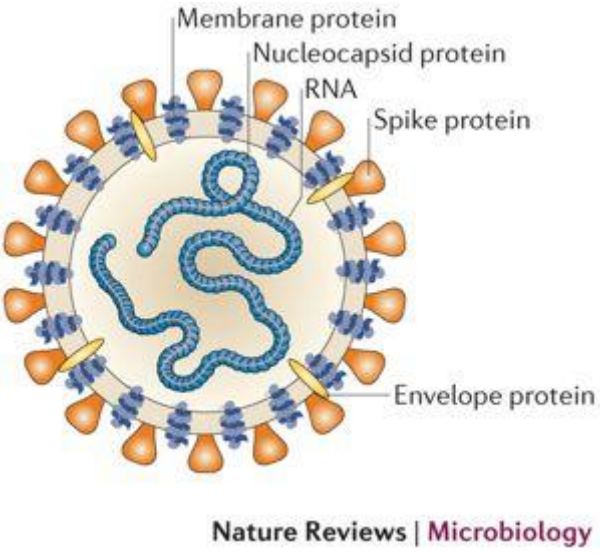
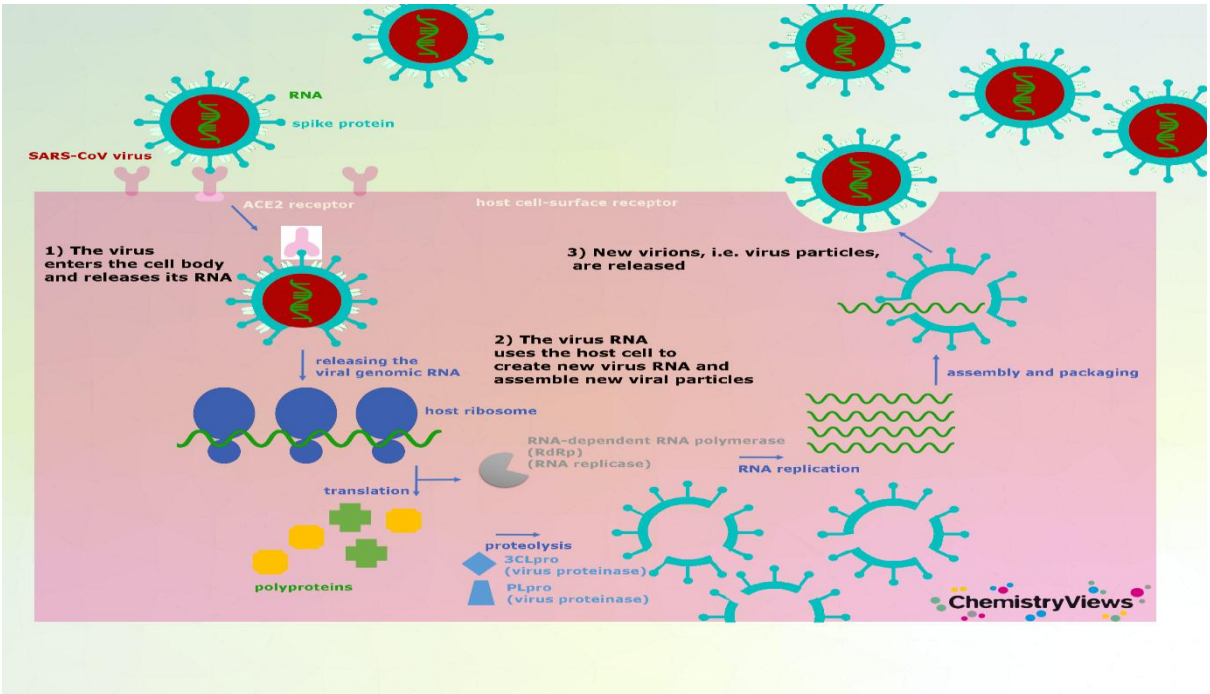
STRUCTURE

Like other coronaviruses, SARS-CoV-2 particles are spherical and have proteins known as spikes protrusive from their surface. These spikes latch onto human cells, then endure a structural amendment that enables the microorganism membrane to fuse with the semipermeable membrane. The microorganism genes will then enter the host cell and genome is copied and multiplies to new multiple viruses. Recent work shows that, just like the virus that caused the 2002 severe acute respiratory syndrome irruption, SARS-CoV-2 spikes bind to receptors on the human cell surface known as angiotensin-converting catalyst two (ACE2).



The researchers used a method, cryo-electron microscopy to require careful pictures of the structure of the spike protein. This involves freezing virus particles and firing a stream of high-energy electrons through the sample to form tens of thousands of pictures. These images are then combined to yield a close 3D view of the virus.[2]





Molecular Biology: The SARS-CoV-2 could be a β-coronavirus, that is enveloped non-segmented positive-sense RNA virus (subgenus sarbecovirus, Orthocoronavirinae subfamily). Coronaviruses (CoV) are divided into four genera, together with α−/β−/γ−/δ-CoV. α- and β-CoV are able to infect mammals, and whereas tend to infect birds. Previously, six CoVs are known as human-susceptible virus, among that α-CoVs HCoV-229E and HCoV-NL63, and β-CoVs HCoV-HKU1 and HCoV-OC43 with low pathogenicity, cause mild respiratory symptoms almost like a

common cold, respectively. Other 2 known β-CoVs, SARS-CoV and MERS-CoV result in severe and probably fatal Respiratory tract infections.

Genome sequence of SARS-CoV-2 is found to be 96.2% identical to a bat CoV RaTG13, whereas it shares 79.5% identity to SARS-CoV, supported virus genome sequencing results and evolutionary analysis, bat has been suspected as natural host of virus origin, and SARS-CoV-2 can be transmitted from bats via unknown intermediate hosts to infect humans.

It's clear currently thatSARS-CoV-2 might use (ACE2), a similar receptor as SARS-CoV. The researchers found that the severe acute respiratory syndrome-CoV-2 spike was ten to twenty times additional likely to bind ACE2 on human cells than the spike from the SARS virus from 2002. This might alter SARS-CoV-2 to unfold additional chance to infect from person to person than the previous virus.

Despite similarities in sequence and structure between the spikes of the 2 viruses, 3 totally different antibodies against the 2002 severe acute respiratory syndrome virus (SARS VIRUS) couldn't successfully bind to the SARS-CoV-2 spike protein. This means that potential vaccine and antibody-based treatment methods can ought to be distinctive to the new virus and it'll take a minimum of one year to come back out vaccine against this deadly virus as per expert opinion.[3,4,1]

ANTIVIRAL TREATMENTS

Various research teams and countries are working on measures to prevent the pandemic through discovering and identifying effective treatment or prophylactic agents are crucial. Several existing approved antivirals and similar agents has been using for other infection and connected altern ative infection are selected by several analysis team s to ascertain if it's effective against covid-19. Several agents are tried with some effectiveness to COVID-19 in humans, however principally through case reports or preliminary information from clinical trials with little sample sizes. Several on-going randomised controlled trials are presently being conducted to further ensure these results. With the joint effort of the healthcare professionals and the scientific community worldwide, new proof for managing COVID-19 is anticipated to be discovered shortly. In this article, we are discussing various agents tried by different research groups and medical teams across the world and those with promising positive results are mainly discussed in this article. Based on the experience of fighting the epidemic SARS-CoV and MERS-CoV previously, we may learn some lessons for some treatment strategies against coronavirus. Antiviral drugs and systemic corticosteroid treatment commonly used in clinical practice previously, including neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, etc), ganciclovir, acyclovir, and ribavirin, as well as methylprednisolone for influenza virus, are invalid for COVID-19 and not recommended.

Remdesivir: Remedesavir is a adenosine nucleotide analogue and has broad spectrum of antiviral activity and mechanism of action is by inhibiting RNA dependent RNA polymerase (RdRps).Originally developed by Gilead sciences for the treatment of Ebola virus and Marburg virus infections this medication causes premature termination of RNA Transcription and thereby inhibit viral replication.

A recent InVitro study demonstrated that RDV potentially inhibited viral replication and reduced viral loads in mice infected with SARS –CoV2 and improved pulmonary function. Holshuetal demonstrated clinical improvement of symptoms in patient infected with Covid-19 in US after treatment with Remedisavir.Several randomised control has been conducted by many research group to confirm the efficacy and safety of RDV in patients with COVID-19.

In February 2020 two phase-3 clinical trials are startedin china in patients with mild/moderate symptoms (NCT04252664) or severe (NCT04257656) covid-19 infection. Remedesavir was given in a dose of 200mg on day 1 and 100mg once daily for 9 days vs placebo. Results of the study is about to be released. Another three international Phase III trials were started in U.S and Asia in hospitalised adult patients infected with Covid-19.

NCT04280705- RDV 200 mg on day 1 and 100 mg once daily up to a 10 days course vs. placebo.

NCT04292730-patients with moderate COVID-19 are given RDV 200 mg on day 1 and 100 mg once daily for 4 days vs. RDV 200 mg on day 1 and 100 mg once daily for 9 days,.

NCT04292899-patients with severe COVID-19 were given RDV 200 mg on day 1 and 100 mg once daily for 4 days vs. RDV 200 mg on day 1 and 100 mg once daily for 9 days. Two of this study is expected to be completed in May 2020.

In phase-, III clinical trial of remedisavir is showing promising results and preliminary results showed that 50% of patients with covid-19 treated with remedisavir were improved and more than half were discharged from hospital within two weeks.

From these studies Remdesivir, is seems to have more promising future. This drug has shown in vitro and in animals a high capacity to block infection and viral replication with attainable concentrations in human plasma.[5,6]

Chloroquine and Hydroxychloroquine (HCQ): Hydroxychloroquine (HCQ) and Chloroquine (CQ) are belonging to chemical group aminoquinolines. These two drugs have been used to treat malaria and autoimmune diseases for over 50 years. These are weak diprotic bases and that elevate the pH of the endosome, which prevents viral fusion and entry in to the cell.

Chloroquine is a repurposed drug with great potential to treat COVID-19., and the mechanism of action is not well understood.
Several mechanism of action that can be possible is proposed:

1. Anti-viral and anti-inflammatory activities of chloroquine may have a role in the treatment of patients with novel COVID-19.
2. Chloroquine can raise endosomal pH and interferes with the glycosylation of cellular receptor of SARSCoV and thereby it has the potential to block viral infection.
3. In addition, chloroquine also inhibits the Quinone reductase-2, which is involved in sialic acid biosynthesis (an acidic monosaccharides of cell transmembrane proteins required for ligand recognition) that makes this agent a broad antiviral agent.

Human coronavirus, HCoV-O43 use sialic acid moieties as a receptor. Moreover, chloroquine changes the pH of lysosomes and likely inhibits cathepsins, results in formation of the auto phagosome which cleaves SARS-CoV-2 spike protein. Recent researches on a combination ofremdesivir with chloroquine found to be effectively inhibit the recently emerged SARS-CoV-2 in vitro.

There was a study conducted in china with sample size of more than 100 covid patient with chloroquine 500mg twice daily it was found that chloroquine is effective in reducing duration of symptoms, exacerbation of pneumonia and chest X and -ray .The detailed result is still not come and need to be conducted with big sample size.Based on the study National Health Commission of the People's Republic of China recommended to include chloroquine also in the gudelines for Treatment of covid-19.

Another study which was conducted in France, Gautretetalused Hydroxychloroquine alone and in combination with azithromycin and found that both the combination and alone effective in reducing nasopharyngeal viral load in 3-6 days in covid 19 subjects when compared to control. After 6 days, viral clearance of HCQ vs control was 70% versus 12.5% respectively. The study was an open label, nonrandomized trial and the outcome was measured by polymerase chain reaction (PCR).

Virological clearance at day-6 post-inclusion in HCQ plus azithromycin, HCQ and control arm was 100%, 57.1% and 12.5% respectively ($p<0.001$).From these data they concluded that there is synergistic effect of azithromycin with HCQ. Hydroxy chloroquine was given in a dose of 200mg Tid for 10 days and azithromycin was given 500mg on day one and 1250 mg once daily for 4 days.Eventhough these studies found to be promising most of these are conducted with small sample size, small group further studies larger trials needed to verify and confirm the efficacy.

One post exposure study with Hydroxychloroquin is under evaluation in U.S using a dose of 800mg once followed by 600mg in 6-8 hr and then 600mg once a day for 4 consecutive days. The results of this study are little bit lesspromising as they find some sudden deaths with cardiac symptoms in corona patients in the study group. Based on these FDA cautions against use of hydroxychlorquinand chloroquine for covid patient outside of the hospital setting due to risk of heart rhythm problems and close supervision is recommended.

Chloroquine and HCQ were used as a treatment option by many countries in absence of any other valid treatment option. Also the low cost of chloroquine and HCQ was also a reason to consider it as a strategy to counter COVID-19. Currently considering the risk- benefit ratio of chloroquine and Hydroxochloroquin, its no longer used as a treatment option across the world.[7,8]

Lopinavir/Ritonavir: Antiretroviral protease inhibitor Lopinavir /Ritonavir combination has been used for the treatment of HIV (AIDS) since 2000.RTV act as pharmacokinetic enhancer and it increase the half-life of LPV by inhibiting cytochrome 450.This combination has been tested for SARS –CoV-1 and MERS-CoV-1 and gave promising results and probable mechanism of action is by inhibiting viral 3-chymotrypsin-like protease (3CLpro).

A randomise ,controlled ,open label study was initiated by LOTUS china trial to study about the efficacy and safety of LPV/RTV given orally to patients infected with SARS –CoV-2 in adult patient admitted in hospital set up. A total of 199 patients with laboratory-confirmed SARS-CoV-2 infection underwent randomization; 99 were

assigned to the lopinavir-ritonavir group, and 100 to the standard-care group. Patients were randomised in a ratio of 1:1 and LPV/RTV (400mg/100mg) was given orally twice daily in addition to standard care or standard care alone for 14 days. There was not much clinical improvent among two groups and mortality rate after 28 days is similier in both the groups. Based on this study author of the study concluded that there is not much benefit

In another study LPV/RTV was started from day 8(day 10 of illness) in patients infected with covid-19 in a dose of two tablets orally two times a day ((lopinavir 200 mg/ritonavir 50 mg. It was observed that viral load was observed from the next day of the LPV/RTV drug administration.
More data is needed to confirm the efficacy of LPV/RTV in treatment of covid-19 as there is a possibility that the decrease in viral load may be due to natural healing process rather than the effect of drug and should be ruled out by conducting trial with bigger population.[9]

Interferon [12,10]
Interferons(IFN) are heterogeneous group of proteins capable of inhibition of viral replication in human cells and it was discovered in 1957.Viruses multiply inside the cell by decreasing level of interferons naturally produced inside the cells and thus interferons can limit the replication of virus inside the cells.

Tong *et al* in1997 demonstrated that Type 1 interferon (alpha/beta) is effective in treatment of hepatitis C virus and it has been in use for that purpose since then *Sperber* and *Hayden* demonstrated that interferons were effective against human corona virus 229E that causes a mild upper respiratory tract infection. Interferons alfa and beta has tested for its effect against SARS covidInVitro and interferon beta has shown potent activity to inhibit viral replication of MERS-Cov.

Loutfvetal, 2003 used Interferon alfacon1 along with cortecosteroids in a pilot study recently to test potential clinical benefit and safety in patients infected with SARS CoV. Based on the study they concluded that it was safe and suggested a therapeutic benefit .Interferon alfacon 1 ha invitro ability to to inhibit the SARS COV replication invitro and further investigations are needed to demonstrate the mechanisms to use as potential therapeutic agent against SARS Cov.[12,10]

Tocilizumab[10,11]
Interleukin (IL)-6 was reported to be released significantly in SARS and MERS patients and would possibly have a role in the pathologic process of those diseases. A recent report on the clinical options of COVID-19 patients additionally found higher plasma levels of cytokines in patients ICU patients. Tocilizumab is a recombinant humanized monoclonal antibody that acts as IL-6 receptor antagonist, and has been used in the treatment of autoimmune disorders like Rheumatoid arthritis.One of the study conducted in china in 21 patients infected with Covid-19 given Toclizumab 400mg once through IV infusion and and 3 patients has another dose due to continued fever. It was observed that 75 % patients had lowered need of oxygen supplement and 19 patients discharged on average 13.5 ± 3.1 days hospitalisation after treatment with Toclizumab.

It has been demonstrated that Toclizumab effectively improved clinical symptoms and prevent further deterioration of Covid -19 patients with severe symptoms. US FDA has given approval for Phase III clinical trial of Toclizumab for evaluating the efficacy of Covid-19 patients with severe pneumonia.(NCT04320615).Another IL-6 receptor antagonist sarlizumab also entered Phase II/III clinical trial to evaluate its efficacy in patients with severe COVID-19 infection (NCT04315298).[10,11]

Ivermectin: Ivermectin is an FDA-approved broad spectrum anti-parasitic agent1 have shown to have anti-viral activity against a broad range of viruses in vitro in recent years along with other groups,. Studies of Ivermectin against HIV (human immunodeficiency virus-1) identified that it inhibit IN nuclear import and HIV-1 replication.

Studies on SARS-CoV proteins have revealed a potential role for IMPα/β1 during infection in signal-dependent nucleocytoplasmic shutting of the SARS-CoVNucleocapsid protein16-18 that may impact host cell division. In addition, the SARS-CoV accessory protein ORF6 has been shown to antagonize the antiviral activity of the STAT1 transcription factor by sequestering IMPα/β1 on the rough ER/Golgi membrane. SARS-CoV-2 is very closely related to the SARS-CoV and these two factors taken together suggested that Ivermectinmight be effective in the treatment of Covid-19 due to its nuclear transport inhibitory activity.

An Invitro study conducted in Australia with cells infected with SARS –CoV-2 and samples were treated with ivermectinafter 3 days there was a reduction in 93% viral RNA compared to the vehicle DMSO.

Cells infected with SARS-CoV-2 were treated with serial dilutions of ivermectin 2 h post infection to additional verify the effectiveness of ivemectin, and supernatant and cell pellets collected for real-

time RT-PCR at 48 h (Fig. 1C/D). .As above, a >5000 reduction in viral RNA was ascertained in each supernatant and cell pellets from samples treated with five µM ivermectin at forty-eight h, equating to a 99.98% reduction in viral RNA in these samples. Again, no toxicity was ascertained with ivermectin at any of the concentrations tested.

Based on these results of invitro activity of Ivermectin against SARS-CoV-2 researchers hypothesis that Ivermectin is likely to act through inhibition of IMPα/β1-mediated nuclear import of viral proteins. Further studies are going on for confirmation of the mechanism of inhibition and to identify the specific SARS-CoV-2 and host component impacted. Ivermectin could be possible promising antiviral agent to limit viral load, prevent severe disease progression and limit person to person.[13]

Favipiravir

Favipiravir (FPV) is a guanosine analogue that selectively inhibits RNA dependent RNA enzyme (RdRP) of RNA viruses and has been approved for the treatment of novel influenza since 2014. In vitro study showed inhibition of SARS-CoV-2 by favipiravir.

Cai et al conducted an open label, controlled study, examine the effects of FPV by giving 1600 mg twice daily on day 1 and 600 mg twice daily on days 2–14) versus LPV/RTV (400 mg/100 mg twice daily. They also gave , in addition to interferon-α1b 60 mg twice daily by inhalation for the treatment of COVID-19. The preliminary results reported significant clinical differences between FPV (35 patients) and LPV/RTV (45 patients) with median viral clearance time (4 days vs. 11 days, $p<0.001$) and chest image improvement rate (91.43% vs. 62.22%, $p=0.004$).
Wang et al recently, reported from. His studies and showed that both FPV and remdesivir are effective in reducing the SARS-CoV-2 infection in vitro .

Haizheng Pharmaceutical Co., conducted studies, FPV (200 mg per tablet) was given orally in a dose 1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2−14 and LPV/RTV (AbbVie Inc., 200 mg/50 mg per tablet were given orally in a dose 400 mg/RTV 100 mg twice daily. Both FPV and LPV/RTV were continued until the viral clearance was confirmed or until 14 dys had passed. In addition, all participants received IFN-α1b 60 µg (Beijing Tri-Prime Gene Pharmaceutical Co., 30 µg per ampule) twice daily by aerosol inhalation. Standard care included oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, and antiemetic drugs.

From 30 January 56 patients with laboratory-confirmed COVID-19 were screened, of which 35 were eligible for the FPV arm of the study. A total of 91 laboratory-confirmed COVID-19 patients who had started treatment with LPV/RTV between 24 January and 30 January 2020 were screened, of which 45 were eligible for the control arm of this study. All enrolled patients finished the therapy and were followed up for 14 d after the treatment began. All the baseline characteristics were compared between the FPV arm and the control. There were no significant differences between the baseline characteristics of the two arms.

The current study also found that early viral clearance contributed to the improvement of chest imaging on Day 14. This finding suggests that improvement of the disease may depend on inhibition of the SARS-CoV-2, and that FPV controls the disease progression of COVID-19 by inhibiting the SARS-CoV.

Study investigated the effect of FPV versus LPV/RTV on the treatment of COVID-19. It was found that FPV was independently associated with faster viral clearance and a higher improvement rate in chest imaging. Faviperavir is now included in treatment plan of covid in many countries.[15,16]

Camostat Mesylate

Camostat is a serine antiviral agent and is approved in japan for treatment of chronic pancreatitis and postoperative reflux esophagitis. Researchers are attempting to repurpose this drug for treatment of covid-19 because of its proteolytic enzyme repressing action that shall be targeted to stop viruscellentry.

A team of German virology, genomic and pharmaceutical scientists at the leibniz Institute for Primate research has identified CamostatMesylate (trade name: Foipan) might be effective against SARS-CoV-2 coronavirus. The new analysis initially started with understanding the entry of the SARS-CoV-2 coronavirus into the human host cells and to develop a method to block it. Dr Markus Hoffmann, PhD, researcher within the Infection Biology Unit of the German Primate Center, leibniz Institute for Primate analysis, Göttingen, germany and 1st author of the paper told Thailand Medical News, "We found that SARS-CoV-2, like SARS-CoV, uses the host proteins ACE2 and TMPRSS2 to enter cells. each coronaviruses ought to so infect similar cells inpatients and should cause disease via similar mechanisms."SARS-CoV-2 exploits the cell entry receptor protein angiotensin converting enzyme II (ACE-2) to access and infect human cells. The interaction between ACE2 and also the spike protein isn't within the site.

This process needs the serine proteolytic enzyme TMPRSS2.

Camostat Mesilate may be a potent serine antiviral agent. Utilizing research on severe acute respiratory syndrome coronavirus (SARS-CoV) and also the closely connected SARS-CoV-2 cell entry mechanism, it's been incontestable that SARS-CoV-2 cellular entry is blocked by camostat mesilate. In mice, mesilate treated at concentrations like the clinically accomplishable concentration in humans reduced mortality following SARS-CoVinfection from 100% to 30-35%. A trial involves giving2x100 mg pills three times daily for five days with 185 participants goes on sponsored by University of Arhus.[14]

Comparison of covid-19 antivirals in Various treatment guidelines.

COVID-19 Treatment Guidelines-NIH, US[17]

Last Updated: November 3, 2020

Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19.

Drug Name	Dosing Regimen	Monitoring Parameters
Chloroquine	Dose Previously Suggested in an EUA for Adults and Adolescents Weighing ≥50 kg: CQ 1 g PO once on Day 1, then CQ 500 mg PO once daily for 4–7 days of total treatment. Treatment duration should be based on clinical evaluation	CBC, hepatic panel, blood glucose, SCr, potassium, magnesium Baseline ECG Follow-up ECG if CQ is given with QTc-prolonging drugs or if the patient has underlying cardiac disease
Hydroxychloroquine	Adults: Various loading and maintenance doses have been reported in studies or in clinical care. Dose Previously Suggested in an EUA for Hospitalized Adults and Adolescents Weighing ≥50 kg: HCQ 800 mg PO once on Day 1, then HCQ 400 mg PO once daily for 4–7 days of total treatment. Treatment duration shouldbe based on clinical evaluation.	CBC, hepatic panel, blood glucose, SCr, potassium, magnesium Baseline ECG Follow-up ECG if HCQ is given with QTc-prolonging drugs (e.g., AZM) or if the patient has underlying cardiac disease
Lopinavir/Ritonavir	Adults: LPV 400 mg/RTV 100 mg PO twice daily for 10–14 days Neonates Aged ≥14 Days with a PMA ≥42 Weeks and Children Aged <18 Years: LPV 300 mg/m2 plus RTV 75 mg/m2 (maximum dose: LPV 400 mg/RTV 100 mg) PO twice daily for a total of 7 days	HIV antigen/antibody testing at baseline Serum transaminase levels Consider monitoring ECG when LPV/RTV is given with other QTc-prolonging medications.
Remdesivir Note: RDV is FDA approved for the treatment of COVID-19.	For Hospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg) For Patients Who Are Not Mechanically Ventilated and/or on ECMO: RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 5 In patients who have not shown clinical improvement after 5 days of therapy, treatment may be extended up to 10 days. For Mechanically Ventilated Patients	infusion reactions Renal function, hepatic function, and prothrombin time should be monitored before and during treatment as clinically indicated Not recommended if eGFR is <30 mL/min RDV may need to be discontinued if ALT levels increase to >10 times the ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.3

	and/or Patients on ECMO: RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 10 Suggested Dose in EUAa for Hospitalized Pediatric Patients Weighing 3.5 kg to <40 kg or Aged <12 Years and Weighing ≥3.5 kg For Patients Weighing 3.5 kg to <40 kg: RDV 5 mg/kg IV over 30–120 minutes on Day 1, followed by RDV 2.5 mg/kg once daily starting on Day 2 For patients who are not mechanically ventilated and/or on ECMO, the recommended treatment duration is 5 days. If patients have not shown clinical improvement after 5 days of therapy, treatment may be extended up to 10 days. For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days. For Patients Aged <12 Years and Weighing ≥40 kg: Same dose as for adults and children aged >12 years and weighing >40 kg	

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial **(AI)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

- The Panel **recommends against** using **lopinavir/ritonavir(AI)** or **other HIV protease inhibitors (AIII)** to treat COVID-19, except in a clinical trial.
- Ivermectin -The Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

National Guidelines for clinical Managment and Treatment of Covid-19-UAE
April 19th, 2020 Version 3[18]

Confirmed COVID19 **URTI without Pneumonia For 5 Days**	Hydroxychloroquine 400mg PO BID x2 doses, followed by 200mg PO BID OR Chloroquine Phosphate 500 mg PO BID OR Lopinavir-Ritonavir (200/ 50 mg) 2 tablets PO BID [7] (If patient cannot be monitored to give 500mg BID day 1 then 250mg BID for 4 days) Consider addition of Camostat 100 mg po TID if available
Confirmed COVID19 **Pneumonia For 7 days**	Hydroxychloroquine 400mg po BID, then 200mg po BID + Favipiravir1600 mg PO BID on day 1, then 600 mg PO BID from day 2 OR Chloroquine Phosphate 500 mg PO BID + Favipiravir 1600

	mg PO BID on day1, then 600 mg po BID from day2 OR Lopinavir-Ritonavir (200/ 50 mg) 2 tablets PO BID [7] + Hydroxychloroquine 400 mg po BID X 2 doses, then 200 mg PO BID (alternatively Chloroquine 500 mg PO BID X 2 doses, followed by 250 mg POBID) OR Remdesivir 200 mg IV on day 1, followed by 100 mg IV daily [8,15] Consider addition of Camostat 100 mg po TID if available
Confirmed COVID19 **Severe Pneumonia /Critically ILL patients** **For 10 days**	• Hydroxychloroquine 400mg PO X 2 doses followed by 200mg po BID + Favipiravir1600 mg PO BID on day 1, then 600 mg PO BID from day 2 ORChloroquine Phosphate 500 mg PO BID + Favipiravir 1600 mg PO BID on day1, then 600 mg po BID from day2 ORKaletra (Lopinavir-Ritonavir 200/50) 2 tablets PO BID to the above regimen -CASE BY CASE BASIS ORRemdesivir 200 mg IV on day 1, followed by 100 mg IV daily. Consider adding *Tocilizumab 4-8 mg/kg (max 800mg) IV x 2 dose in case of cytokine storm (see below indication) if available.

Covid -19 Interim Treatment guideline line -kerala-India[19]
Categories

A	Mild sorethroat,cough,rhinitis,diarrhoea
B	Fever and/or severe sorethroat,cough OR CATEGORY-A plus two or more of the following Lung, Heart, Liver, Kidney, neurological disease, hypertension, haemtological disorder, uncontrolled diabetes, cancer, HIV-AIDS On long term steroids Pregnant ladies Age more than 60 OR cardiological disorders.
C	Breathlessness, chest pain, drowsiness, fall in blood pressure, haemotypsis,cyanosis. Children with ILI(Influenza like Illness)Red Flag Signs Worsening of underlying chronic conditions.

	Treatment Strategies according to clinical conditions	
Category	**Treatment**	**Precautions**
A	**Symptomatic treatment**	Categorization should be reassessed every 28-48 hours for Category A
B	1.Tab HCQ 400mg 1-0-1x 1day followed by 200mg 1-0-1 for 4 days. Children:(6.25mg/kg)dose PO BID day 1 followed by 3.25mg/kg dose PO BID X 4 days. OR 1.Tab .Chloroquine base 600mg(10mg/kg) at diagnosis and 300mg (5mg/kg)12h later followed by 300mg (5mg/kg) BD upto 5 days. PLUS Tab .Azithromycin 500mg 1-0-0 1 day and 250mg 1-0-0 x 4days. Children:10mg/kg(max 500mg) day 1 followed by 5mg/kg /day on days 2 to 5. 3. TabOseltamivir 75mg 1-0-1 in all symptomatic patients with influenza like illness until PCR	Contraindications to chloroquine/HCQS. QTC>50msec, Porphyria, Myastheniagravis,Retinalpathology,Epilepsy. Pregnancy is NOT a contraindication. If baseline QT is prolonged, frequent ECG monitoring is required.

	report.Children:3mg/kg/dose BD.Dose adjustment required for all renal insufficiency cases.	
C	1.Tab HCQ 400mg 1-0-1x 1day followed by 200mg 1-0-1 for 4 days.Children:(6.25mg/kg)dose PO BID day 1 followed by 3.25mg/kg dose PO BID X 4 days. OR 1.Tab .Chloroquine base 600mg(10mg/kg) at diagnosis and 300mg (5mg/kg)12h later followed by 300mg (5mg/kg) BD upto 5 days PLUSInj.Azithromycin 500mg IV STAT and 250mg IV OD for 5days.Children:5mg/kg (max 500mg) on DAY 1 followed by 5mg/kg/day on days 2 to 5. 2.Tab.Lopinavir/Ritonavir (400/100)1-0-1 for 14 days or for7 days after becoming asymptomatic. Children 14 daysto 6 months:16mg/kg(based on lopinavircompontent)PO BD; <15kg:12mg/kgPO(based on lopinavir component BD) 15-25kg:200mg-50mg PO BD ; 26-35kg:300mg-75mg PO BD ;>35kg: 400mg-100mg PO BD Lopinavir/Ritonavir is to be used only if HCQS/chloroquine is contraindicated.It should be used only on a compassionate ground after informed consent.It has to be started within 10 days of symptom onset.	For chloroqiune and derivatives, as discussed above.For protease inhibitors, assessdrg-drug interactions before starting. Monitor liver function test.Discontinue these agents upon discharge regardless of duration**.**

China's National Health Commission Guidelines for COVID-19[22]

Novel Coronavirus Treatment Guidelines – 7th Edition

Antiviral therapy: Hospitals can try Following

Alpha-interferon (5 million U or equivalent dose each time for adults, adding 2ml of sterilized water, atomization inhalation twice daily.

lopinavir/ritonavir (200 mg/50mg per pill for adults, two pills each time, twice daily, no longer than 10 days),

Ribavirin (suggested to be used jointly with interferon or lopinavir/ritonavir, 500 mg each time for adults, twice or three times of intravenous injection daily, no longer than 10 days).

Chloroquine phosphate (500 mg bid for 7 days for adults aged 18-65 with body weight over 50 kg; 500 mg bid for Days 1&2 and 500 mg qidfor Days 3-7 for adults with body weight below 50 kg).

Arbidol (200 mg tid for adults, no longer than 10 days).

Be aware of the adverse reactions, contraindications (for example, chloroquine cannot be used for patients with heart diseases) and interactions of the abovementioned drugs. Further evaluate the efficacy of those drugs currently being used. Using three or more antiviral drugs at the same time is not recommend; if an intolerable toxic side effect occurs, the respective drug should be discontinued. For the treatment of pregnant women, issues such as the number of gestational weeks, choice of drugs having the least impact on the fetus, as well as whether pregnancy is terminated before treatment should be considered with patients being informed of these considerations.

Antibiotic drug treatment: Blind or inappropriate use of antibiotic drugs should be avoided, especially in combination with broad-spectrum antibiotics.

COVID 19 THERAPEUTIC PROTOCOL-Italy [23]

COVID-19 positive patient with asymptomatic or mild symptoms: (Fever (> 37.5 ° C), cough, cold symptoms without dyspnoea), age <70 years and without risk factors (COPD, diabetes and heart disease) and X-ray negative chestVolume-up - Clinical observation, supportive therapy.

Patient positive for COVID-19 with mild respiratory symptoms but aged> 70 years and / or with risk factors (COPD, diabetes and heart disease) or symptomatic or with mild symptoms (Fever (> 37.5 ° C), cough, dyspnea

lopinavir / ritonavir cps 200/50 mg, 2 x 2 / day (alternatively darunavir 800 mg 1 cp / day + ritonavir 100 mg 1 cp / day or darunavir / cobicistat 800/150 mg 1 cp / day), + chloroquine 500 mg , 1 x 2 / day or hydroxychloroquinecp 200 mg, 1 x 2 /

day. Duration of therapy: from 5 to 20 days, with timing to be established according to clinical evolution.

In case of need for oxygen therapy or rapid clinical deterioration, (see paragraph "supportive measures" and COVID respiratory severity scale) request Remdesivir for compassionate use. At the time of its availability, suspend LPV / RTV (or DRV / b) and continue with:

Remdesivir 150 mg vials: 1 day 200 mg iv in 30 minutes then 100 mg iv / day for a further 9 days in combination with **chloroquine 500** mg, 1 x 2 / day or **hydroxychloroquine 200 mg**, 1 x 2 / day (duration of therapy: from 5 to 20 days, with timing to be established according to clinical evolution).

If patient has BCRSS score ³2 evaluate**dexamethasone 20 mg / day** for 5 daysthen 10 mg / day for 5 days (on intensive care indication) and / or **tocilizumab** (see specific paragraph on page 11)

COVID-19 positive patient with severe pneumonia, ARDS or global respiratory failure, haemodynamic decompensation, need for mechanical (or non-invasive) ventilation:

Remdesivir1 day 200 mg IV as a loading dose, then 100 mg / day iv (days 2-10) + chloroquine 500 mg, 1 x 2 / day or hydroxychloroquine 200 mg x 2 via SNG (duration of therapy: 5 to 20 days, with timing to be established according to clinical evolution).

Until remdesivir is available, start therapy with LPV / RTV 5 mL x 2 / day (or alternatively DRV / r oral suspension or crushed and dispersed DRV / c) via SNG + hydroxychloroquine 200 mg x 2 via SNG.

ARDS patients: 24 hours after the diagnosis of ARDS: dexamethasone 20 mg / day for 5 days then 10 mg / day for 5 days (according to intensive care) and / or tocilizumab

Drug interactions and drug shortages- The Working Group recommends that full attention to be paid to possible pharmacokinetic interactions, particularly of lopinavir / ritonavir with other drug classes. In case of concomitant intake of other drugs, the working group recommends consulting the website: http://www.covid19-druginteractions.org/

Patient type	**Clinical presentation**	**Supportive and immunomodulatory treatment**	**Antiviral treatment**	**notes**
Asymptomatic patient		None - surveillance	None	
Patient with mild respiratory symptoms	Fever (> 37.5 ° C), cough, cold symptoms without dyspnoea	Symptomatic treatment	None	
Patient with mild respiratory symptoms but age> 70 years and / or presence of comorbidities or risk of increased mortality **- Patient with moderate respiratory symptoms and / or chest x-ray with pneumonia**	Fever (> 37.5 ° C), cough, mild to moderate dyspnoea	Symptomatic treatment - O2 therapy If patient BCRSS score ³2 Evaluate: dexamethasone 20 mg / day for 5 daysthen 10 mg / day for 5 days (on intensive indication). and / or Tocilizumab (see specific paragraph on page 11)	**Lopinavir / ritonavir** 200/50 mg 2 cp BID + Chloroquine 500 mg BID for 20 days OR Hydroxychloroquine 200 mg BID Alternative regimen to lopinavir / ritonavir: darunavir 800 mg 1 cpQD + ritonavir 100 mg 1 cp QD or darunavir / cobicistat 800/150 mg QD(duration of	if oxygen therapy is required it may be reasonable to request Remdesivir (see Patient with severe symptoms

			treatment from 5 to 20 days, with duration to be established according to clinical evolution	
Patient with severe symptoms	ARDS or global respiratory failure, haemodynamic decompensation	Necessary resuscitation evaluation and transfer to intensive care. ARDS patients: 24 hours after the diagnosis of ARDS: dexamethasone 20 mg / day for 5 days then 10 mg / day for 5 days (on intensive indication) and / or Tocilizumab (see specific paragraph on page 11)	**Remdesivir** (if available) first day loading dose of 200 mg / ev followed by a maintenance dose of 100 mg / ev / day from day 2 to day 10 + Chloroquine or Hydroxychloroquine (see above) Or Lopinavir / ritonavir (see above) + Chloroquine or hydroxychloroquine (see above) Alternative to lopinavir / ritonavir: darunavir + ritonavir or darunavir / cobicistat (see above	

Antivirals, immunomodulatory and other adjunctive therapies for COVID-19 –WHO interim guidelines.[21]

WHO interim guidelines recommend that the following drugs not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials:

• Chloroquine and hydroxychloroquine (+/- azithromycin), including but not limited to: • Antivirals, including but not limited to: Lopinavir/ritonavir Remdesivir Umifenovir Favipiravir • Immunomodulators, including but not limited to: Tocilizumab Interferonβ-1a • Plasma therapy.

Remarks:

1. Existing published literature on the agents listed above is mostly observational in nature, with few clinical trials; and does not provide high-quality evidence in favour of any of these agents. In addition, important side-effects have been described (122-131). • Chloroquine and hydroxychloroquine +/- azithromycin: each can cause QT prolongation and taken together can increase the risk of cardiotoxicity. • Lopinavir/ritonavir: the most common adverse effects are gastrointestinal. • Remdesivir: elevation of hepatic enzymes, GI complications, rash, renal impairment and hypotension. • Umifenovir: diarrhoea, nausea. • Favipiravir: QT interval prolongation. • Interferon-β-1a: pyrexia, rhabdomyolysis. • Tocilizumab: URT infections, nasopharyngitis, headache, hypertension, increased alanine aminotransferase (ALT), injection site reactions.

2. This recommendation has not changed and is consistent with previous WHO guidance documents and other international grade-based guidelines (132).

3. Outside of clinical trials, the following criteria should be met for access to investigational therapeutics:

1) no proven effective treatment exists; 2) it is not possible to initiate clinical studies immediately; 3) data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favourable risk–benefit analysis; 4) the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use; 5) adequate resources are available to ensure that risks can be minimized; 6) the patient's informed consent is obtained; and 7) the emergency use of the intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community

DISCUSSION & CONCLUSION

The current approach in the research of covidantivirals include using the existing antivirals and repurposing the drugs already approved and used for other similar conditions as they already passed animal toxicity studies and human trials. Numerous potential therapies, including supportive intervention, immunomodulatory agents, antiviral therapy, and convalescent plasma transfusion, have been used in clinical practice. Antiviral drugs and systemic corticosteroid treatment commonly used in clinical practice previously, including neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, etc), ganciclovir, acyclovir, and ribavirin, as well as methylprednisolone for influenza virus, are invalid for COVID-19 and not recommended.

Hydroxy chloroquine and chloroquine were included in the treatment plans of most of the countries based on the successful inhibition of the covid 19 virus initial Invitro studies and also clinical trials in small experimental groups. Early reports from China and France suggested that patients with severe symptoms of COVID-19 improved more quickly when given chloroquine or hydroxychloroquine.Trials in big groups are still going on and there is caution from some researchers including FDA that these drugs can cause QT prolongation and sudden cardiac arrest. Close monitoring of the patients is recommended while the patient is on therapy. Moreover, due to all these facts currently chloroquine and hydroxychloroquine are no longer considered as a better treatment strategies.

Lopinavir/Ritonavir also included in most of the treatment guideline as it is found to be giving good result based on the available initial clinical data. Many healthcare facilities started giving favipiravir as this also shown clinical improvement in experimental groups. Camostatmesylate and certulizimab has been in use by many clinicians across the world as they shown giving some clinical benefits and improves the patient conditions.

The antiviral drug remdesivir was FDA approved in October 2020 to treat certain hospitalized patients with COVID-19. Clinical trials suggest that in these patients, remdesivir may modestly speed up recovery time.

The Solidarity Trial published interim results on 15 October 2020. It found that all 4 treatments evaluated (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients.[24]

Existing published literature on the agents listed above is mostly observational in nature, with few clinical trials; and does not provide high-quality evidence in favour of any of these agents as per WHO.As the research, investigation are continuing ,clinical trials in big study groups are still needed further to releasea comprehensive treatment guidelines and protocol from WHO.

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