

INVESTIGATIONAL DRUGS: UNMASK THE MYTHS OF COVID-19

*Tanistha Mumtaz Chatterjee, Subham Chakraborty, Dr. Dhruvo Jyoti Sen and Dr. Beduin Mahanti

Department of Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt Lake City, Sector-V, EM-4, Kolkata-700091, West Bengal, India.

*Corresponding Author: Tanistha Mumtaz Chatterjee

Department of Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt Lake City, Sector-V, EM-4, Kolkata-700091, West Bengal, India.

Article Received on 07/05/2020

Article Revised on 28/05/2020

Article Accepted on 18/06/2020

ABSTRACT

COVID-19: Prevention & Investigational Treatments- COVID-19 is the disease caused by an infection of the SARS-CoV-2 virus, first identified in the city of Wuhan, in China's Hubei province in December 2019. COVID-19 was previously known as 2019 Novel Coronavirus (2019-nCoV) respiratory disease before the World Health Organization (WHO) declared the official name as COVID-19 in February 2020. The SARS-CoV-2 virus belongs to the family of viruses called coronaviruses, which also includes the viruses that cause the common cold, and the viruses that cause more serious infections such as severe acute respiratory syndrome (SARS), which was caused by SARS-CoV in 2002, and Middle East respiratory syndrome (MERS), which was caused by MERS-CoV in 2012. Like the other coronaviruses, the SARS-CoV-2 virus primarily causes respiratory tract infections, and the severity of the COVID-19 disease can range from mild to fatal. Serious illness from the infection is caused by the onset of pneumonia and acute respiratory distress syndrome (ARDS). Currently, there are no FDA approved treatments for COVID-19, and the development of vaccines are still in pipeline.

KEYWORDS: Drug profile, efficacy, clinical research, metabolism, interactions, drug-receptor, inflammatory response, immune complexes.

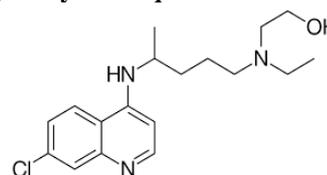
Investigational drug: Hydroxychloroquine (Plaquenil)

Overview: Hydroxychloroquine (HCQ), sold under the brand name **Plaquenil** among others, is a medication used to prevent and treat malaria in areas where malaria remains sensitive to chloroquine. Other uses include treatment of rheumatoid arthritis, lupus and porphyria cutanea tarda. It is taken by mouth. HCQ is being studied to prevent and treat (COVID-19). High-quality evidence of benefit for such use is lacking, with concerns of potential harms from side effects.

Drug profile of plaquenil: Hydroxychloroquine is a racemic mixture consisting of an R and S enantiomer. Hydroxychloroquine is an aminoquinoline like chloroquine. It was developed during World War II as a derivative of quinacrine with less severe side effects. Chloroquine and hydroxychloroquine are both being investigated for the treatment of SARS-CoV-2. Hydroxychloroquine was granted FDA approval on 18 April 1955.

Due to COVID-19, the FDA has issued an emergency use authorization for hydroxychloroquine and chloroquine. This authorization allows for the unapproved use of these medications in light of a public health emergency. A recent study reported a

fatality in the group being treated with hydroxychloroquine for COVID-19.^[1]

Structure of hydroxychloroquine

Chemical formula: C₁₈H₂₆ClN₃O; **IUPAC Name:** 2-[4-[(7-chloroquinolin-4-yl)amino]pentyl-ethylamino]ethanol

The myth around Hydroxychloroquine's efficacy: Whether hydroxychloroquine (HCQ), the controversial anti-malarial drug, can stave off COVID-19 infection will be available by July, a senior scientist of the Indian Council of Medical Research (ICMR). According to ICMR, there are mixed results from all over and the process of establishing efficacy is ongoing. At some point, meta-analysis will be done to examine all studies to determine the effect. In the meantime, the drug is being prescribed with adequate safeguards. This is not an antiviral. It does not kill the virus, only modulates the immune system. The cardiac problems have been

observed when HCQ is given in combination with azithromycin. On the contrary, based on the findings, the scientists said there is no evidence that use of hydroxychloroquine reduced the risk of mechanical ventilation in patients hospitalized with COVID-19. Hydroxychloroquine use with or without co-administration of azithromycin did not improve mortality or reduce the need for mechanical ventilation in hospitalized patients. Early studies done found that HCQ may be the savior which could help millions affected

from the coronavirus infection. In fact, preliminary reports suggested that HCQ helped cut down on the recovery time (Time to Clinical Recovery or TTCR) by shortening the duration of a cold, flu or fever in the body and even absorb pneumonia and promoted improvement in patients with mild to moderate symptoms.^[2]

Comparative antiviral efficacy and mechanism of action of CQ and HCQ against SARS-CoV-2 infection *in-vitro*.

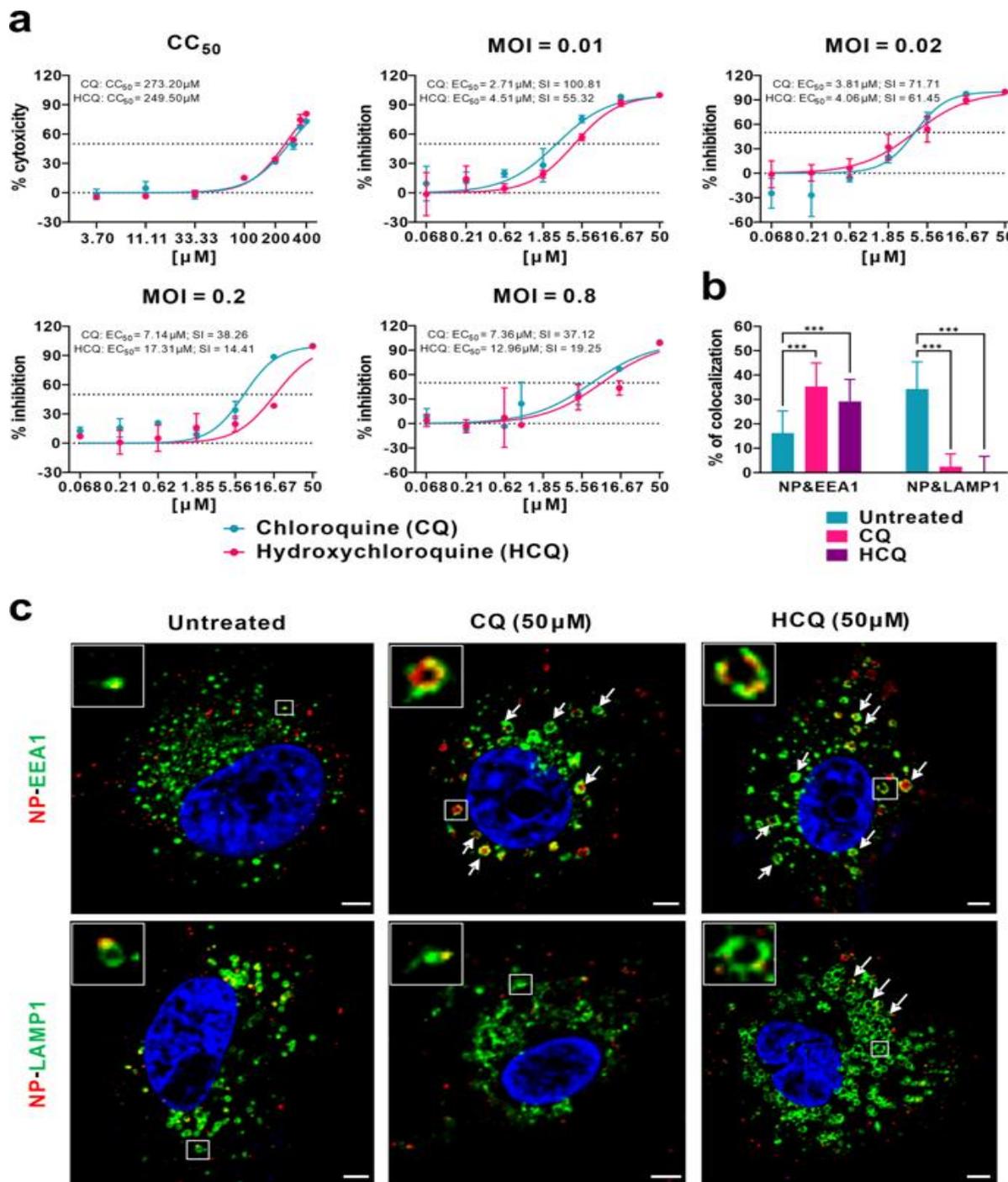


Figure 1: Chloroquine & Hydroxychloroquine mode of action comparative study.

Drug receptor interaction

How the **drug** reacts with the **receptors of Plaquenil** or **Hydroxychloroquine** shows below:

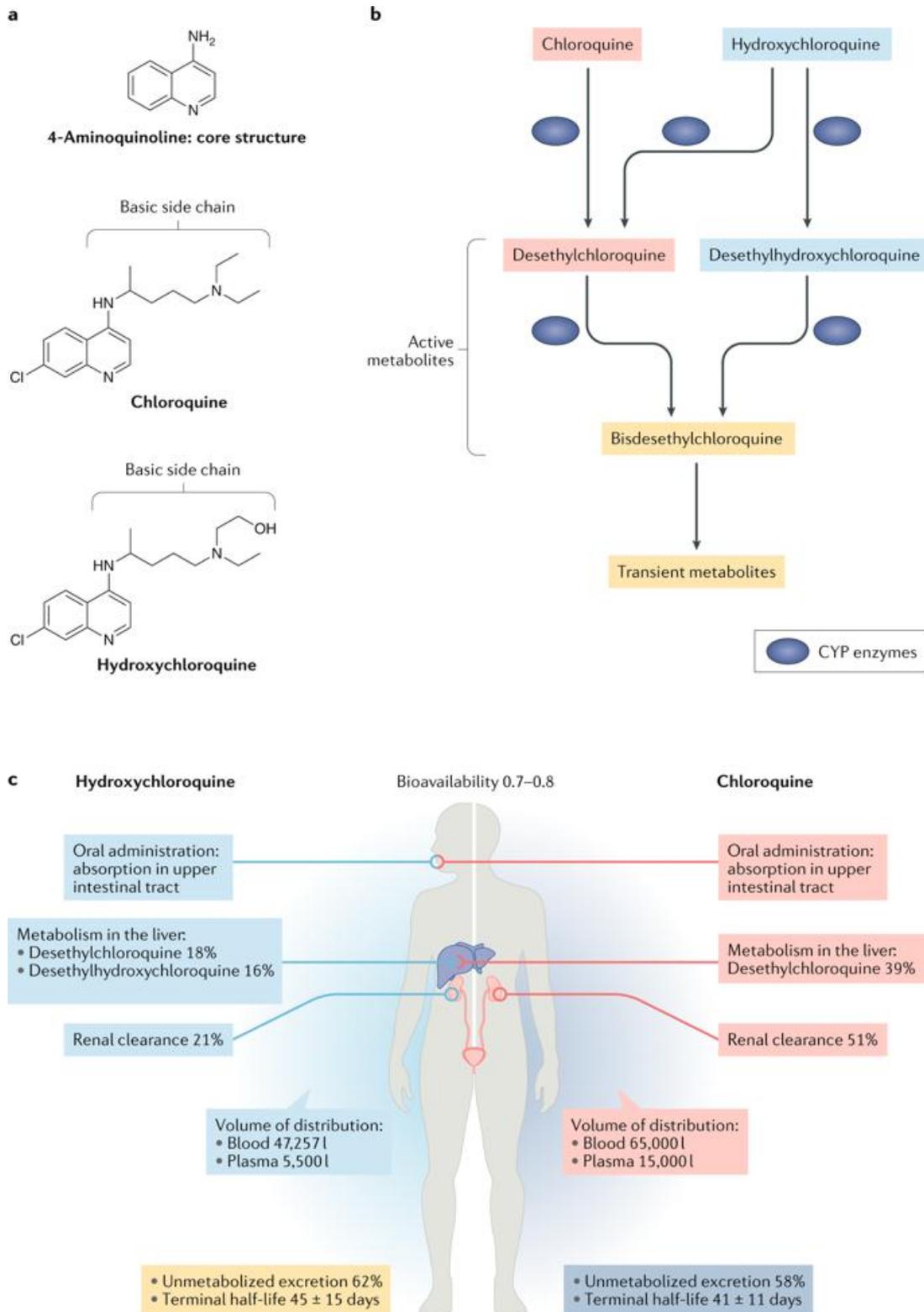


Figure 2: Flowchart of drug with receptor binding.

Pharmacology of plaquenil: Hydroxychloroquine is indicated for the prophylaxis of malaria where chloroquine resistance is not reported, treatment of

uncomplicated malaria (caused by *P. falciparum*, *P. malariae*, *P. ovale*, or *P. vivax*), chronic discoid lupus

erythematosus, systemic lupus erythematosus, acute rheumatoid arthritis, and chronic rheumatoid arthritis.^[3]

Pharmacodynamics: Hydroxychloroquine affects the function of lysosomes in humans as well as plasmodia. Altering the pH of the lysosomes reduces low affinity self-antigen presentation in autoimmune diseases and interferes with the ability of plasmodia to proteolyze hemoglobin for their energy requirements. Hydroxychloroquine has a long duration of action as it may be taken on a weekly basis for some indications. Hydroxychloroquine may lead to severe hypoglycemia and so diabetic patients are advised to monitor their blood glucose levels. Hydroxychloroquine is not effective against malaria in areas where chloroquine resistance has been reported.

Pharmacokinetics: Hydroxychloroquine has similar pharmacokinetics to chloroquine, with rapid gastrointestinal absorption, large distribution volume, and elimination by the kidneys. Cytochrome P450 enzymes (CYP2D6, 2C8, 3A4 and 3A5) metabolize hydroxychloroquine to *N*-desethylhydroxychloroquine. Both agents also inhibit CYP2D6 activity and may interact with other medications that depend on this enzyme.

Mechanism of action: Hydroxychloroquine increases lysosomal pH in antigen-presenting cells. In inflammatory conditions, it blocks toll-like receptors on plasmacytoid dendritic cells. Toll-like receptor 9 (TLR 9), which recognizes DNA-containing immune complexes, leads to the production of interferon and causes the dendritic cells to mature and present antigen to T cells. Hydroxychloroquine, by decreasing TLR signaling, reduces the activation of dendritic cells and the inflammatory process. In 2003, a novel mechanism was described wherein hydroxychloroquine inhibits stimulation of the toll-like receptor (TLR) 9 family receptors. TLRs are cellular receptors for microbial products that induce inflammatory responses through activation of the innate immune system. As with other quinoline antimalarial drugs, the antimalarial mechanism of action of quinine has not been fully resolved. The most accepted model is based on hydrochloroquinine and involves the inhibition of hemozoin biocrystallization, which facilitates the aggregation of cytotoxic heme. Free cytotoxic heme accumulates in the parasites, causing death.

Hydroxychloroquine increases the risk of low blood sugar through several mechanisms. These include decreased clearance of the hormone insulin from the blood, increased insulin sensitivity, and increased release of insulin from the pancreas.^[4]

Metabolism of hydroxychloroquine: The site of metabolism of Hydroxychloroquine is in liver. Hydroxychloroquine (HCQ) and chloroquine (CQ) are well absorbed (0.7-0.8 bioavailability) when given orally. Severe malnutrition (such as kwashiorkor) effects

absorption but diarrhea does not. Both HCQ and CQ have prolonged half-lives, between 40 and 50 days. Protein binding ranges between 30 and 40% with binding to both albumin and alpha₂ glycoprotein. There is differential binding and metabolism of the (R) and (S) stereoisomers. Both drugs bind strongly to pigmented tissues but also bind to mononuclear cells, muscles, etc. There is stereo-selective excretion of both drugs and 40-50% of the drug is excreted renally. Between 21 and 47% is excreted unchanged.

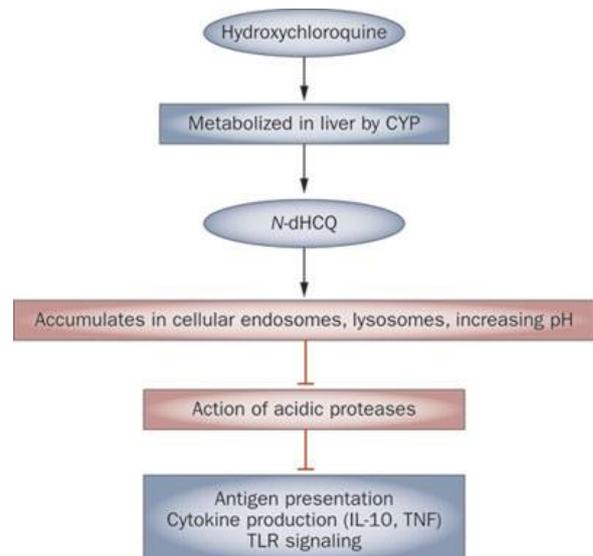


Figure 3: Metabolism of Hydroxychloroquine.

Adverse Effects: Signs of an allergic reaction: hives; difficulty breathing; swelling of your face, lips, tongue, or throat. Taking hydroxychloroquine long-term or at high doses may cause irreversible damage to the retina of your eye. The most common adverse effects are nausea, stomach cramps, and diarrhea. Other common adverse effects include itching and headache. The most serious adverse effects affect the eye, with dose-related retinopathy as a concern even after hydroxychloroquine use is discontinued. Serious reported neuropsychiatric adverse effects of hydroxychloroquine use include agitation, mania, difficulty sleeping, hallucinations, psychosis, catatonia, paranoia, depression, and suicidal thoughts. In rare situations, hydroxychloroquine has been implicated in cases of serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and Drug reaction with eosinophilia and systemic symptoms. Reported blood abnormalities with its use include eosinophilia, and atypical For short-term treatment of acute malaria, adverse effects can include abdominal cramps, diarrhea, heart problems, reduced appetite, headache, nausea and vomiting Other adverse effects noted with short-term use of HCQ include low blood sugar and QT interval prolongation, Idiosyncratic hypersensitivity reactions have occurred.^[5]

The patients confirmed infection with SARS-CoV-2, the virus that causes COVID-19, and be experiencing fever, cough and/or shortness of breath. The investigators

anticipate that many of those enrolled will be 60 years of age or older or have a higher chance associated with developing serious complications from COVID-19, such as cardiovascular disease or diabetes.

Majorly the risk factors arise into the following

QT prolongation
Hypoglycemia
Mild nausea and diarrhea

Serious reported neuropsychiatric adverse effects of hydroxychloroquine use include

Agitation, mania, difficulty sleeping, hallucinations, psychosis, catatonia, paranoia, depression, and suicidal thoughts in rare situations, hydroxychloroquine has been implicated in cases of serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and Drug reaction with eosinophilia and systemic symptoms

Other Risk factors includes

EYES: One of the most serious side effects is retinopathy (generally with chronic use). Toxicity from hydroxychloroquine may be seen in two distinct areas of the eye: the cornea and the macula. The cornea may become affected (relatively commonly) by an innocuous cornea verticillata or vortex keratopathy and is characterized by whorl-like corneal epithelial deposits.

SKIN AND ABDOMINAL PROBLEM: Adverse effects include the acute symptoms, plus altered eye pigmentation, acne, anemia, bleaching of hair, blisters in mouth and eyes, blood disorders, cardiomyopathy, convulsions, vision difficulties, diminished reflexes, emotional changes, excessive coloring of the skin, hearing loss, hives, itching, liver problems or liver failure, loss of hair, muscle paralysis, weakness or atrophy, nightmares, psoriasis, reading difficulties, tinnitus, skin inflammation and scaling, skin rash, vertigo, weight loss, and occasionally urinary incontinence. Hydroxychloroquine can worsen existing cases of both psoriasis and porphyria.

HEART: The heart, they are known to potentially cause liver and kidney problems, nerve cell damage that can lead to seizures (fits) and low blood sugar (hypoglycaemia).^[6]

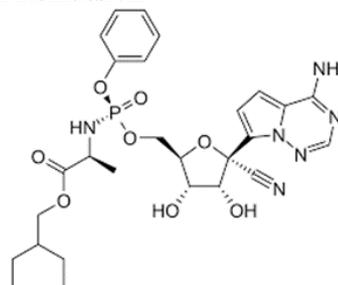
Investigational study of Remdesivir

Overview: Remdesivir is a broad-spectrum antiviral medication developed by the biopharmaceutical company Gilead Sciences. It is administered via injection into a vein. As of 2020, remdesivir is being tested as a specific treatment for COVID-19 and has been authorized for emergency use in the US, India, and approved for use in Japan for people with severe symptoms. It also received approval in the UK in May 2020, however will be rationed due to limited supply. It may shorten the time it takes to recover from the infection. Remdesivir is an investigational drug that has

not been approved by the FDA for any use. It is not yet known if remdesivir is safe and effective for the treatment of COVID-19. The distribution of remdesivir has been authorized only for the treatment of hospitalized patients with severe COVID-19. It is not authorized for the treatment of any other viruses or pathogens.

Drug profile: In January 2020, Gilead began laboratory testing of remdesivir against SARS-CoV-2, stating that remdesivir had been shown to be active against severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in animal models. Remdesivir is an investigational nucleotide analog with broad-spectrum antiviral activity both *in-vitro* and *in-vivo* in animal models against multiple emerging viral pathogens, including Ebola, Marburg, MERS and SARS. In vitro testing conducted by Gilead has demonstrated that remdesivir is active against the virus that causes COVID-19. The safety and efficacy of remdesivir for the treatment of COVID-19 are being evaluated in multiple ongoing Phase 3 clinical trials.^[7]

Structure of Remdesivir



Chemical formula: C₂₇H₃₅N₆O₈P, **IUPAC Name:** (2S)-2-{{(2R,3S,4R,5R)-[5-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxy-tetrahydrofuran-2-ylmethoxy]phenoxy-(S)-phosphorylamino}propionic acid 2-ethyl-butyl ester.

Absorption: A 10mg/kg intravenous dose given to cynomolgus monkeys distributes to the testes, epididymis, eyes, and brain within 4h.

Half-life: A 10mg/kg intravenous dose in non-human primates has a plasma half-life of 0.39h. The nucleoside triphosphate metabolite has a half-life of 14h in non-human primates. The nucleoside triphosphate metabolite has a half-life of approximately 20 hours in humans.

Toxicity: Data regarding overdoses of remdesivir are not readily available. Overdoses of other nucleoside analogs like acyclovir can be managed with symptomatic and supportive treatment.

Affected organisms: SARS-CoV, SARS-CoV-2.

Route of Administration: The majority of pharmacokinetic studies of remdesivir stem from *in vitro*, *in vivo*, and limited clinical studies for the

treatment of Ebola. For the treatment of COVID-19 disease, remdesivir is given as a 200 mg intravenous (IV) injection on Day 1, followed by 100 mg IV on days 2-10. Following IV administration, remdesivir is rapidly converted in plasma to the intermediate metabolite, GS-704277, and to the nucleoside analog, GS-441524. Due to the high first pass hepatic extraction of phosphoramidates and expected low bioavailability, oral administration of remdesivir was not explored.^[8]

Protein Data Bank of Remdesivir: Remdesivir, or GS-5734, is an adenosine triphosphate analog first described in 2016 as a potential treatment for Ebola. In 2017, its activity against the coronavirus family of viruses was also demonstrated. Remdesivir is also being researched as a potential treatment to SARS-CoV-2, the coronavirus responsible for COVID-19. Remdesivir is a nucleoside analogue used to inhibit the action of RNA polymerase. The duration of action is moderate, as it is given once daily. Patients should be counselled regarding the risk of infusion related reactions as well as elevated transaminases. Remdesivir is 74% eliminated in the urine and 18% eliminated in the faeces. 49% of the recovered dose is in the form of the metabolite and 10% is recovered as the unmetabolized parent compound.

Data regarding the protein binding of remdesivir is not readily available.

Mechanism of action: As an adenosine nucleoside triphosphate analog, the active metabolite of remdesivir interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production. In some viruses such as the respiratory syncytial virus it causes the RNA-dependent RNA polymerases to pause, but its predominant effect (as in Ebola) is to induce an irreversible chain termination. Unlike with many other chain terminators, this is not mediated by preventing addition of the immediately subsequent nucleotide, but is instead delayed, occurring after five additional bases have been added to the growing RNA chain. For the RNA-Dependent RNA Polymerase of MERS-CoV, SARS-CoV-1, and SARS-CoV-2 arrest of RNA synthesis occurs after incorporation of three additional nucleotides. Hence, remdesivir is classified as a direct-acting antiviral agent that works as a delayed chain terminator.^[9]

Interaction: To date, there are only limited *in-vitro* transporter and enzyme-mediated drug interaction studies on remdesivir. Remdesivir is a substrate of multiple cytochrome P450 enzymes including CYP2C8, CYP2D6, and CYP3A4, and is also a substrate of the organic anion transporting polypeptide OATP1B1, and P-glycoprotein (P-gp). Remdesivir is also a weak inhibitor of CYP3A4, OATP1B1, OATP1B3, bile acid export pump (BSEP), multidrug resistance associated protein 4 (MRP4), and sodium-taurocholate cotransporter protein (NTCP). However, metabolism of

remdesivir is believed to be mediated predominantly via hydrolases and not CYP enzymes, as noted above. Due to the high extraction ratio of remdesivir, hepatic clearance is likely driven by hepatic blood flow and not metabolic enzyme activity. This, in addition to the short plasma half-life and need for IV administration that avoids hepatic first pass metabolism, likely results in a low potential for drug-drug interactions with the administered drug. This will require further study to determine the full clinical impact of drug-drug interactions with remdesivir therapy.

Metabolism: An adenosine nucleoside triphosphate analogue, the active metabolite of remdesivir viral exoribonuclease (ExoN), causing a decrease in viral RNA production. In some viruses such as the respiratory syncytial virus it causes the RNA-dependent RNA polymerases. For the **RNA-Dependent RNA Polymerase** of MERS-CoV, SARS-CoV-1, and SARS-CoV-2 arrest of RNA synthesis occurs after incorporation of three additional nucleotides. Hence, remdesivir is classified as a direct-acting antiviral agent that works as a delayed chain terminator.

Remdesivir is a ProTide (Prodrug of nucleotide) that is able to diffuse into cells where it is converted to GS-441524 mono-phosphate via the actions of esterase and a phosphoamidase; this in turn is further phosphorylated to its active metabolite triphosphate by nucleoside-phosphate kinases. **Remdesivir drug is at least** partially metabolized by the cytochrome P450 enzymes CYP2C8, CYP2D6, and CYP3A4. Blood plasma concentrations of remdesivir are expected to decrease if it is administered together with cytochrome P450 inducers such as: Rifampicin, Carbamazepine, Phenobarbital, Phenytoin, primidone.

Adverse Effects of Remdesivir: The most common adverse effects in studies of remdesivir for COVID-19 include: Respiratory failure and organ impairment, including low albumin, low potassium, low count of red blood cells, low count of platelets that help with clotting, and yellow discoloration of the skin.

Other reported side effects include gastrointestinal are: Distress, elevated transaminase levels in the blood (liver enzymes), and infusion site reactions.^[10]

Other possible side effects of remdesivir include

Infusion-related reactions. Infusion-related reactions have been seen during a remdesivir infusion or around the time remdesivir was given.

Signs and symptoms of infusion-related reactions may include: low blood pressure, nausea, vomiting, sweating, and shivering.

Increases in levels of liver enzymes, seen in abnormal liver blood tests. Increases in levels of liver enzymes have been seen in people who have received remdesivir,

which may be a sign of inflammation or damage to cells in the liver.

Investigational study of Favipiravir

Favipiravir, sold under the brand name **Avigan**, is an antiviral medication used to treat influenza in Japan. It is also being studied to treat a number of other viral infections. Like the experimental antiviral drugs (T-1105 and T-1106), it is a pyrazine carboxamide derivative. It is being considered to be an effective treatment for covid-19. It is being developed and manufactured by Toyama Chemical (Fujifilm group) and was approved for medical use in Japan in 2014. A study on 80 people in comparison to lopinavir/ritonavir found that it reduced viral clearance time, and that 91% of people had improved CT scans with few side effects. The drug has been approved for use in clinical trials of coronavirus disease 2019 in China. In March 2020, Italy approved the drug for experimental use against COVID-19 and has begun conducting trials in three regions most affected by the disease. The Italian Pharmaceutical Agency, however, has reminded the public that the existing evidence in support of this drug is scant and preliminary. There are plans to study it in three hospitals in Massachusetts, USA as of April 20, 2020. As of early May 2020, a trial is starting in London, UK.^[11]

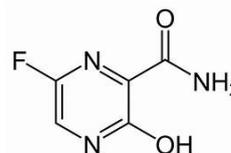
Dosage: 1600 mg/600 mg BID	C _{max} Note2 (µg/mL)	AUC Note2,3 (µg·hr/mL)	T _{max} Note4 (hr)	T _{1/2} Note5 (hr)
	Day1	64.56(28.1)	1.5(0.75,4)	4.8±1.1
	Day 6	64.69(31.9)	1.5(0.75,2)	5.6±2.3

Pharmacodynamics: Favipiravir functions as a prodrug and undergoes ribosylation and phosphorylation intracellularly to become the active favipiravir-RTP. Favipiravir-RTP binds to and inhibits RNA dependent RNA polymerase (RdRp), which ultimately prevents viral transcription and replication.

Mode of action: The mechanism of action of favipiravir is novel compared to existing influenza antivirals that primarily prevent entry and exit of the virus from cells. The active favipiravir-RTP selectively inhibits RNA polymerase and prevents replication of the viral genome. There are several hypotheses as to how favipiravir-RTP interacts with RNA dependent RNA polymerase (RdRp). Some studies have shown that when favipiravir-RTP is incorporated into a nascent RNA strand, it prevents RNA strand elongation and viral proliferation. Studies have also found that the presence of purine can reduce favipiravir's antiviral activity, suggesting competition between favipiravir-RTP and purine nucleosides for RdRp binding. Although favipiravir was originally developed to treat influenza, the RdRp catalytic domain (favipiravir's primary target), is expected to be similar for other RNA viruses. This conserved RdRp catalytic domain contributes to favipiravir's broad-spectrum coverage.^[12]

Absorption: The bioavailability of favipiravir is almost complete at 97.6%. The mean C_{max} for the recommended

Structure



Molecular Formula: C₅H₄FN₃O₂; **IUPAC name:** 5-fluoro-2-oxo-1H-pyrazine-3-carboxamide

Route of administration: The drug is administered orally. Note: 1200 mg + 400 mg on Day 1, then 400 mg twice daily on Days 2 to 6 followed by 400 mg once daily on Day 7. The approved dosage of favipiravir is "1600 mg orally twice daily for 1 day followed by 600 mg orally twice daily for 4 days."

Pharmacokinetics: Blood Concentrations

The following table shows pharmacokinetic parameters of favipiravir after an oral administration in 8 healthy adults at 1600 mg twice daily for 1 day, then 600 mg twice daily for 4 days followed by 600 mg once daily for 1 day (1600 mg/600 mg BID).

dosing schedule of favipiravir is 51.5µg/mL. Studies comparing the pharmacokinetic effects of multiple doses of favipiravir in healthy American and Japanese subjects are below: Japanese subjects First Dose: C_{max}=36.24µg/mL T_{max}=0.5hr AUC=91.40µg·hr/mL. American subjects First Dose: C_{max}=22.01µg/mL T_{max}=0.5hr AUC=44.11µg·hr/mL. Japanese Subjects Final Dose: C_{max}=36.23µg/mL T_{max}=0.5hr AUC=215.05µg·hr/mL. American Subjects Final Dose: C_{max}=23.94µg/mL T_{max}=0.6hr AUC=73.27µg·hr/mL

When favipiravir was given as a single dose of 400 mg with food, the C_{max} decreased. It appears that when favipiravir is given at a higher dose or in multiple doses, irreversible inhibition of aldehyde oxidase (AO) occurs and the effect of food on the C_{max} is lessened.

Protein Data Bank of Favipiravir (Avigan) Drug

Favipiravir is a modified pyrazine analogue that was initially approved for therapeutic use in resistant cases of influenza. The antiviral targets RNA-dependent RNA polymerase (RdRp) enzymes, which are necessary for the transcription and replication of viral genomes. Favipiravir is 54% plasma protein-bound. Of this fraction, 65% is bound to serum albumin and 6.5% is bound to α1-acid glycoprotein.

Drug metabolism of Favipiravir Drug: Favipiravir was not metabolized by cytochrome P-450 (CYP), mostly metabolized by aldehyde oxidase (AO), and partly metabolized to a hydroxylated form by xanthine oxidase (XO). In studies using human liver microsomes, formation of the hydroxylate ranged from 3.98 to 47.6 pmol/mg protein/min, with an inter-individual variation of AO activity by 12 times at maximum. A glucuronate conjugate was observed in human plasma and urine as a metabolite other than the hydroxylated form.^[13]

Excretion: Favipiravir was mainly excreted as a hydroxylated form into the urine, and little amount unchanged drug was observed. In an oral 7-day multiple dose study with 6 healthy adults, cumulative urinary excretion ratio of the unchanged drug and the hydroxylated form was 0.8% and 53.1%, respectively, during 48 hours after the last administration.

Interactions: The antiviral agent favipiravir is likely to be co-prescribed with acetaminophen (paracetamol). The present study evaluated the possibility of a pharmacokinetic interaction between favipiravir and acetaminophen, *in-vitro* and *in-vivo*. Favipiravir inhibits acetaminophen sulfate formation *in-vitro* and *in-vivo*. However, the increase in systemic exposure to acetaminophen due to favipiravir co-administration, though statistically significant, is small in magnitude and unlikely to be of clinical importance. Acetaminophen (paracetamol) plays an important role in treatment of seasonal influenza virus infection. As such, co-administration of favipiravir and acetaminophen is likely to happen in clinical practice. Favipiravir has potent antiviral activities against influenza virus and RNA viruses.

Adverse effects of Favipiravir: There is evidence that use during pregnancy may result in harm to the baby.

Brand name Avigan, and it has shown a great “antiviral” activity against both the influenza type A and type B.

Azithromycin (Azithral)

What antibiotics kill coronavirus? Azithromycin (Zithromax) is a macrolide antibiotic that is being investigated as a potential treatment for people with COVID-19, the disease caused by the new coronavirus (SARS-CoV-2). It is already used for the treatment of community-acquired pneumonia caused by designated, susceptible bacteria, and for the treatment of other bacterial infections. Azithromycin is also thought to have antiviral and anti-inflammatory activity and may work synergistically with other antiviral treatments. In *in-vitro* laboratory studies azithromycin has demonstrated antiviral activity against Zika virus and against rhinoviruses, which cause the common cold.

The current clinical evidence for using azithromycin to treat COVID-19: Interesting results have been reported from a very small clinical trial, which enrolled 20

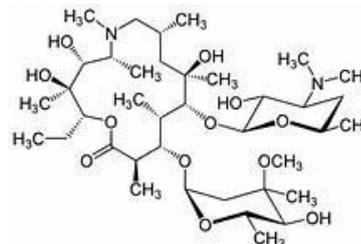
patients with COVID-19 in France. Patients were treated with hydroxychloroquine (Plaquenil) alone or in combination with azithromycin. Viral loads were significantly reduced in patients receiving hydroxychloroquine compared with those who did not receive the treatment. Patients taking hydroxychloroquine also appeared to clear the virus from their system more quickly. Virus elimination was even more efficient in the 6 patients in the trial who received both azithromycin and hydroxychloroquine. However, results from another small trial conducted in 30 patients in China do not back up the results from the trial in France. In the Chinese trial patients did not receive azithromycin, but were treated with hydroxychloroquine or standard care. Unlike in the other trial, treatment with hydroxychloroquine did not appear to reduce viral load or shorten the time to viral elimination.^[14]

Overview: Azithromycin is an antibiotic used for the treatment of a number of bacterial infections. This includes middle ear infections, strep throat, pneumonia, traveler's diarrhea, and certain other intestinal infections. It can also be used for a number of sexually transmitted infections, including chlamydia and gonorrhea infections. Along with other medications, it may also be used for malaria. It can be taken by mouth or intravenously with doses once per day.

Pharmacodynamics: Macrolides stop bacterial growth by inhibiting protein synthesis and translation, treating bacterial infections. Azithromycin has additional immunomodulatory effects and has been used in chronic respiratory inflammatory diseases for this purpose.

Mode of action: In order to replicate, bacteria require a specific process of protein synthesis, enabled by ribosomal proteins. Azithromycin binds to the 23S rRNA of the bacterial 50S ribosomal subunit. It stops bacterial protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit. This results in the control of various bacterial infections. The strong affinity of macrolides, including azithromycin, for bacterial ribosomes, is consistent with their broad-spectrum antibacterial activities. Azithromycin is highly stable at a low pH, giving it a longer serum half-life and increasing its concentrations in tissues compared to erythromycin.^[15]

Chemical structure



Protein Data Bank: In order to replicate, bacteria require a specific process of protein synthesis, enabled by ribosomal proteins. Azithromycin binds to the 23S rRNA of the bacterial 50S ribosomal subunit. It stops bacterial protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit. This results in the control of various bacterial infections. The strong affinity of macrolides, including azithromycin, for bacterial ribosomes, is consistent with their broad-spectrum antibacterial activities.

Azithromycin is highly stable at a low pH, giving it a longer serum half-life and increasing its concentrations in tissues compared to erythromycin. The **serum protein binding** of azithromycin varies in humans, decreasing from **51% at 0.02g/mL to 7% at 2 g/mL**.

Half-life: Terminal elimination half-life: 68 hours.

Clearance: Mean apparent plasma clearance=630 mL/min (following single 500 mg oral and i.v. dose)

Toxicity: Possible major adverse effects include cardiovascular arrhythmias and hearing loss. Macrolide resistance is also an ongoing issue. Hepatotoxicity has been since in rare cases

A note on the risk of liver toxicity: Due to the fact that azithromycin is mainly eliminated by the liver, caution should be observed when azithromycin is given to patients with decreased hepatic function.^[16]

A note on potential renal toxicity: Because limited data in patients with renal GFR <10 mL/min, caution should be exercised when prescribing azithromycin to these patients.

Use in Pregnancy: This drug is categorized as a pregnancy category B drug. Reproduction studies have been done in rats and mice at doses up to moderately maternally toxic doses (for example, 200 mg/kg/day).

Metabolism: *In-vitro* and *in-vivo* studies to assess the metabolism of azithromycin have not been performed, however, this drug is eliminated by the liver. **Azithromycin** prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, thus inhibiting translation of mRNA. Nucleic acid synthesis is not affected. **Azithromycin** is an acid-stable antibiotic, so it can be taken orally with no need of protection from gastric acids. It is readily absorbed, but absorption is greater on an empty stomach. Time to peak concentration (T_{max}) in adults is 2.1 to 3.2 hours for oral dosage forms. Due to its high concentration in phagocytes, azithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations are released. Azithromycin's half-life allows a large single dose to be administered and yet

maintain bacteriostatic levels in the infected tissue for several days. Following a single dose of 500 mg, the apparent terminal elimination half-life of azithromycin is 68 hours.

Adverse effects: Most common adverse effects are diarrhea (5%), nausea (3%), abdominal pain (3%), and vomiting. Fewer than 1% of people stop taking the drug due to side effects. Nervousness, skin reactions, and anaphylaxis have been reported. *Clostridium difficile* infection has been reported with use of azithromycin. Azithromycin does not affect the efficacy of birth control unlike some other antibiotics such as rifampin. Hearing loss has been reported. Occasionally, people have developed cholestasis hepatitis or delirium. Accidental intravenous overdose in an infant caused severe heart block.

CONCLUSION

All examined treatments, although potentially effective against **COVID 19**, need either appropriate drug development or clinical trial to be suitable for clinical use. No specific therapies/vaccine are yet available for the treatment of COVID 19. Nevertheless, while waiting for effective preventive measures i.e., Vaccines, many clinical trials on drugs belonging to different therapeutic classes are currently underway. Their results will help us in defining the best way to treat **COVID 19 and reducing its symptoms and complications**.

REFERENCES

1. Aronson JK Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions. Elsevier, 2015; 261.
2. Callahan MV, et al. "Rethinking the role of hydroxychloroquine in the treatment of COVID-19". *FASEB Journal*, 2020; 34(5): 6027–6037.
3. Schrezenmeier E, Dörner T "Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology". *Nature Reviews. Rheumatology*, 2020; 16(3): 155–166.
4. Siegel, D., Hui, H.C., Doerffler, E., Clarke, M.O., Chun, K., Zhang, L., et al Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. *J Med Chem*, 2017; 60: 1648-1661.
5. Mulangu, S., Dodd, L. E., Davey Jr, R. T., Tshiani Mbaya, O., Proschan, M., Mukadi, D., & Ali, R. A randomized, controlled trial of Ebola virus disease therapeutics. *New England Journal of Medicine*, 2019; 381(24): 2293-230.
6. Hayden FG, Shindo N Influenza virus polymerase inhibitors in clinical development. *Curr Opin Infect Dis.*, 2019; 32(2): 176-186.
7. Jin Z, Smith LK, Rajwanshi VK, Kim B, Deval J "The ambiguous base-pairing and high substrate efficiency of T-705 (Favipiravir) Ribofuranosyl 5'-triphosphate towards influenza A virus polymerase". *PLOS One*, 2013; 8(7): e68347.

8. Baranovich T, Wong SS, Armstrong J, Marjuki H, Webby RJ, Webster RG, Govorkova EA "T-705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro". *Journal of Virology*, 2013; 87(7): 3741–51.
9. Guedj J, Piorkowski G, Jacquot F, Madelain V, Nguyen TH, Rodallec A, et al. "Antiviral efficacy of favipiravir against Ebola virus: A translational study in cynomolgus macaques". *PLOS Medicine*, 2018; 15(3): e1002535.
10. Smee DF, Hurst BL, Egawa H, Takahashi K, Kadota T, Furuta Y "Intracellular metabolism of favipiravir (T-705) in uninfected and influenza A (H5N1) virus-infected cells". *The Journal of Antimicrobial Chemotherapy*, 2009; 64(4): 741–6.
11. Naesens L, Guddat LW, Keough DT, van Kuilenburg AB, Meijer J, Vande Voorde J, Balzarini J "Role of human hypoxanthine guanine phosphoribosyltransferase in activation of the antiviral agent T-705 (favipiravir)". *Molecular Pharmacology*, 2013; 84(4): 615–29.
12. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, Barnard DL, et al. "T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections". *Antiviral Research*, 2009; 82(3): 95–102.
13. Gielen V, Johnston SL, Edwards MR Azithromycin induces anti-viral responses in bronchial epithelial cells. *European Respiratory Journal*, 2010; 36: 646-654.
14. Schogler A, Kopf BS, Edwards MR et al Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells. *European Respiratory Journal*, 2015; 45: 428-439.
15. Wang E, Lew K, Barecki M, Casciano CN, Clement RP, Johnson WW Quantitative distinctions of active site molecular recognition by P-glycoprotein and cytochrome P450 3A4. *Chem Res Toxicol.*, 2001; 14(12): 1596-603.
16. Sparreboom A, Altman RB, Klein TE PharmGKB summary: Macrolide antibiotic pathway, pharmacokinetics/pharmacodynamics. *Pharmacogenet Genomics*, 2017; 27(4): 164-167.