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A systematic search and emerging use of Chloroquine (CQ) and Hydroxychloroquine (HCQ) in the treatment of coronaviruse Disease-2019 (COVID-19)

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ABSTRACT:

The severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) First broke out in Wuhan (China) and subsequently spread worldwide. No drugs are currently approved for COVID-19 although some have been tried. Chloroquine and hydroxychloroquine has been used in treating SARS-COV-2 infection, but it's more tolerable safety profile makes it the preferred drug to treat malaria and autoimmune condition, Clinical safety profile of hydroxychloroquine is better than of chloroquine and fewer concerns about drug-drug interaction. In this we evaluate the role of Hydroxychloroquine on respiratory viral load and other search include clinical pharmacology, usage, precautions, drug-drug interaction and adverse reactions. We propose that the immunomodulatory effect of Hydroxychloroquine also may be useful in controlling the cytokine storm that occurs late phase in critically ill SARS-COV-2 Infected patients.

Considering minimal risk upon user, a long experience of use in other disease, cost effectiveness and easy availability across in India. Since hydroxychloroquine has been also approved for treatment of diabetes in India, it should be further research in diabetes and Coronavirus disease-19 (COVID-19)

KEYWORDs: SARS-COV-2, Chloroquine, Hydroxychloroquine, COVID-19.

INTRODUCTION:

Coronaviruses are eneloped positive sense single- stranded RNA viruses belonging to the family Coronaviridae and are broadly distributed in human and other vertebraes, eventually causing damage in digestive, respiratory and even multiple system. In December 2019, a series of pneumonia cases of unknown etiology appeared in Wuhan, Hubei, china[1]. Sequencing analysis of throat swabs sample and electron microscope observations indicated a novel Coronavirus, which was named SARS-COV-2 (formely known as 2019-nCoV)[2]. On 11th March 2020, The World Health Organization (WHO) declared this disease as pandemic.[3] Chinese centre for disease control and prevention showed an increased mortality in people with diabetes (2.3% Vs 7.3% ; overall Vs. in patient with diabetes respectively) from a report of 72,314 case of COVID-19[4]. People with diabetes and COVID-19 may need special attention and clinical care [5]. As of March 20, 2020 more than two hundred thousand confirmed cases have been identified globally, for a total of 8778 death [6]. As the epidemic is spreading to many countries, COVID-19 poses a severe threat to global health [7]. Therefore, it is urgent to develop effective drugs against COVID-19.

Now a day's many drug have been tried recently in the treatment for COVID-19 that includes a low cost antimalarial drugs, chloroquine and its derivatives hydroxychloroquine (HCQ) along with several other antiviral drug. Chloroquine is a widely used antimalarial with immunomodulatory effect [8]. A recent paper repotan inhibitor effect of remdesivir (a new antiviral drug) and chloroquine on the growth of SARS-COV-2 in vitro[9] and an early clinical trial conducted in COVID-19 Chinese patients, showed that chloroquine had a significant effect, both in terms of clinical outcomes and viral clearance, when comparing to control group[10,11].

Hydroxychloroquine (an analogue of Chloroquine) has been demonstrated to have an anti SARS-COV-2 activity in vitro[12]. Hydroxychloroquine (HCQ) has similar therapeutic effect and fewer adverse effects. Hydroxychloroquine clinical safety profile is better than that of Chloroquine (during long term use) and allow higher daily dose and has fewer concern about drug-drug interaction. Based on its characteristics of immunity regulation, antithrombotic activity and inflammatory improvement, hydroxychloroquine has been routinely used in the clinical treatment of systemic lupus erythematouses (SLS). However the efficacy of Hydroxychloroquine in COVID-19 remain unknown [13].

The molecular mechanisms of action of Chloroquine and hydroxychloroquine have been not fully elucidated. Finding from previous studies have suggested that chloroquine and hydroxychloroquine may inhibit the Coronavirus through a series of steps. Firstly, the drug can change the pH at the surface of the cell membrane and thus, inhibit the fusion of the virus to the cell membrane. It can also inhibit nucleic acid replication, glycosylation of Viral Protein, virus assembly, new virus particles transport, virus release and other processes to achieve its antiviral effect [14]

Hydroxychloroquine has been approved in the treatment of type-2 diabetes in India since 2014 as a third or fourth line drug, it would be interesting to research it's impact in patient with diabetes, infected with COVID-19. In this review article, we have systematically searched the medical database and collated all y available evidence that

have emerged so far on the efficacy of Chloroquine and hydroxychloroquine in the treatment of patient with COVID-19 with or without diabetes.[15-17]

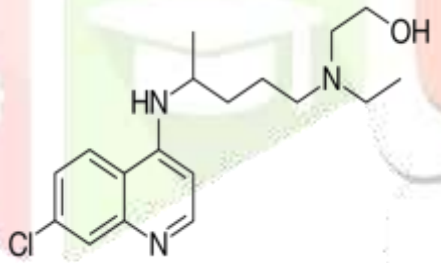
Hydroxychloroquine Tablet:

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[18].It is taken by mouth. It is also being studied as a treatment for coronavirus disease 2019 (COVID-19[19]).

Ex. Hydroxychloroquine sulphate tablet USP

Description:[20]

Hydroxychloroquine sulfate is a white or practically white, crystalline powder, freely soluble in water; practically insoluble in alcohol, chloroform, and in ether. Hydroxychloroquine sulfate tablets contain 200 mg hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration

Chemical Name	2-{[4-[(7-chloro-4-quinolyl)amino]pentyl]ethylamino}eyhanol
Structural formula	
Molecular formula	$C_{18}H_{26}ClN_3O.H_2SO_4$
Molecular weight	433.95gm

Inactive ingredients:[20]

Dibasic calcium phosphate USP, hypromellose USP, magnesium stearate

NF, polyethylene glycol 400 NF, polysorbate 80 NF, corn starch, titanium dioxide USP,

Carnauba wax NF, shellac NF, black iron oxide NF.

Pharmacokinetics:

Hydroxychloroquine has similar pharmacokinetics to chloroquine, with rapid gastrointestinal absorption [21], large distribution volume. About 50% get bound in plasma and is concentrated in liver, spleen, kidney, lungs, skin, leukocyte and some other tissues. it's selective accumulation in retina is responsible for the ocular toxicity seen with prolonged use[22].

It is elimination by the kidney. Cytochrome P450 enzymes (CYP2D6, 2C8, 3A4 and 3A5). It has significant level of three metabolites, desethylhydroxychloroquine (DHCQ), desethylchloroquine (DCQ), Bidesethylhydroxychloroquine (BDCQ) have been found in plasma and blood with DHCQ being the major metabolites.

The absorption half life was approximately 3 to 4 and the terminal half life ranged from 40 to 50 dayy. The long half life can be attributed to extensive tissue uptake rather than through decrease excretion [20].

Pharmacokinetics Data [29]

Bioavialabity	Variable (74% on average) T_{max}= 2-4.5
Protein binding	45%
Metabilism	Liver
Elimination $t_{1/2}$	32-50 days
Excretion	Mostly kidney (23-25% as unchanged drug) Also biliary (<10%)

Pharmacodynamics:

Antimalarials are lipophilic weak bases and easily pass plasma membranes. The free base form accumulates in lysosomes (acidic cytoplasmic vesicles) and is then protonated[23], resulting in concentrations within lysosomes up to 1000 times higher than in culture media. This increases the pH of the lysosome from four to six[24]. Alteration in pH causes inhibition of lysosomal acidic proteases causing a diminished proteolysis effect [25]. Higher pH within lysosomes causes decreased intracellular processing, glycosylation and secretion of proteins with many immunologic and nonimmunologic consequences [26]. These effects are believed to be the cause of a decreased immune cell functioning such as chemotaxis, phagocytosis and superoxide production by neutrophils[27].

Hydroxychloroquine is a weak diprotic base that can pass through the lipid cell membrane and preferentially concentrate in acidic cytoplasmic vesicles. The higher pH of these vesicles in macrophages or other antigen-

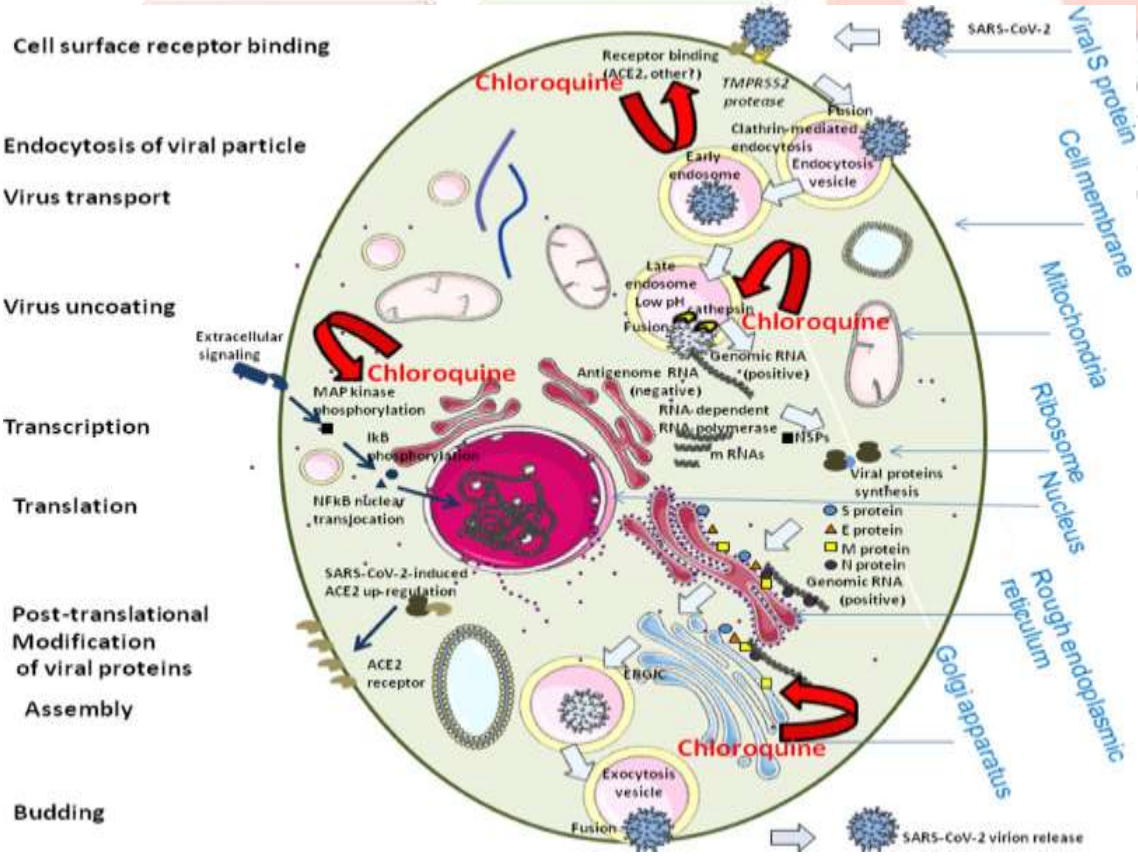
presenting cells limits the association of autoantigenic (any) peptides with class II MHC molecules in the compartment for peptide loading and/or the subsequent processing and transport of the peptide-MHC complex to the cell membrane[28].

Mechanisms of action:

The precise mechanism by which Hydroxychloroquine exhibit activity against plasmodium is not known. Hydroxychloroquine, like chloroquine is a weak base and may exert its effect by concentrating on the acid vesicles of the parasite and by inhibiting polymerization of heme. It can also inhibit certain enzyme by its interaction with DNA[20].

Hydroxychloroquine increase lysosomal PH in antigen presenting cells. In inflammatory conditions, it blocks toll-like receptor on plasmacytoid dendritic cells (PDCs). Toll-like receptor (TLR 9), which recognises DNA containing immune complexes, lead to the production of interferon and causes the dendritic cells to mature and present antigen to T- cells. Hydroxychloroquine by decreasing TLR signalling, reduces the activation of dendritic cells and the inflammatory process.[30]

In 2003, a novel mechanism was described wherein Hydroxychloroquine inhibit stimulation of the toll-like receptor (TLR)9 family receptor. TLRs are cellular receptor for microbial products that induce inflammatory response through activation of the innate immune system[31].



This is a host cell having lysosome inside cytoplasm and ACE 2 receptor on its outer surface which helps in attachment of the virus. COVID-19 virus has spike protein on its outer surface for attachment to the host cell. Chloroquine and hydroxychloroquine interferes with the glycosylation of ACE 2 receptor and block the virus fusion with the host cell, therefore the binding of the virus through the receptor on the cell is impended and infection is consequently prevented.

Once hydroxychloroquine and chloroquine enter cell, they are both concentrated in the organelle with low pH such as endosomes and lysosome. These drug increase the pH of lysosome. creating problem in cleavage of the surface spike protein. Without the cleavage function replication of and infection by CORONA VIRUSES are block. Hydroxychloroquine are considered to bo immunomodulator rather than immunosuppressant preventing T-cell activation

Uses:

Hydroxychloroquine is used to treat systemic lupus erythematous, rheumatic disorders like rheumatoid arthritis, porphyria cutanea tarda and Q fever and certain types of malaria. It y considered the first line treatment for systemic lupus erythematouses. Certain types of malaria resistant strains and complicated cases require different or additional medication [18]. It is widely used in the treatment of post-lyme arthritis. It may have both an anti- spirochaete activity and anti-inflammatory activity [32].

In the desperate search to find effective treatment for coronaviruse disease 2019(COVID-19), 2 generic drug used largely by rheumatologist and dermatologist to treat immune medicated disease. Hydroxychloroquine and chloroquine have demonstrated antiviral activity against severe acute respiratory syndrome Coronavirus 2(SARS-COV-2) in vitro and in small, poorly controlled or uncontrolled clinical studies[33-35]. Data to support the use of Hydroxychloroquine and chloroquine for coronaviruse disease 2019(COVID-19) are limited and inconclusive. The drug have some in-vitro activity against severe viruses, including Coronavirus and influenza have been negative [36, 37]. The evidence for the use of this drug to treat immune mediated disease is not. For example hydroxychloroquine is a cornerstone of therapy for SLE. Hydroxychloroquine can effectively treat disease manifestations, such as joint pain and rashes; reduce thrombotic event; and prolong survival [38].

Given the like hood that shortage will continue in the near term, we propose that manufacturers, clinicians, pharmacies, health system and government health agencies continue to cordinate an aggressive response to ensure that antimalarial drugs use is appropriately managed during the Coronavirus disease 2019 pandemic[39].

Adverse effect:[20]

The following adverse reaction has been identified during post approval use of hydroxychloroquine.

Blood and lymphatic system disorders: Bone marrow failure, anemia, aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Hemolysis reported in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

Cardiac disorders: Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome. HCQ prolongs the QT interval. Ventricular arrhythmias and torsade de pointes have been reported in patients taking hydroxychloroquine.

Ear and labyrinth disorders: Vertigo, tinnitus, nystagmus, nerve deafness, deafness.

Eye disorders: Irreversible retinopathy with retinal pigmentation changes (bull's eye appearance), visual field defects (paracentral scotomas) and visual disturbances (visual acuity), maculopathies (macular degeneration), decreased dark adaptation, color vision abnormalities, corneal changes (edema and opacities) including corneal deposition of drug with or without accompanying symptoms (halo around lights, photophobia, and blurred vision).

Gastrointestinal disorders: Nausea, vomiting, diarrhea, and abdominal pain.

General disorders and administration site conditions: Fatigue.

Hepatobiliary disorders: Liver function tests abnormal, hepatic failure acute.

Immune system disorders: Urticaria, angioedema, bronchospasm

Metabolism and nutrition disorders: Decreased appetite, hypoglycemia, porphyria, weight decreased.

Musculoskeletal and connective tissue disorders: Sensorimotor disorder, skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups, depression of tendon reflexes and abnormal nerve conduction.

Nervous system disorders: Headache, dizziness, seizure, ataxia and extrapyramidal disorders such as dystonia, dyskinesia, and tremor have been reported with this class of drugs.

Psychiatric disorders: Affect/emotional lability, nervousness, irritability, nightmares, psychosis, suicidal behavior.

Skin and subcutaneous tissue disorders: Rash, pruritus, pigmentation disorders in skin and mucous membranes, hair color changes, alopecia. Dermatitis bullous eruptions including erythema multiforme, Stevens-Johnson

syndrome, and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), photosensitivity, dermatitis exfoliative, acute generalized exanthematous pustulosis (AGEP). AGEP has to be distinguished from psoriasis, although PLAQUENIL may precipitate attacks of psoriasis. It may be associated with pyrexia and hyperleukocytosis.

Contraindications:

The drug label advises that hydroxychloroquine should not be prescribed to individuals with known hypersensitivity to 4-aminoquinoline compounds [40]. There are a range of other contraindications [41,42] and caution is required if patients have certain heart conditions, diabetes or psoriasis.

Precautions:[20]

Hydroxychloroquine should be administered with caution in patients having glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Dermatological reaction to hydroxychloroquine may occur and therefore proper care should be exercised when it is administered to any patient receiving a drug with a significant tendancy to produce dermatitis. It uses with caution in patients with gastrointestinal, neurological or blood disorder and hepatic/ renal disease and in those with a sensitivity to quinine.

Interaction:

The drug transfers into breast milk [43]and should be used with care by pregnant or nursing mothers. Care should be taken if combined with medication altering liver function as well as aurothioglucose (Solganal), cimetidine (Tagamet) or digoxin (Lanoxin). HCQ can increase plasma concentrations of penicillamine which may contribute to the development of severe side effects. It enhances hypoglycemic effects of insulin and oral hypoglycemic agents. Dose altering is recommended to prevent profound hypoglycemia. Antacids may decrease the absorption of HCQ. Both neostigmine and pyridostigmine antagonize the action of hydroxychloroquine[44].

The US Food and Drug Administration's drug label for hydroxychloroquine lists the following drug interactions[40]:

- Digoxin- wherein it may result in increased serum digoxin levels.
- Insulin or anti-diabetic medication- wherein it may enhance the effects of a hypoglycemic treatment.
- Hydroxychloroquine taken along with arrhythmogenic drug they prolongs the QT interval and may increase the risk of inducing ventricular arrhythmias if used concurrently[45].
- Mefloquine and other drugs known to lower the convulsive threshold, may increase risk of convulsions.
- Antiepileptics- concurrent use may impair the antiepileptic activity

- Cyclosporin- wherein an increased plasma cyclosporin level was reported when used together.

Dosage and Administration:[20]

Hydroxychloroquine sulphate 400mg given twice daily for 1 day, followed by 200mg twice daily for 4 more day is recommended to treat SARS-COV-2 infection.It is given by oral route. **Overdose:**

Serious symptoms of overdose generally occur within an hour of ingestion [46]. These symptoms may include sleepiness, vision changes, seizures, stopping of breathing, and heart problems such as ventricular fibrillation and low blood pressure [46,47]. Loss of vision may be permanent [48]. Low blood potassium, to levels of 1 to 2 mmol/L, may also occur [46,49].

Chloroquine has a risk of death in overdose in adults of about 20%, while hydroxychloroquine is estimated to be two or three fold less toxic[46]. While overdoses of hydroxychloroquine have historically been uncommon, one report documented three deaths out of eight cases[50].

Treatment recommendations include early mechanical ventilation, cardiac monitoring, and activated charcoal [46]. Intravenous fluids and vasopressors may be required with epinephrine being the vasopressor of choice. Gastric lavage may also be used [50]. Seizures may be treated with benzodiazepines. Intravenous potassium chloride may be required; however this may result in high blood potassium later in the course of the disease. Dialysis has not been found to be useful [46].

Regulatory Approval:

On 17 March 2020, the AIFA Scientific Technical Commission of the Italian Medicines Agency expressed a favorable opinion on including the off-label use of chloroquine and hydroxychloroquine for the treatment of COVID-19[51].

In the US, several state pharmacy boards reported that some doctors and dentists were writing prescriptions for hydroxychloroquine and a related drug[52], chloroquine, to themselves, family members, and staff. Sudden demand spikes caused by hospital use for severely ill COVID-19 patients and prescriptions for prophylaxis have resulted in shortages; doctors have expressed concern that patients who have long taken hydroxychloroquine for other approved indications, like lupus and rheumatoid arthritis, will be unable to procure needed medicine [53,54].

On 28 March 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to allow hydroxychloroquine sulfate and chloroquine phosphate products donated to the Strategic National Stockpile (SNS) to be distributed and used for certain people who are hospitalized with COVID-19[55,56].

In anticipation of product shortages, the FDA issued product-specific guidance for chloroquine phosphate and for hydroxychloroquine sulfate for generic drug manufacturers [57].

In vitro antiviral activity of Hydroxychloroquine against SARS-COV-2:[58]

Method:

The pharmacological activity of Chloroquine and hydroxychloroquine was test using SARS-COV-2 Infected Vero cells. Physiologically based pharmacokinetics model (PBPK) were implemented for both drug separately by integrating their in vitro data. Using the PBPK model, hydroxychloroquine concentration in lung fluid were stimulated under five different dosing regimen to explore the most effective regimen while considering drug safety profile.

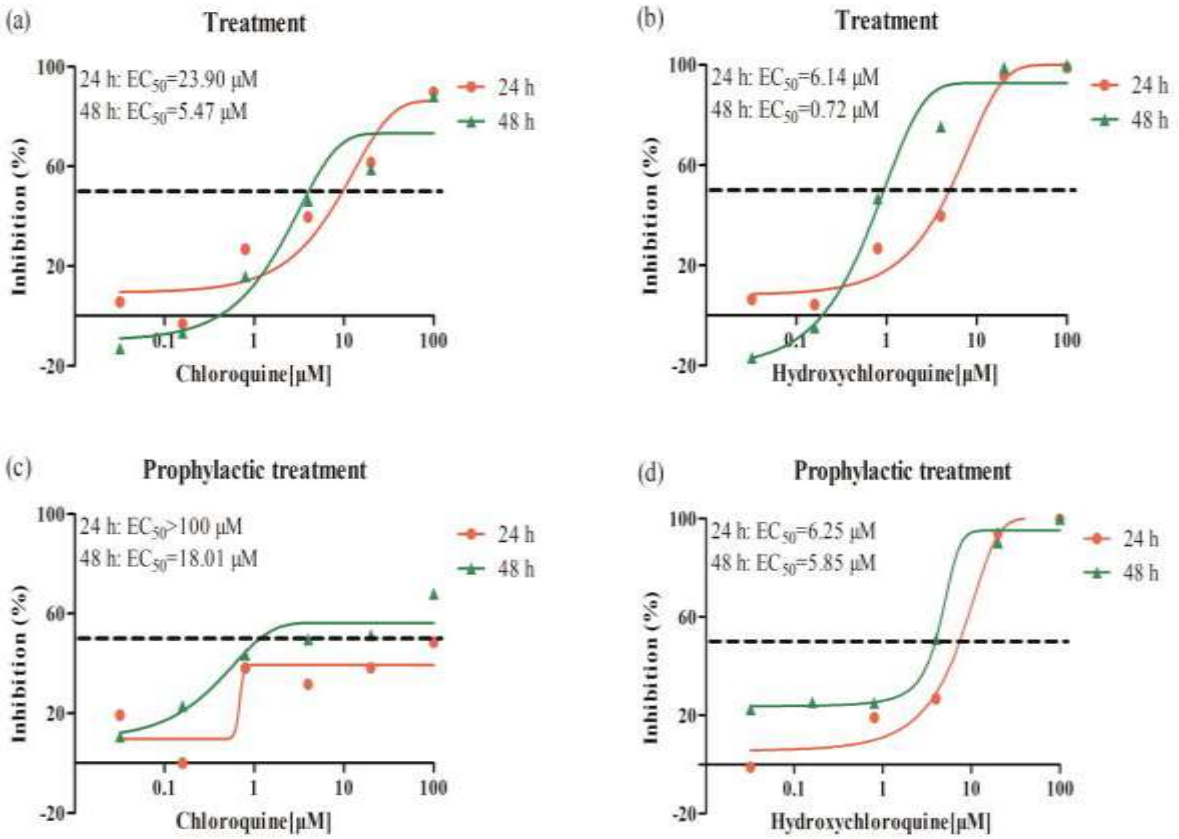
Result:

Hydroxychloroquine (EC_{50}=0.72 uM) was found to be more potent than chloroquine(EC_{50}=5.47 uM) in vitro. Based on PBPK model result , a loading dose of 400mg twice daily of Hydroxychloroquine sulphate given orally, followed by a maintenance dose of 200mg given twice daily for 4 day is recommended for SARS-COV-2 infection, as it reaches three times the potency of Chloroquine phosphate when given 500mg twice daily 5 day in advance.

Figure:

The antiviral activities of Chloroquine and hydroxychloroquine for therapeutic and prophylactic use were tested on the Vero cells infected with SARS-COV-2 clinically isolated strain. (a) and (b) : For treatment group, Chloroquine and hydroxychloroquine were added medium after the Vero cells infected and cells were incubated with medium contained drug for 24 or 48 hrs.

(C) and (d): For prophylactic treatment group, the Vero cells were pre-treated with chloroquine and hydroxychloroquine for 2 hrs and then viruses were added to medium to infect cells. After that, the medium was removed and replaced with Fresh medium without drug or viruses and cells were incubated for 24 or 48 hrs. The viral yield in the cell supernatant was quantified by RT-PCR.



Conclusion:

Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-COV-2 in vitro. And it including hydroxychloroquine has a more tolerable safety profile in comparison to chloroquine.

In our study we noted that the EC50 value for hydroxychloroquine and chloroquine decreased with longer incubation time. This suggests that incubation time may influence the drug antiviral activity. The optimal dosing regimen for hydroxychloroquine was evaluating in in silico by using PBPK modelling and simulation techniques.

The potential of Hydroxychloroquine in the treatment of COVID-19 has been partially. considering that their is no better option at present, it is a promising practice to apply hydroxychloroquine to Covid-19 under reasonable management. However, large scale clinical and basic research is stil needed to clarify it's specific mechanism and to continuously optimised the treatment plan.

In April 2020, the US National Institute of Health (NHH) began a trial to assess whether hydroxychloroquine is safe and effective to treat COVID-19.

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