

## Hydroxychloroquine emergence of a COVID Warrior ?

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### Abstract -

Hydroxychloroquine is a safer derivative of chloroquine that is being used in the treatment and prophylaxis of COVID19. Evidence of its efficacy is sparse, two small studies demonstrating clinical, radiological and serological improvement. However, scarcity of available treatment options has projected this drug into prominence. Drug interactions and risk of QT prolongation are to be kept in mind during use.

**Key Words :** treatment, prophylaxis, COVID19, QT prolongation

The Corona Virus Disease 2019 or COVID 19 was declared a pandemic by WHO on 11th March 2020.

Hydroxychloroquine (HCQ) is being advocated as a treatment modality as well as a prophylactic drug in the management of COVID 19. Though not substantiated by any large randomized trial, in the absence of any other definitive therapeutic option, hydroxychloroquine has emerged as a viable option in the present scenario.<sup>1</sup>

Hydroxychloroquine Sulphate was synthesized in the late forties as a hydroxy-derivative of chloroquine. Chloroquine phosphate was first synthesized in India in 1934 by the Bengal Chemical Works founded by Acharya Prafulla Chandra Ray. Hydroxychloroquine is produced by adding a hydroxyl moiety to chloroquine and is found to be about 40% less toxic. Both these drugs are weak bases with large volume of distribution and long half-lives, because of which their actions are persistent for a considerable time after discontinuation. They have been used in autoimmune diseases for a long time. The antiviral activity of this drug has been investigated for more than a decade with variable results.

### Conventional indications

Rheumatoid arthritis

SLE

Anti-Phospholipid Syndrome

Primary Sjogren Syndrome

### Newer indications

Prevention/treatment of Type 2 diabetes retinopathy is a concern

Treatment and prophylaxis of COVID 19 talk of the day.

### Actions

Anti-inflammatory

Immunomodulatory

Anti-viral activity- prevents viral entry, transport in cells

and post entry events.

Anti-thrombotic activity

Anti-hyper glycaemic activity

Antihyperlipidemic activity

### Recommendations for treatment(2)

For severe illness requiring ICU management

Hydroxychloroquine 400mg BD on Day 1, then 200mg BD for 4 days

Along with Azithromycin 500mg OD for 5 days

### Recommendations for prophylaxis of COVID 19-

Asymptomatic healthcare worker caring for suspected or confirmed case of COVID19.

Household contacts of confirmed case of COVID19.

Dose 400mg weekly for 7 weeks with meals for healthcare workers, for 3 weeks in house hold contacts

### Important points to remember

1. The drugs are to be taken only by prescription of a registered medical practitioner.
2. It should not in still a false sense of security- to maintain hand hygiene, respiratory hygiene, PPE where necessary.
3. If anyone becomes symptomatic on prophylaxis to contact health facility for testing and management
4. Pharmacovigilance of adverse drug reactions through self-reporting via app/helpline is advocated

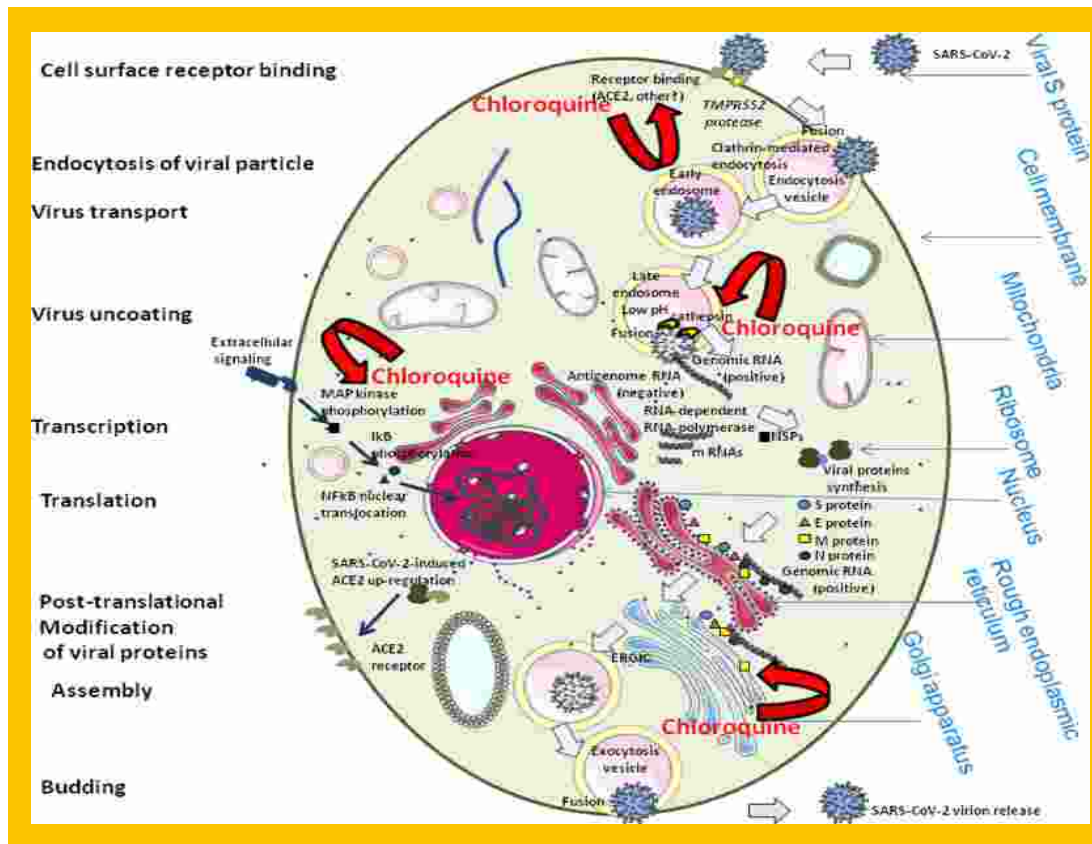
### Mechanism of action

Though not clearly delineated, this weak base causes changes in PH in endosomes and lysosomes that has been postulated as a major factor leading to various alteration of viral functions.

In vitro studies indicate that the drug inhibits infection of cells by SARS CoV-2 by glycosylation of the cellular receptors of the viral cell surface that is it cannot bind to the angiotensin-converting enzyme 2 (ACE2) expressed in lung, heart, kidney and intestine.<sup>3</sup>

The drug also inhibits the quinone reductase-2, which is involved in sialic acid biosynthesis (an acidic monosaccharides of cell transmembrane proteins

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required for ligand recognition) that makes this drug a broad antiviral agent. There is formation of an autophagosome which cleaves SARS-CoV-2 spike protein.<sup>4,5</sup>

Through the inhibition of MAP-kinase it interferes with SARS-CoV-2 molecular crosstalk, besides altering the virion assembly, budding and interfering with the proteolytic processing of M Protein of the virus.<sup>6</sup>

There is inhibition of immune activation by inhibiting Toll like receptor signalling and cytokine production in T cells. This may be helpful in the prevention of cytokine storm found in severe COVID 19.<sup>6</sup>

Though having similar mechanism of action hydroxychloroquine was found to be more effective antiviral activity than chloroquine in vitro (EC50 6.25micro MVS 100 micro M respectively at 24 hours)

A Chinese study involving more than 100 patients of COVID-19, that represents the first human trial, found chloroquine superior to the control group in reducing symptom duration, exacerbation of pneumonia including radiological improvement and promoting virus-negative seroconversion without any severe side effects<sup>7</sup>

The second human study which is currently available was conducted with HCQ. In an open-label, non-randomized trial (n ¼ 36) conducted in Marseille, France, Gautret et al. found that HCQ alone and combination of HCQ plus azithromycin was highly and significantly effective in clearing viral nasopharyngeal carriage<sup>8</sup>

**Side Effects**

- Nausea, vomiting, diarrhoea
- QTc prolongation
- Cardiomyopathy in rheumatologic patients

- Retinopathy
- Hypersensitivity reaction
- Myopathy
- Hypoglycaemia in diabetics on other antivirals(9)
- Caution in G6PD deficiency

**Monitoring**

Complete hemogram, serum electrolytes, blood glucose (because of hypoglycemic potential of HCQ) hepatic as well as renal function tests. Due to potential to prolong QTc, routine electrocardiography is essential prior to starting these drugs.

**Drug Interactions**

Co-administration of other drugs known to prolong the QTc interval (such as anti-arrhythmic, anti-depressants, anti-psychotics, antihistaminic) are to be done with cautious monitoring e.g addition of azithromycin to HCQ as done in French trial by Gautret et al. may increase the risk of QTc prolongation. ECG is to be performed daily if QTc is 450e500 msec.

Hypo glycemia as well as anticipated QTc prolongation must be looked for in patients with diabetes especially with concurrent use of chloroquine/HCQ and lopinavir/ritonavir.<sup>10</sup>

**Contraindications**

Hypersensitivity to this drug, retinopathy, porphyria, epilepsy, pre-existing maculopathy, G6PD deficiency, recent myocardial infarction and QTc >500 msec.

Hydroxychloroquine and Chloroquine are not contraindicated in pregnancy'

To conclude, although documentation of chloroquine and Hydroxychloroquine efficacy in COVID19 is limited (based

on the experimental data and only two small human trials), the potentially favourable benefit-risk ratio of chloroquine and HCQ in absence of any other valid treatment option has been taken into account. Therefore such treatment has been recommended by various official bodies in the current scenario of pandemic of COVID-19.

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