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Relevance and Role of Hydroxychloroquine in Prophylaxis and Therapy of COVID-19

Authors
Dr Arjun Baidya[1*], Dr Anand Shankar[2], Dr Rishad Ahmed[3], Dr Amit Kumar Das[4]
[1]Associate Professor, Department of Endocrinology, NRS Medical College & Hospital, Kolkata, India
[2]Diabetologist, Shankar Diabetes Care Centre, Patna, Bihar
[3]Associate Professor, Department of Medicine, KPC Medical College & Hospital, Kolkata
[4]Diabetologist, Shree Hospital & Maternity, Muzaffarpur, Bihar
*Corresponding Author
Dr Arjun Baidya
Associate Professor, Department of Endocrinology, NRS Medical College & Hospital, Kolkata,
West Bengal, India

Abstract
A rapidly spreading novel corona virus infection, COVID-19 (Corona virus disease, 2019), a global pandemic has already reported to cause death of approximately 2.5% of total infected individuals. Being more immunodeficient uncontrolled diabetic individuals have more chance to be symptomatic with COVID-19 than the nondiabetic individuals. There are some recent updates regarding the efficacy of hydroxychloroquine as a monotherapy or with adjunct therapy to improves the condition of COVID-19 infected patients and even the molecule hasthe property to regulate blood glucose level without much hypoglycemia. This review article highlighted the proposed mechanisms of hydroxychloroquine by which it provides beneficial effect in nondiabetic individuals who became symptomatic with COVID-19 as well as being an approved anti diabetic agent how it reduces the chance of infection with COVID-19 in patients with diabetes.
Keyword: *Hydroxychloroquine, Coronavirus, COVID-19, Diabetes.*

Introduction

Novel Coronavirus COV-2 (COVID-19) pandemic is one of the biggest threats to the mankind and society today. Till the date of writing this article, there are several lakhs of COVID-19 confirmed diagnosed patients worldwide including India and several thousands have died. COVID-19 was first reported in December 2019 in Wuhan City in China. It has since spread across the world and significantly impacted the community health. Till now as there is no specific therapy for COVID-19 prevention of spread of infection is only way to contain this deadly virus. To help stopping the virus spreading everyone should practice good hygiene including washing hands regularly, using a tissue and covering mouth when cough or sneeze and avoiding close contact with others. People are strongly

encouraged to participate in social distancing behaviors.

Though the evidences are fewer still evidences are pouring in in the scientific literatures regarding the role of chloroquine and its derivative hydroxychloroquine (HCQ) in prophylaxis and therapy of COVID-19 and recommendations has also been evolved. Therefore, in this review we discuss the relevance and role of hydroxychloroquine in prophylaxis and therapy of COVID-19.

COVID-19 and Its Impact

Coronaviruses are a family of viruses that cause respiratory illnesses. Most of them cause illness in animals, but seven known types of coronaviruses cause illness in humans. Some people even have no symptoms, or only the mild symptoms of common cold[1]. SARS-CoV-2 is one of those viruses which causes the illness. SARS-CoV-2 is related to other coronaviruses that cause illness in humans such as those that cause SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome). Coronaviruses are enveloped positive strand RNA viruses with the largest known RNA genomes, of 30–32 kb[2].

Based on genome sequencing, corona viruses are divided into three groups (alpha, beta and gamma coronaviruses). Betacoronavirus, murine coronavirus (MuCoV), mouse hepatitis virus (commonly referred to as MHV) are the few types of well-studied coronaviruses. While most coronavirus infections cause the self-limiting common cold in humans, the emergence of the agent for severe acute respiratory syndrome (SARS), the SARS-associated coronavirus (SARS-CoV), also a betacoronavirus, demonstrated the potential for further significant human diseases[3].

The success of coronaviruses in their ability to jump between species may be attributed, in part, to the diverse array of virus entry strategies they deploy to infect target cells[4]. Coronavirus entry inside the cells is largely controlled by the spike surface envelope glycoprotein (S) since it bears both receptor binding and membrane fusion capabilities[5]. Assuch, the S-glycoproteinis a crucial determinante of tissue and cell tropism as well as host range. Coronaviruses are notable because at each step of virus entry, which includes receptor binding, activation of fusion, and internalization, a multitude of mechanisms and strategies have evolved[6]. Coronaviruses can enter cells via fusion either directly at the cell surface or can be internalized through the endosomal compartment. The mouse hepatitis virus (MHV) is a prime example of the flexibility in entry mechanisms used. A variant of the MHV-4strain was shown to be able to fuse directly at the cell surface at neutral pH and also enter cells through an endocytic route[7]. Importantly, coronaviruses employ a diversity of cues, such as receptor binding, low pH and proteolytic activation, to activate the S protein, allowing a timely release of the fusion peptide into target membranes[4].

COVID-19 is usually a mild disease and around 98% of people affected survive. The majority of cases (>80%) are mild (showing only minimal flu-like symptoms) and people can recover at home. Some cases (around 14%) are severe and very few (around 5%) can result in critical illness like severe pneumonia with respiratory failure or even death. This is more common in people who have other health problems, particularly the elderly, those with cardiovascular disease, chronic lung disease and hypertension. People with diabetes are among those high-risk categories that can have serious illness if they get the virus.

Diabetes and COVID-19

Among 72,314 cases, diabetes subjects had 7.3% higher mortality rates compared to nondiabetic subjects who had 2.3% mortality as reported by Wu Z et al[6]. Xiaobo Yang et al also confirmed that the most distinctive comorbidities of COVID-19 were cerebrovascular diseases (22%) and diabetes (22%) and documented 32 non-survivors from a group of 52 intensive care unit patients[8]. In another study, comorbidities of hypertension (23·7%), diabetes mellitus (16·2%), coronary

heart diseases (5·8%), and cerebrovascular disease (2·3%) documented in 1099 patients with confirmed COVID-19[9].

Relevance of Hydroxychloroquine in COVID-19

Hydroxychloroquine will as a prophylactic drug and is acting as a therapeutic agent against COVID-19 infection and it is a game changer in fight against the COVID-19.

Hydroxychloroquine acts on host target respiratory cells by increasing the endosomal pH required for the virus- host target cell fusion. Firstly, increase in the pH disrupts the normal viral function. Secondly, in SARS-coronavirus, which is a sister to COVID-19, hydroxychloroquine was found to interfere with the glycosylation of cellular receptors of the virus. This interference eventually resulted in no association between the host target cell and the virus (Figure 1). This interference eventually resulted in no association between the host target cell and the virus (Figure 1). Thirdly, hydroxychloroquine acts as an ionophoric agent for Zinc ions and thus increases the influx of Zinc ions into the cytoplasm of host target cells regardless whether the host target cells are infected or not [10]. Zinc ions adhere to the RNA dependent RNA polymerase enzyme of the virus and stops COVID-19 polymerization intracellularly.

All the above-mentioned mechanism is on the host cells and COVID-19 can't mutate and cause resistance to these three mechanisms. First two mechanisms inhibit the virus-target host cell union. ACE-2 (Angiotensin converting enzyme-2) is a surface receptor found on target host cell.

Hydroxychloroquine results in disablement of ACE2 terminal glycosylation which leads to the morphological change. This results in the disruption in the association between the COVID-19 and target host cell as COVID-19 requires ACE-2 receptor to attach to a cell[11].

Because the action is on the target host cell, hydroxychloroquine won't develop resistance therapeutically. If a person not yet exposed to the COVID-19 infection and subsequently after taking hydroxychloroquine some viruses enters inside the body and try to infect target host cells, hydroxychloroquine first and second mechanism will prevent the union of virus-target host cell. If some of the viruses enters the target host cell, Zinc ions present inside the cells adhere to the RNA dependent RNA polymerase enzyme of the virus and stops COVID-19 polymerization intracellularly. If COVID-19 mutates inside the cell several times, even then the Zinc ions would actively inhibit the viral multiplication inside the host respiratory cells, irrespective of the viral strain. Even if COVID-19 virus manages to escape from Zinc ions trap and releases from the host target cell cytoplasm into the interstitial matrix, intercellular space, and tried to re-infect some of the healthy target host cells, Hydroxychloroquine will prevent the re-union of viral genome with target host cells via the first two mechanisms and the infection will halt in the preliminary stages itself and complications like COVID-19 pneumonia will not develop. Hydroxychloroquine molecules will not lose it's effectively in an individual pre and post infection.
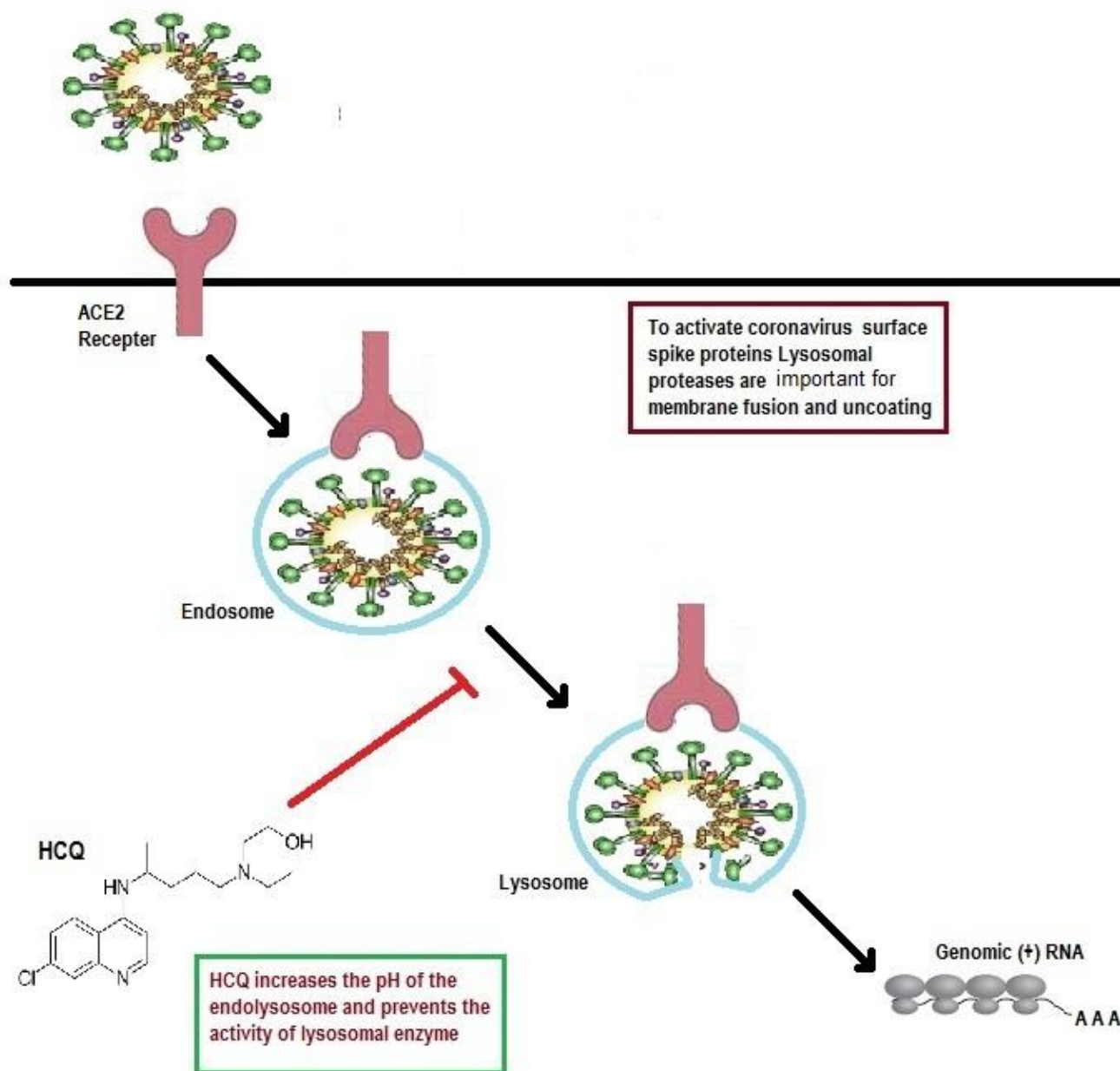
Figure 1: The mechanisms of action of hydroxychloroquine (HCQ) against COVID-19

Lysosomal pH elevation with hydroxychloroquine was reported from about 4.5 to 6.5 at 100 μM[12]. It was reported that safe dosage i.e. 6 to 6.5 mg/kg per day of hydroxychloroquine could generate serum level of 1.4 - 1.5 μM in human[13]. A recent study in line with this, also confirm that safe dosage of hydroxychloroquine concentration in the above tissues is likely to be achieved to inhibit COVID-19 infection[14]. This trial also concludes that, hydroxychloroquine not only attenuate the inflammatory response but also decrease the level of cytokines which generally higher in patients infected with SARS-CoV-2. One study found that hydroxychloroquine is more potent than chloroquine in inhibiting SARS-CoV-2[15].

A recent study shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin[16].

The precise mechanism by which hydroxychloroquine improves glycemic control has not been certainly elucidated. The drug is purported to act by increasing the metabolic effect of insulin by reducing its lysosomal degradation. The drug has been demonstrated to inhibit the production of inflammatory markers such as TNF-α, IL-1, IL 6 and interferon-γ which are linked to the development of insulin resistance[17]. Animal studies have demonstrated that administration of hydroxychloroquine has contributed to the lowering of IL-1β, IL-6 and TNF-α and transforming growth factor β1, which in turn resulted in the preservation of islets of Langerhans structure[18]. Mercer et al. Have demonstrated that 6 weeks of hydroxychloroquine therapy has contributed to significant increase in insulin sensitivity from 4.5 to 8.9 in obese non-diabetic subjects[19].

In India current recommendation is to use hydroxychloroquine in combination with sulphonylurea and metformin. The 2018 Research Society for the Study of Diabetes in India (RSSDI) guidelines have placed hydroxychloroquine as third line of drug indicated for the management of T2DM[20].

Role of Hydroxychloroquine in COVID-19
In treatment
So far till date (25th March, 2020) no authority has issued confirmed dosing recommendations for Hydroxychloroquine for the treatment of COVID-19 infection. Therefore, the dosing regimen of Hydroxychloroquine reported in the recently published articles have been discussed below.

In French Study of Hydroxychloroquine and Azithromycin as a treatment of COVID- 19 (N=20 hydroxychloroquine-treated patients and 16 control patients), Hydroxychloroquine sulfate 200 mg, three times per day for ten days was the dosing regimen used. Among hydroxychloroquine-treated patients six patients received Azithromycin (500mg on day1 followed by 250mg per day, the next four days) to prevent bacterial super-infection under daily electrocardiogram control[16].

Regimen based on simulated lung concentration based on in-vitro study Yao X et al recommended hydroxychloroquine 400mg BID at day 1 and 200mg BID Day-2 to Day-5[15].

For infants and childrenIranian Expert's Consensus Statement recommend hydroxychloroquine sulfate, i.v.,3 – 5 mg/kg/day (max dose 400 mg), BID for 5 days[21].

Recommendations for COVID-19 clinical management Rome, Italy recommended Clinical management based on case severity and for following categories of patients Hydroxy-chloroquine has been recommended

- Asymptomatic or mild infection
- Patient affected by respiratory symptoms, clinically unstable, not in critical conditions (e.g.: MEWS clinical deterioration score 3-4)
- Critical patient (e.g. MEWS clinical deterioration score >4)[22]

Hydroxychloroquine phosphate recommended dosage for above categories is 400 mg tablet, 1 tabletas loading dose, followed by 200 mg tablet, 1 tablet q12hour, for 10 days. They have also recommended that before chloroquine and hydroxychloroquine administration, G6PD deficiency test should be performed[22].

In prophylaxis
Asymptomatic healthcare workers involved in care of suspected or confirmed cases of COVID-19: 400mg twice a day on day 1, followed by 400mg once weekly for next 7 weeks; to be taken with meals. Asymptomatic household contacts of laboratory confirmed cases: 400mg twice a day on day 1, followed by 400mg once weekly for next 7 weeks; to be taken with meals[23].

Interim clinical guidelines for supportive care & antiviral treatment of hospitalized patients with suspected or confirmed COVID-19 in Belgium are given in the table below[24].

Table: Interim guidelines for supportive care & antiviral treatment of hospitalized patients with suspected or confirmed COVID-19[24].

Clinical category	Supportive Care	Additional antiviral therapy	Precautions
Confirmed COVID-19 • Mild-to moderate disease (no O2 requirement/no evidence of pneumonia) • Risk group #[1] ([#1]Risk groups: age > 65 years AND/OR underlying end organ dysfunction (lung, heart, liver,...), diabetes, coronaropathy, chronic obstructive pulmonary disease, arterial hypertension)	Symptomatic treatment	Consider to start hydroxychloroquine if no contra-indication ● 400 mg at suspicion/diagnosis; ● 400 mg 12 h later ● Followed by 200 mg BID up to Day 5 *NB:* *stop hydroxychloroquine if follow-up at home* If no hydroxychloroquine available, consider chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5 or chloroquine phosphate 1000mg at diagnosis and 500mg 12h later, followed by 300mg BID up to day 5	**Contra-indications** • QTc > 500 msec • Check for drug interaction • Interaction potential of hydroxychloroquine is likely the same as chloroquine • Myasthenia gravis • Porphyria • Retinal pathology • Epilepsy NB: pregnancy is not a contra-indication as such (large safety experience with chloroquine); see risk/benefit balance Perform ECG daily if initial QTc 450-500 msec, and biochemistry according to underlying disease
Confirmed COVID-19 Severe disease • ≥ 1 of the following: • Respiratory rate ≥30/min (adults); ≥40/min (children < 5) • Blood oxygen saturation ≤93% • PaO2/FiO2 ratio <300 • Lung infiltrates >50% of the lung field within 24-48 hours	Optimal supportive care in hospital WARD (or ICU) Provide 02 Consider carefully antibiotics or antifungals according to local epidemiology	**Start hydroxychloroquine if no contra-indication** • 400 mg at diagnosis; • 400 mg 12 h later • Followed by 200 mg BID up to Day 5 NB: If no hydroxychloroquine available, consider chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5 OR chloroquine phosphate 1000mg at diagnosis and 500mg 12h later, followed by 300mg BID up to day 5 Consider lopinavir/ritonavir 400/100 mg (= 2 tablets of 200/50 mg) BID for 14 days) as second choice **ONLY if hydroxychloroquine/chloroquine contra-indicated and provided it can be administered within 10 days after symptoms onset** (check also drug interaction!); or in children < 10 kg (after IDS advice)	**Contra-indications** • QTc > 500 msec • Check for drug interaction • Interaction potential of hydroxychloroquine is likely the same as chloroquine • Myasthenia gravis • Porphyria • Retinal pathology • Epilepsy NB: pregnancy is not a contra-indication as such (large safety experience with chloroquine); see risk/benefit balance Perform ECG daily if initial QTc 450-500 msec, and biochemistry according to underlying disease Perform basic biochemistry daily and ECG daily if initial QTc > 450 msec (+ other indicated investigations) Avoid quinolones if possible, or monitor closely the QT if these antibiotics are needed In case antibiotics must be provided, consider to add azithromycin (given its possible synergistic effect with hydroxychloroquine) BUT with a particular caution for interaction and QTc prolongation (daily ECG or cardiac monitoring)

Conclusion

There are only few small trialswhich confirmed the beneficial effects of hydroxychloroquine to treat recent COVID-19 global pandemic. For prevention of COVID-19 hydroxychloroquine is the drug choice as of now. As hydroxychloroquine has already been shown antidiabetic effect and approved in India for uncontrolled T2DM, adding this molecule in uncontrolled T2DM might provide dual benefit in the current scenario of COVID-19 pandemic. But before large scale use larger randomized controlled trial is warranted.

Disclosure

The authors report no conflicts of interest in this work.

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