



Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries

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ARTICLE INFO

Article history:

Received 21 March 2020

Received in revised form

22 March 2020

Accepted 22 March 2020

Keywords:

COVID-19

Chloroquine

Hydroxychloroquine

Diabetes

ABSTRACT

Background and aims: No drugs are currently approved for Coronavirus Disease-2019 (COVID-19), although some have been tried. In view of recent studies and discussion on chloroquine and hydroxychloroquine (HCQ), we aimed to review existing literature and relevant websites regarding these drugs and COVID-19, adverse effects related to drugs, and related guidelines.

Aims and methods: We systematically searched the PubMed database up till March 21, 2020 and retrieved all the articles published on chloroquine and HCQ and COVID-19.

Results: Two small human studies have been conducted with both these drugs in COVID-19, and have shown significant improvement in some parameters in patients with COVID-19.

Conclusion: Considering minimal risk upon use, a long experience of use in other diseases, cost-effectiveness and easy availability across India, we propose that both these drugs are worthy of fast track clinical trial for treatment, and may be carefully considered for clinical use as experimental drugs. Since HCQ has been approved for treatment of diabetes in India, it should be further researched in diabetes and COVID-19, a subgroup where significant mortality has been shown.

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1. Introduction

Novel coronavirus (2019-nCoV), officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of the (Corona Virus Disease 2019) COVID-19, emerged in Wuhan, Hubei province, China. On 11th March 2020, The World Health Organization (WHO) declared this disease as pandemic [1]. Chinese Centre for Disease Control and Prevention showed an increased mortality in people with diabetes (2.3% vs. 7.3%; overall vs. in patients with diabetes respectively) from a report of 72,314 cases of COVID-19 [2]. People with diabetes and COVID-19 may need special attention and clinical care [3]. In the absence of any

known efficient therapy and because of the situation of a “public-health emergency”, many drugs have been tried recently in the treatment for COVID-19 that includes a low-cost antimalarial drug chloroquine and its derivative hydroxychloroquine (HCQ), along with several other antiviral drugs. Because HCQ 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 its impact in patients with diabetes, infected with COVID-19.

Reports gathered so far have suggested that a number of drugs could be potential candidates for the treatment of COVID-19, although the clinical effectiveness of these drugs have not yet been fully evaluated. The list of these drugs has been summarized in Table 1 [4–6].

In this review article, we have systematically searched the medical data base until March 21, 2020 and collated all the available evidences that have emerged so far on the efficacy of chloroquine and hydroxychloroquine, in the treatment of patients with COVID-

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Table 1
Drugs in pipeline for COVID-19^{4–6}

Drugs	Types	Mechanisms of action	Past evidences
Chloroquine	4-aminoquinoline	Not clearly known, changes the pH of endosomes and believed to prevent viral entry, transport and post-entry events	Inhibits infection of cells by SARS-CoV-2 <i>in vitro</i> , approved for malaria treatment and prophylaxis
Hydroxychloroquine	4-aminoquinoline	Not clearly known, changes the pH of endosomes and believed to prevents viral entry, transport and post-entry events	Inhibits infection of cells by SARS-CoV-2 <i>in vitro</i> , approved for malaria prophylaxis and autoimmune disease (e.g. rheumatic diseases). Approved for treatment of T2DM in India
Remdesivir	Adenosine nucleotide analogues	Inhibits viral application	Effective against SARS and MERS
Ribavirin	Nucleoside analogue	Inhibits viral RNA synthesis and mRNA capping	No evidence in SARS (potential harm) and MERS
Ribavirin plus Interferon		Inhibits viral replication	Mixed result against MERS
Camostat Mesilate	Protease inhibitors	Blocks viral maturation and entry to cells	Effectively blocked SARS-CoV-2 in lung cells <i>in vitro</i>
Lopinavir/Ritonavir	Protease inhibitors	Blocks viral cellular entry	Effective against SARS-CoV-1 both <i>in vitro</i> and human studies, approved for HIV-1 treatment
Darunavir/Cobicistat	Protease inhibitors	Blocks viral cellular entry	Established anti-HIV medication. No activity against coronaviruses or other respiratory viruses. No <i>in vitro</i> or clinical data.
Favipiravir	RNA polymerase inhibitors	Inhibits viral RNA-dependent polymerase	Broad-spectrum anti-viral against influenza, arenavirus, bunyavirus and filovirus
Umifenovir	Fusion inhibitor	Inhibits fusion between viral and cellular membrane	Antiviral against other Corona viruses
Interferon-β1	Cytokines	Stimulate innate antiviral immunity.	MERS-CoV appears to be more sensitive than SARS-CoV <i>in vitro</i> studies. Anti-MERS-CoV action noted in animal studies.
Interferon beta plus Lopinavir/Ritonavir		Interferon beta inhibits viral replication	Ongoing study for SARS-Cov-2 and MIRACLE trial for MERS
Aerosolized interferon α	Cytokines	Stimulate innate antiviral immunity.	Case report suggested benefit in MERS
Oseltamivir	Neuraminidase inhibitor	Inhibits viral replication	No effect in SARS <i>in vitro</i> studies. No evidence in SARS and MERS
Baloxivir marboxil	Viral endonuclease inhibitor	Inhibits influenza virus multiplication	Approved for uncomplicated influenza only. Oral route.
Tocilizumab, Sarilumab, Eculizumab	Monoclonal antibody	IL-6 inhibitor, blocks cytokine storm.	No data on SARS or MERS. Tocilizumab reduced fever and oxygen requirement in COVID-19, approved for rheumatoid arthritis.
SARS-Cov-2 specific protease drug candidate	Protease inhibitors	Blocks viral infectivity	No data available
SARS-Cov-2 specific antibodies	Antibody	Binds to virus and block infection, binds to infected cells and change the immune system	Inhibits SARS-CoV-2 entry into cells <i>in vitro</i>

SARS- severe acute respiratory syndrome, MERS- Middle-East respiratory syndrome, HIV- Human Immunodeficiency syndrome, T2DM – type 2 diabetes, COVID-19- Corona virus disease 19.

19, with or without diabetes and present a perspective on both these compounds. Additionally, we have also pooled the currently on-going trials with both these compounds against the COVID-19.

2. Methods

We systematically searched the PubMed database up till March 21, 2020 using key words chloroquine AND COVID-19, and hydroxychloroquine AND COVID-19 and retrieved a total of 13 articles. The two articles that were written in Chinese were excluded. In addition, we also accessed and retrieved the full text of the cross references of importance from these 11 articles written in English. Moreover, we also accessed the currently ongoing trials with both these compounds from [ClinicalTrials.gov](https://clinicaltrials.gov).

3. Results

3.1. Studies of chloroquine and hydroxychloroquine conducted *in vitro*

Experimental studies have suggested that chloroquine is a

proven anti-malarial drug that has the capability of inhibiting the replication of several intracellular micro-organisms including coronaviruses *in vitro*. It is also believed that chloroquine may have a varied mechanism of action which may differ depending upon the pathogen studied. It has been increasingly learnt that the anti-viral and anti-inflammatory activities of chloroquine may have a role in the treatment of patients with novel COVID-19. Chloroquine increases endosomal pH and interferes with the glycosylation of cellular receptor of SARS-CoV and thereby it has the potential to block viral infection [7]. 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. It is important to note that both human coronavirus HCoV-O43 and orthomyxoviruses uses sialic acid moieties as a receptor. Moreover, chloroquine changes the pH of lysosomes and likely inhibits cathepsins, that leads to the formation of the autophagosome which cleaves SARS-CoV-2 spike protein. Furthermore, chloroquine through the inhibition of MAP-kinase interferes with SARS-CoV-2 molecular crosstalk, besides altering the virion assembly, budding and interfering with the proteolytic processing of

the M protein [7,8]. Previous experimental studies have also demonstrated that chloroquine has potent anti-SARS-CoV-1 effects *in vitro*, primarily attributable to a deficit in the glycosylation receptors at the virus cell surface, so that it cannot bind to the angiotensin-converting enzyme 2 (ACE2) expressed in lung, heart, kidney and intestine. Since SARS-CoV-2 utilizes the similar surface receptor ACE2, it is believed that chloroquine can also interfere with ACE2 receptor glycosylation thus prevents SARS-CoV-2 attachment to the target cells [6–9]. Chinese researchers who studied the effect of chloroquine *in vitro* (using Vero E6 cell line infected by SARS-CoV-2) found chloroquine to be highly effective in reducing viral replication that can be easily achievable with standard dosing due to its favorable penetration in tissues including the lung [6,10].

Since the structure and mechanism of action of chloroquine and hydroxychloroquine (HCQ) are exactly same except an additional hydroxy moiety in one terminal in HCQ, both act as a weak base that can change the pH of acidic intracellular organelles including endosomes/lysosomes, essential for the membrane fusion. It is believed that both the agents could be effective tools against SARS-CoV-1 and SARS-CoV-2 [10,11]. However, an important question that still remains is whether HCQ has a similar effect on SARS-CoV-2 infection. Some data show HCQ effectively inhibited both the entry, transport and the post-entry stages of SARS-CoV-2, similar to the chloroquine and one study found HCQ to be a more potent agent than chloroquine in inhibiting SARS-CoV-2 *in vitro* [12,13]. In addition, HCQ acts effectively on other intracellular bacterial infections such as *Coxiella burnetii* (Q fever) and *Tropheryma whipplei* (Whipple's disease) [14,15]. Addition of hydroxyl molecule makes HCQ less permeable to blood-retinal barrier and allows faster clearance from retinal pigment cell, thereby suggesting a lesser risk of retinal toxicity with HCQ, as compared to chloroquine [16]. Furthermore, the narrow therapeutic and safety index margin with chloroquine makes HCQ a safer option than chloroquine.

An additional issue to be considered in severely sick patients is cytokine storm associated with disease severity of SARS-CoV-2 [17]. The significant decrease in the production of pro-inflammatory markers and cytokines with HCQ has made this agent a successful disease modifying anti-inflammatory agent in the treatment of various autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus and Sjogren's syndrome. Long-term clinical safety profile of HCQ is better than that of chloroquine, that allows higher daily dose of HCQ with less drug-drug interactions.

3.2. Studies conducted with chloroquine and hydroxychloroquine in human COVID-19

The anti-viral and anti-inflammatory actions of chloroquine have led to numerous trials urgently in the face of global health emergency. A Chinese study involving more than 100 patients of COVID-19 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 [18]. This represents the first human trial ever conducted with chloroquine against COVID-19. Although the detailed results of this trial are not yet published and only available in a letter form, interestingly, this early result led China to include chloroquine in the prevention and treatment of COVID-19 pneumonia. Moreover, The National Health Commission of the People's Republic of China recommended inclusion of chloroquine in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19. In this study, chloroquine was given in dose of 500 mg of chloroquine twice daily in mild to severe COVID-19 pneumonia (see Table 1).

The second human study which is currently available was conducted with HCQ. In an open-label, non-randomized trial ($n = 36$) 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 (measured by polymerase chain reaction [PCR]) in only three-to six days in COVID-19 subjects, compared to control. The virological clearance day-6 post-inclusion (primary outcome) with HCQ vs. control was 70.0% versus 12.5%, respectively ($p = 0.001$). In addition, the virological clearance at day-6 post-inclusion in HCQ plus azithromycin, HCQ and control arm was 100%, 57.1% and 12.5% respectively ($p < 0.001$). This data suggests a synergistic effect of azithromycin with HCQ. Indeed, azithromycin has shown an antiviral effect against Zika and Ebola viruses in *in vitro* studies; however, it is not yet known whether it has any action against COVID-19 as well [19]. These results of converting a potential carrier to a seronegative patient are of importance with regards to preventing community transmission of COVID-19. Since the data from Wuhan, China showed that some patients were carrier as long as up to 37 days (usually around 20 days), results of this study are very encouraging in the context of converting a patient to a seronegative subject within 6 days. Interestingly, this study also showed that the effect of HCQ was significantly higher ($p < 0.05$) in symptomatic patients as compared to asymptomatic patients with COVID-19. The authors have acknowledged limitations of the study; a small sample size, dropout of six patients and limited follow-up, apart from the non-randomized and open-label nature of the trial. A close look in to this study also suggests that the Cycle threshold (Ct) value for nasopharyngeal swab PCR to call it as a sample negative, was lower (Ct value > 35 was deemed as negative for virus) compared to conventional Ct threshold of >40 . Ct is defined as the number of cycles to be run for the PCR test to turn positive. In other words, lower the number of Ct denotes more virus is present and lesser number of cycles are required to hit the threshold. Moreover, nasopharyngeal swab PCR is a less sensitive tool, compared to PCR of Broncho-alveolar lavage and sputum in COVID-19. Furthermore, exclusion of five patients (26%) receiving HCQ from the overall analysis, exaggerate the final results of this study.

Nevertheless, based on limited available evidences to date, and given the prevailing pandemic of COVID-19, some of the institutions and or organizations have already recognized the utility of chloroquine and HCQ [20]. The expert consensus from the Department of Science and Technology and Health Commission of Guangdong province published on 20th February (based on *in vitro* evidence and still unpublished clinical experience) chloroquine phosphate tablet at a dose of 500 mg twice per day for 10 days for patients diagnosed as mild, moderate and severe cases of SARS-CoV-2 pneumonia in the absence of contraindication to the drug [21]. A Central Clinical Task Force from Korea who have treated 27 cases of COVID-19 recommend using lopinavir 400mg/Ritonavir 100 mg BID or Chloroquine 500 mg orally per day or Hydroxychloroquine 400 mg orally per day for 7–10 days, in moderate to severe case of COVID-19 [22]. Similarly, The Dutch Center of Disease control in a public document on its website, also suggested the use of chloroquine in those having severe COVID-19 infection admitted in the intensive care unit [23]. Table 2 summarizes the recommendation and dosing from all the various groups [21–28].

4. Discussion

The antiviral activity of chloroquine and HCQ have been identified in the *in vitro* studies and the growth of many different viruses have been inhibited in the cell culture line by both the agents, including the SARS coronavirus. Mice studies have also demonstrated activity of these agents against human coronavirus OC43,

Table 2Available Guidelines (as of March 21, 2020) in the treatment of COVID-19 for Chloroquine and Hydroxychloroquine.^{19,21–28}

Study/Guidelines/Country	Dose (adults)
Expert consensus from Department of Science and Technology and Health Commission of Guangdong province, China ²¹ Central Clinical Task Force, Korea ²²	Chloroquine phosphate 500 mg BID for 10 days. <u>Moderate to severe COVID-19:</u> Lopinavir 400mg/Ritonavir 100 mg BID or Chloroquine 500 mg orally per day or Hydroxychloroquine 400 mg orally per day for 7–10 days. <u>URTI plus positive PCR:</u> • Chloroquine phosphate 500 mg BID for 5 days. • Oseltamivir 150 mg BID for 5 days.
Centre for Disease Control and Prevention, Atlanta, MICC Version 1 (March 12, 2020) ²³	<u>COVID-19 Pneumonia:</u> • Chloroquine phosphate 500 mg BID for 5 days plus Darunavir 800 mg/ Cobicistat 150 mg OD for 2 weeks. • Atazanavir 400 mg OD for 2 weeks plus Oseltamivir 150 mg BID for 5 days. 600 mg of Chloroquine base followed by 300 mg after 12 h on day 1, then 300 mg × 2/day per person on days 2–5.
The Dutch Center of Disease Control ²⁴	<u>Mild to moderate COVID-19:</u> Lopinavir/ritonavir plus Chloroquine 500 mg × 2/day or Hydroxychloroquine 200 mg per day for 10 days.
Italian Society of Infectious and Tropical Diseases (Lombardy Section) ²⁵	<u>Severe or critical COVID-19:</u> Remdesivir plus Chloroquine 500 mg × 2/day or Hydroxychloroquine 200 mg per day for 10–20 days.
Mount Sinai Health System, Canada ²⁶	<u>Moderate to severe COVID-19:</u> Hydroxychloroquine 400 mg BID x 2 doses then 12 h later start 400 mg OD for 5–10 days.
Surviving Sepsis Campaign, The Society of Critical Care Medicine and the European Society of Intensive Care Medicine. ²⁷	Insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19 at this point of time.
Clinical guidance for patients with suspected or confirmed COVID-19 in Belgium ²⁸	<u>Mild/Moderate/Severe COVID-19:</u> Hydroxychloroquine 400 mg at diagnosis, 400 mg 12 h later, followed by 200 mg BID for 5 days, Or, Chloroquine 600 mg at diagnosis and 300 mg 12 h later followed by 300 mg BID for 5 days (Consider lopinavir 400 mg/ritonavir 100 mg BID for 14 days as a second choice only if HCQ and chloroquine is contraindicated, provided it can be administered within 10 days after onset of symptoms) <u>Critical COVID-19:</u> Remdesivir 200 mg loading dose i.v within 30 min followed by 100 mg OD for 2–10 days (Hydroxychloroquine is second option if Remdesivir is unavailable)
Clinical guidance for patients with suspected or confirmed COVID-19 in Netherland ²⁸	<u>Mild/moderate/severe COVID-19:</u> Chloroquine 600 mg on day 1, then 300 mg BID for 5 days (lopinavir/ritonavir as second option) <u>Critical COVID-19:</u> Remdesivir for 10 days plus chloroquine for 5 day Hydroxychloroquine 200 mg TID for 10 days.
Gautret et al., Marseille, France ¹⁹	

OD-once daily, BID-twice daily, TID-thrice daily, URTI- upper respiratory tract infection, PCR-polymerase chain reaction, i.v - intravenous.

enterovirus EV-A71, Zika virus and influenza A H5N1. However, no benefit of chloroquine was seen in the prevention of influenza and dengue infection in a randomized, double-blind, placebo-controlled, clinical trial [29,30]. Similarly, chloroquine was active in *ex vivo* studies but not in the *in vivo* studies against ebolavirus, nipah and influenza viruses [31–33]. Data of chloroquine against chikungunya virus is even more intriguing. While chloroquine had satisfactory antiviral activity against chikungunya *in vitro*, animal studies showed increase in virus replication, aggravation of fever and incomplete viral clearance [34]. Human trials of chloroquine showed no improvement in chikungunya acute illness and rather an increase in chronic arthralgia was observed during post-illness period, compared to the controls [35]. The role of chloroquine against Human Immunodeficiency Virus was inconclusive [36]. The only viral disease where chloroquine was modestly effective so far before COVID-19 era was chronic hepatitis C suggesting an increased virological response to pegylated interferon plus ribavirin [37]. Therefore, the results of chloroquine and HCQ so far done against COVID-19, more promising than previous trial in other viral diseases. Moreover, these drugs are of low cost, reasonably safe (see below), and widely available in countries where malaria is endemic.

4.1. Cautions and contraindication with chloroquine and hydroxychloroquine

Expectedly, some precautions will be needed while using both these drugs that include frequent monitoring of hematological parameters (RBC, WBC and platelet counts), measurement of

serum electrolytes, blood glucose (because of hypoglycemic potential of HCQ) and hepatic as well as renal functions. Since both these drugs have the potential to prolong QTc, routine electrocardiography is essential prior to starting these drugs. Co-administration of other drugs known to prolong the QTc interval (such as anti-arrhythmic, anti-depressants, anti-psychotics, anti-histaminic, teneligliptin, ondansetron and moxifloxacin etc.) must be avoided [38,39]. Moreover, addition of azithromycin to HCQ as done in French trial by Gautret et al. may increase the risk of QTc prolongation. Perform ECG daily if QTc is 450–500 msec. Additionally, hypoglycemia must be looked for in patients with diabetes especially with concurrent use of chloroquine/HCQ and lopinavir/ritonavir. Chloroquine and HCQ should not be used concurrently with lopinavir/ritonavir and remdesivir for anticipated QTc prolongation. Finally, pharmacovigilance on visual and mental disturbance is also closely required.

Although there are sporadic case reports of chloroquine-induced cardiomyopathy and reversible heart failure in the literature, many studies and large meta-analysis conducted in patients with rheumatoid arthritis pointed to a reduced cardiovascular risk with both these compounds [40]. Nevertheless, since both the drug has potential to prolong QTc, a baseline ECG should be done in patients with established cardiovascular disease.

All clinicians using these drugs must know contraindication to both these compounds; hypersensitivity to these agents, retinopathy, porphyria, epilepsy, pre-existing maculopathy, G6PD deficiency, recent myocardial infarction and QTc >500 msec. Chloroquine is not contraindicated in pregnancy.

Table 3

Based on the available evidence so far (including *in vitro*, *ex vivo* and *in vivo* studies – both experimental and two human studies) and considering the benefit-risk ratio as well as the low cost of chloroquine and hydroxychloroquine in Indian context, we propose the following regime, until more evidence is available –

Timing of intervention	Proposed
Chemoprophylaxis	<ul style="list-style-type: none"> No conclusive evidence so far; however, chloroquine or HCQ could be researched as a prophylactic agent in endemic areas. Recent guidelines from Indian Council of Medical Research recommend it as prophylactic agent (see reference 42 for indication and dose) Note: HCQ can be used as an adjunct to control glycemia in adult patients with type 2 diabetes (approved for treatment in India). However, role of such adjunctive treatment for testing its potential role as a prophylaxis of COVID-19 in diabetes, has not been researched but could be attempted (in view of above) considering a higher mortality in patients with diabetes, as compared to non-diabetic subjects with COVID-19.
Confirmed COVID-19	<p>A. Chloroquine phosphate: [@]</p> <ol style="list-style-type: none"> COVID-19 URTI: 500 mg BID for 5 days. COVID-19 LRTI: 500 mg BID for 10 days. <p>B. Hydroxychloroquine: [@]</p> <p>Loading dose: 400 mg BID day 1, then</p> <p>Maintenance dose: 200 mg BID for 5–10 days.</p> <p>C. Monitor and watch for side effects*</p>

@ watch for hypoglycemia in diabetes especially with concurrent use of lopinavir/ritonavir, \$ should not be used concurrently with lopinavir/ritonavir and remdisivir due to increased QTc prolongation, * complete blood count, renal, hepatic profile and ECG – watch for QTc prolongation, URTI- upper respiratory tract infection, LRTI- lower respiratory tract infection, HCQ-hydroxychloroquine, BID – twice daily.

Table 4

Ongoing trials with chloroquine and hydroxychloroquine as of March 21, 2020.

Study title	Types of intervention	Intervention vs. comparator	n	Country	ClinicalTrial.Org identifier
Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COVID19: A Randomized Control Trial (THDMS-COVID19)	Treatment	Antiviral drugs plus Chloroquine PBO	80	Thailand	NCT04303299
Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV)	Prophylaxis	Chloroquine PBO	10,000	UK	NCT04303507
Treatment of Mild Cases and Chemoprophylaxis of Contacts as Prevention of the COVID-19 Epidemic (HCQ4COV19)	Treatment and prophylaxis in two separate groups	Darunavir/Cobicistat plus Chloroquine PBO	3040	Germany	NCT04304053
The Clinical Study of Carrimycin on Treatment Patients With COVID-19	Treatment	Carrimycin Lopinavir/ritonavir Arbidol Chloroquine PBO	520	China	NCT04286503
Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients with Mild Coronavirus Disease (COVID-19)	Treatment	Lopinavir/ritonavir HCQ	150	Korea	NCT04307693
Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV)	Treatment	HCQ PBO	30	China	NCT04261517
Post-exposure Prophylaxis for SARS-Coronavirus-2	Post exposure prophylaxis	HCQ PBO	1500	United States	NCT04308668

HCQ-hydroxychloroquine, PBO- placebo, N - number.

5. Conclusion

Although evidence of chloroquine and HCQ is limited (based on the experimental data and only two small human trials), considering the potentially favorable benefit-risk balance of chloroquine and HCQ in absence of any other valid treatment option, we believe that such treatment could be useful in the current context of pandemic COVID-19 outbreak. We have summarized current consideration and proposed line of management in Table 3. The low cost of chloroquine and HCQ could also be an effective strategy to counter COVID-19 (especially in patients with diabetes and other co-morbidities in whom mortality is high) in resource constrained and COVID-19 overburdened health care systems in middle- and low-income countries including India.

Future directions:

1. Intervention trials planned for COVID-19: Several trials are currently underway with both chloroquine and HCQ in patients with COVID-19 at different doses. A search of The ClinicalTrial.org database dated March 21, 2020 showed 4 trials with chloroquine and 3 trials with HCQ which is currently under progress and have been summarized in Table 4. A list of 23 trials are already enlisted with both compounds at Chinese Clinical Trial Registry (<http://www.chictr.org.cn>) [41]. We believe that it

would be wise to conduct a quick interim analysis from these trials as soon as possible to find out the results that can be applied to the masses across the globe to curb the menace of COVID-19 pandemic.

2. Research for resistance to drugs in already mutating virus strains: Another area which needs to be explored further is resistance to chloroquine and HCQ that may be present with different strains of the virus.
3. Role of these drugs in COVID-19 chemoprophylaxis: Another knowledge gap that still remains is about role of these drugs in chemoprophylaxis. We still do not know whether these compounds can be useful to prevent the transmission of the virus, especially for healthcare workers. This needs to be tested in further studies.
4. Use of HCQ in patients with diabetes in India where it is already approved for treatment: It would be interesting to research COVID-19 infection in patients with diabetes who are already on HCQ for treatment of diabetes. Further, the effect of HCQ on glycemia, cardiovascular function and viral load, in patients with diabetes needs to be researched.

Declaration of competing interest

We hereby declare that we have no conflict of interest related to

this article.

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