Use Of Chloroquine And Hydroxychloroquine In COVID-19 Patients- A Dilemma

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ABSTRACT: The terror of COVID-19 is present universally. The number of cases is on rise. There is always debate about use of chloroquine and hydroxychloroquine as a prophylaxis. Healthcare workers being the front line soldiers need additional protection as compared to general population. This review article highlighted the mechanism of action of both drugs and their role in COVID-19 patients.

Key words: Chloroquine, COVID-19, Hydroxychloroquine

Key message: COVID-19 infection is spreading globally and hence the use of chloroquine and hydroxychloroquine may be beneficial.

1. INTRODUCTION

In December 2019 in Wuhan city of China, there was sudden outburst of coronavirus disease 2019 (COVID-19) which extended over 90% of countries universally and became health emergency of international concern.¹ A novel coronavirus was affirmed as causative agent of COVID-19 by Chinese center for disease control and prevention on January 8th, 2020.² World Health Organization (WHO) on January 30, 2020 confirmed this outbreak as a public health disaster of international status with mortality rate to be 3.4%. Considering its spread all over the world, WHO in March 2020 declared it as Pandemic disease.³

Structure

Coronaviruses are single stranded RNA viruses and the term novel is being used considering it to be new virus to already existing coronavirus family Coronaviridae. The term corona designates to crown shape of the proteins that coat them. This virus is highly infectious and its resemblance to coronavirus species seen in bats and potentially pangolins have been confirmed in recent research thus it is found to be zoonotic in origin ie animals to humans transmission.⁴
Severe acute respiratory syndrome coronavirus (SARS-CoV) was first recognized in year 2002, and the middle-east respiratory syndrome coronavirus (MERS-CoV) was first acknowledged in year 2012. Covid-19 is now called as SARS-CoV-2.\[5\]

**Epidemiology**

In India, as on 17 September 2020, 08:00 IST (GMT+5:30), there are total cases of 51,18,253, of which, 83198 deaths reported.\[6\] [Table 1] As reported by WHO, Globally, as of 5:18pm CEST, 11 August 2020, there have been 19,936,210 confirmed cases of COVID-19, including 732,499 deaths.\[7\] [Table 2]

Globally, as of 10:53am CEST, 17 September 2020, there have been 29,679,284 confirmed cases of COVID-19, including 936,521 deaths, reported to WHO.

**Clinical symptoms**

Patient present with prodromal symptoms such as cold- or flu-like symptoms usually appears 2–4 days after a coronavirus infection. However, there can be variations in symptoms from person-to-person. The most common symptoms are high grade fever, dry cough, shortness of breath or dyspnea and fatigue or tiredness.\[8\] Some patients may experience myalgia or muscle pain, headache, sore throat, vomiting and diarrhea. There can be diminished sense of smell (hyposmia) and abnormal taste sensation (dysguesia).\[9\] Computed tomographic (CT) scan shows ground-glass opacities, bilateral patchy shadows and bilateral pneumonia in the chest. Severe patients may develop arrhythmia and shock which need ventilatory support.\[10\]

**Management**

The management of positive cases is by supportive therapy only. Many clinical trials are being conducted worldwide but till date no vaccine has been invented. According to Center of Disease control (CDC) so far, there are no US Food and Drug Administration (FDA)-approved drugs for the management of COVID-19 infected patients.\[11\] The treatment is focused on prevention of infection by adhering to universal WHO recommended safety measures which includes proper hand washing with soap for atleast 20 seconds, disinfection of frequently touched surfaces, maintaining physical distance of 3 meters or 6 feet, usage of mask and preventing social gathering.\[12\] Supportive care comprise of use of hydration, antipyretics, analgesics, and antitussives. Asymptomatic patients are advised to self-isolate for at least 7 days after a positive test result. Symptomatic positive COVID-19 patients are hospitalized where they remain under close observations for 21 days and are managed based on symptoms.\[13\] There oxygen level is maintained via high-flow oxygen or noninvasive positive pressure ventilators. In severe cases, patient may develop acute respiratory distress syndrome which requires intubation with mechanical ventilation in an intensive care unit setting.\[14\]

Many antiviral drugs such as remdesivir, favipiravir, chloroquine (CQ)/hydroxychloroquine (HCQ), convalescent plasma, IL-6 inhibitors and lopinavir- ritonavir have been proposed in the treatment of COVID-19 time to time.\[15\] Their effectiveness is being assessed and they are under clinical trials.

**Chloroquine/ Hydroxychloroquine**

Chloroquine (CQ) was first synthesized in 1934 and is the main drug for the prevention and treatment of malaria. They are routinely used in autoimmune conditions including systemic lupus erythematosus (SLE), porphyria cutanea tarda, rheumatoid arthritis, Q fever and also acts as immunomodulating agent.\[16\] Later on in year 1955, Hydroxychloroquine (HCQ), a derivative of CQ became available in the market. It proved to be better with additional outcomes and less side effects.\[17\] They are lipophilic weak bases that quickly pass across cell membranes and gather in acidic organelles, such as lysosomes, golgi and endoplasmic reticulum. These drugs are active against Plasmodium parasites, the causative agent of malaria which acts by interacting with parasites DNA causing inhibition of the polymerization of heme.\[18\]
HCQ shows its anti-inflammatory properties by increasing the pH within intracellular vacuoles and endosomes, thus interferes with antigen processing in macrophages and antigen-presenting cells. CQ/HCQ shows antibacterial, antiviral and antifungal activities. It is found to be active against HIV, polio virus, rabies virus, herpes simplex virus and hepatitis B virus. Chloroquine is available for oral administration in tablet form as Chloroquine phosphate 500 mg and hydroxychloroquine sulfate 200 mg. A maximum dose of 2000 CQ and HCQ are used in active malarial cases. The mean half life of CQ is 22 days and for HCQ is 20-60 days. The peak plasma concentration of CQ found to be 30 minutes and that of HCQ is 3-4 hours.

Nausea, vomiting and diarrhea are frequent side effects of these drugs. Arnaout et al[21] assessed the use of CQ and observed nausea and abdominal cramps in 24% and diarrhea in 17% of breast cancer patients. Furst et al[22] found GIT side effects with dose of 800 mg HCQ in patients of rheumatoid arthritis.

**Mechanism of action**

The mechanism of action of hydroxychloroquine/chloroquine against COVID-19 is still to be fully explained. Chloroquine was first studied in SARS-CoV for the SARS coronavirus epidemic in year 2002–2003. There is 79% of genetic sequence similarity of SARS-CoV and SARS-CoV-2.[23]

**Hindrance of cell membrane fusion**

Various cellular proteases such as trypsin, elastase, cathepsin L etc. actively participate in cell membrane fusion of SARS-CoV-2 by after causing endocytosis in the presence of triggering factors such as proteolytic activation.[24] CQ/HCQ may involve the interference of the endosome acidification process, which might inactivate lysosomal proteases, thus interfering with the fusion of virus and host membranes.[25]

**Inhibition of receptor recognition process**

SARS-CoV-2 virus has its S protein which when enters in host body is broken down into two subunits such as S1 and S2. SARS-CoV-2 attaches to the angiotensin-converting enzyme 2 (ACE2) receptors whereas S2 binds with cell membrane. CQ and HCQ may inhibit terminal glycosylation by preventing virus attachment to receptors.[26]

de Wilde et al[27] assessed the efficacy of CQ against MERS-CoV and HCoV-229E in the human hepatoma cell line (Huh-7) and found that CQ was effective in hindering replication cycle of MERS-CoV. There was 3.0 μM concentration of CQ and 3.3 μM of HCQ. Study provided that the selectivity indexes of CQ were 19.4 and for HCQ were more than 15. It was found that addition of 16μm of CQ 1 hour before MERS-CoV infection decreased the production of virus by 1-log and with 32μM concentrations of CQ by 2-logs. Cortegiani et al[28] in their invitro study evaluated the role of HCQ on Vero E6 cells infected with SARS-CoV-2 found significant reduction in viral replication with an effective concentration (EC) 90 of 6.90 μM.

**Inhibition of T cell activation and cytokine production**

CQ/HCQ prevents T cell activation and obstructs expression of CD154 on the surface of CD4 + T cells. They cause change in pH of endosomes, thus decrease cytokines production such as interleukin (IL)-1, IL-6 and tumor necrosis factor-α (TNF-α) from T cells and B cells.[29] Huang et al[30] and Chen et al[31] in their studies have observed increased level of cytokines and pro-inflammatory factors such as IL-6 and IL-10 in SARS-CoV-2 patients, concluding that cytokine release syndrome (CRS) is associated with disease severity.

**Alteration of cell signaling pathway and host defense mechanism**

It is established that there is transmission of signals from surface of cell to its nucleus such as SARS-CoV through mitogen-activated protein kinase (MAPK) pathway delivers.[32] HCQ could lead to formation of cellular reactive oxygen species (ROS), which are necessary for
activation of innate immunity. Thus, CQ/HCQ can both suppress the activation of p38 MAPK pathway and affect the host defense mechanism.\textsuperscript{[10]}

Gao et al\textsuperscript{[33]} conducted a clinical study in more than ten Chinese hospitals to assess the efficacy of chloroquine on pneumonia associated in COVID-19 positive patients. They recommended 500 mg of chloroquine per day for ten days to their patients. They suggested that chloroquine is efficacious in treating pneumonia in COVID-19 positive patients because of its anti-viral and anti-inflammatory properties.

Yao et al\textsuperscript{[34]} in their in vitro study evaluated pharmacological properties of chloroquine and hydroxychloroquine on SARS-CoV-2 infected Vero cells. It was found that chloroquine was highly efficient in controlling 2019-nCoV infection. Hydroxychloroquine was more potent than chloroquine in inhibiting SARS-CoV-2 in vitro.

It is not very clear whether to consume or not to consume CQ or HCQ as a precautionary measure or to treat COVID-19 in malaria endemic areas. It may have impact on local malaria prevalence. Subjects consuming CQ or HCQ by its own without medical consultation would become plasmodium asymptomatic carriers.\textsuperscript{[35]} This may lead to decrease or inhibition of parasite count and mostly if CQ-sensitive strains supplants CQ-resistant strains. After stopping of drugs, there are chances that malaria would rebound itself because of deficiency of control measures. In addition, as CQ-resistant strains are still circulating, CQ intake could result in selection of resistant strains bearing mutations on some Plasmodium genes involved in drug resistance. Coppee et al\textsuperscript{[36]} assessed possible association between some Plasmodium genes and altered activity of other antimalarials such as Artemisinin-based combination therapy. Author suggested that long use of CQ or HCQ may lead to emergence of malarial resistant strains. Singh et al\textsuperscript{[37]} in their meta-analysis of 3 studies on assessing the efficacy of hydroxychloroquine (HCQ) on control as well as on COVID-19 subjects which focused on viral clearance measured by reverse transcriptase polymerase chain reaction (RT-PCR) found no benefit on COVID-19 subjects. There were more deaths with the use of HCQ as compared to control. Authors found increase mortality rate with HCQ.

2. CONCLUSION

Chloroquine and hydroxychloroquine are relatively cheap, readily available and has few side effects. There are few clinical trials who warned the use of CQ/HCQ in COVID-19 patients due to high mortality rates compared to control whereas other found good results too. There is insufficient evidence that strongly recommend these drugs in management of COVID-19 positive patients. The present study has not sufficient data to support the use of CQ/HCQ in COVID-19 patients and increasing care should be taken about the application of CQ/HCQ in COVID-19.

| Location   | Total cases | Cases per 1 million | Recovered | Death |
|------------|-------------|---------------------|-----------|-------|
| Maharashtra| 11,21,221   | 9,819               | 7,92,832  | 30,883|
| Andhra Pradesh | 5,92,760 | 12,002             | 4,97,376  | 5,105 |
| Tamil Nadu | 5,19,860   | 7,661               | 4,64,668  | 8,559 |
| Karnataka | 4,84,990   | 7,571               | 3,75,809  | 7,536 |
| Uttar Pradesh | 3,30,265 | 1,617               | 2,58,573  | 4,690 |
| Delhi     | 2,30,269   | 12,130              | 1,94,516  | 4,839 |
| West Bengal | 2,12,383  | 2,351               | 1,84,113  | 4,123 |
| Odisha    | 1,67,161   | 3,823               | 1,29,859  | 669   |
| Telangana | 1,65,003   | 4,688               | 1,33,555  | 1,005 |
| Bihar     | 1,62,463   | 1,641               | 1,48,656  | 848   |
| Assam     | 1,48,969   | 4,814               | 1,19,367  | 511   |

Table 1 COVID-19 statistics in India
| Region                  | Confirmed cases |
|-------------------------|-----------------|
| Americas                | 15,095,403      |
| South East Asia         | 5,768,599       |
| Europe                  | 4,957,363       |
| Eastern Mediterranean   | 2,165,277       |
| Africa                  | 1,127,164       |
| Western Pacific         | 564,790         |

Data last updated: 2020/9/17, 10:53am CEST

| Table 3 Studies of HCQ compared to placebo in patients with COVID-19 |
|---------------------------------------------------------------|
| **Study** | **Patient’s mean age** | **Country** | **Case: Control** | **HCQ dose/day X Day** | **Primary outcome** | **Secondary outcome** |
|---------------------|-------------------------|--------------|-------------------|------------------------|---------------------|----------------------|
| Molina et al38      | 42.5 years              | France       | 11:0              | 600g/day X 10 days+ Azithromycin 500 mg X 3 days | Improvement in pneumonia symptoms | 1 died, 2 transferred to ICU |
| Barbosa              | 62.7                    | USA          | 32:31             | 800 mg/d X              | Requirement         | Change in           |
et al.19

1-2 days followed by 200-400 mg OD X 3-4 days of respiratory support/ intubation on day 5

lymphocyte count, NLR and mortality

Gautret et al.40

45.1 years France 20:16 600g/day X 10 days Viral load by RT-PCR + vs. - at day 6 Improvement in symptoms

Mahevas et al.41

60 France 84:97 600g/day X 7 days ICU transfer and death on day 7 All-cause mortality on day 7, Occurrence of ARDS within 7 days

Jun et al.42

NR China 15:15 400g/day X 5 days Viral load by RT-PCR + vs. - at day 7 NR

3. REFERENCES
[1] https://www.pasteur.fr/fr/centre-medical/fiches-maladies/coronaviruswuhan. [Accessed 26 March 2020].
[2] https://www.who.int/fr/emergencies/diseases/novel-coronavirus2019/advice-for-public/q-a-coronaviruses. [Accessed 26 March 2020].
[3] https://www.who.int/docs/default-source/coronaviruse/situationreports/20200402-sitrep-73-covid-19.pdf?sfvrsn=5ae25bc7_4. [Accessed 2 April 2020].
[4] Zhu NA, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
[5] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected Pneumonia. N Engl J Med 2020. doi:10.1056/NEJMoa2001316.
[6] https://www.mygov.in/covid-19.
[7] https://covid19.who.int/
[8] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, Liu L, Shan H, Lei C-L, Hui DS, et al. 2020. Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv. doi:10.1101/2020.1102.1106.20020974.
[9] Yang Y, Lu Q, Liu M, Wang Y, Zhang A, Jalali N, Dean N, Longini I, Halloran ME, Xu B, et al. 2020. Epidemiological and clinical features of the 2019 novel coronavirus outbreak in China. medRxiv. doi:10.1101/2020.1102.1110.20021675.
[10] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. 2020. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA [epub ahead of print 7 Feb 2020] in press. doi:10.1001/jama.2020.1585.
[11] Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today’s diseases? Lancet Infect Dis 2003;3:722–7.
[12] Disposition of Non-Hospitalized Patients with COVID-19. Centers for Disease Control and Prevention. Available at: www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-inhome-patients.html. Accessed Apr 10, 2020.
[13] Return-to-Work Criteria for Healthcare Workers. Centers for Disease Control and Prevention. Available at: www.cdc.gov/coronavirus/2019-ncov/hcp/return-to-work.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2FHealthcare-facilities%2Fhfc-p-return-work.html. Accessed Apr 13, 2020.

[14] Management of Patients with Confirmed 2019-NCoV. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Centers for Disease Control and Prevention. Available at: www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidancemanagement-patients.html. Accessed Apr 6, 2020.

[15] Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020 [Epub ahead of print].

[16] Tönnesmann E, Kandolf R, Lewalter T. Chloroquine cardiomyopathy - A review of the literature. Immunopharmacol Immunotoxicol 2013; 35:434–42.

[17] Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. Clin Rev Allergy Immunol 2012; 42:145–53.

[18] Concordia Pharmaceuticals Inc. Plaquenil Hydroxychloroquine Sulfate Tablets, USP; 2017.

[19] Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Semin Arthritis Rheum 1993;23(2 Suppl 1):82–91.

[20] Ducharme J, Farinotti R. Clinical pharmacokinetics and metabolism of chloroquine. Focus on recent advancements. Clin Pharmacokinet 1996; 31:257–74.

[21] Arnaout A, Robertson SJ, Pond GR, et al. A randomized, double-blind, window of opportunity trial evaluating the effects of chloroquine in breast cancer patients. Breast Cancer Res Treat 2019; 178:327–35.

[22] Furst DE, Lindsley H, Baethge B, et al. Dose-loading with hydroxychloroquine improves the rate of response in early, active rheumatoid arthritis: a randomized, double-blind six-week trial with eighteen-week extension. Arthritis Rheum 1999; 42:357–65.

[23] Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395:565–74.

[24] Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses. 2012;4(6):1011-1033.

[25] Simmons G, Zmora P, Gierer S, Heinrich P, Pöhlmann S. Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. J Antimicrob Chemother. 2013;100(3):605-614.

[26] de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother. 2014;58(8):4875-4884.

[27] Cortegiani A, Ingoglia G, Ippolito M. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care 2020 March https://doi.org/10.1016/j.jcrc.2020.03.005.

[28] Jang CH, Choi JH, Byun MS, Jue DM. Chloroquine inhibits production of TNF-alpha, IL-1beta and IL-6 from lipopolysaccharide-stimulated human monocytes/macrophages by different modes. Rheumatology (Oxford). 2006;45(6):703-710.
[29] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. 47.
[30] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-51.
[31] Kopecky-Bromberg SA, Martinez-Sobrido L, Palese P. 7a protein of severe acute respiratory syndrome coronavirus inhibits cellular protein synthesis and activates p38 mitogen-activated protein kinase. J Virol. 2006;80(2):785-793.
[32] Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020. https://doi.org/10.5582/bst.2020.01047.
[33] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. In Vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). Clin Infect Dis 2020 Mar 9.
[34] Mvumbi DM, Bobanga L, Melin P, De Mol P, Kayembe N, Situakibanza NT, et al. High prevalence of Plasmodium falciparum infection in asymptomatic individuals from the Democratic Republic of Congo. Malar Res Treat 2016, Article ID 5405802. pmid:26942036.
[35] Coppée R, Sabbagh A, Clain J. Structural and evolutionary analyses of the Plasmodium falciparum chloroquine resistance transporter. Sci Rep 2020;10:4842.
[36] Singh AK, Singh A, Singh R, Misra A. Hydroxychloroquine in patients with COVID-19: A Systematic Review and meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14: 589-596.
[37] Molina JM, Delaquerre C, Goff JL, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect 2020; In Press
[38] Barbosa J, Kaitis D, Ryan F, Kim L, Xihui L. Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: a quasi-randomized comparative study. Biblio 2020.
[39] Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.32205204.
[40] Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medRxiv 2020. 2020.04.10.20060699.
[41] Jun C, Danping L, Li L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ 2020. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03.