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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.[19] 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.[20]

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 interferance 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 SARSCoV-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.[10]

Gao et al [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 [34] in their 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.[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 [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 [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.

Table 1 COVID- 19 statistics in India

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

Kerala	1,22,394	3,517	87,345	490
Gujarat Rajasthan	1,17,547 1,07,680	1,875 1,563	98,029 89,352	3,256 1,279
Haryana	98,622	3,890	77,166	1,026
Madhya Pradesh Punjab	95,515 87,184	1,302 3,116	71,535 63,570	1,844 2,592
Chhattisgarh Jharkhand	73,966 66,074	2,298 2,071	35,885 51,357	611 579
Jammu and Kashmir Ladakh	58,244 3,535	4,641 12,888	37,809 2,536	932 46
Uttarakhand	35,947	3,565	24,432	447
Goa+ Puducherry	26,139+ 21,111	14,386 15,139	20,445 15,923	319 418
Tripura	20,676	5,652	12,956	222
Himachal Pradesh	10,795	1,575	6,558	91
Manipur	8,320	2,913	6,521	48
Arunachal Pradesh Nagaland	6,692 5,263	5,332 2,313	4,787 3,987	13 15
Meghalaya	4,195	1,582	2,264	29
Andaman and Nicobar Islands	3,574	8,231	3,318	52
Sikkim Mizoram	2,221 1,480	3,588 1,327	1,722 922	19 0

Covid India As On: 17 September 2020, 08:00 IST (GMT+5:30)

Table 2 COVID- 19 cases worldwide

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 al[38]	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[39]				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

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