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CHLOROQUINE AND HYDROXYCHLOROQUINE ARE AVAILABLE TREATMENT OPTIONS TO FIGHT WITH COVID-19

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ABSTRACT

The corona virus SARS-CoV-2 caused pandemic Covid-19 disease. At present there is no vaccine or drug approved by FDA to treat Covid-19 disease. The high fatality rate and extreme fast spreading of disease in the community make researchers to invent possible therapeutic inventions a global priority. Recent studies suggested that Chloroquine (ChQ) and Hydroxychloroquine (HChQ) can be used for the treatment of Covid-19 patients. In-vitro tests suggest ChQ and HChQ have good efficiency towards SARS-CoV-2 virus. In this report, we have reviewed latest literature information about ChQ and HChQ drugs to use for the treatment of this pandemic.

INTRODUCTION

The epidemic of corona virus was declared for the first time in 2019 December in Wuhan city of China. This is a new SARS-CoV-2 virus which belongs to corona family. On 7th January, 2020, there was an official announcement from Chinese health officials related to discovery of carona virus. By this time the new virus SARS-CoV-2 affected 11 million people in the Wuhan metropolis city. Later on 30th January 2020 the World Health Organization (WHO) officially declared health emergency globally. Later WHO named the disease caused by this novel virus as Covid-19. Due to the exponential increase of virus effected patients globally the WHO upgraded the situation epidemic to pandemic on 11th March 2020 (1, 2).

The SARS-CoV-2 virus main target in the diseased patients is lower respiratory tract which cause cold, cough and throat infections. Serious symptoms such as difficulty in breathing or shortness of breath and chest pain appeared in the Covid-19 patients. On average it takes 5-6 days to observe the symptoms from when someone is infected with the virus; however it can take up to 14 days. It is notable that adult patients with Covid-19 in early stage, observed with a keen decrease in CD^{4+} and CD^{8+} T-cell subsets (3, 4).

Accordingly the victims suffered with acute respiratory distress condition for 7 to 10 days after infected with Covid-19 due to the swift growth of virus in the body. The virus replication in the body also increases the pro-inflammatory cytokines as well as chemokine response and inflammatory cell infiltrates (4, 5). The incubation period of SARS-CoV-2 virus differs from 2 days to 14 days in different persons, the vague incubation period make it difficult for early diagnosis. The late diagnosis affecting more on the community spread and majorly initiation of treatment in early stage of disease (5, 6).

Epidemiology of corona virus:

After an epidemic breakout in China in January of 2020 the outbreak status has been advanced internationally with the rapid growth in South Korea, Singapore and Japan. Soon after researchers noticed rapid growth of Covid-19 affected patients in Italy and Iran. In the above countries it is witnessed as a community transmission with the persons came from China. The number of Covid-19 patients reached to peak after two months the virus appeared in China. In March first week the Chinese officials declared that the number of new patients are decreasing actively in the country and government reopened the public places. However by that time all the European countries are badly affected with the corona virus (1),

Precisely Italy, Span and France countries. By the March 16th the WHO announced almost as many cases appeared in China are appeared worldwide with 81,077 Covid-19 patients in China and 86,438 patient's rest of the world which includes 143 countries. The WHO announced that as of May 11th 2020, there were 4,088,848 confirmed Covid-19 cases and 283,153 deaths.

Treatment options:

The center of Disease control and prevention (CDC) on 21st March 2020 in a public document informed that there is no vaccine or precise medicine for SARS-CoV-2 (7). The speedy outbreak of corona virus worldwide and the distressing more number of deaths encouraged the scientific community accelerates the invention of all possible and innovative controlling methods of this disease(8).

Quite a few interventional treatment options come up for controlling Covid-19 disease with indefinite efficiency and safety measures (9). Recent studies recommended a well-known anti-malarial drug Chloroquine (ChQ) and Hydroxychloroquine (HChQ) to treat the Covid-19 patients. These FDA approved drugs are used to treat malaria and specific inflammatory conditions at present. In this epidemic situation WHO lists ChQ and HChQ as essential drugs, so these medicines should be available all times in affordable price (10, 11).The ChQ and HChQ molecules showed in-vitro activity against SARS-CoV, SARS-CoV-2, and other corona viruses. It is reported that the HChQ is having relatively high potency than ChQ against SARS-CoV-2 virus (12-14).

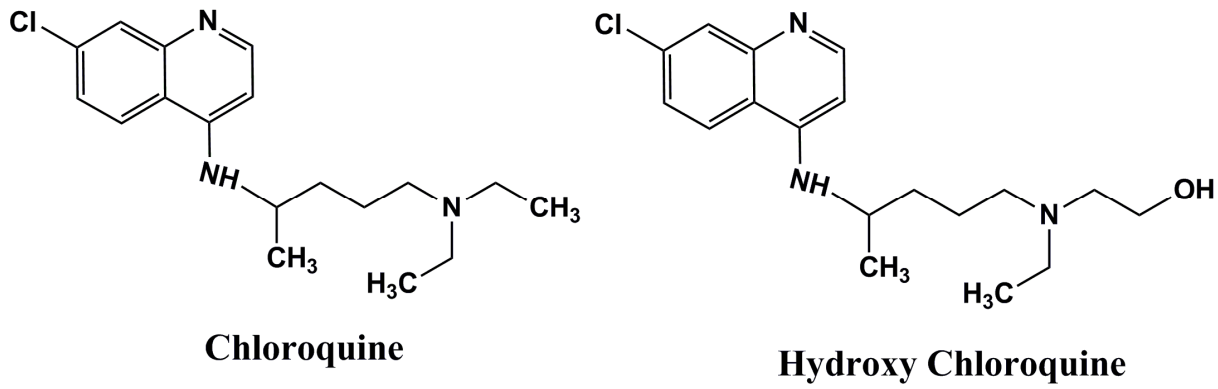

Figure 1: The chemical structures of Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine antiviral activities against COVID-19

The ChQ and HChQ have chemical structure similarities and they are approved by FDA for anti-malarial and anti-rheumatic treatment. For the literature these drugs also known for their antiviral activity with various mechanisms (15- 17). In this epidemic outbreak, ChQ and HChQ have been proposed as anti-SARS-CoV-2 drugs as ChQ inhibited the virus in cell culture

experiments (18, 19), and they also emerge to decrease virus growth in Covid-19 patients in an open label non-randomized trail (20).

These drugs showed excellent anti-viral properties in-vitro, with its effect on primitive stages of virus replication through preventing virus-endosome fusion, by growing endosomal pH (21). It is shown that Corona viruses are able to reach the target cells using pH dependent mechanism, while acidic pH of lysosome results in to fusion of virus and endosomal membranes. It is known that results of uncoating of viral particle and successively viral nucleic acid release in the cytoplasm (22). The ChQ also damages the post translational alterations of virus proteins by interfering with prolytic processes (23). ChQ also shows inhibition of glycosylation through inhibiting sugar modifying enzymes or glycosyltransferases (24).

Previous studies show that ChQ molecule inhibits the access of the SARS-CoV into human cells by interfering with the glycosylation of its cellular receptor angiotensin converting enzyme 2 receptor (ACE2). Recent literature reveals that SARS-CoV-2 also enters into the human body through ACE2 receptor. This suggests that a possible inhibition effect of ChQ on SARS-CoV-2 at this viral replication step (25). On the other hand, because of its anti-inflammatory activity ChQ and HChQ drugs are used to treat multiple diseases where inflammation is effect such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and osteoarthritis (26). In this regard, the central symptom of COVID-19, the virus induces lungs inflammation, this symptom can be an advantageous effect of ChQ and HChQ as both the drugs have capacity to reduce the inflammation.

Efficacy and Toxicity

The ChQ drug in-vitro tests on Vero E6 cells infected by SARS-CoV-2 showing the EC_{90} of 6.90 μM, is became a promising choice of using ChQ in clinical treatment of SARS-CoV-2 as completely off-label (27). On the other hand, HChQ drug is considerably more effective compare to ChQ was observed *in vitro* results as the EC_{50} values of HChQ is 0.72 μM and ChQ is with 5.47 μM, and HChQ showing less efficiency for drug interactions in comparison to ChQ.

Further, physiologically based pharmacokinetic models in vitro inhibition of SARS-COV-2 reveals that the drug molecule HChQ sulfate is showing better results around five days faster than the drug ChQ phosphate (28).

The most common adverse effects of these two drugs are diarrhea, skin rashes, anorexia, nausea (29), and a rare Acute Liver failure (30), a type of severe skin toxic epidermal necrolysis (31) and Long QT syndrome along with cardiotoxicity (32-34).

Over many years people are using both Chloroquine and Hydroxychloroquine drugs in treating the diseases like SLE and RA and these drugs are in the exhibit proper safety lines in these diseases. HChQ is showing lesser toxicity in some of the animal studies, in comparison with the usage of ChQ. Still there is no particular evidence of clinical trial to support the safety levels of the HChQ molecule to compare the toxicity(35-38). It is require to consume larger doses than the regular RA and SLE disease doses to treat SARS-CoV-2 and the effect of the large doses will affect the health and may leads to side effects over the period of life.

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