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Short Commentary

A Quick Review on Hydroxychloroquine in the Treatment of COVID-19

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Abstract

The aim of this investigation is was to review briefly the literature of the anti-viral activity for hydroxychloroquine, how has been used in the treatment of the novel coronavirus disease COVID-19, pathogenesis of COVID-19, and the mechanism of action for hydroxychloroquine in treatment of COVID-19. Hydroxychloroquine likely to attenuate the sever progression of COVID-19, Inhibiting the cytokine storm by suppressing T cell activation, also act by increase the pH of intracellular organelles. The study concludes and gave a well-supported document for quick review of the anti-viral activity of hydroxychloroquine used in the treatment of novel coronavirus COVID-19.

Keywords: *Hydroxychloroquine (HCQ), Chloroquine (CQ), SARS-COV-2, Antiviral, Pathogenesis*

Introduction

The novel corona virus COVID-19 was first reported on the month of December 2019 in Wuhan city-China and it has rapidly spread to all over the world [1]. On February 2020 the world health organization (WHO) named it as (COVID-19), simultaneously the international virus classification commission announced that the new corona virus was named as sever acute respiratory syndrome cornoavirus-2 (SARS-coV2) [2,3]. COVID-19 belongs to the family of genera betacoronaviridae, it is enveloped, single stranded, positive sense RNA virus, the name corona virus derived from the spike proteins that surrounded the outer member of virus [4,5]. COVID-19 is not the first virus from the family of coronaviruses, in the year 2003 a severe respiratory diseases known as sever acute respiratory syndrome (SARS) was reported as an epidemic and 8000 of people being infected with total 10% of cases death. In 2012 another corona virus has outbreak in middle east called as middle east respiratory syndrome (MERS) and infected about 2500 clinical cases with total 35% death. COVID-19 incubation period is about 4-14 days, the shedding period of virus 8-37 days but in severe cases takes about 19 days and in the critical condition takes 24 days [5]. Hydroxycholorquine used as anti-malarial drug and autoimmune diseases such as lupus and rheumatoid arthritis, recently hydroxychloroquine reported in the treatment of novel corona virus (SARS-coV19) [6]. Hydroxychloroquine is a derivative of chloroquine that chemically belongs to 4-aminoqinolines, chloroquine discovered in the year 1934 as anti-malarial drug. Chloroquine also used in the treatment of various infectious diseases [7]. Both Chloroquine as well as hydroxychloroquine acts by the same mechanism of action on coronavirus (COVID-19), that both of chloroquine and hydroxychloroquine are weak bases and they know to increase the intracellular organelles acidic pH, also prevent the binding of virus spike glycoprotein with ACE2 receptors [6].

Hydroxychloroquine (HCQ)

Hydroxychloroquine has similar structure to that of chloroquine (Figure 1). Chloroquine shows inhibitory action on the novel corona virus, but due its several adverse drug reactions chloroquine not suite for the treatment of SARS-coV-2. Hydroxychloroquine has proposed due to its antiviral activity, it is also shows better effect comparing to chloroquine [8]. chloroquine-(N4-(7-Chloro-4-quinolinyl)-N1,N1-diethyl-1,4-pentanediamine) is an amnio acidotropic form of quinine and first synthesized in Germany in the year of 1934 and used in the treatment of malarial and many other autoimmune diseases. Chloroquine has antiviral activity against several diseases like HIV, hepatitis A and C viruses, Influenza A and B viruses, Influenza A H5N1 virus, Dengue virus, chikungunya virus, poliovirus, lassa virus and Zika virus. Hydroxychloroquine sulphate is a derivative of chloroquine and was first synthesized in the year 1946 by addition of hydroxyl group (OH) into chloroquine structure, so produced hydroxychloroquine with less toxicity in animal. Hydroxychloroquine share the same therapeutic uses as well as mechanism of action to that of chloroquine [6,9,10]. Both Hydroxychloroquine and chloroquine have been shown anti-viral activity in SARS-coV-2

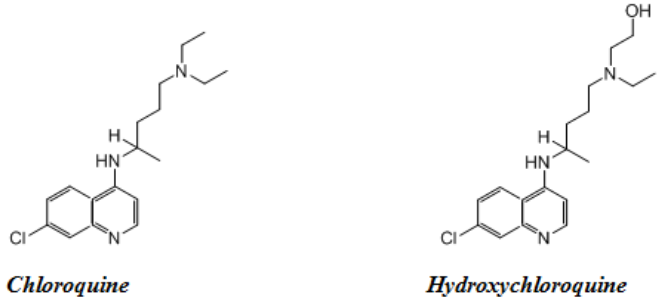

Figure 1: Structures of chloroquine and hydroxychloroquine.

when administrated as prophylactic – pre-treated as well as post-viral entry, indicating multiple mechanisms of action. HCQ and CQ are weak bases so they know to increase the pH inside the intracellular organelles including (lysosomes, endosomes and golgi vesicles), specific enzymes present in the lysosomes active only at low pH around 4.5, as the novel coronavirus SARS-coV-2 needs that enzymes for the process of replication and survive, Chloroquine and hydroxychloroquine increases the pH of lysosomes and interfere the activity of this enzymes and inhibits the SARS-coV-2, help in the treatment of the virus. In addition to that hydroxychloroquine can inhibit SARS-coV-2 entry through the changing the glycosylation of angiotensin converting enzyme-2 (ACE-2) receptor as well as spike protein, experimentally confirmed that hydroxychloroquine inhibits the entry and post-entry steps of the virus. hydroxychloroquine and chloroquine also block the transport of SARS-coV-2 from early endosomes (EEs) to endolysosomes (ELs) which is important required in the release of genome in SARS-coV-2. Due to the altered pH of the endosomes and interfere the binding between tall-like receptors (TLR7, TLR9) and their RND/DNA ligands, TLR signals suppressed due hydroxychloroquine. In the cytoplasm hydroxychloroquine interfere with the interaction of cytosolic DNA and the nucleic acid sensor cyclic (GMP-AMP) synthase. Hydroxychloroquine acts as immune modulator, inhibit receptor binding and membrane fusion, also it has been shown to down regulate pro-inflammatory cytokines including IL6 levels, and minimize cytokines release syndrome / ARDS. Dose of hydroxychloroquine in COVID-19 was recommended as 400 mg twice in a day for two days, then 200 mg twice per a day for another 3 more days. Hydroxychloroquine has better therapeutic approach compared to chloroquine in the treatment of SARS-COV-2 infection [5-8,11-13] (Figure 1).

Pathogenesis

The pathogenesis of SARS-COV-2 not clearly understood, but the mechanism of SARS-COV, and MERS give us a huge information to understand the pathogenesis of novel coronavirus SARS-COV-2 [2]. The genome structure of coronaviruses are well known compared with other RNA viruses.coronaviruses RNA contain encodes viral polymerase, RNA synthesis material and non-structural polyproteins which not involved in host response modulation. Additionally the genome encodes also contain 4 structural proteins these proteins are, spike (S), envelope (E), membrane (M) and nucleocapsid (N) [14] (2019 NOVEL COVID-19). The novel coronavirus SARS-COV-2 mainly act by targeting the respiratory system and cause severe pneumonia and acute cardiac injury with high blood levels of cytokines and chemokines [15]. Virus Enter into host cell, the envelope spike glycoprotein bind to angiotensin converting enzyme-2 (ACE-2) for SARS-COV-2, CD29L (a C-type lectin also known as l-SIGN). After the entry of SARS-COV-2 into the cell the viral RNA genome is release into cytoplasm and converted to 2 polyproteins and structural proteins, then genome begins replication process. The genome that newly formed inserted into the membrane of the endoplamic reticulum, the vesicles carrying the virus particles fuse with the plasma membrane to release the virus. Due to antigen presentation the body stimulate humoral and cellular immunity which are mediated by virus specific B and T-cells that similar to common acute viral infections the antibody profile against SARS-COV virus has typical of IgM and IgG production. The infected patient with SARS-COV-2 shows the number of CD4 and CD8 T-cells in the peripheral blood significantly reduced. The main death cause of novel coronavirus SARS-COV-2 due to the high levels of cytokines and chemokines that released by body immunity. The different types of cytokines that released (IFN-a, IFN-g, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-a, TGFb) and chemokines (CCL2, CCL3, CCL5 CXCL8, CXCL9, CXCL10). High levels of these inflammation mediators lead to multiple organ failure and finally may lead to death in severe cases in SARS-COV-2 [2].

Conclusion

The authors succeeded in compiling the data and made the brief literature survey. In summary, Hydroxychloroquine serve as a better therapeutic approach than chloroquine for the treatment of COVID-19, due to inhibition of cytokine storm by reducing CD154 expression in T-cell. Hydroxychloroquine showed fewer side effects, safe during the pregnancy.

Conflicts of Interests

Authors do not have any conflicts of interest with the publication of the manuscript.

Acknowledgment

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