Journal of Pharmaceutical Research International

32(9): 52-60, 2020; Article no.JPRI.56879
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Chloroquine and Hydroxychloroquine could be an Available Weapons to Treat COVID-19 Associated Pneumonia

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i930482
Editor(s):
(1) Dr. Q. Ping Dou, Barbara Ann Karmanos Cancer Institute, Wayne State University, USA.
Reviewers:
(1) Victor B. Oti, Nasarawa State University, Nigeria.
(2) Marema Ephraim Makgatho, University of Limpopo, South Africa.
Complete Peer review History: http://www.sdiarticle4.com/review-history/56879

Review Article

Received 22 April 2020
Accepted 07 May 2020
Published 10 June 2020

ABSTRACT

Aims: This study aims to review the efficacy of chloroquine and hydroxychloroquine to treat coronavirus disease 2019 (COVID-19) associated pneumonia.
Methodology: This review includes searching Google scholar for publications about the use of hydroxychloroquinein the treatment of COVID-19 using the words of (Covid-19) AND hydroxychloroquine.
Results: Chloroquine and hydroxychloroquine have proven effective in treating coronavirus in China *in vitro*, but till now only few clinical trials are available and these trials were conducted on a small sample size of the patients. The efficacy of chloroquine and hydroxychloroquine is mainly due to its effect on angiotensin-converting enzyme II (ACE2).
Conclusion: The use of chloroquine and hydroxychloroquine could be very promising but more trials are needed that include larger sample size and more data are required about the comparison between chloroquine and hydroxychloroquine with other antivirals.

Keywords: Chloroquine; hydroxychloroquine; antivirals; COVID-19; pneumonia; SARS-CoV-2.

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1. INTRODUCTION

The outbreaks of the current coronavirus disease 2019 (COVID-19) pandemics in December 2019 in Wuhan - China, Middle East respiratory syndrome (MERS) in September 2012 in Kingdom of Saudi Arabia and severe acute respiratory syndrome (SARS) in February 2003 in Guangdong – China are all caused by coronaviruses, and patients mainlyexpired because of the acute respiratory distress syndrome [1].

In December 2019, several pneumonia cases of the unidentified cause were reported in Wuhan, Hubei Province, China, and were linked to a seafood wholesale market [2-4]. This disease is now called COVID-19. It has spread rapidly, with cases now confirmed in multiple countries [5].

The main feature of COVID-19 and other two coronaviruses caused infections, the middle east respiratory syndrome and severe acute respiratory syndrome in severe cases were acute respiratory distress syndrome and pneumonia. Moreover, in advanced cases, several patients have multi-organ failure and shock [6].

This virus has50% genomic similarity to the middle east respiratory syndrome coronavirus (MERS-CoV), 75–80% genomic similarity to the severe acute respiratory syndrome coronavirus (SARS-CoV), and uses the same cell receptor which is angiotensin-converting enzyme II (ACE2), that is used by SARS-CoV [2,7,8].

Among the cases which were reported to the World Health Organization, 82% are mild; 15% are severe and 3% are critical [9]. Pauline reported that the estimated overall case fatality rate is around 2%, but nowadays the fatality rate is much higher than 2% [10].

The outbreak of the novel coronavirus disease which is caused by the new coronavirus 2019-CoV is now offcially identified as severe acute respiratory syndrome-related coronavirus or SARS-CoV-2. It is now representing a pandemic threat to public health globally [11,12].

Similar to MERS-CoV and SARS-CoV, SARS-CoV-2 attacks the lower respiratory system and lead to viral pneumonia, but additionally it may affect other systems such as heart, kidney, gastrointestinal system, central nervous system and liver, leading to multi-organ failure [13].

The clinical presentation of COVID-19 includes mainly cough, fever and pneumonia. Although the initial cases were related to a seafood market in Wuhan, the virus origin, intermediate hosts and how the virus was spread to humans are still generally [2]. This study aims to review the efficacy of chloroquine and hydroxychloroquine to treat COVID-19 Associated Pneumonia.

2. METHODOLOGY

This review includes searching Google scholar for publications about the use of hydroxychloroquine in the treatment of COVID-19 using the words of (Covid-19) AND hydroxychloroquine. The search was conducted in 18-03-2020 at 10:20 AM, there were 43 results, many of the publications were written in a language other than English. Moreover, several publications were under review. So the publications that were under review and publications written in languages other than English were excluded. After exclusion, there were 15 publications included in the review. Additionally, I add more researches from the references in these publications.

3. PATHOGENESIS OF THE INFECTION

Du L et al., Wrapp D et al. and Hoffmann M et al. reported that the genome of beta coronavirus encodes numerous structural proteins, including S protein that is considered a main inducer of host immune responses [14]. This S protein mediates host cell invasion by both SARS-CoV-2 and SARS-CoV via binding to a receptor protein known as angiotensin-converting enzyme 2 (ACE2) that is located on the surface membrane of host cells [14-16].

Other recent studies have shown that this invasion process requires the host cell produced serine protease TMPRSS211 to facilitate S protein priming. Additionally, the viral genome also encodes several proteins including coronavirus main protease (3CLpro), papain-like protease (PLpro) and RNA-dependent RNA polymerase (RdRp) [17,18].

Moreover, Glowacka et al and Wu Y reported that ACE2 involvement with coronavirus infection is of additional interest since ACE2 is a potent negative regulator limiting over-activation of the renin-angiotensin system that may be involved in elicitation of inflammatory lung disease and also it is well-known to have role in regulation of blood pressure and the balance of body electrolytes and fluid [19,20].

The infection process is initiated by the interaction between viral S protein and ACE2 on the host cell surface. It is revealed that the binding affinity of SARS-CoV-2 S protein to ACE2 is about 10−20 times higher than that the S protein of SARS-CoV [15,21]. It is hypothesized that this may contribute to the higher transmissibility and contagiousness of SARS-CoV-2 as compared to SARS-CoV [22].

Manisha et al reported that the life cycle of CoV in host cells is initiated by the binding of S proteins of CoV to cellular receptor ACE2 which is followed by the entry of viral RNA genome into the host cell and translation of non-structural and structural proteins [23].

4. THE CURRENT COVID-19 RELATED RESEARCHES

Cynthia et al. reported that Since SARS-CoV-2 is a newly discovered pathogen, they are no specific drugs have been identified or are currently available to treat it [24].

In the Chinese Clinical Trial Registry, a total of 233 trials are registered till the date of Feb 24, 2020 for the keywords 2019-nCov and COVID-19. In these trials there were many pharmacotherapeutic agents evaluated such as high-dose vitamin C, adalimumab, favipiravir, dihydro-artemisinin piperaquine, dipyridamole leflunomide, chloroquine or hydroxychloroquine, suramin sodium, IFN-alpha 2b, lopinavir/ritonavir and arbidol (umifenovir) tablets. Other important agents being evaluated including traditional Chinese medicines in addition to the use of stem cells [25].

Wang et al reported that chemical drug research involved 32 types, and their concentration was relatively good, mainly concentrated on drugs such as lopinavir/ritonavir, interferon, chloroquine, hydroxychloroquine, glucocorticoids and remdesivir. He also reported that till 22-feb-2020, there are 6 chemical drugs were used in interventional clinical researches related to COVID-19. Out of the 57 protocols, 10 interventional clinical types of research related to COVID-19 use chloroquine and 8 researches used hydroxychloroquine [26]. Moreover, Yaseen M et al stated that there are several randomized and nonrandomized studies for the treatment of COVID-19 using a variety of interventions including corticosteroids, different combinations of ribavirin, lopinavir/ritonavir, chloroquine, hydroxychloroquine, interferons, remdesivir and other agents [6].

Therefore, the drug that should be used for COVID-19 treatment should have an effect on one of the enzymes or proteins involved in the pathogenesis of the COVID-19 infection. For example, there are many studies about the use of lopinavir because it affects 3CLpro and PLpro; remdesivir and ribavirin could be effective because they affect RdRp; arbidol could be effective because it affects S protein and ACE2; camostat mesylate could be effective because it may affect TMPRSS2; chloroquine and hydroxychloroquine could be effective because theyaffect ACE2; Favipiravir could be effective because it affects RdRp; in addition to other drugs that may be effective [24].

5. THE RATIONAL OF USING HYDROXYCHLOROQUINE AND CHLOROQUINE FOR THE TREATMENT OF COVID-19

Since the late 1960's, the in vitro antiviral efficacy of chloroquine has been identified [27-29]. In 2004, Keyaerts E et al. reported that the growth of many different viruses can be inhibited in cell culture by both chloroquine and hydroxychloroquine, including the SARS coronavirus [30].

Helal et al. found that the only modest effect of chloroquine in the therapy of human virus infection was found for chronic hepatitis Cand he said that this was not enough to include chloroquine in the standardized therapeutic [31].

Touret F and de Lamballerie X reported that the assessment of preceding trials shows that, to date, no acute virus infection has been successfully treated by chloroquine in humans [32].

Wang, M reported that chloroquine and several other drugs were tested *in vitro* and have proven effective in treating coronavirus in China [33]. Additionally, many other antiviral agents are also listed, but this study is conducted in vitro. Endosome/ ACE2 is the target for chloroquine. Chloroquine could be effective for treating COVID-19 because it can elevate endosomal pH and interfere with ACE2 glycosylation [33,34].

Previous studies also demonstrated that chloroquine also has a potential broad-spectrum

antiviral activity by many mechanisms include interfering with the glycosylation of cellular receptors of SARS-CoV and by increasing the endosomal pH required for virus/cell fusion. The efficacy of chloroquine in treating COVID-19 pneumonia may be due to the anti-viral and anti-inflammatory activities of chloroquine [35,36].

Naidi Yang and Han-Ming reported that there is immense evidence suggesting that the endocytic pathway plays a key role in mediating viral entry for many CoVs including SARS-CoVs, MERS-CoVs and possibly plays a main role in facilitating viral entry for SARS-CoV-2 [37]. As a result, several medications targeting the endocytic pathway could have the therapeutic potential in treating COVID-19 associated pneumonia, including chloroquine (a lysosomotropic agent) and chlorpromazine (a clathrin-mediated endocytosis inhibitor) [5,33,38,39].

Dyall et al. stated that hydroxychloroquine sulfate and chloroquine diphosphate was identified with in vitro activity against MERS or SARS [40].

Besides, Vincent et al. found that chloroquine, an antimalarial agent, inhibits SERS-CoV by the elevation of endosomal pH and alters the terminal glycosylation of ACE-2, which eventually interferes with the receptor binding of the virus [41].

Also one of the reasons to use chloroquine is its used widely for malaria, this means that the drugs are readily available in numerous locations around the world and for which doctors are also familiar with its side effect profile [42].

Touret F and de Lamballerie X stated that the option of using chloroquine in the treatment of SARS-CoV-2 should be examined with attention in light of the recent promising announcements and also the potential detrimental effect of the drug that observed in previous attempts to treat acute viral diseases should be examined [32].

Although some studies said that chloroquine and hydroxycloroquine didn't show good efficacy in human for the previous viral infections, there are many in vitro study showed their efficacy for the treatment of SARS-CoV-2 and nowadays some few studies in human shows their efficacy in human. Moreover, the drugs are readily available around the world and the health care professionals are familiar with their side effect profile.

6. THE RESULTS OF THE STUDIES ABOUT THE USE OF CHLOROQUINE AND HYDROXYCHLOROQUINE FOR THE TREATMENT OF COVID-19

The State Council of China held a news briefing on February 17, 2020 indicating that the use of chloroquine phosphate had demonstrated a marked efficacy and acceptable safety in the treatment of pneumonia that is associated with COVID-19 in a multicenter clinical trials conducted in China [43].

Subsequently, several clinical trials have been conducted quickly in China to test the safety and efficacy of hydroxychloroquine or chloroquine in the treatment of COVID-19 associated pneumonia, these studies were conducted in more than 10 hospitals in Wuhan, Guangzhou, Jingzhou, Beijing, Chongqing, Shanghai and Ningbo [44]. Thus far, the results were obtained from more than 100 patients and have demonstrated that chloroquine phosphate is superior to the control group in inhibiting pneumonia exacerbation, promoting a virus-negative conversion, improving lung imaging findings and also shortening the course of the disease according to the news briefing.

Gao and colleagues reported that Chloroquine phosphate is shown to have apparent efficacy and acceptable safety against COVID-19 associated pneumonia in multicenter clinical trials conducted in China [5]. Franck Touret and Xavier de Lamballerie stated that these results represented the first successful usage of chloroquine in humans for the management of acute viral disease, they said also that this drug is cheap and widely available [32].

In the early *in vitro* studies, chloroquine was found to block COVID-19 infection at low-micromolar concentration, with a half-maximal effective concentration (EC50) of 1.13 μM and a half-cytotoxic concentration (CC50) greater than 100 μM [33]. Moreover, Wang et al reported that chloroquine or hydroxychloroquine is highly expected to be an encouraging anti-SARS-CoV-2 activity *in vitro* [33].

Xueting et al. reported in his study that hydroxychloroquine was found to be more potent than chloroquine at inhibiting SARS-CoV-2 *in vitro*. Moreover, hydroxychloroquine exhibited better in vitro anti-SARS-CoV-2 activity than chloroquine. Xueting et al. recommend the combination between low dose

hydroxychloroquine with an anti-inflammatory drug to alleviate the cytokine storm in critically ill SARS-CoV-2 patients [45].

Jianjun et al. reported that chloroquine phosphate is safe and cheap and has been used for more than 70 years, and because of the urgent clinical need, it is recommended to treat pneumonia caused by a COVID-19 in larger populations in the future [5].

In the Handbook of COVID-19 Prevention and Treatment that was published in China, chloroquine phosphate is considered second line on adults between 18-65 years old and used if the basic regimen is not effective. But also the treatment should be monitored for the adverse drug effects of it and its drug - drug interactions [46].

Abdollah K et al. in the Algorithmic Approach to Diagnosis and Treatment of Coronavirus Disease 2019 (COVID-19) in Children in Iran reported that hydroxychloroquine could be used but as a combination with other antivirals not a single agent in children. But serious adverse reactions were reported chloroquine [47].

In addition to that, Biot et al. additionally stated that hydroxychloroquine was reported to have anti-SARS-CoV activity in vitro and less drug-drug interactions than chloroquine and may be a potential pharmacological agent for the treatment of COVID-19 infection [48]. Fox RI stated that the molecular mechanism of action of chloroquine and hydroxychloroquine has not been fully clarified [49]. But Hamming et al. found that the ACE2 protein expresses abundantly in the epithelia of the human lung and small intestine [50]. This may explain the efficacy of chloroquine and hydroxychloroquinebecause SARS-CoV-2 as SARS-CoV binds to the same ACE2 receptor so SARS-CoV-2 is also susceptible to the inhibitory effect of chloroquine as reported by Zhou et al. and Wang et al. [7,33].

CUI et al. compared the efficacy of chloroquine and lopinavir/litonavir antiviral and reported that chloroquine has shown better clinical antiviral efficacy than lopinavir/litonavir in clinical trials of small size and reported that the mechanism of actions of hydroxychloroquine is similar to chloroquine but hydroxychloroquine is safer than chloroquine. More studies are needed to know the clinical pharmacology of it to use it in the treatment of COVID-19 [51].

Franck Touret and Xavier de Lamballerie said that it is also necessary to determine if the benefit of chloroquine therapy depends on the age class, the clinical presentation or the stage of the disease [32].

There are no FDA-approved therapeutics or drugs to treat, cure or prevent COVID-19. Nowadays' The FDA has been working closely with other government agencies and academic centers to investigate the use of the chloroquine to determine whether it can be used to treat patients with mild-to-moderate COVID-19 in order to potentially lessen the duration of symptoms, as well as viral shedding, which can help in preventing the disease spreading. Studies are ongoing to determine the efficacy in using chloroquine to treat COVID-19 [52].

7. ADVERSE DRUG REACTIONS AND SAFETY ISSUES

Generally, the side-effects of chloroquine and hydroxychloroquine are generally mild and transitory and they are considered to be safe. Yet, the margin between the therapeutic and toxic dose is narrow and severe poisoning has been associated with cardiovascular disorders that could be life-threatening [53].

Additionally, Jianjun et al reported that chloroquine phosphate is cheap and safe and has been used for more than 70 years [5]. CUI et al. stated that hydroxychloroquine is safer than chloroquine [51].

The serious adverse effects of chloroquine phosphate include atrioventricular block, cardiomyopathy, heart failure, prolonged QT interval, torsades de pointes, ventricular fibrillation, ventricular tachycardia, hypoglycemia, hemolytic anemia, anaphylaxis, extrapyramidal disease, seizure, disorder of macula of retina and retinal disorder [54].

The serious adverse effects of hydroxychloroquine sulfate include torsades de pointes, hypoglycemia, agranulocytosis, aplastic anemia, thrombocytopenia, a disorder of muscle, retinal disorder, hearing loss, angioedema and also although rare, suicidal behavior has been reported [55].

In the Handbook of COVID-19 Prevention and Treatment that was published in china, the authors said that chloroquine phosphate treatment should be monitored for the adverse drug reactions of it that include nausea, vomit,

dizziness, headache, diarrhea, different kinds of skin rash, ocular toxicity and cardiac arrest as a result an electrocardiogram needs to be examined before taking the drug and chloroquine should be prohibited for patients with retinal disease, arrhythmia or hearing loss. Moreover, it has several contraindicated and major interactions specially with the medications that may lead to the prolonged Q-T interval such as azithromycin, moxifloxacin, amiodarone and others [46].

Abdollah Karimi et al. reported that serious adverse reactions were reported for Chloroquine that include QT interval prolongation, torsades de pointes and ventricular arrhythmias especially in concurrent use with Kaletra. Therefore, it should be used with caution in patients with a history of ventricul ararrhythmias, cardiac disease, uncorrected hypokalemia and/or hypomagnesemia, or bradycardia. He also reported that electrocardiography needs to be examined prior to starting chloroquine and after onset of drug, cardiac monitoring is recommended [47]. Furthermore, Wang and colleagues concluded that it is important to assess the chloroquine safety track record in human patients suffering from the novel coronavirus disease [33].

Due to the severe adverse reactions of chloroquine and hydroxychloroquine, the safety profile should be monitored. Franck Touret and Xavier de Lamballerie stated that the self-treatment of these 2 drugs is not recommended and that their use should be subject to strict rules [32].

8. CONCLUSION

Nowadays there is a confusion regarding which drugs is the first drug of choice for the treatment of COVID-19 because of the lacking in clinical trials for treating COVID-19.

Generally, the majority of the studies about the use of chloroquine or hydroxychloroquine for the treatment of pneumonia and acute respiratory distress syndrome in COVID -19 are *in vitro* not in human. The use of chloroquine and hydroxychloroquine could be very promising but till now only few clinical trials are available and these trial were conducted on a small sample size of the patients, so more trials are needed that include larger sample size and more data are required about the comparison between chloroquine and hydroxychloroquine with other antivirals.

Additionally, more trials are needed because also there is confusion regarding is it better to use hydroxychloroquine alone or as a combination with other. Furthermore, more trials are also needed to discuss if the benefit of chloroquine therapy depends on specific factors such as age class, the clinical presentation or the stage of the disease and is there a difference in the response rate between different individuals and between different countries.

Finally, chloroquine and hydroxychloroquine are effective *in vitro* and in small sample size clinical trial. They are cheap, safe and available. But could cause rare but severe adverse effects and can cause many drug – drug interactions, so they should have prescribed under physician supervision and some cardiovascular tests should be done before and after using these drugs. So the physicians should decide if the benefit of using the medications in their patients is more than the risk or no.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

This Publication was supported by the Deanship of Scientific Research at Prince Sattam Bin Abdulaziz University.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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