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Review

Chloroquine and hydroxychloroquine in covid 19: a systematic review

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SUMMARY

Since 100 years, current coronavirus pandemic (COVID-19) caused by SARS-CoV-2 is themost dangerous healthcare crisis and unprecedented in absense of prophylactic or therapeutic drugs. The world's major health systems have had no large-scale therapeutic choice and at an acceptable cost apart from Chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) to treat Covid-19.These drugs have anti-inflammatory activity and are already used to treat rheumatoid arthritis, lupus. However, these drugs have raised a great worldwide controversy between the pros and cons of their uses to treat patients with Covid-19

In these systematic review, we analyzed articles published until 28 august in pubmed, sciences direct and ClinicalTrials.gov by using these keywords: chloroquine and COVID-19 or hydroxychloroquine and COVID-19. these online preprint publications have offered inconclusive preliminary results as well as clinical trials not yet finished. Although CQ / HCQ have antiviral activity against Sars cov 2 in vitro, antiviral activity in vivo is questionable..

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan, Hubei Province, China in December 2020. On March 11, 2020, the World Health Organization (WHO) declared this pandemic disease (Castagnoli R *et al.,* 2020). Recent publications have brought attention to the possible benefit of chloroquine, a broadly used antimalarial drug, in the treatment of patients infected by the novel emerged coronavirus (SARS-CoV-2). Based on these publications and *in vitro* results, chloroquine (CQ) and its hydroxychloroquine derivative (HCQ) are drugs that have been taken to treat COVID-19 (Liu et al., 2020).

The use of chloroquine and hydroxychloroquine is now authorized for the treatment of COVID-19 by the United States Food and Drug Administration, and advocated by the Indian Council for Medical Research (Ferner et al., 2020).

Our work is a systematic review, which consists of a synthesis of the scientific literature on the use of chloroquine and hydroxychloroquine in the treatment of COVID-19.

1. Material and methods

We searched the PubMed database until 28 august, 2020 using the keywords chloroquine AND COVID-19 (we retrieved a total of 826 articles with 794 in English, 13 clinical trial, 25 Systematic Review, 5 Meta-Analysis, 2 Retracted Publication, 9 Preprint), then hydroxychloroquine AND COVID-19 (we retrieved a total of 1176 articles with 1150 in English, 9 clinical trial, 12 Systematic Review, 6 Meta-Analysis, 2 Retracted Publication, 16 Preprint). All articles were published in 2020.

In addition, we also searched for Meta-Analysis and Randomized Controlled Trial we found 2 items.Of all the articles published in 2020, two articles was retracted until publication of this paper (Castagnoli R *et al.,* 2020; Mehta *et al.,* 2020; Touret *et al.,* 2020).

We also accessed the trials currently underway with these two compounds from ClinicalTrials.gov.

No trial of 24 clinical trials has been completed to date.

On ScienceDirect we searched by keywords: chloroquine AND COVID-19 we found 1041 publications until August 27, 2020 including 1 publication in 2019 and 1037 publications in 2020 and 3 publications for 2021 (318 research articles and 316 journal articles)

On ScienceDirect we searched by keywords: hydroxychloroquine AND COVID-19 we found 1728 publications until August 27, 2020 including 1 publication in 2019 and 1022 publications in 2020 and 5 publications for 2021. (451 Research articles and 359 articles from review)

2. Results

On both the pubmed and scienceDirect databases we found a lot of articles on the place of chloroquine and hydroxychloroquine in COVID-19.

With ease of consultation of the articles since they are all free access.

We preferred Pubmed, which gives us more filter for the search especially for retracted articles.

We found two retracted articles in two world renowned journals with a great impact factor, which prompted us to raise ethical considerations for scientific publication (Castagnoli R *et al.,* 2020; Mehta *et al.,* 2020; Touret *et al.,* 2020).

Chloroquine is an antimalarial that can inhibit the replication of several intracellular microorganisms. The chloroquine (Nivaquine*) and Hydroxychloroquine (Plaquenil*) have both been commercialised in Morocco as antimalarial drugs. Hydroxychloroquine is now broadly used in autoimmune diseases such as lupus and

rheumatoid arthritis. Of note, chloroquine and hydroxychloroquine are considered to be safe and side-effects are generally mild and transitory (Touret et al., 2020).

In addition, chloroquine has antiviral and anti-inflammatory activity, which may play a role in the treatment of patients with COVID-19 (Liu et al., 2020).

The *in vitro* antiviral activity of chloroquine has been identified since the late 1960's and the growth of many different viruses can be inhibited in cell culture by both chloroquine and hydroxychloroquine, including the SARS coronavirus (Touret et al., 2020). Chloroquine increases the endosomal pH and interferes with the glycosylation of cellular SARS-CoV receptors and thus has the potential to block viral infection (Liu et., 2020 ; Mehta et al., 2020 ; Touret et al., 2020 ; Wang et al., 2020).Chloroquine also inhibits quinone reductase-2, which is involved in the biosynthesis of sialic acid (an acid monosaccharide of cellular transmembrane proteins required for the recognition of ligands) which makes this agent a broad antiviral agent(Liu et., 2020). Chloroquine changes the pH of lysosomes and probably inhibits cathepsins, which promotes the formation of the autophagosome which cleaves the advanced protein SARS-CoV-2 (Liu et., 2020).

Experimental studies have also shown that chloroquine has potent anti-SARS-CoV-1 effects in vitro, mainly due to a deficiency of glycosylation receptors on the surface of viral cells, so that it cannot bind to angiotensin 2 converting enzyme (ACE2) expressed in the lungs, heart, kidneys and intestine.

Since SARS-CoV-2 uses the similar surface receptor ACE2, chloroquine may also interfere with the glycosylation of the ACE2 receptor, thereby preventing the attachment of SARS-CoV-2 to target (Wang et al., 2020; Colson et al., 2020; Zhou et al., 2020).

Chinese researchers have found that chloroquine is very effective in reducing viral replication, which can be easily obtained with a standard dosage due to its favorable penetration into tissues, including the lungs (Gao et al, 2020). Some studies show that HCQ inhibits the entry, transport and post-entry stages of SARS-CoV-2, similar to chloroquine (Liu et., 2020b). One study found that HCQ was a more potent agent t chloroquine for inhibiting SARS-CoV-2 *in vitro* (Yao et al., 2020; Raoult et al., 2020).

HCQ is less permeable to the blood-retinal barrier and allows faster clearance of retinal pigment cells, therefore a lower risk of retinal toxicity with HCQ, compared to chloroquine (Marmor et al., 2020).

Chloroquine causes a significant decrease in the production of pro-inflammatory markers and cytokines which makes it an anti-inflammatory agent in the treatment of severe forms of SARS-CoV-2 disease Raoult et al., 2020).

The first Chinese human trial with chloroquine against COVID-19 involving more than 100 COVID-19 patients found chloroquine superior to the control group in reducing the duration of symptoms, exacerbation of pneumonia, including l improvement and acceleration of negative seroconversion to the virus without any serious side effects (Gao et al., 2020b). In this study, chloroquine was administered at a dose of 500 mg of chloroquine twice a day in mild to severe COVID-19 pneumonia. The treatment with hydroxychloroquine is significantly associated with a reduction or disappearance of the viral load in COVID-19 patients and its effect is reinforced by azithromycin (Gautret., 2020).

Given the COVID-19 pandemic, the available evidence base is limited to certain institutions and / or organizations that have already recognized the usefulness of chloroquine and HCQ (Touret et al., 2020b).

based on a clinical experience not yet completed one tablet of chloroquine phosphate at a dose of 500 mg twice a day for 10 days for patients diagnosed as mild, moderate and severe cases of SARS-CoV-2 pneumonia in the absence of contraindication to the drug (Multicenter collaboration group ., 2020)

Dose (adults) Chloroquine phosphate 500 mg BID for 10 days (Multicenter collaboration group ., 2020)

In Morocco the protocol does not include chloroquine or hydroxy chloroquine in pregnant women, and the therapeutic management of confirmed cases is based on:

First-line protocol:

Chloroquine 500mg 2 times a day for 10 days, Or Hydroxychloroquine sulfate 200 mg 3 times a day for 10 days. In combination with azithromycin 500 mg the first day then 250 mg per day from 2nd day to 7th day.

3. Discussion

Chloroquine is an antimalarial, the story of which begins with quinine, which is an active compound in cinchona bark, the medicinal properties of which have long been known to the natives of South America in the tropical regions of the Andes. The Spanish introduced it to Europe in the 1600s.

The pure compound was extracted in 1820 by Caventou and Pelletier. The chloroquine was synthesized in 1934 by Hans Andersag at Bayer, but it was too toxic for human use.

Hydroxychloroquine appeared in the 1950s with an additional OH group which detaches from one of these N-ethyls at the end of the chain;

Chloroquine is administered orally as chloroquine phosphate.

It can also be administered by intramuscular injection in the form of chloroquine hydrochloride.

Chloroquine is effective against susceptible strains of malaria parasites Plasmodium vivax, P. oval and P. falciparum as well as certain parasitic worms and amoebas.

It is also used in the treatment of inflammatory rheumatic diseases, such as lupus erythematosus and rheumatoid arthritis.

Side effects may occur with the use of chloroquine.

Examples of mild side effects are headaches abdominal cramps, which are common to antimalarials.

Sometimes also a rash, muscle weakness, nausea, vomiting, tinnitus (ringing in the ears) and behavioral changes.

Visual impairment, in the form of retinal damage, can occur with long-term use under the name of chloroquine retinopathy.

Chloroquine interacts with a number of other drugs, including antacids, certain types of antibiotics: ampicillin and erythromycin, and antiarrhythmics.

Possible side effects of HCQ and CQ, such as prolonging the QT interval with an increased risk of arrhythmia, should be taken into account by monitoring the ECG every 48 hours.

Intense pruritus, a common complaint among black Africans taking the drug, is usually relieved by antihistamines.

Rarely, chloroquine can cause extrapyramidal toxicity of the nervous system and should be avoided in people with a history of epilepsy.

The Indian Council of Medical Research has recommended the use of HCQ in the phylaxis of:

- All health care workers those who are involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals.
- Asymptomatic household contacts of laboratory confirmed cases may be prescribed 400 mg twice a day on day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals.

Currently, clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or

treatment of SARS-CoV-2 infection is lacking from CDC due to absence of randomized clinical trials (RCTs) (Agrawal et al., 2020).

Finally, chloroquine can induce the uptake of zinc into the cytosol of the cell, which is capable of inhibiting RNA-dependent RNA polymerase and ultimately halting the replication of coronavirus in the host cell (Shittu et., 2020).

4. Conclusion

The SARS-CoV-2 pandemic showed a rapid spread of the covid 19 virus with a high mortality rate over a short period of time, which caused a collapse of health systems and devastating effects on the world economy. .

In the absence of a preventive vaccine solution, the world's major health systems have had no large-scale therapeutic choice and at an acceptable cost apart from CQ)and HCQ.

Many clinical trials have started around the world, but so far no trials have published their final results. A large number of open access and preprint scientific publications with preliminary and inconclusive results.

This requires conducting a large-scale, double-blind, randomized, placebo-controlled clinical trial, in order to obtain more reliable evidence, on the therapeutic or preventive protocol based on chloroquine (CQ) and its derivative hydroxychloroquine (HCQ).

Conflicts of Interest

Authors declare no conflict of interest.

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