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SAFETY AND EFFICACY PROFILE OF CHLOROQUINE AND HYDROXYCHLOROQUINE IN THE MANAGEMENT OF COVID-19: A REVIEW

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ABSTRACT

At the end of December 2019, a completely unique coronavirus (COVID-19) caused a virulent disease in Wuhan, and has quickly spread to all provinces in China and 26 other countries around the world, leading to a heavy situation for epidemic prevention. Coronavirus pandemic is currently a world public health emergency. At the moment there's not any pharmacological treatment is thought to treat this condition, and there's a necessity to review the available treatments. Previous studies have shown that the role of Chloroquine and Hydroxychloroquine in various viral conditions, there's limited information about the utilization of them in COVID-19. The purpose of this systematic review is to summarize the available evidence regarding the role of chloroquine in the treatment of coronavirus infection. Here we found that treating the patients diagnosed as novel coronavirus pneumonia with chloroquine might improve the success rate of treatment, shorten hospital stay and improve patient outcome and hence pneumonia like symptoms can be treated. **Conclusion:** Considering minimal risk upon use, a protracted experience of use in other diseases, cost effectiveness and straightforward availability across India. We propose that both these drugs are deserve means last treatment, and may be carefully considered for clinical use as experimental drugs. Since HCQ has been approved for treatment of diabetes in India, it should be further research in COVID-19, a subgroup where significant mortality has been shown.

KEYWORDS

Chloroquine, Hydroxychloroquine, Pneumonia and COVID-19.

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INTRODUCTON

An outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2 or COVID-19) was reported in Wuhan, China, in December 2019, which spread to the remainder of China and lots of other countries across the earth. Globally the amount of individuals diagnosed with COVID-19

infection is increasing exponentially, and it's been declared a virulent disease by WHO. At present, no pharmacological agent has been approved by regulatory agencies for the treatment of SARS-CoV-2 infection, and a review of medication found to be effective against COVID-19 is that the need of the hour. Chloroquine (CQ) used as an antimalarial agent with immunomodulatory effects. A derivative of CQ, Hydroxychloroquine sulfate (HCQ) was synthesized first in 1946 by adding a bunch to CQ and is far less toxic than CQ in animal studies. CQ has been utilized in SARS Coronavirus infection because of its antiviral properties. Recently CQ has also been found to possess Anti-COVID-19 activity in vitro. For these reasons, CQ and HCQ is that the potential drug for treating COVID-19 infection. To date, there's no any clinical evidence to support the utilization of CQ or HCQ for treating SARS-CoV-2 infection though many clinical trials with these drugs are already underway. The purpose of this study is to review the available literature for the utilization of CQ or HCQ in treating COVID-19 infection.

In the early in vitro studies, chloroquine was found to dam COVID-19 infection at low-micromolar concentration, with a half-maximal effective concentration (EC50) of 1.13μM and a half-cytotoxic concentration (CC50) greater than 100μM. the variability of subsequent clinical trials are quickly conducted in China to test the efficacy and safety of chloroquine or hydroxychloroquine within the treatment of COVID-19 associated pneumonia in quite 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo. Thus far, results from quite 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a scourge negative conversion, and shortening the disease course keep with the news briefing. Severe adverse reactions to chloroquine phosphate weren't noted within the aforementioned patients. Given these findings, a conference was persisted February 15, 2020; participants including experts from government and regulatory authorities and organizers of clinical trials reached an agreement that chloroquine phosphate has potent activity against COVID-19. The drug is usually recommended for inclusion within the following version of the foundations for the Prevention, Diagnosis, and Treatment of Pneumonia caused by COVID-19 issued by the National Health Commission of the People's Republic of China.

Chloroquine is employed to prevent and treat malaria and is efficacious as an anti-inflammatory agent for the treatment of arthritis and lupus erythematous. Studies revealed that it also has potential broad-spectrum antiviral activities by increasing endosomal pH required for virus/cell fusion, also as interfering with the glycosylation of cellular receptors of SARS-CoV. The anti-viral and anti-inflammatory activities of chloroquine may account for its potent efficacy in treating patients with COVID-19 pneumonia. Chloroquine could even be an inexpensive and safe drug that has been used for quite 70 years. In light of the urgent clinical demand, chloroquine phosphate is usually recommended to treat COVID-19 associated pneumonia in larger populations within the long term.

BACKGROUND

Chloroquine (CQ) was first used as prophylaxis and treatment for malaria. Hydroxychloroquine (HCQ) could even be a more soluble and fewer toxic metabolite of chloroquine, which causes less side effects and is, therefore, safer. More recently, CQ/HCQ has been accustomed manage conditions like systemic LE and arthritis. CQ/HCQ has been utilized within the treatment of HIV with mixed results. The facility of CQ/HCQ to inhibit certain coronaviruses, like SARS-COV-1, has been explored with promising results. Both drugs are affordable and widely available internationally. With decades of experience administering these drugs, their safety profiles are well established. It's likely to want many months for novel, specific treatments of COVID-19 to become available. As a result, there has been growing interest within the utilization of CQ and HCQ as potential treatments within the interim.

METHODS

We performed a systematic review of the Pub Med and EMBASE databases from inception to 10th April, 2020 to find articles providing information on the efficacy and safety of Chloroquine and Hydroxychloroquine related formulations in patients with SARS-CoV-2 pneumonia and articles describing related in-vitro studies. We also searched the Chinese Clinical Trial Registry, Clinicaltrial.gov and the International Clinical Trials Registry Platform (WHO ICTRP) to identify ongoing trials.

Literature Review and Data Sources

Pub Med and Google Scholar were used for searching the articles, reporting on the topics of the role of CQ in COVID 19 infection. The search was conducted using the following keywords: "Chloroquine," "Hydroxychloroquine," "COVID-19," and "SARS-CoV-2" with a publication time range up to 30th March, 2020. The abstract & purpose of the articles found during the literature search were reviewed. Articles describing the role of CQ or HCQ in COVID-19 infection were selected for full-text review.

Screening

Titles, also because the abstracts of things within the search results, were screened. The full-text of the chosen articles was downloaded. Relevant information about the utilization of CQ and HCQ from all the chosen articles was extracted. The information from selected articles were studied independently by two investigators (VG and MD), and consensus was achieved with mutual discussion.

Pharmacology of chloroquine and hydroxychloroquine

Drug structure and chemistry

Hydroxychloroquine and chloroquine belong to a category of medication called 4-aminoquinolines, whereas other less frequently used antimalarial drugs belong to other groups (such because the endoperoxidases (artemisinin) or acridines (mepacrine) Both drugs have a flat aromatic core structure and are weak bases due to the presence of a basic side chain (Figure No.1). The essential side chain is believed to contribute to the build-up of these drugs in intracellular compartments, especially lysosomal compartments, which seems to be crucial for his or her activity and also the potential interaction of these drugs with nucleic acids. Both hydroxychloroquine and chloroquine occur as enantiomers (R and S isomers). (R) (-) hydroxychloroquine (the stereochemical 'rectus' configuration of hydroxy chloroquine) is present at higher concentrations within the blood than (S) (+) hydroxychloroquine (the stereochemical 'sinister' configuration of hydroxychloroquine), suggesting the existence of stereo-selective processes within the deposition and/or metabolism of this drug. The efficacy and safety of the drug enantiomers may additionally differ. However, the (R)(-) and (S)(+) isomers of chloroquine have similar effects in vitro, and also the embryo toxicity of chloroquine enantiomers in rats is additionally equivalent. Stereoisomer specific drug formulations are developed to chop back adverse effects like risk of retinopathy, but their effects require further clinical investigation.

Biological Mechanism of Chloroquine and Hydroxychloroquine

A number of potential mechanisms of action of CQ/HCQ against SARS-CoV-2 are postulated. The virus is believed to enter cells by binding to a cell surface enzyme called angiotensin-converting enzyme 2 (ACE2). ACE2 expression is additionally believed to be upregulated by infection with SARS-CoV-2. Chloroquine may reduce glycosylation of ACE2, thereby preventing COVID-19 from effectively binding to host cells. Furthermore, Savarino *et al*, hypothesis that CQ might block the assembly of pro-inflammatory cytokines (such as interleukin-6), thereby blocking the pathway that subsequently finally ends up in acute respiratory distress syndrome (ARDS). Some viruses enter host cells through endocytosis; the virus is transported within the host cell during a cell-membrane derived vesicle called an endosome, within which the virus can replicate. When the endosome fuses with the acidic intracellular lysosome, this finally ends up in rupture of the endosome with the discharge of the viral contents. Chloroquine has been found to accumulate in lysosomes, interfering with this process. Chloroquine is additionally believed to lift

the pH level of the endosome, which may interfere with virus entry and/or exit from host cells.

SARS-CoV2, like other human coronaviruses, harbours three envelope proteins, the spike (S) protein (180–220 kDa), the membrane (M) protein (25–35 kDa) and also the envelope (E) protein (10–12 kDa), which are required for entry of infectious virions into target cells. The virion also contains the nucleocapsid (N), capable of binding to viral genomic RNA, and nsp3, a key component of the replicase complex. A subset of beta coronaviruses use a hemagglutinin-esterase (65 kDa) that binds sialic acids at the surface of glycoproteins. The S glycoprotein determines the host tropism. There's indication that SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) expressed on pneumocytes. Binding to ACE2 is predicted to trigger conformational changes within the S glycoprotein allowing cleavage by the transmembrane protease TMPRSS2 of the S protein and also the discharge of S fragments into the cellular supernatant that inhibit virus neutralisation by antibodies. The virus is then transported into the cell through the primary and late endosomes where the host protease cathepsin L further cleaves the S protein at low pH, leading to fusion of the viral envelope and phospholipidic membrane of the endosomes resulting in release of the viral genome into the cell cytoplasm.

Replication then starts and also the positive-strand viral genomic RNA is transcribed into a negative RNA strand that's used as a template for the synthesis of viral mRNA. Synthesis of The negative RNA strand peaks earlier and falls faster than synthesis of the positive strand. Infected cells contain between 10 and 100 times more positive strands than negative strands. The ribosome machinery of the infected cells is diverted in favour of the virus, which then synthesises its non-structural proteins (NSPs) that assemble into the replicase-transcriptase complex to favourviral subgenomic mRNA synthesis.

Following replication, the envelope proteins are translated and inserted into the endoplasmic reticulum and then move to the Golgi compartment. Viral genomic RNA is packaged into the nucleocapsid and then envelope proteins are incorporated during the budding step to make mature virions. The M protein, which localises to the trans-Golgi network, plays a very important role during viral assembly by interacting with the alternative proteins of the virus. Following assembly, the newly formed viral particles are transported to the cell surface in vesicles and are released by exocytosis. It's possible that chloroquine interferes with ACE2 receptor glycosylation, thus preventing SARS-CoV-2 binding to target cells. Chloroquine could also possibly limit the biosynthesis of sialic acids which will be required for cell surface binding of SARS-CoV-2. If binding of some viral particles is achieved, chloroquine may modulate the acidification of endosomes thereby inhibiting formation of the autophagosome. Through reduction of cellular mitogen-activated protein (MAP) kinase activation, chloroquine may additionally inhibit virus replication. Moreover, chloroquine could alter M protein maturation and interfere with virion assembly and budding.

RESULTS

Studies of Chloroquine and Hydroxychloroquine conducted *in vitro*

Experimental studies have suggested that chloroquine may be a proven anti-malarial drug that has the aptitude of inhibiting the replication of several intracellular micro-organisms including coronaviruses *in vitro*. It's also believed that chloroquine may have a varied mechanism of action which can differ depending upon the pathogen studied. It's been increasingly learnt that the anti-viral and anti-inflammatory activities of chloroquine may have a task within the treatment of patients with novel COVID-19. Chloroquine increases endosomal pH and interferes with the glycosylation of cellular receptor of SARS-CoV and thereby it's the potential to dam virus infection. Additionally, chloroquine also inhibits the Quinone reductase-2, which is involved in sialic acid biosynthesis (an acidic monosaccharides of cell transmembrane proteins required for ligand recognition) that creates this agenta broad medicinal drug. It's important to notice that both human

coronavirus HCoV-O43 and orthomyxoviruses uses sialic acid moieties as a receptor.

Moreover, chloroquine changes the pH of lysosomes and certain inhibits cathepsins, that ends up in the formation of the autophagosome which cleaves SARS-CoV-2 spike protein. Furthermore, chloroquine through the inhibition of MAP-kinase interferes with SARS-CoV-2 molecular crosstalk, besides altering the virion assembly, budding and interfering with the proteolytic processing of the M protein. Previous experimental studies have also demonstrated that chloroquine has potent anti-SARS-CoV-1 effects *in vitro*, primarily because of a deficit within the glycosylation receptors at the virus cell surface, so it cannot bind to the angiotensin-converting enzyme 2 (ACE2) expressed in lung, heart, kidney and intestine. Since SARS-CoV-2 utilizes the similar surface receptor ACE2, it's believed that chloroquine may interfere with ACE2 receptor glycosylation thus prevents SARS-CoV-2 attachment to the target cells [6e9]. Chinese researchers who studied the effect of chloroquine *in vitro* (using Vero E6 cell line infected by SARS-CoV-2) found chloroquine to be highly effective in reducing viral replication that may be easily achievable with standard dosing because of its favorable penetration in tissues including the lung.

Potential antiviral effect of chloroquine against SARS-CoV-2

Because of its broad spectrum of action against viruses, including most coronaviruses and particularly its close relative SARS- CoV-1, and since coronavirus cell entry occurs through the endolysosomal pathway, it made sense during a situation of a public- health emergency and therefore the absence of any known efficient therapy to analyze the possible effect of chloroquine against SARS-CoV- 2. A recent paper reported that both chloroquine and therefore the medicine remdesivir inhibited SARS-CoV-2 in vitro and suggested these drugs be assessed in human patients affected by COVID-19. Recently, the China National Center for Biotechnology Development indicated that chloroquine is one amongst the three drugs with a promising profile against the new SARS-CoV-2 coronavirus that causes COVID-19. Chloroquine repurposing was investigated in hospitals in Beijing, in central China's Hunan province and South China's Guangdong province. Per preliminary reports from the Chinese authorities suggesting that approximately 100 infected patients treated with chloroquine experienced a more rapid decline in fever and improvement of lung CAT (CT) images and required a shorter time to recover compared with control groups, with no obvious serious adverse effects, the Chinese medical planning board has suggested chloroquine inclusion within the SARS-CoV-2 treatment guidelines. As a result, chloroquine is maybe the primary molecule to be utilized in China and abroad on the front for the treatment of severe SARS- CoV-2 infections. A survey of SARS-CoV- 2-infected patients for adverse effects of chloroquine therapy remains to be performed. However, chloroquine is currently among the simplest available candidates to impact the severity of SARS-CoV-2 infections in humans. Currently, a minimum of ten clinical trials are testing chloroquine as an anti-COVID-19 therapy.

Precautions with Chloroquine and Hydroxychloroquine

Expectedly, some precautions are needed while using both these drugs that include;

Frequent monitoring of hematological parameters (RBC, WBC and platelet counts) Measurement of serum electrolytes,

Blood glucose (because of hypoglycemic potential of HCQ) and hepatic similarly as renal functions.

Since both these drugs have the potential to prolong QTc, routine electrocardiography is important before starting these drugs.

Co-administration of other drugs known to prolong the QTc interval (such as anti-arrhythmic, anti-depressants, anti-psychotics, antihistaminic, teneligliptin, ondansetron and moxifloxacin etc.) must be avoided.

Moreover, addition of azithromycin to HCQ as exhausted French trial by Gautret *et al.* May increase the chance of QTc prolongation. Perform ECG daily if QTc is 450e500 msec.

Additionally, hypoglycemia must be looked for in patients with diabetes especially with concurrent use of chloroquine/HCQ and lopinavir/ritonavir.

Chloroquine and HCQ should not be used concurrently with lopinavir/ritonavir and remdesivir for anticipated QTc prolongation.

Finally, pharmacovigilance on visual and mental disorder is additionally closely required.

Contraindications

All clinicians using these drugs must know contraindication to both these compounds;

Hypersensitivity to those agents

Retinopathy

Porphyria

Epilepsy,

Pre-existing maculopathy

G6PD deficiency

Recent myocardial infarct and QTc >500 msec.

Chloroquine isn't contraindicated in pregnancy.

DISCUSSION

Chloroquine (CQ) may be a well-known 4-aminoquinoline that has been in clinical use since 1944. Hydroxychloroquine sulfate (HCQ) was synthesized in 1946 with the addition of a hydroxyl group to CQ. CQ has been used extensively in treating malaria and also for the treatment of autoimmune diseases like autoimmune disorder, systemic lupus erythematous, etc. Because of its immunomodulatory role.

CQ exerts its antiviral effects through various mechanisms within the cell.

CQ is weakly alkaline in nature, and it can change the pH of endosomes. Thus it can exert a serious inhibitory effect on viral infections, which invade cells via the endosome pathway like Zika virus and Borna disease virus.

Many other viruses like Ebola (EBOV) depend on the naturally low pH of acidic endosomes for activating and triggering the fusion by their envelope glycoproteins. Thus a 'fusion inhibitor' could target the host cell machinery by preventing the acidification of the endosome to inhibit virus entry. The cell entry by EBOV, FLU-H5, and MARV is inhibited due to the increase within the endosome pH by CQ due to its ability to forestall the acidification of intracellular organelles. The data on the kinetics of chloroquine uptake indicated the drug attained near-maximum intracellular concentrations in 1 hr and a drug level of 60μg/ml produced a decrement within the cellular biosynthesis of protein, RNA, or DNA. Herpes simplex replication was found to be sensitive to the current drug because the extent of progeny virus production was depressed by 95% in 24 hr. CQ also affects viral replication by inhibiting viral natural phenomenon. CQ incorporates a capability to vary the pattern of glycosylation in HIV-1 gp120 envelope during In vitro and in vivo tests.

CQ also inhibits the replication of the HIV virus in CD4 + T cells. Both CQ and HCQ are weakly alkaline bases and affect the acid vesicles causing the dysfunction of enzymes required for post-translational protein modifications. These drugs increase the pH of acidic vesicles, cause disruption of several enzymes like acid hydrolases and cause inhibition of the post-transcriptional modification of newly synthesized proteins.

CQ has been found to be effective in inhibiting the infection and spread of SARS CoV in cell culture. CQ inhibits the virus replication by reducing the terminal glycosylation of angiotensin-converting enzyme 2 (ACE2) receptors on the Vero E6 cells' surface and interfering with the binding of SARSCoV to the ACE2 receptors. CQ had a serious inhibitory antiviral effect when the susceptible cells were treated either before or after infection, suggesting a possible prophylactic and therapeutic use. CQ interferes with COVID-19's attempt to acidify the lysosomes and probably inhibits cathepsins, which needs a coffee pH for optimal cleavage of COVID-19 spike protein, a requirement for the formation of the autophagosome.

As of 23rd February 2020, seven clinical trial registries are found within the Chinese clinical trial Registry for using HCQ to COVID-19 treatment. It has been reported that the safe dosage of HCQ (66.5mg/kg per day) could reach serum levels of 1.4-1.5μM in humans. In animals, CQ and HCQ share similar tissue distribution, with concentrations within the liver, spleen, kidney, and lung reaching levels, which are 200-700 times above those within the plasma. Therefore an extremely high concentration within the above tissues is perhaps visiting be achieved with the safe dosage of HCQ

for inhibiting SARS-CoV-2 infection. This possibility, however, awaits confirmation by clinical trials. In patients with COVID19 infection, CQ can interact with lopinavir/ritonavir, Causing QT interval prolongation. Hence HCQ is taken into account instead of CQ when the latter isn't available for COVID-19 treatment.

HCQ has been found to be more potent than CQ at inhibiting SARS-CoV-2 in vitro. HCQ Sulfate 400mg twice daily for in some unspecified time within the future, followed by 200 mg twice daily for four more days, has been recommended for treating COVID-19 infection.

Supported CQ's antiviral mechanisms, its laboratory activity against COVID-19, additionally as CQ's pharmacokinetics supported its use for malaria and autoimmune diseases, safe and potentially efficacious dose regimens are recommended for protection against COVID-19. This protocol has pre-exposure prophylaxis of 250-500mg CQ daily and post-exposure prophylaxis at 8mg/kg/day CQ for 3 days.

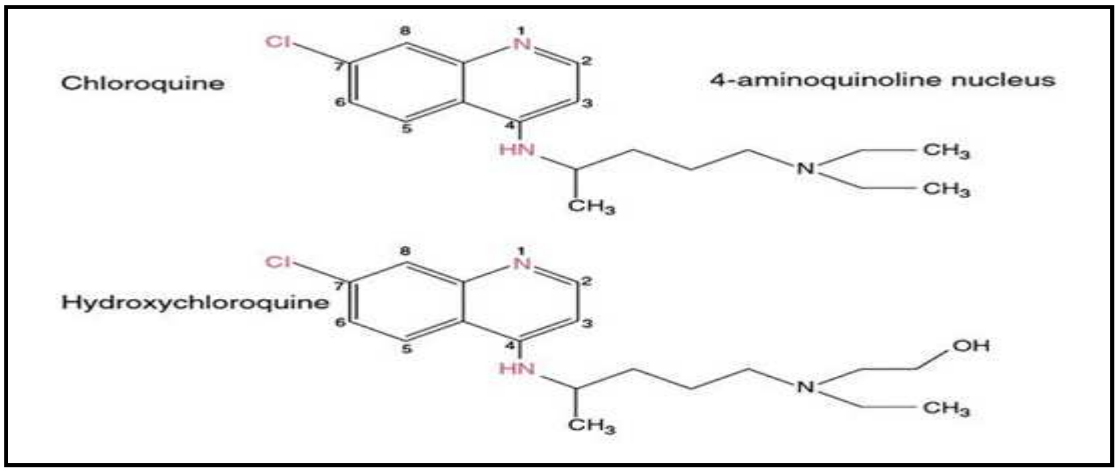

Figure No.1: Structure of Chloroquine and Hydroxychloroquine

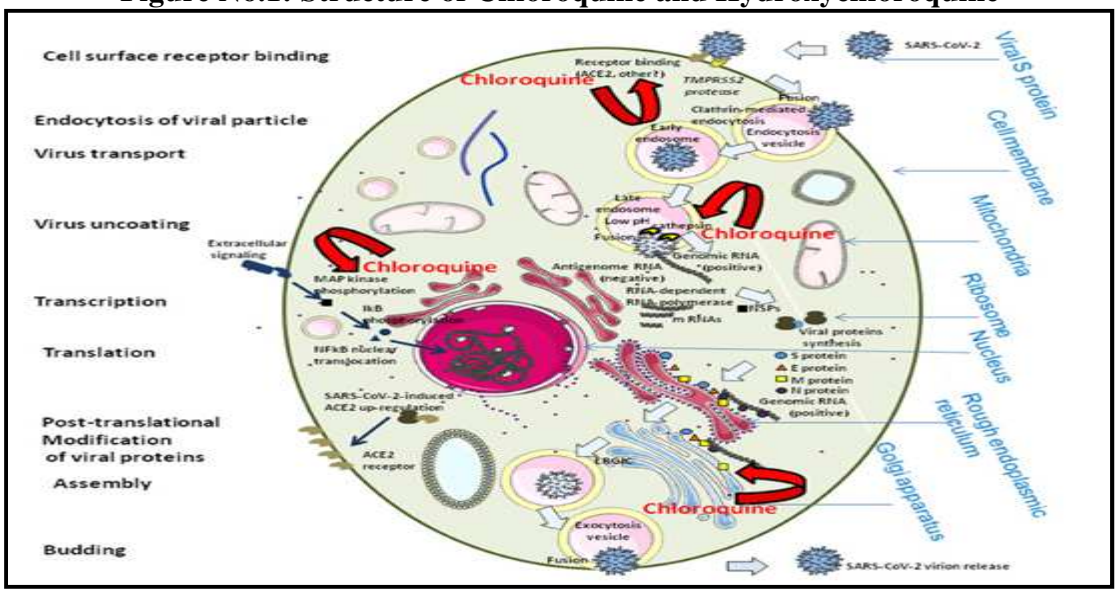

Figure No.2: Schematic representation of the possible effects of chloroquine on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication cycle

CONCLUSION

The results of *in vitro* studies and those of recent clinical trials using CQ and HCQ in COVID-19 infection are quite promising. A worldwide strategy for allowing the employment of promising drugs like CQ and HCQ for COVID-19 should be made. Considering the low cost, easy availability, and minimal adverse effects, CQ and HCQ should be prescribed to COVID-19 patients under medical supervision.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Cooper R G, Magwere T. Chloroquine: Noveluses and manifestations, *Indian J Med Res,* 127(4), 2008, 305-316.
2. Sharma V P. Battling the malaria iceberg with chloroquinein India, *Malar J,* 6(1), 2007, 105.
3. Ansah E K, Gyapong J O, Agyepong I A, Evans D B. Improving adherence to malaria treatment for children. He use of pre-packed chloroquine tablet svs. Chloroquine syrup, *Trop Med Int Heal,* 6(7), 2001, 496-504.
4. Mc Chesney E W. Animal toxicity and pharmacokinetics of hydroxy chloroquine sulphate, *Am J Med,* 75(1A), 1983, 11-18.
5. Savarino A, Boelaert J R, Cassone A, Majori G, Cauda R. Effects of chloroquin eon viral infections, an old drug against today diseases, *Lancet Infect Dis,* 3(11), 2003, 722-727.
6. Wang Metal. Remdesivir and chloroquine effective lyinhibit the recent yemerged novel coronavirus (2019-nCoV) *in vitro*, *Cell Res,* 30(3), 2020, 269-271.
7. Zhu R, Gao R, Robert S H, Gao J, Yang S, Zhu C. Systematic Review of the Registered Clinical Trials of Coronavirus Disease 2019 (COVID-19), *Med Rxiv,* 2020, 1-43.
8. Gordon C, Amissah-Arthur M B, Gayed M *et al*. The British Society for Rheumatology guide line forth emanagement of systemic lupusery the matosus in adults, *Rheumatology (Oxford*), 57(1), 2018, e1-e45.
9. Schrezenmeier E, Dorner T. Mechanism so faction of hydroxylchloroquine and chloroquine, implications for rheumatology, *Nat Rev Rheumato,* 16(3), 2020, 155-166.
10. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. https://www.who.int/dg/speeches/detail/who-directorgeneral-s-opening-remarks-atthe-media-briefing-on-covid-19-11-march2020.
11. Wu Z, Mc Googan J M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China, summary of a report of 72 314 cases from the Chinese Center for disease control and prevention, *J Am Med Assoc,* 323(13), 2020, 1239-1242.
12. Gupta R, Ghosh A, Singh A K, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic, Diabetes, *Metab Syndrome Clin Res Rev,* 14(3), 2020, 211e2.
13. Chloroquine US prescribing information (Last accessed March 21, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf.
14. Delang L, Abdelnabi R, Neyts J. Favipiraviras a potential counter measure against neglected and emerging

RNA viruses, *Antiviral Res,* 153, 2018, 85-94.
15. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral R N A polymerase, ProcJpnAcad, *Ser B, PhysBiol Sci,* 93(7), 2017, 449-463.
16. News.http://www.szdsyy.com/News/0a6c1e58-e3d0-4cd1867a-d5524bc59cd6.html (accessedFebruary22, 2020). (In Chinese).
17. Sheehan T P, Sims a C, Leist S R, *et al.* Comparative the rape tic efficacy of redesivir and combination lopinavir, ritonavir, and interferon beta against MERS CoV, *Nat Commun,* 11, 2020, 222.
18. Arya R, Das A, Prashar V, Kumar M. Potential inhib it or against papa in, like protease of novel coronavirus (SARS-CoV-2) from F D A approved drugs, *Chemrxiv Org,* 2020, 1-8.
19. Chang R, Sun W Z. Repositioning Chloroquine as Ideal Antiviral Prophylactic against COVID-19, *Time snow,* 2020.
20. Kearney J. Chloroquineasa Potential Treatment and Prevention Measure for the 2019 Novel Coronavirus, *A Review, Pre-prints,* 2020.
21. Zhu N, Zhang D, Wang W, *et al.* A Novel Coronavirus from Patients with *Pneumonia* in China, *New Eng l J Med,* 382(8), 2019, 27-733.
22. Gorbalenya A E, Baker S C, Baric R S, *et al.* Severe acute respire to rysyndrome-related coronavirus: The species and its viruses –a statement of the Corona virus Study Group, *Bio Rxiv,* 2020, 2020-2022.
23. Li Q, Guan X, Wu P, *et al.* Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. The New England journal of medicine. 2020. Touret F, deLamballerie X. of chloroquine and COVID-19, *Antiviral Res,* 177, 2020, 1047-1062.
24. Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquino lines Against Coronavirus Disease 2019 (COVID-19): Chloro quineor Hydroxy chloroquine, *Int J Antimicrob Agents,* 55(4), 2020.

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