REVIEW ARTICLE

Chloroquine and Hydroxychloroquine in Coronavirus Disease-19: The Real Savior or a False-positive Testament

Muhammad Shahid Iqbal[1], Anam Liaqat[2], Muhammad Asad[3], Muhammad Faheem[2], Muhammad Zahid Iqbal[4], Salah-Ud-Din Khan[5]

[1]Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, 11942, Saudi Arabia, [2]Department of Pharmacology, Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad, Pakistan, [3]Armed Forces Institute of Cardiology, National Institute of Heart Disease, Rawalpindi, Pakistan, Pakistan, [4]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, AIMST University, 08100 Bedong, Kedah, Malaysia, [5]Department of Biochemistry, College of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

Abstract

Objective: A novel coronavirus disease (COVID-19) has spread all around the world. The progression from initial signs to a diagnosis of acute respiratory failure is usually related to spontaneous cytokine production. There is a growing need to classify appropriate medicines for treatment care. The inhibitory effect of chloroquine (CQ) is potential. However, CQ can lead to serious side effects. Various studies recommend hydroxychloroquine (HCQ) have similar antiviral effect as of CQ and maybe a better therapeutic solution. Therefore, we aim to explore the mechanism by which HCQ can inhibit replication of coronavirus. **Materials and Methods:** A retrospective study was carried out using online databases from 2003 to 2020. **Results:** The obtained results showed that HCQ can inhibit viral replication and entry inside the cell through raising lysosomal pH and binding to specific receptors on the cells, thereby, preventing viral entry. **Conclusion:** HCQ has a better safety profile than CQ and also modulates cytokine syndrome. However, further studies are needed to explore this mechanism.

Key words: Chloroquine, coronavirus disease-19, hydroxychloroquine, severe acute respiratory syndrome coronavirus-2

INTRODUCTION

In late December 2019, an emerging coronavirus disease (COVID-19) outbreak caused by a novel coronavirus (named severe acute respiratory syndrome coronavirus [SARS-CoV-2]) later started in Wuhan, China, and expanded rapidly in China and worldwide.[1,2] On March 12, 2020, the World Health Organization announced the COVID-19 outbreak as a pandemic.[3] According to recent studies, approximately more than 80% of the infected patients presented with moderate-level infections and the total case-fatality rate is more than 5% but exceeds 12% in patients aged 70–79 and 20% in those aged 80 years.[4] Therefore, there is an immediate need for adequate care to treat symptomatic patients but also to decrease the length of the propagation of the virus to reduce population transmission.

Among potential candidate drugs to treat COVID-19, repositioning old drugs for use as antivirals are an interesting strategy because of information about the safety profile, side effects, and dosage and drug interactions.[5,6] A number of studies have been recently shown to evaluate an appropriate therapeutic protocol for COVID-19. A recent study about chloroquine (CQ) phosphate which is an old antimalarial agent endorsed its inhibitory effect on the growth of SARS-CoV-2.[7] According to the clinical trial conducted among COVID-19 Chinese patients, findings showed that CQ had a significant effect, both in terms of

Address for correspondence:
Dr. Muhammad Shahid Iqbal, Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-kharj, 11942, Saudi Arabia.
E-mail: m.javed@psau.edu.sa

Received: 09-07-2020
Revised: 15-08-2020
Accepted: 29-08-2020

clinical outcome and viral clearance when compared to control groups.[8,9]

On March 28, 2020, the U.S. Food and Drug Administration permitted CQ and hydroxychloroquine (HCQ) to be utilized among severely infected COVID-19 patients, especially if they hospitalized. Moreover, for decades, these two drugs (CQ and HCQ) have been widely used for the treatment and management of malaria and several autoimmune diseases. Several clinical trials in China have shown that CQ is effective against COVID-19. CQ has also played a positive role in handling outbreaks of the Zika virus and SARS-COV.[10] Experts suggest that patient diagnosed with a mild, moderate, and severe cases of COVID-19 pneumonia, without CQ contraindications, be treated with 500 mg of CQ twice daily for 10 days.[11] Studies revealed that CQ confers its significant wide-spectrum antiviral effects through interrupting the fusion process of these viruses by increasing the intracellular endosomal and lysosomal pH. CQ also alters the glycosylation of the cellular receptors of coronaviruses.[12] Further, another study demonstrates that CQ and HCQ act as zinc ionophores, allowing zinc to enter into the cells, zinc concentration increases in cytosol, and zinc inhibits RNA-dependent RNA polymerase.[13] HCQ, which is an analog of CQ, also shown to have similar *in vitro* anti-SARS-CoV activity.[14] However, the clinical safety profile of HCQ is greater than that of CQ and allows for a higher daily dose,[15] with fewer concerns about drug-drug interactions.[16] Replacement of N-diethyl group of CQ with N-hydroxyethyl side chain in HCQ makes it more soluble with fewer side effects. HCQ increases pH just like CQ and, therefore, exhibits antiviral effects.

In addition, it shows a modulating effect on activated immune cells and downregulates the expression of toll-like receptors (TLRs) and, therefore, ultimately decreases the production of interleukin (IL)-6. Retinopathy is a dosage-limiting side effect of HCQ, and a secure daily dosage seems to correlate to an ideal body weight of 6.5 mg/kg and actual bodyweight of 5.0 mg/kg. Although more clinical data are available on CQ anti-coronavirus activity as compared to HCQ, both drugs are theoretically identical with respect to antiviral activity. Furthermore, CQ may show interaction with lopinavir/ritonavir in patients with COVID-19 and lead to prolongation of QT interval. Hence, HCQ consideration is safer than CQ in this perspective as well since other therapeutic agents for COVID-19, that is, antiviral agents (oseltamivir, lopinavir/ritonavir, ribavirin, etc.), interferons, and intravenous immunoglobulins that do not show drug-drug interaction with HCQ.[17,18]

METHODOLOGY

A retrospective study from the literature was conducted between 2003 and 2020 by setting a criterion from an extensive literature review about CQ and HCQ studies done during early months (February 2020–June 2020) of COVID-19 pandemic. The main objectives were determined and finalized.

Statistical analyses

For data analysis, descriptive statistics were used and data were analyzed using Statistical Package for the Social Sciences version 24.0.

RESULTS

This study had some main valuable points that were explored. These are presented in Table 1.

Table 2 shows the major adverse drug events of CQ. However, they are varied among varied populations but more or less are common.

Table 3 illustrates the major adverse drug events of HCQ. Similarly, like CQ, they are varied among different populations but more or less are common.

Table 4 demonstrates the toxicity profile of CQ. Depending on the severity of the patients' condition, age, comorbidities, and drug dose adjustments, they may be varied among different populations.

Table 5 presents the toxicity profile of HCQ. Depending on the severity of the patients' condition, age, comorbidities, and drug dose adjustments, they may be varied among different populations.

Table 1: The major highlights of the study

No.	Statements
1	COVID-19 is a major global threat nowadays
2	No specific treatment has been established for the COVID-19 infection yet
3	CQ and HCQ mechanism of action in COVID-19 disease infection could play a role
4	CQ and HCQ could inhibit viral replication through a mechanism of alkalization of endosomes and may prevent virus attachment to ACE receptors in COVID-19 patients

COVID: Coronavirus disease, HCQ: Hydroxychloroquine, ACE: Angiotensin-converting enzyme

Table 2: Main adverse drug events of CQ

Headache
GIT cramps
Nausea
Vomiting
Blurred vision
Hair color change or loss

Table 3: Adverse drug events of HCQ

a) Most frequent
Nausea
Vomiting
Headache
Skin rash
Dizziness
Vertigo
GIT upset
b) Less frequent
Liver disorders
Light phobia
Skin scars
Hypoglycemia

HCQ: Hydroxychloroquine

Table 4: Toxicity profile of CQ

Dyspnea
Inflammation
Mouth/throat infections
Sunlight phobia
Skin disorders
Tiredness
Hearing loss
Mood disorders

Table 5: Toxicity profile of HCQ

a) Short term
Heart problems
ECG abnormalities
Cardiac arrest
Cardiac death
b) Long term
Microvascular
Myopathies
Neuropathies
Retinopathies

HCQ: Hydroxychloroquine

Table 6: Prominent drug interactions of CQ and HCQ

Antifungals
Antidepressants
Macrolides
Antiemetics
Quinolones
Antiarrhythmics
Cytochrome 450 inhibitors
P-glycoprotein eliminators
CQ and HCQ metabolism competitors
CQ and HCQ absorption reducers

HCQ: Hydroxychloroquine

Table 6 shows the most noticeable drug interactions of CQ and HCQ. Depending on the severity of the patients' condition, age, comorbidities, and drug dose adjustments, they may be varied among different populations.

DISCUSSION

Several antiviral drugs were tested for effectiveness in inhibiting replication of COVID-19 (SARS-CoV-2) in cell culture, and CQ is a drug renowned due to its efficacy in the management of malaria and autoimmune disease.[8,19] Many trials were carried out to assess the action of CQ and HCQ in COVID-19 patients. Therapeutic outcomes were more prevalent in fever suppression, changes in CT imaging, as well as disease retardation. In the sixth edition of the latest pneumonia diagnosis and treatment program published through China's National Health and Care Commission in February 2020, CQ has officially declared a therapeutic agent for COVID-19. The suggested regimen in adults is 500 mg/day that is the human body average safe dose.[5,19]

HCQ is among the antirheumatic disease-modifying medications (DMARDs) having close chemical composition to that of CQ. The DMARDs display high immunomodulatory ability, which prevents the progression of inflammation as well as organ damage.[20] In general, HCQ can contribute to higher intracellular pH and thus impede lysosomal function in antigen-presenting cells, plasmacytoid dendritic cells as well as in B cells, thereby stopping the processing of antigens and major histocompatibility complex class II-mediated autoantigen exposure to T cells. This eventually diminishes the stimulation of T-cell differentiation or costimulatory protein expression (e.g., CD154 on CD4+ T cells),[21] also cytokines formation such as IL, (i.e., IL-1, IL-6, and TNF). In the meantime, because of altered endosomal pH along with disrupted binding among TLR7, TLR9, and their RNA/DNA ligands, TLR processing gets inhibited due to HCQ treatment.

HCQ also works by interfering with the interaction of DNA and nucleic acid sensor cyclic GMP-AMP (cGAMP) synthase (cGAS) in the cytoplasm. Since TLR signaling and cGAS interferon gene activation (the STING pathway) become hindered through HCQ, resultant pro-inflammatory signaling stimulation and cytokine formation including are attenuated.[22-26] These mechanisms strongly support the view that HCQ is expected to confer a capacity to control cytokine release syndrome due to overactivation of

the immune system stimulated through SARS-CoV-2 and ultimately attenuate the disease's progression from mild to serious.[27]

In addition to the function of immune regulation, CQ and HCQ prevent the attachment to receptors as well as membrane fusion, the two key steps required by coronaviruses for cellular uptake. CQ is believed to have an antiviral activity during pre-/post-infection situations through interfering with angiotensin-converting enzyme 2 (ACE2) glycosylation (SARS-CoV cell receptor) and blocking viral fusion with the cell membrane.

Impeded glycosylation of ACE2 can decrease the association between ACE2 with the spike protein SARS-CoV. Consequently, the virus attachment to cell receptors is obstructed, ultimately preventing infection. When CQ and HCQ join a cell, they localize inside the low pH endosomes, Golgi vesicles, and lysosomes. They utilize endosomes as a tool for cell access which results in raising the pH of endosomes to impart a negative effect among virus and endosomes' fusion process.[28] By splitting the coronavirus surface spike proteins, lysosomal proteases induce the cell's fusion with the virus membrane, and increasing the pH of lysosomes reduces its protease function and fusion mechanism. COVID-19 spread inhibition was noticed with CQ treatment before or in later infection hence indicating prophylactic and therapeutic advantages of CQ. Since HCQ displays identical mechanisms as of CQ, it would be highly possible that HCQ can function likewise in early protection and prevention of the disease.[29]

Patients with prolonged use of CQ and HCQ may experience serious adverse effects and drug interactions, including retinopathy, circular defects, retina diametric defects, and cardiomyopathies. Older patients prescribed with CQ and HCQ therapy, may experience toxic effects if the dose is exceeded their recommended dose limits. HCQ, on the other hand, has a bit lower tissue accumulation level, which could demonstrate the implication linked to less adverse outcomes as compared to CQ. Yet, it is effectively used in malaria treatment and prevention. However, prolonged ingestion of HCQ over 5 years of the period could contribute to retinopathy.[30] In addition, CQ exhibits a range of adverse events on fetal, hence, HCQ is also recommended for pregnant patients since it protects from congenital heart block episodes because of a possible suppression of type I interferon formation in autoimmune diseases.[31,32]

CQ and HCQ in COVID-19 patients

Despite the fact that CQ and HCQ have considerable safety margins, yet their use in severely ill COVID-19 patients may cause various instances of severe complications and/or deaths.[19,33-35] These complications usually could arise due to multiple factors like their high dose than the recommended or prescribed, concomitant use of some other antimicrobials like azithromycin, and very severe COVID-19 patients.[36-40] There may be a need of a specialized stepwise pharmaceutical care plan for patients suffering from severe COVID-19 infections.[41,42] But again, there should be very careful and thorough monitoring under the proper care of a qualified health-care professional is a must thing to tackle any unwanted effects and drug interactions. Such unwanted and side effects could range from a simple drug allergy to congenital long QT interval syndrome.

Both CQ and HCQ have some mild-moderate side effects and drug interactions with many regularly used drugs, which if ignored, can cause a severe health risk for COVID-19 patients, especially with severe shortness of breath. Such drug interactions and side effects must need to be identified and addressed. Besides, if there are some severely life-threatening side effects appear among COVID-19 patients, then both of the drugs, that is, CQ and HCQ should be stopped immediately, tapered down their dose, adjust their dose, or alter the drug regimens especially when given concomitantly with other drugs.[19,40-42]

Although, simultaneous use of CQ or HCQ with azithromycin may be of great significance but to avoid or minimize longer QT syndrome, such patients must be observed under critical care or intensive care. To determine that a drug should be avoided or contraindicated in patients, usually risk score is thought to be ≥11 to declare long QT syndrome. On the other side, where this risk is higher than 11, the drug is considered as contraindicated. For this substantial and life-threatening issue, all COVID-19 patients which are on HCQ therapy should have monitored regularly for their QT interval.[19,36-39]

Regarding some cardiac adverse effects in COVID-19 patients, electrolyte imbalance should also be observed which could lead to cardiac complications. And to avoid these imbalances, use of diuretics especially loop diuretics should be started and patients sign and symptoms should be monitored to reduce the severe chances of cardiotoxicity. In the case of stable tachycardia after administering HCQ, magnesium sulfate should be immediately administered over 15 min.[19,42,43] In the case, where patient does not respond, isoproterenol infusion at 2–10 mcg/min can be given. Besides, pacing to a rate of 100–120 depolarizations per minute to suppress tachycardia can also be started.[19,35-38]

Current scenario in COVID-19

The beneficial role of CQ and HCQ in COVID-19 patients' management is a vibrant element and could rapidly change once the results of randomized trials in different parts of the world are evident. Based on the site of action, both CQ and HCQ have antiviral properties which made them a

choice to manage COVID-19 patients. Both of these drugs are immunomodulators and downregulate the cytokine production which can mitigate the effects of SARS-CoV-2 virus infection in target vital organs such as the lungs, heart, liver, and gut.[43,44] Although, there are considerable evidences *in vitro* studies that both CQ and HCQ have strong antiviral properties, yet most of the health professionals are against the use of HCQ in management and post-exposure prophylaxis of COVID-19 patients.[45,46] Despite this, both CQ and HCQ have a narrow margin of safety that can cause severe side effects, drug interactions, and unwanted effects in terms of cardiotoxicity.[19,47]

CONCLUSION

It is recommended that HCQ for the treatment of SARS-CoV-2 infection in COVID-19 patients could function as a better therapeutic option than CQ because HCQ dampens the extreme advancement of COVID-19 infection by suppressing storm of cytokine release through decreasing the expression of CD154 on T cells. Furthermore, HCQ can have comparable antiviral effect in both early and later infection stages than CQ and due to the fact that it has fewer side effects, is healthy individuals, especially in pregnant women, and is widely available than CQ. Given the increasingly rising COVID-19-infected patients, with the immediate requirement of efficient and safe medicines, it is also more realistic to identify and develop precise, particular, and more suitable medications than the secondary supportive medications such as CQ and HCQ.

ACKNOWLEDGMENT

The authors would like to thank the Deanship of Scientific Research at Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia, to support this publication.

REFERENCES

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020;55:105920-4.
2. Wang LS, Wang YR, Ye DW, Liu QQ. A review of the 2019 novel Coronavirus (COVID-19) based on current evidence. Int J Antimicrob Agents 2020;55:105944-8.
3. World Health Organization, Director-General's Opening Remarks at the Media Briefing on COVID-19; 2020.
4. Wu Z, McGoogan JM. 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. JAMA 2020;323:1239-42.
5. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel Coronavirus SARS-CoV-2. Int J Antimicrob Agents 2020;55:105923.
6. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents 2020;55:105928-32.
7. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, *et al*. Remdesivir and chloroquine effectively inhibit the recently emerged novel Coronavirus (2019-nCoV) *in vitro*. Cell Res 2020;30:269-71.
8. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72-3.
9. Chinese Clinical Trial Registry. Available from: http://www.chictr.org.cn. [Last accessed on 2020 Jun 25].
10. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: An old drug against today's diseases. Lancet Infect Dis 2003;3:722-7.
11. Expert consensus on chloroquine phosphate for the treatment of novel Coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E019.
12. Lim HS, Im JS, Cho JY, Bae KS, Klein TA, Yeom JS, *et al*. Pharmacokinetics of hydroxychloroquine and its clinical implications in chemoprophylaxis against malaria caused by *Plasmodium vivax*. Antimicrob Agents Chemother 2009;53:1468-75.
13. Te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn^{2+} inhibits Coronavirus and arterivirus RNA polymerase activity *in vitro* and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010;6:e1001176.
14. Biot C, Daher W, Chavain N, Fandeur T, Khalife J, Dive D, *et al*. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. J Med Chem 2006;49:2845-9.
15. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology 2016;123:1386-94.
16. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, *et al*. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020;71:732-9.
17. Jorge AM, Melles RB, Zhang Y, Lu N, Rai SK, Young LH, *et al*. Hydroxychloroquine prescription trends and predictors for excess dosing per recent ophthalmology guidelines. Arthritis Res Ther 2018;20:133.
18. Tan YW, Yam WK, Sun J, Chu JJH. An evaluation of chloroquine as a broad-acting antiviral against hand, foot and mouth disease. Antiviral Res 2018;149:143-9.
19. Khuroo MS. Chloroquine and hydroxychloroquine in Coronavirus disease 2019 (COVID-19). Facts, fiction and the hype: A critical appraisal. Int J Antimicrob

Agents 2020;56:106101.
20. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: A systematic review. Ann Rheum Dis 2010;69:20-8.
21. Wu SF, Chang CB, Hsu JM, Lu MC, Lai NS, Li C, *et al*. Hydroxychloroquine inhibits CD154 expression in CD4+ T lymphocytes of systemic lupus erythematosus through NFAT, but not STAT5, signaling. Arthritis Res Ther 2017;19:183.
22. van den Borne BE, Dijkmans BA, de Rooij HH, Le Cessie S, Verweij CL. Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. J Rheumatol 1997;24:55-60.
23. Kužnik A, Benčina M, Švajger U, Jeras M, Rozman B, Jerala R. Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. J Immunol 2011;186:4794-804.
24. Ewald SE, Lee BL, Lau L, Wickliffe KE, Shi GP, Chapman HA, *et al*. The ectodomain of toll-like receptor 9 is cleaved to generate a functional receptor. Nature 2008;456:658-62.
25. Häcker H, Mischak H, Miethke T, Liptay S, Schmid R, Sparwasser T, *et al*. CpG-DNA-specific activation of antigen-presenting cells requires stress kinase activity and is preceded by non-specific endocytosis and endosomal maturation. EMBO J 1998;17:6230-40.
26. Vollmer J, Tluk S, Schmitz C, Hamm S, Jurk M, Forsbach A, *et al*. Immune stimulation mediated by auto-antigen binding sites within small nuclear RNAs involves toll-like receptors 7 and 8. J Exp Med 2005;202:1575-85.
27. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, *et al*. Chloroquine is a potent inhibitor of SARS Coronavirus infection and spread. Virol J 2005;2:69.
28. Schrezenmeier E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: Implications for rheumatology. Nat Rev Rheumatol 2020;16:155-66.
29. Al-Bari MA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. Pharmacol Res Perspect 2017;5:e00293.
30. Jorge A, Ung C, Young LH, Melles RB, Choi HK. Hydroxychloroquine retinopathy-implications of research advances for rheumatology care. Nat Rev Rheumatol 2018;14:693-703.
31. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, Khamashta MA, Kim MY, Saxena A, *et al*. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation 2012;126:76-82.
32. Lisney AR, Szelinski F, Reiter K, Burmester GR, Rose T, Dörner T. High maternal expression of SIGLEC1 on monocytes as a surrogate marker of a Type I interferon signature is a risk factor for the development of autoimmune congenital heart block. Ann Rheum Dis 2017;76:1476-80.
33. World Health Organization. The Cardiotoxicity of Antimalarials. WHO Evidence Review Group Meeting, 13-14 October 2016, Malaria Policy Advisory Committee (MPAC) Meeting 22-24 March. Geneva, Switzerland: World Health Organization; 2017.
34. Ursing J, Rombo L, Eksborg S, Larson L, Bruvoll A, Tarning J, *et al*. High-dose chloroquine for uncomplicated plasmodium falciparum malaria is well tolerated and causes similar QT interval prolongation as standard-dose chloroquine in children. Antimicrob Agents Chemother 2020;64:e01846-19.
35. Guastalegname M, Vallone A. Could chloroquine/hydroxychloroquine be harmful in Coronavirus disease 2019 (COVID-19) treatment? Clin Infect Dis 2020;71:888-9.
36. Borba MG, Sobo CT. Chloroquine Diphosphate in two Different Dosages as Adjunctive Therapy of Hospitalized Patients with the Severe Respiratory Syndrome in the Context of Coronavirus (SARS-CoV-2) Infection: Preliminary Safety Results of a Randomized, Double-Blinded, Phase IIb Clinical Trial (CloroCovid-19 Study), medRxiv; 2020.
37. Simpson TF, Kovacs RJ, Stecker EC. Ventricular arrhythmia risk due to hydroxychloroquine-azithromycin treatment for COVID-19: Cardiology magazine. Am Coll Cardiol 2020. Available from: https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19. [Last accessed on 2020 Jun 25].
38. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881-90.
39. The Cardiotoxicity of Antimalarials. WHO Evidence Review Group Meeting, 13-14 October 2016, Varembé Conference Centre. Geneva, Switzerland: World Health Organization; 2017.
40. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac complications attributed to chloroquine and hydroxychloroquine: A systematic review of the literature. Drug Saf 2018;41:919-31.
41. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes 2013;6:479-87.
42. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: Mechanisms and clinical management. Ther Adv Drug Saf 2012;3:241-53.
43. Rathi S, Ish P, Kalantri A, Kalantri S. Hydroxychloroquine prophylaxis for COVID-19 contacts in India. Lancet Infect Dis 2020;20:1118-9.
44. Taccone FS, Gorham J, Vincent JL. Hydroxychloroquine in the management of critically ill patients with

COVID-19: The need for an evidence base. Lancet Respir Med 2020;8:539-41.
45. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary Results from a Multi-Centre, Randomized, Controlled Trial, medRxiv No. 20151852; 2020.
46. World Health Organization. "Solidarity" Clinical Trial for COVID-19 Treatments. Geneva: World Health Organization; 2020.
47. Chorin E, Dai M, Shulman E, Wadhwani L, Bar-Cohen R, Barbhaiya C, *et al*. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med 2020;26:808-9.

Source of Support: Nil. **Conflicts of Interest:** None declared.