AIJR Preprints
Section: Coronavirus
Article Id: 58, Version: 1, 2020
URL: https://preprints.aijr.org/index.php/ap/preprint/view/58

{Click on above link to see the latest available version of this article}

NOT PEER-REVIEWED

A Systematic Review on the Potency and How Safe Chloroquine is for the Treatment of COVID-19

Aborode Abdullahi Tunde

Department of Chemistry, Faculty of Physical Sciences, University of Ilorin, PMB 1515, Ilorin, Nigeria

E-mail: **********

Version 1: Received: 08 May 2020 / Approved: 12 May 2020 / Online: 12 May 2020

ABSTRACT

Coronavirus disease 2019(COVID-19) is a global health emergency of serious health concern. However, there is no current medical treatment, although it is much needed for patient contracting the severe form of the disease. This systematic review was to explain the information regarding chloroquine for the treatment of COVID-19 via the data obtain from PubMed and other three trial Registries which were searched for review and the use of chloroquine in patients with COVID-19. Four articles were included (one narrative letter, one in-vitro study, one commentary and one editorial) and review on other 14 ongoing clinical trials in China. Chloroquine seems to have great potential in reducing the replication of SARS-CoV-2 (virus causing COVID-19) in vitro. There is high chance, pre-clinical evidence of effectiveness and information of safety from long-time clinical use for other indications to describe the clinical research on Chloroquine in patients with COVID-19. However, clinical description should either adhere to the Monitored Emergency Use of Unregistered Interventions (MEURI) framework or be ethically approved as a trial as stated by the World Health Organization. Safety data and data from high-quality clinical trials are urgently needed.

Keywords: SARS-CoV-2; COVID-19; Chloroquine; Pneumonia; Coronavirus

1 Introduction

COVID-19 (Coronavirus Disease-2019) is a global health emergency that needs serious response. Patients having the acute type of the infection are approximately 15% of the cases (Wu and McGoogan, 2020). However, during this pandemic there is no special, effective and proven medical treatment. *In vitro* report has described that chloroquine, is an immunomodulant drug anciently used to cure malaria, is active in limiting viral multiplicity in other infections, including the SARS-associated coronavirus (CoV) and MERS-CoV (Savarino *et al.,* 2003).

Chloroquine has been used globally for more than 70 years, and it is part of the World Health Organization (WHO) model list of essential medicines. It is also less expensive and has a necessary clinical safety profile (Colson *et al.,* 2020). However, chloroquine does not treat pneumonia but it stops viral replication which in turn prevent further infection. Treatment of cloroquine is combined with antibiotics Azithromycin to treat the pneumonia infection (Golden and John, 2020). Some researcher suggested that pulmonary fibrosis and embolism is the primary cause of the pneumonia associated with Covid-19. That this is one of the major reasons, ventilating the lungs does not improve the lungs function.

A systematic review was obtained from PubMed databases from inception to 1-March- April 2020 to search for articles that are providing information using the following keyword to search on the potency, efficacy and safety of chloroquine and chloroquine related formulations in patients with SARS-CoV-2 pneumonia and articles describing related in-vitro studies.

The information obtained on COVID-19 are coming from Asia, no language restrictions were imposed. The search was expanded using a snowballing method applied to the references of retrieved papers. The search paper also focuses on the Chinese Clinical Trial Registry, Clinical trial. gov and the International Clinical Trials Registry Platform (WHO ICTRP) to identify ongoing trials.

Table 1: Characteristics of clinical trials studying the efficacy and safety of Chloroquine or related formulation in patients with new coronavirus pneumonia (COVID-19) (Gao *et al.*, 2020).

ID	Recruiting Status	Number of centers and Study design	Country	Population (n patients)	Intervention Group(s)	Comparison Group(s)	Primary Outcomes
ChiCTR2000030417	Not yet recruiting	Single Center RCT	China	COVID-19 pneumonia (n = 30)	Chloroquine phosphate aerosolized inhalation solution	Water for injection atomized inhalation combined	Temperature normal for more than 3 days, respiratory symptoms, pulmonary imaging, test (Gao *et al.*, 2020).
ChiCTR2000030054	Pending approval	Single Center RCT	China	Mild and common COVID-19 pneumonia (n = 100)	Hydroxychloroquine sulfate group: Hydroxychloroquine sulfate and Chloroquine phosphate group: First dose of chloroquine phosphate	Standard treatment	Clinical recovery time (Wang *et al.*, 2020).
ChiCTR2000030031	Recruiting	Single Center RCT	China	Mild and common COVID-19 pneumonia (n = 120)	2 tablets Chloroquine phosphate BID	2 tablets placebo BID	Time of conversion to be negative of novel coronavirus nucleic acid (Yang *et al.*, 2020)
ChiCTR2000029992	Pending approval	Single Center RCT	China	Severe COVID-19 pneumonia (n = 100)	Chloroquine phosphate group: Chloroquine phosphate 1.0 g × 2 days, then 0.5 g × 12 day from the third day Hydroxychloroquine sulfate group:	Standard treatment	Clinical recovery time; Changes in viral load of upper and lower respiratory tract

					Hydroxychloroquine sulfate 0.2 g BID x 14 days		samples compared with the baseline (Huang *et al.,* 2020).
ChiCTR2000029988	Recruiting	Single Center RCT	China	Severe COVID-19 pneumonia (n = 80)	Chloroquine phosphate	Standard treatment	Time to Clinical Recovery (Gao *et al.,* 2020)
ChiCTR2000029975 Chin	Pending approval	Single Center Single-arm clinical trial	China	COVID-19 pneumonia (n = 10)	150 mg chloroquine phosphate dissolved in 5 ml of normal saline, q12h, inhaled by atomization for one week	No comparison group	Viral negative-transforming time; 30-day cause-specific mortality; Co-infections; Time from severe and critical patients to clinical improvement (Lenk and Duttge, 2020)
ChiCTR2000029939	Recruiting	Single Center RCT	China	COVID-19 pneumonia (n = 100)	Chloroquine phosphate	Standard treatment	Length of hospital stay (Geo *et al.*, 2020)
ChiCTR2000029935	Recruiting	Single CenterSingle-arm clinical trial	China	COVID-19 pneumonia (n = 100)	Chloroquine phosphate	No comparison group	Length of hospital stay (Gao *et al.,* 2020)
ChiCTR2000029803	Pending approval	Single Center RCT	China	Close contacts with suspected or confirmed cases, and positive test of COVID-19 nucleic acid (n = 320)	Group A1: Hydroxychloroquine, small dose; Group A2: Hydroxychloroquine, high dose	Group B1: Abidol hydrochloride low dose; Group B2: Abidol hydrochloride high dose	Progression to suspected or confirmed disease within 24 days (Wang *et al.,* 2020)

ChiCTR2000029761	Recruiting	Multi-Center RCT	China	Common COVID-19	Low-dose group: Low-dose hydroxychloroquine;	Standard treatment	Negative conversion rate of COVID-19 nucleic acid; lung
ChiCTR2000029740	Recruiting	Single Center RCT	China	COVID-19 pneumonia (n = 78)	Oral intake hydroxycholoroquine 0.2 g BID	Standard Treatment	Negative conversion rate of COVID-19 nucleic acid; prognosis; oxygen index; respiratory rate; lung radiography; temperature; count of lymphocyte; temperature; other infections (Huang *et al.,* 2020)
ChiCTR2000029542	Recruiting	Single center prospective cohort study	China	COVID-19 pneumonia (n = 20)	Oral chloroquine 0.5 g BID for 10 days	Standard treatment	Negative conversion rate of COVID-19 nucleic acid; 30-day cause specific mortality (Gao *et al.,* 2020)
NCTO4261517	Not yet recruiting	Single center RCT	China	COVID-19 pneumonia (n = 30)	Hydroxychloroquine 400 mg/day for 5 days	Standard treatment	Mortality rate at day 14; Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 3,5,7 (Guan *et al.,* 2020)

The number of patients in the Population columns refers to the reported sample size.

2 Discussion

The initial search identified 50 sources (30 were from PubMed, 25 was found in EMBASE and 5 from other sources). Following screening of titles and abstracts and removing duplicates, evaluation was made on eight articles in full text, among these, four relevant articles (one narrative letter, one research letter, one editorial and one commentary) (Gao *et al.,* 2020; Wang *et al.,* 2020). Fourteen trials were found in the trial registries (Table 1).

The research letter, written by a group of Chinese researchers, studied the effect of chloroquine in vitro, using Vero E6 cells infected by SARS-CoV-2 at a multiplicity of infection (MOI) of 0.05. The study demonstrated that Chloroquine was highly effective in reducing viral replication, with an Effective Concentration (EC) 90 of 6.90 μM that can be easily achievable with standard dosing, due to its favorable penetration in tissues, including in the lung (Wang *et al.,* 2020). The authors explained that chloroquine is known to block virus infection by increasing endosomal pH and by interfering with the glycosylation of cellular receptor of SARSCoV. The authors also speculated on the possibility that the known immunomodulant effect of the drug may enhance the antiviral effect in vivo (Zhonghua *et al.,* 2020).

Since cases were reported in 85 countries so far (5th March 2020), the low cost of chloroquine is a major benefit for both the highly stressed healthcare systems of involved high-income countries and the underfunded healthcare systems of middle- and low-income counties (Farner, 2020). The expert consensus was published on 20th February by a multicentre collaboration group of the Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province paper and related specifically to the use of Chloroquine phosphate (Zhonghua *et al.,* 2020). No information was provided on the method used to achieve consensus.

Based on in vitro evidence and still unpublished clinical experience, the panel recommended chloroquine phosphate tablet, at a dose of 500 mg twice per day for 10 days, for patients diagnosed as mild, moderate and severe cases of SARS-CoV-2 pneumonia, provided that there were no contraindications to the drug. The panel recommended using several precautions, including blood testing to rule out the development of anemia, thrombocytopenia or leukopenia as well as serum electrolyte disturbances and/or hepatic and renal function dysfunction.

Also recommended were routine electrocardiographies to rule out the development of QT interval prolongation or bradycardia and patient interviews to seek the appearance of visual and/or mental disturbance/deterioration. The panel recommended avoiding concurrent administration of other drugs known to prolong the QT interval (i.e. chinolones, macrolides, ondansetron) as well as various antiarrhythmic, antidepressant and antipsychotic drugs (Gao *et al.,* 2020).

The Dutch Center of Disease control (CDC), in a public document on its website, suggested to treat severe infections requiring admission to the hospital and oxygen therapy or admitted to the ICU with Chloroquine (James *et al.,* 2020). However, the study also stated that treating patients only with optimal supportive care is still a reasonable option, due to lack of supportive evidence. The suggested regimen in adults consists of 600 mg of chloroquine base (6 tablets A-CQ 100 mg) followed by 300 mg after 12 h on day 1, then 300 mg × 2/daily per os on days 2–5 days. This study also underlined the needs for stopping the treatment at day 5 to reduce the risk of side effects, considering the long half-life of the drug (30 h); 2) the need to differentiate between regimens based on Chloroquine phosphate and Chloroquine base since 500 mg of the first correspond to 300 mg of the second (Yang *et al.,* 2020).

Another guideline document by the Italian Society of Infectious and Tropical disease (Lombardy section) recommend the use of chlorochine 500 mg × 2/daily or hydroxychloroquine 200 mg die for 10 days, although the treatment may vary from 5 to 20 days according to clinical severity. The suggested target

population ranged from patients with mild respiratory symptoms and comorbidities to patients with severe respiratory failure (Haung *et al.,* 2020).

Search also identified ongoing 14 trials, all in China (Table 1). The trials varied in study design, severity of the disease in the target population and in dosing and duration of the treatment. Indeed, the trial registrations varied also in quality of the reported information. That so many such studies are being conducted in parallel suggests that that the scientific community is making a huge effort to clarify this question, but this effort is probably insufficiently coordinated. In support of this observation, the Chinese authorities have recently issued a directive to regulate and coordinate clinical trials studying potential pharmacological treatments for COVID-19. The results of these trials will be the first available on humans, since studies published to date on the characteristics and management of patients with COVID-19 did not report data about Chloroquine use (Wang *et al.,* 2020).

Of note, the WHO published a generic protocol for randomized clinical trials to investigate the clinical efficacy and safety of drugs in hospitalized patients with COVID19 (i.e. a "master template" for researching drugs in this setting) (Farner, 2020). The vital ethical issue is whether administration of chloroquine in the setting of COVID-19 is experimental, and therefore requires ethical trial approval, or off-label (i.e. ethically justifiable as the best available treatment). Additional information on chloroquine will soon be released in the context of the evolving outbreak (Guan *et al.,* 2020).

Timely release of this information can be of importance due to the growing number of infected patients, and the absence of licensed specific drugs. Meanwhile, the recommendations for "Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected", published by the WHO, confirm that there is currently no evidence from RCTs to inform on specific drug treatment of COVID-19 and that unlicensed treatments should be administered only in the context of ethically-approved clinical trials or the Monitored Emergency Use of Unregistered Interventions Framework (MEURI), under strict monitoring (Wu and McGoogan, 2020).

The WHO therefore seems to view Chloroquine as experimental. The authors tend to agree with this viewpoint. But even off-label use of Chloroquine may be accompanied by several concerns; the first is patient safety. Such use should be accompanied by close monitoring. An epidemic is hardly the ideal setting to do this. The ethical approach to off-label drug use also differs between countries, raising questions regarding equity. Finally, chloroquine remains a pivotal drug in the treatment of malaria in many places in the world. Off label drug use can create major drug shortages.

3 Conclusion

There is sufficient pre-clinical information, data and evidence regarding the potency and activeness of chloroquine for treatment of COVID-19 as well as evidence of safety from long-time use in clinical practice for other indications to describe clinical research on the topic. The current situation explained the prioritization of the systematic review of study proposals above other. Although the use of chloroquine may be supported by expert opinion, clinical use of this drug in patients with COVID-19 should adhere to the MEURI framework or after ethical approval as a trial as stated by the WHO. Data from high-quality, coordinated, clinical trials coming from different locations worldwide are greatly required.

4 Declarations

4.1 Acknowledgments

Sincere thanks to Dr. Atolani for his supervision and review for the valuable inputs and help in writing the manuscript.

4.2 Competing Interests

The author declares that no conflict of interest exists in the publication.

How to Cite:

Aborode Abdullahi Tunde. "A Systematic Review on the Potency and How Safe Chloroquine is for the Treatment of COVID-19". *AIJR Preprints*, 58, version 1, 2020. (URL: https://preprints.aijr.org/index.php/ap/preprint/view/58).

References

Colson, P., Rolain, J.M., and Raoult, D. (2020). Chloroquine for the 2019 novel coronavirus SARSCoV-2. *Int J. Antimicrob Agents.* 13:105-123.

Farner, K. (2020). Chloroquine use as a Global Challenge. *Italian Society of Infectious and Tropical disease.* 2:23-26.

Gao, J., Tian, Z., and Yang, X. (2020). Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci. Trends.* 1: 4-7.

Golden, K.L., and John, D.E. (2020). Priority Disease Key action on Table of Therapeutics. *Int J Antimicrob Agents*. 2: 76-79.

Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., and He, J.X. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2:20-32.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., and Hu, Y. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395:497–506.

James, K., Daniel, M., and Garner, D. (2020). Re-emergency of Chloroquine use. *The Dutch Center of Disease control (CDC)*. 1:2-4.

Lenk, C., and Duttge, G. (2014). Ethical and legal framework and regulation for off-label use: European perspective. *Ther Clin Risk Manag*. 10:537–546.

Savarino, A., Boelaert, J.R., Cassone, A., Majori, G., and Cauda, R. (2003). Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis*. 3:722–7.

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., and Zhang, J. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *Jama*. 1:15-18.

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., and Xu, M. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2:8-12.

Wu, Z., and McGoogan, J.M. (2020). 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*. 1:1-5.

Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., and Liu, H. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 13:26-30.

Zhonghua, J., He, H., Xi, H., and Zhi, Z. (2020). Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. *Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia.* 43:9-14.