Serious Cardiovascular Adverse Event Associated with Hydroxychloroquine with Azithromycin in Patient with COVID-19: A Pharmacovigilance Analysis of the FDA Adverse Event Reporting System (FAERS)

Lomeshkhairstar1, Vijay Pawar2

1,2 Swami Vivekananda Sanstha’s Institute of Pharmacy, Mungase, Malegaon.

Abstract

The use of Hydroxychloroquine combine with Azythromycin for the treatment of coronavirus disease (COVID-19) it may increases the risk of serious cardiovascular adverse events. WHO not recommended for the use of HCQ to treat the COVID-19 because it has serious side effect on heart like Arrhythmia ,cardiac toxicity. In the following describe the risk of serious cardiovascular adverse event using HCQ is combined with Azythromycin it compared with that therapeutic alternatives. Some clinical trial that reporting the combine of HCQ with AZ demonstrated better efficacy than signal drug combination of HCQ and AZ has synergestic effect against viral infectious. The FAERS that evaluate adverse effect reports ,medication error reports and product quality complaint resulting in adverse effect that were submitted to FDA. The performing the test to analysis to case series using the US FDA Adverse Event Reporting System (FAERS).

Keywords: COVID-19, Hydroxychloroquine, Azythromycin, Cardiovascular Risks

INTRODUCTION –

The first cases of the Covid-19 were identified in Wuhan, China, in late 2019, and the Covid-19 rapidly spread throughout the world, infecting more than 168 million individuals and causing 3.5 million deaths worldwide as of May 28, 2021. Respiratory failure is the primary cause of death, cardiovascular complications, such as acute myocardial injury and myocarditis, cardiac fibrosis, arrhythmias, endothelial dysfunction, dysautonomia, and thrombotic events, may also contribute to overall morbidity and mortality of COVID-19 patients. Covid-19 symptoms was found such as fever, sore throat, lesions in the lungs, difficulty in breathing, dry cough, lymphopenia, fatigue, anorexia, arrhythmia, and shock. These symptoms depend on the person's immune system and on its potential role in virulence. Coronaviruses belong to the family Coronaviridae and can be classified into four genera: Alpha-coronavirus, Beta-coronavirus, Gamma-coronavirus, and Delta-coronavirus.

A pandemic of historic impact, coronavirus disease 2019 (COVID-19) has potential consequences on the cardiovascular health of millions of people who survive infection worldwide. Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), the etiologic agent of COVID-19, can infect the heart, vascular tissues, and circulating cells through ACE2 (angiotensin-converting enzyme 2), the host cell receptor for the viral spike protein. Acute cardiac injury is a common extrapulmonary manifestation of COVID-19 with potential chronic consequences.
HYDROXYCHLOROQUINE

Hydroxychloroquine is the most widely prescribed drug since 1940s. Physicians firstly used to treat the malarial infections. It’s most often used to treat autoimmune disorders. Now a days it is prefererely used to treat the rheumatoid arthritis (RA). We all heard that in covid pandemic, HCQ is also for the treatment of covid 19. It may lead some adverse effects like damaging joints, muscle inflammation and sometimes internal organs\(^{(3)}\).

HCQ increases pH within intracellular vacuoles and altering the process of protein degradation by acidic hydrolases in the lysosome and macromolecules in the endosomes. This results inhibition of formation of peptide-MHC protein complexes required to stimulate CD\(^{4}\) T cells and result in down-regulation of the immune response against autoantigenic peptides\(^{(4,5)}\).

Diagrammatic MOA of HCQ: \(^{(6)}\)

| Mode of actions                                    | Molecular mechanisms                                                                 | References |
|----------------------------------------------------|--------------------------------------------------------------------------------------|------------|
| Impairment of lysosomal activity and autophagic process | HCQ accumulate in lysosomes and inhibit their functions. HCQ impair autophagosome-lysosome fusion | 7 and 8    |
| Interference with TLR signalling                   | Accumulation of HCQ in lysosome raises endosomal pH and hinders the signalling of TLR 3,7,9. | 9 and 10   |
Role of HCQ in covid-19:-

Corona virus mainly affects the respiratory system and the major organs like lungs. There are four stages of COVID-19 have been identified: the first stage is characterized by upper respiratory tract infection; the second by the onset of dyspnoea and pneumonia; the third by a worsening clinical scenario dominated by a cytokine storm and the consequent hyperinflammatory state; and the fourth by death or recovery.\(^{(11)}\)

SARS-CoV-2 is an enveloped virus with a positive-sense single-stranded RNA genome, and the viral envelope is coated by spike (S) protein trimers that bind to angiotensin converting enzyme 2 (ACE2) receptor, which is required for SARS-CoV-2 infection on host cells\(^{(12)}\).

As shown in above figure, the replication cycle of SARS-CoV-2 consists of the following 5 steps \(^{(13)}\):

(i) Attachment: the virus attach to the host receptor ACE2 via the viral spike protein, which will facilitates its internalization; (ii) Endocytosis: viral membrane fuses with the host cell membrane and gets entry via the host endocytic pathway (endosomes and lysosomes); (iii) Release of viral RNA: the internalized virus releases its genome into the cytosol to be replicated (lysosomes); (iv) Synthesis of viral RNA: genomic RNA experiences transcription and translation to produce relevant viral proteins; (v) Package and release: the viral components assemble together to form new virion which exit to extracellular space through exocytosis\(^{(14)}\).

Common side effects of HCQ\(^{(15)}\):-

- Diarrhoea
- Fatigue
- Bradycardia

Direct binding of HCQ to nucleic acid prevents their recognition and inhibit TLR – ligand interaction.
- Skin rashes
- Chest tightness
- Nausea

The above images show the voltage surface on a rabbit heart with and without HCQ. Without the drug (normal) the electrical activation spreads homogeneously, while with HCQ, waves propagate unevenly, generating complex spatiotemporal patterns and arrhythmias. An elongation of the T wave, a portion of the heart cycle during which voltages normally dissipate in preparation for the next beat. By extending the QT portion of one wave cycle, the drug sets the stage for disturbances in the next wave, potentially creating an arrhythmia. Such disturbances can transition to fibrillation that interferes with the heart’s ability to pump.\(^{18}\)

WHO has not recommend hydroxychloroquine as a treatment for COVID-19. They has recommendation is based on 30 trials with more than 10 000 COVID-19 patients. Hydroxychloroquine not reduce mortality, the need for or duration of mechanical ventilation. More Taking
hydroxychloroquine to treat COVID-19 may increase the risk of heart rhythm problems, blood and lymph disorders, kidney injury, liver problems and failure.\(^{(19)}\)

**Azithromycin -**

Azithromycin is used in the treatment of bacterial infections. It is used in bacterial infections of tonsils, sinus, ear, nose, throat, skin and soft tissues and lungs (pneumonia). Azithromycin is an antibiotic. It works by preventing synthesis of essential proteins required by bacteria to carry out vital functions. Thus, it stops the bacteria from growing, and prevents the infection from spreading. It has some side effects: Vomiting, Nausea, Abdominal pain, Diarrhea.\(^{(20)}\)

Combination of HCQ and Azithromycin:

In France, one clinical trial with 36 participants indicated that combination of HCQ with AZ demonstrated a better efficacy than single drug, based on the virus clearance rate.\(^{(21)}\) In the New York the retrospective study say that the combination of HCQ with AZ leads to synergistic effect. There is no any adverse effect of this combination. The electrocardiogram is abnormal and the hospital mortality had no significant difference from control group.\(^{(22)}\) In USA suggested that risk of ventilation had no significant difference in HCQ+AZ group from control group.\(^{(23)}\)

The synergistic effect of HCQ and AZ in the treatment of SARS-CoV-2 is still questionable, as summarized in below table:-

| Agents     | Type of study               | Design of Treatment                                                                 | Main Findings                                                                                           | Side effects | Ref |
|------------|-----------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------|-----|
| HCQ + AZ   | Phase I clinical trial (open-label non-randomized) | n=42; 26 received HCQ+AZ (600 mg/day), 16 were control group | HCQ treatment associated with viral load reduction or disappearance; this effect is reinforced by AZ | N. A         | 21  |
| HCQ + AZ   | Retrospective study         | n=1,438; 735 in HCQ+AZ group, 271 in HCQ group, 221 in AZ group | Abnormal electrocardiogram and in-hospital mortality had no significant difference from control group | N. A         | 22  |
| HCQ + AZ   | Retrospective study         | n=368; 97 in HCQ group, 113 in HCQ+AZ group, 158 in no HCQ group | significant difference from control group; No reduced risk of mechanical ventilation after treatment | N. A         | 23  |
There are two studies consistently claimed that the combination of HCQ and AZ causes side-effects, including heart failure and cardiovascular fatality within 30-days treatment period in COVID-19 patients.\(^{(24)}\)

The FAERS that evaluate adverse effect reports, medication error reports and product quality complaint resulting in adverse effect that were submitted to FDA.\(^{(25)}\)

The performing the test to analysis to case series using the US FDA Adverse Event Reporting System (FAERS).\(^{(25)}\)

FDA says that Hydroxychloroquine have not been shown to be safe and effective for treating or preventing COVID-19. The safety recommendation by physicians and the public of risk information set out in the hydroxychloroquine and chloroquine healthcare provider fact sheets that were required by the EUA. Hydroxychloroquine can cause abnormal heart rhythms such as QT interval prolongation. These risks may increase when these medicines are combined with other medicines known to prolong the QT interval, including azithromycin.\(^{(26)}\)

Method

1) Study design and data sources-

The retrospective analysis has used FAERS pharmacovigilance monitoring database to analyzing adverse reactions related to HCQ. There is an extraction of the pertinent data of HCQ from the FAERS database to perform pharmacovigilance disproportionality analysis. The analysis adopted the validated pharmacovigilance tool, The analytic uses cleaned FDA data by removing duplicates and incomplete reports Data in the event report include case ID, suspected drug, indication, adverse events, event date, serious outcomes, reporter country, and reporter type. These reports also include the sex (male, female, or unknown) and age of the patient, but do not include their name and date of birth.\(^{(27)}\)

We designed eight comparison groups to estimate the SCAEs associated with HCQ in patients with COVID-19:

- HCQ/CQ + azithromycin versus HCQ/CQ + amoxicillin.
- HCQ/CQ + azithromycin versus lopinavir/ritonavir.
- HCQ/CQ + azithromycin versus remdesivir.
- HCQ/CQ + azithromycin versus all other drugs except for HCQ/CQ, azithromycin, lopinavir/ritonavir, and remdesivir (e.g., insulin, simvastatin, etc.).\(^{(28)}\)

2) Study patients-

The patients suffering from covid-19 were transferred to the study specialised centre after patient having positive test for RT-PCR to the Medical City Hospitals. COVID-19 patients were classified according to clinical evaluation to mild cases (no pneumonia on a CT scan), moderate cases (pneumonia on a CT scan), severe cases (respiratory rate ≥ 30 breaths/min, oxygen saturation ≤ 93% or patients with pneumonia on a CT scan) and critical cases (respiratory failure/need mechanical ventilation). All
patients were treated according to the MOH treatment protocol which relies on patient severity status.  

| Therapy regimen                                                                 | Case Severity                                 |
|----------------------------------------------------------------------------------|-----------------------------------------------|
| Hydroxychloroquine PO (400mg BID first day then 200 mg BID for 5 days)            | Covid 19 patients without                      |
| Azithromycin PO (500mg on the first day, then 250 mg daily for 5 days)            | Pneumonia                                     |
| Hydroxychloroquine PO (400mg BID first day then 200 mg BID for 14 days), Azithromycin PO (500mg on the first day, then 250 mg daily for 14 days), Tamiflu 75 mg PO BID for 5 days | Covid 19 patients with pneumonia in the ward |

**CONCLUSION**

COVID-19 are the challenge to identify effective therapies for prevention and treatment on patient. The study says that potential cardiovascular adverse events associated with the use of HCQ with or without azithromycin, to treat the in patients with COVID-19 by analyzing adverse events reported in the FAERS database. The test of CVAEs are associated with HCQ treatment of non-COVID-19 patients, particularly cardiomyopathy, QT prolongation, cardiac arrhythmias and heart failure.

**REFERENCE**

1. Cardiovascular complications of COVID-19. Farnaz Farshidfar, Navid Koleini, and Hossein Ardehali. Published online 2021 Jul 8. doi: 10.1172/jci.insight.148980
2. Fareeda. Begum Shaik a, Swarna Latha a, Chandra Mohan b, Anu Thomas c, Rajasekhar Chikati c, G. Sandeep d, Narendra Maddu d. https://doi.org/10.1016/j.jnutos.2021.12.004  https://www.sciencedirect.com/journal/clinical-nutrition-open-science
3. COVID-19 and Cardiovascular Disease. Mina K. Chung, David A. Zidar, Michael R. Bristow, Scott J. Cameron, Timothy Chan, Clifford V. Harding, III, Deborah H. Kwon, Tamanna Singh, John C. Tilton. Published online 2021 Apr 16. doi: 10.1161/CIRCRESAHA.121.317997
4. WebMD https://www.webmd.com/lung/hydroxychloroquine#1 James F. Fries MD (Professor of Medicine) Catherine A. Williams MPH (Research Analyst) Semin Arthritis Rheum 1993 Oct;23 https://doi.org/10.1016/S0049-0172(10)80010-1
5. MINI REVIEW article Front. Immunol., 02 July 2020 Sec. Inflammation https://doi.org/10.3389/fimmu.2020.01409
6. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. PMID: 32034323 DOI: 10.1038/s41584-020-0372-x
7. Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hijlkema K-J, et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy. (2018) 14:1435–55. MID: 29940786 PMCID: PMC6103682, DOI: 10.1080/15548627.2018.1474314
8. I Mellman, R Fuchs, A Helenius. Acidification of the endocytic and exocytic pathways. Annu Rev Biochem. (1986) 55:663–700. PMID: 2874766 DOI: 10.1146/annurev.bi.55.070186.003311
9. Ewald SE, Lee BL, Lau L, Wickliffe KE, Shi G-P, Chapman HA, et al. The ectodomain of Toll-like receptor 9 is cleaved to generate a functional receptor. *Nature*. (2008) 456:658–62. PMID: 18820679 □ MCID: PMC2596276, DOI: 10.1038/nature07405
10. C. Stasi, S. Fallani, F. Voller, C. Silvestri Treatment for COVID-19: An overview Eur J Pharmacol, 889 (2020), p. 17364
11. Kim D, Lee JY, Yang JS, Kim JW, Kim VN, Chang H. The Architecture of SARS-CoV-2 Transcriptome. Cell. 2020;181:914–21.e10
12. Nour AM, Modis Y. Endosomal vesicles as vehicles for viral genomes. Trends Cell Biol. 2014;24:449–54. PMID: 24746011
13. Soderstrom K. Viral Replication. In: BylundSJEdBB, editor. xPharm: The Comprehensive Pharmacology Reference. Elisevier: East Carolina University, Greenville, USA, Copyright © 2007 Elsevier Inc. 2008
14. Srinivasa A, Tosounidou S, Gordon C. Increased Incidence of Gastrointestinal Side Effects in Patients Taking Hydroxychloroquine: A Brand-related Issue? J Rheumatol. 2017;44:398. PMID: 28250164
15. Schrezenmeier E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020;16:155–66.
16. **Jia Liu,** #1**Ruiyuan Cao,** #2**Mingyue Xu,** #1,3**Xi Wang,** #1 a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.
17. Scitechdaily [https://scitechdaily.com/study-shows-hydroxychloroquines-harmful-effects-on-heart-rhythm-urges-for-covid-19-use-restrictions/Coronavirus----disease----(COVID-19): Hydroxychloroquine](https://scitechdaily.com/study-shows-hydroxychloroquines-harmful-effects-on-heart-rhythm-urges-for-covid-19-use-restrictions/Coronavirus----disease----(COVID-19): Hydroxychloroquine)
18. [https://www.1mg.com/generics/azithromycin-209411](https://www.1mg.com/generics/azithromycin-209411)
19. L, Mailhe M. et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56:105949. [PMC free article] [PubMed] [Google Scholar] [Ref list]
20. Rosenberg ES, DuFort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J. et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State.
21. Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS, Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19.
22. 24) Lane JCE, Weaver J, Kostka K, Duarte-Salles T, Abrahao MTF, Alghoul H. et al. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. Lancet Rheumatol. 2020;2:e698–e711.
23. [FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)](https://www.fda.gov/.../FDA-ADVERSE-EVENT-REPORTING-SYSTEM-FAERS)
24. [FDA CAUTIONS AGAINST USE OF HYDROXYCHLOROQUINE OR CHLOROQUINE FOR COVID ...](https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-cautions-against-use...)
25. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7355808/#B21-jcm-09-01867](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7355808/#B21-jcm-09-01867)
26. Ying Zhao1 · Jingu Zhang2 · Kai Zheng3 · Sydney Thai4 · Ross J. Simpson Jr. Drugs - Real World Outcomes (2022) 9:231–241 PMID: 35386046
27. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7744890/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7744890/)
28. Wiley Public Health Emergency Collection Int J ClinPract. 2021 Apr; 75(4): e13856.