

Article Review

Potential Toxicity of The Combination of Hydroxychloroquine and Azithromycin for Covid-19 Therapy: Literature Review

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ABSTRACT

One of the therapies often used for COVID-19 patients is a combination of Hydroxychloroquine and Azithromycin. Although only short-term treatment, Hydroxychloroquine and Azithromycin may increase the risks of QTc and TdP intervals prolongation. This literature review aims to determine the potential toxicity of the combination of Hydroxychloroquine and Azithromycin for COVID-19 therapy. This study involved the PubMed, NCBI, Science Direct, NIH MEDLINE, Google Scholar and ProQuest databases. The 24 articles collected were then selected. Finally, 15 articles were found feasible for references in a literature review. The study results showed that combined Hydroxychloroquine and Azithromycin in COVID-19 therapy could increase the risk of QTc and TdP waves prolongation. It can be concluded that the combination of Hydroxychloroquine and Azithromycin carried the risk of prolongation of QTc and TdP waves in the heart rhythm cycle. There is a need for monitoring and/or recommendation regarding instructions for the use of combination therapy of the two types of drugs among patients with COVID-19.

Keywords : Hydroxychloroquine (HCQ), Azithromycin (AZM), Therapy, COVID-19

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INTRODUCTION

In 2019, precisely in December, it was reported a kind of pneumonia in Wuhan, China. Upon identification, the pathogen became known as acute respiratory syndrome coronavirus (novel coronavirus) or COVID-19. Since then, the virus has spread internationally and infected millions of people resulting in high mortality rate¹.

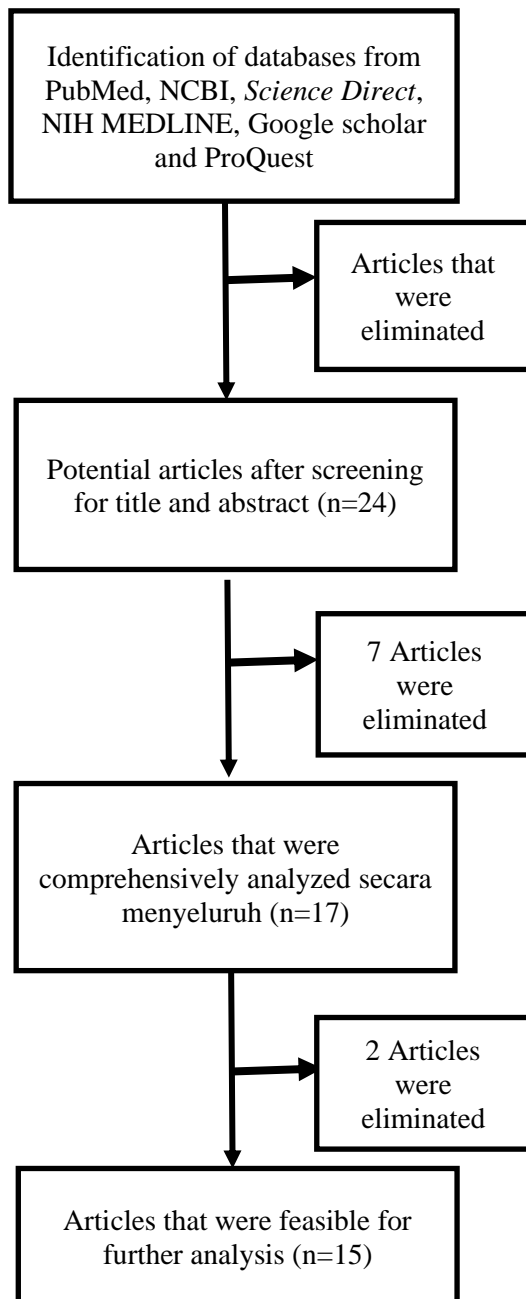
Drugs used as therapy for acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are preferred due to their effectiveness against earlier strains of coronavirus (SARS-CoV and Middle East Respiratory Syndrome Coronavirus). One of the drugs often used in therapy for COVID-19 patients is a combination of Hydroxychloroquine (HCQ) and Azithromycin (AZM)².

Several studies have addressed the toxicity of HCQ and AZM combination drug administration in Covid-19 patients³. Even though HCQ is generally well tolerated, doctors and patients must remain concern about the serious side effects that may occur. Even if it is only a short-term treatment, one of the potential risks of treatment is prolongation of the QTc interval. Such potency will increase if it is used in combination with AZM. In addition, the administration of drug combination therapy can also result in drug interactions⁴.

METHOD

A systematic review was conducted using databases obtained through PubMed, NCBI, Science Direct, NIH MEDLINE, Google scholar and ProQuest by searching for

appropriate keywords such as: potential toxicity in the use of the combination of Hydroxychloroquine and Azithromycin on COVID-therapy and words related to the effects of Hydroxychloroquine and Azithromycin treatment. Literature selection was performed based on inclusion criteria, namely articles with title, abstract, accessible full text and were published in the last 5 years. The exclusion criteria were articles that only showed the abstract or journal manuscripts that could not be accessed in full text.



Graph 1. Literature Review Selection Process

RESULTS

Based on the search results using the database, 24 journals were found and selected. Based on the results of the review and selection of journals, 15 research journals were obtained with the feasible category to be involved as samples and further analyzed in this review literature.

DISCUSSION

Hydroxychloroquine (HCQ) has been used to prevent and treat malaria and chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus⁴. However, hydroxychloroquine (HCQ) in vitro had also shown its efficiency as antiviral against SARS-CoV-2^{4,5} by changing the endosomal pH required for virus-cell fusion as well as the ability to interfere with glycosylation of SARS-CoV cellular receptors^{1,4,5}. It seems that hydroxychloroquine (HCQ), combined with Azithromycin (AZM), have a certain level of effectiveness against viruses that was faster to cure compared to using HCQ as a single monotherapy. However, the use of combination therapy must be implemented with caution due to the side effects of the drugs given which can be potentially life-threatening⁶.

The antimalarial drug of HCQ and the macrolide antibiotic of AZM used in combination for COVID-19 therapy are known to increase the QT interval. COVID-19 patients who were hospitalized and treated with HCQ and AZM showed a much greater increase in the corrected QT interval when compared to monotherapy of HCQ drug^{1,3}.

Azithromycin (AZM) is a macrolide antibiotic that can broadly inhibit gram-positive and negative bacteria with a target on disrupting bacterial ribosomal protein synthesis. AZM and HCQ work simultaneously by inhibiting Sars-CoV-2 in vitro⁷.

The administration of HCQ and AZM was correlated with a three-fold higher risk of QTc interval prolongation than no treatment. In addition, the administration of HCQ was also correlated with an increased risk of QTc and TdP intervals prolongation through blockade of HERG/Kv potassium channels. The torsadogenic potential of these drugs could be mutually reinforcing if other QTc-prolonging drugs such as azithromycin were administered together⁸.

Furthermore, Hydroxychloroquine (HCQ) works by inhibiting signals mediated by Toll-Like Receptors (TLR), including TLR-7 and TLR-9, endosomal innate immune sensors capable of detecting single-stranded RNA, modulating complement-dependent antigen/antibody reactions, activating Regulatory T cells, and inhibiting the production of proinflammatory cytokines such as interleukin-6, tumor necrosis factor- α and interferon- γ . Therefore, HCQ immediately attenuates the inflammatory response directed against SARS-CoV-2 causing a cytokine storm, which is considered severe COVID-19⁶.

hydroxychloroquine can also interfere with ventricular repolarization, which leads to prolongation of the QTc interval and increased risk of torsades de pointes (TdP)⁹. At the cellular level, HCQ prolongs the duration of cardiac action potentials, increases automaticity, and reduces maximum diastolic potential. Consequently, HCQ causes prolongation of the QT and QRS intervals on the EKG view. In addition, patients receiving the combination of HCQ + AZM showed a greater change in the median QT interval compared to those receiving HCQ alone^{2,11}. Other potentially serious dangers include hypoglycemia, neuropsychiatric effects, idiosyncratic hypersensitivity reactions, and drug interactions if used simultaneously with AZM^{4,10}.

The administration of HCQ and AZM requires careful cardiac monitoring, especially in menp with a high-risk Tisdale score, and patients with an initial QTc interval score of ≥ 450 milliseconds⁵. Treatment should be discontinued if there are any danger signs: QTc of >550 ms or the appearance of VES or TdP¹⁶.

These two drugs have been widely used over the past few decades. According to the 2013 IMS Health in the United States, approximately 52.5 million prescriptions were written for Azithromycin in 2012 and approximately 4.5 million prescriptions were written for hydroxychloroquine. However, to date, there are very limited data on the safety of combined use among COVID-19 patients^{13,14,15}.

Potential antiviral activity could be achieved at usual doses of the drug Hydroxychloroquine (400-600 mg daily) which was considered clinically safe. The clinically effective dose of Hydroxychloroquine for combination therapy with Azithromycin in Covid-19 had not yet been determined^{6,14}.

Therefore, further studies regarding the appropriate dosage for Covid-19 therapy is required. Similarly, the level of safety regarding the level of QTc prolongation for HCQ+AZM therapy among patients with COVID-19 needs further studies in order to investigate the prevalence of arrhythmias and the risk of death¹².

CONCLUSION

The combination of Hydroxychloroquine and Azithromycin had a higher risk of QTc and TdP waves prolongation. So, there is a need for monitoring or recommendation regarding instructions for the use of combination therapy of the two types of drugs among patients with COVID-19.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCE

1. Saleh M, Gabriels J, Chang D, Soo Kim B, Mansoor A, Mahmood E, Makker P, Ismail H, Goldner B, Willner J, Beldner S. Effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. *Circulation: Arrhythmia and Electrophysiology*. 2020 Jun;13(6):e008662.
2. Özdemir İH, Özlek B, Özen MB, Gündüz R, Çetin N, Bilge AR. Hydroxychloroquine/azithromycin treatment, QT interval and ventricular arrhythmias in hospitalised patients with COVID-19. *International journal of clinical practice*. 2021 Feb;75(2):e13896.
3. Yendrapalli U, Ali H, Green JL, Edwards J. Effects of cardiac toxicity of combination therapy with hydroxychloroquine and azithromycin in COVID-19 patients. *Journal of Infection and Public Health*. 2021 Nov 1;14(11):1668-70.
4. Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine

- and azithromycin in the management of SARS-CoV-2 infection. *Cmaj*. 2020 Apr 27;192(17):E450-3.
5. Eftekhari SP, Kazemi S, Barary M, Javanian M, Ebrahimpour S, Ziaei N. Effect of hydroxychloroquine and azithromycin on QT interval prolongation and other cardiac arrhythmias in COVID-19 confirmed patients. *Cardiovascular Therapeutics*. 2021 Feb 27;2021:1-7.
 6. Mégarbane B, Scherrmann JM. Hydroxychloroquine and azithromycin to treat patients with COVID-19: both friends and foes?. *Journal of clinical pharmacology*. 2020 Jul;60(7):808.
 7. Li C, Cheng G. Will hydroxychloroquine still be a game-changer for COVID-19 by combining azithromycin?. *Frontiers in Immunology*. 2020 Aug 7;11:1969.
 8. Huang HD, Jneid H, Aziz M, Ravi V, Sharma PS, Larsen T, Chatterjee N, Saour B, Aziz Z, Nayak H, Trohman RG. Safety and effectiveness of hydroxychloroquine and azithromycin combination therapy for treatment of hospitalized patients with COVID-19: a Propensity-Matched study. *Cardiology and Therapy*. 2020 Dec;9:523-34.
 9. Voisin O, le Lorc'h E, Mahé A, Azria P, Borie MF, Hubert S, Ménage E, Guillermin JC, Mourad JJ. Acute QT interval modifications during hydroxychloroquine-azithromycin treatment in the context of COVID-19 infection. In *Mayo Clinic Proceedings* 2020 Aug 1, 95,(8), 696-1700. Elsevier.
 10. Echarte-Morales J, Minguito-Carazo C, del Castillo-García S, Borrego-Rodríguez J, Rodríguez-Santamarta M, Sánchez-Muñoz E, Bergel-García R, González-Maniega C, Prieto-González S, Menéndez-Suarez P, Tundidor-Sanz E. Effect of hydroxychloroquine, azithromycin and lopinavir/ritonavir on the QT corrected interval in patients with COVID-19. *Journal of Electrocardiology*. 2021 Jan 1;64:30-5.
 11. O'Connell TF, Bradley CJ, Abbas AE, Williamson BD, Rusia A, Tawney AM, Gaines R, Schott J, Dmitrienko A, Haines DE. Hydroxychloroquine/azithromycin therapy and QT prolongation in hospitalized patients with COVID-19. *Clinical Electrophysiology*. 2021 Jan 1;7(1):16-25.
 12. Hache G, Rolain JM, Gautret P, Deharo JC, Brouqui P, Raoult D, Honoré S. Combination of hydroxychloroquine plus azithromycin as potential treatment for COVID-19 patients: safety profile, drug interactions, and management of toxicity. *Microbial Drug Resistance*. 2021 Mar 1;27(3):281-90.
 13. Tuncer T, Karaci M, Boga A, Durmaz H, Guven S. QT interval evaluation associated with the use of hydroxychloroquine with combined use of azithromycin among hospitalised children positive for coronavirus disease 2019. *Cardiology in the Young*. 2020 Oct;30(10):1482-5.
 14. Ramireddy A, Chugh H, Reinier K, Ebinger J, Park E, Thompson M, Cingolani E, Cheng S, Marban E, Albert CM, Chugh SS. Experience with hydroxychloroquine and azithromycin in the coronavirus disease 2019 pandemic: implications for QT interval monitoring. *Journal of the American Heart Association*. 2020 Jun 16;9(12):e017144.
 15. Ouarradi AE, Abdeladim S, Oualim S, Filali RA, Bensahi I, Elharass M, Hafid S, Tazi H, Naitlhou A, Bouaiti EA, Moustaghfir A. Hydroxychloroquine and azithromycin as a treatment of Covid-19: electrocardiogram variability. *Journal of the Saudi Heart Association*. 2020;32(3):350.

16. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LC, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, Junqueira DL. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *New England Journal of Medicine*. 2020 Nov 19;383(21):2041-52.