Open Access

Journal of Biomedical Sciences

CURRENT RESEARCH TRENDS

DOI: https://doi.org/10.3126/jbs.v7i2.33997

Azithromycin and Hydroxychloroquine combination: The future pharmacotherapy of COVID-19

Shukla A[1], Mohabeer P[2], Kashyap A[3], Robinson J[4], Banerjee I[5]*

Corresponding author:

Dr. Indrajit Banerjee

Associate Professor, Department of Pharmacology, Sir Seewoosagur Ramgoolam Medical College, Mauritius

Email: indrajit18@gmail.com ORCID

Information about the article:

Received: Nov 01, 2020
Accepted: Dec 28, 2020
Published online: Dec 31, 2020

Cite this article:

Shukla A, Mohabeer P, Kashyap A, Robinson J, Banerjee I. Azithromycin and Hydroxychloroquine combination: The future pharmacotherapy of COVID-19. Journal of Biomedical Sciences. 2020;7(2):54-57

Publisher

Nepal Health Research Society, Bahundhara -6, Gokarnesowor Municipality, Kathmandu, Nepal
eISSN 2382-5545, ISSN 2676-1343 (Print)

ABSTRACT

Background

In response to the urgency of increasing death toll due to COVID-19, caused due to SARS CoV-2, various drugs are under clinical trial, as there is no specific drug for its treatment. In an international survey that was recently conducted in which about 7500 physicians participated from all over the world considered that Hydroxychloroquine and Azithromycin were among the most effective ones for the pharmacotherapy of COVID-19. Azithromycin is a macrolide antibiotic whose mechanism of action against COVID-19 is still unknown, but various theories have been postulated. In vitro and in vivo studies have been conducted; however, their results are quite contradictory. Azithromycin is said to increase the risk of QT prolongation in elderly patients and when given in combination with Hydroxychloroquine can increase the risk of Torsade's de pointes. Therefore, caution has to be paid before prescribing Azithromycin.

Conclusion

The mass loss of human lives is regrettable and needs to be stopped as soon as possible. Azithromycin could be the future drug for COVID-19, but such limited data is insufficient to support the drug's safety or efficacy and needs to be reconsidered.

Keywords

Adverse effects, macrolides, pandemics, pharmacology, therapeutics, SARS-CoV-2

Background

COVID-19, caused by the SARS CoV-2 virus that began to spread in late December 2019 in Wuhan city, China has infected millions of people worldwide, in context to which, on 11th March 2020 it was declared a pandemic by WHO [1, 2]. It is the fourth worst-hit pandemic in history that has claimed a large number of lives till date. During this state of urgency, where no specific drugs are present against COVID-19, loads of existing drugs are currently under clinical trial [3]. WHO and its partners had also launched an international Clinical trial named "solidarity", to rapidly discover the drugs that either weigh down the disease's progression or improve survival [3]. A recent international survey involving 7500 physicians from across 30 countries found that hydroxychloroquine and azithromycin were the most effective treatment for the treatment COVID-19 [4].

Azithromycin

Azithromycin is a wide -spectrum Macrolide, with a long half-life and large volume of distribution, antibacterial activity, immunomodulatory effects and anti-inflammatory effects. Azithromycin is primarily used to treat various bacterial infections such as respiratory, enteric and genitourinary bacterial infections but, has proved efficacy for treatment against rhinovirus, influenza virus, respiratory syncytial virus, Zika, and Ebola virus as well [5, 6]. It's being employed internationally off label to treat patients suffering from COVID-19 and, in an online survey that was conducted in late March 2020 within which about 6227 physicians participated from 30 different countries found that Azithromycin was the second most typically used prescribed treatment for COVID-19 after simple analgesia [7]. Following the given figures, it becomes imperative to evaluate the drug's effectiveness and safety with regards to COVID-19.

Mechanism of Action

The precise mechanism of action against viruses remains unknown, but various theories have been postulated. In an in vitro study conducted by Poschet and colleagues, acidic pH is required for the maturation and functioning of the endosome. As Azithromycin is a weak base, it accumulates in endosomal vesicles and lysosomes, which increases the pH levels and blocks endocytosis and /or viral genetic shedding from lysosomes, and thus limiting viral replication. Enveloped viruses like influenza and HIV requires an acidic environment for uncoating, and probably the same mechanism could also be there for coronavirus [6]. SARS CoV-2 virus is believed to possess a furin cleavage present within the spike protein. Poschet et al. found that Azithromycin decreases the enzyme furin levels within the host cell and thus interferes with the viral entry [7]. Azithromycin can also mediate its antiviral effects by causing amplification of host interferon pathway-mediated antiviral responses [6]. According to Damle B et al. Azithromycin can induce pattern recognition of viral replication. Additionally, its direct action on bronchial epithelial cells maintains their function and reduces mucus secretion to facilitate lung function [6].

Research Data

In-vitro

Two studies have been conducted until now. Touret et al., assessed the ability of about 1,520 approved drugs to inhibit SARS CoV-2 replication in vitro Multiplicity of Infection of 0.002. Among all of these drugs, Azithromycin had an EC50 of 2.12µM, CC50 of >40µM, and SI of >19. From the following figures, the authors concluded that Azithromycin could probably be used to treat COVID-19 [8].

The other study was conducted by Andreania et al., in which they assessed the activity of Azithromycin and Hydroxychloroquine against SARS CoV-2. Azithromycin was tested at different concentrations (2,5 and 10µM) against the virus at both high and low multiplicity of infection (0.25 and 2.5). It could not inhibit the viral replication, but when Multiplicity of Infection was low, and 5 or 10 µM of Azithromycin was combined with 5µM of Hydroxychloroquine, inhibited viral replication. Even at high Multiplicity of Infection when 10µM of Azithromycin was combined with 2µM of Hydroxychloroquine, also inhibited viral replication. Still, it was stated that the concentration of both the drugs is the ones that are achieved in lung tissue in vivo.

From the given figures, the value of multiplicity of infection is different in both the studies, the value being lowered by a factor of 100 in the study of Touret et al. This might be a contributory factor that led to the finding that Azithromycin alone has the activity to inhibit SARS CoV-2 viral replication which was found by Touret et al [7].

In-vivo

A study conducted by Gautret and his colleagues in France where 20 participants out of 30, were given Hydroxychloroquine (200mg t.d.s for ten days) and 16 were control patients. Out of the total patients treated with Hydroxychloroquine 6 of them received Azithromycin (500 mg on day 1 followed by 250mg per day for the next four days) to prevent bacterial superinfection and their ECG were being monitored daily. The study found that the patients treated with the combination of Hydroxychloroquine and Azithromycin were likely to be tested negative on day 3, 4 and 5 compared to those treated with Hydroxychloroquine only. On Day 6,100 % of the patients who were treated with Azithromycin and Hydroxychloroquine were tested negative as compared to 57.1% who were tested negative on being treated with Hydroxychloroquine and 12.5% patients in the control group ($p<0.001$) [9].

But it is essential to mention some limitations, as discussed by Gbinigie K et al. in his research that having small sample size will cause the analysis of the results to be underpowered, leading to false-positive results. As well as that the decision to treat the patient with Azithromycin depends on clinical presentation, which has been stated in a study, however, the criteria used to make the decision was not clear. Furthermore, there was an exception in the study where a patient treated with combination tested negative on Day 6 but was tested positive on Day 8 at low titre [7]. The same team also conducted a study that involved a cohort of about 80 patients treated with a combination of Azithromycin and Hydroxychloroquine for further assessment of the combination regimen. Patients with no contraindications were given a combination of Hydroxychloroquine 3 times per day for ten days and Azithromycin 500mg on day one, followed by 250mg per day for the next four days. Before the treatment, a twelve-lead ECG was performed on each patient two days after the treatment began. Finally, the study revealed that about 97.5% were tested negative on Day 5, 83 % on Day 7 and 93% on Day 8. The authors also reported that patients experienced only a few and mild side effects ranging from 2 cases of nausea, 4 cases of diarrhoea, and one case of blurred vision. However, the sample size being small, and the absence of a control group are the limitations to be stated [10].

However, in contrast to the findings of the study by Gautret et al. a study conducted by Molina J.M. et al where they assessed the prospective study virologic and clinical outcomes found that about 8 out of 10 patients' nasopharyngeal swab was still positive even after 5 and 6 days after initiation of the dose regimen as stated by Gautret et al.

In addition to this, a study conducted in China on COVID-19 patients has found no difference on the rate of virologic clearance at 7 days with or without 5 days of Hydroxychloroquine and in clinical outcomes as well [11].

Safety

As it is a commonly used antibiotic for various bacterial infections, there are various adverse effects for present indications ranging from gastrointestinal upset to uncommon ones, such as prolonged QT interval. Also, care had to been taken while administering it in patients with severe hepatic failure or renal failure [7].

Regarding COVID 19, the following studies that are mentioned above do not assess the safety of Azithromycin. However, safety considerations have been stated by David N. Juurlink, asserting that it increases the risks of arrhythmias when Azithromycin is used in combination with Hydroxychloroquine [12] as well as antibiotic resistance can also arise which is a major concern all around the world nowadays due to prolong usage of antibiotic which is used to treat the coinfection by bacterial species along with coronavirus. As this pandemic has also shifted the face-to-face visits of a patient to telehealth consultations, it has also led to increased antibiotic usage, which may also play a role in developing antibiotic resistance [13]. Recent evidence shows that the combination of Azithromycin and Hydroxychloroquine has been associated with a higher mortality rate in COVID-19 patients than those treated with Hydroxychloroquine alone [14].

Conclusion

The mass loss of human lives is miserable and needs to be stopped as soon as possible. Azithromycin could be the future drug for COVID-19, but such limited data is not sufficient to support the drug's safety or efficacy and needs to be reconsidered.

Abbreviation

Coronavirus disease 2019 (COVID19), Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), World Health Organization (WHO)

Acknowledgments

We extend our intense gratitude to the Chairman Mr. RPN Singh and Prof. Namrata Chhabra, Principal In charge, Sir Seewoosagur Ramgoolam Medical College, Belle Rive, Mauritius, for providing us with huge support to conduct the research study effectively.

Authors' contribution

a. Study planning: AS, IB
b. Manuscript writing: AS
c. Manuscript revision: AS, PM, AK, JR, IB
d. Final approval: AS, PM, AK, JR, IB
e. Agreement to be accountable for all aspects of the work: AS, PM, AK, JR, IB

Funding

There was no funding for this work.

Availability of data and materials

All data and materials available as part of the article, and no additional source data are required.

Competing interests

There is no conflict of interest for any author of this manuscript.

Publisher's Note

NHRS remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

The publisher shall not be legally responsible for any types of loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused

arising directly or indirectly in connection with or arising out of the use of this material.

Author information

[1]Ananya Shukla, 2nd Professional medical student, Sir Seewoosagur Ramgoolam Medical College, Mauritius ORCID

[2]Poornasha Mohabeer, 2nd Professional medical student, Sir Seewoosagur Ramgoolam Medical College, Mauritius ORCID

[3]Abhishek Kashyap, 2nd Professional medical student, Sir Seewoosagur Ramgoolam Medical College, Mauritius ORCID

[4]Jared Robinson, 2nd Professional medical student, Sir Seewoosagur Ramgoolam Medical College, Mauritius ORCID

[5]Dr Indrajit Banerjee, Associate Professor, Department of Pharmacology, Sir Seewoosagur Ramgoolam Medical College, Mauritius ORCID

References

1. Banerjee I, Robinson J, Kashyap A, Mohabeer P, Shukla A, Leclézio A. The changing pattern of COVID-19 in Nepal: A Global concern- A Narrative Review. Nepal J Epidemiol. 2020 Jun 30;10(2):845-855. https://doi:10.3126/nje.v10i2.29769
2. Banerjee I, Robinson J, Sathian B, van Teijlingen ER. South Africa and its COVID-19 prohibition predilection. Nepal J Epidemiol. 2020 Sep 30;10(3):874-877. https://doi.org/10.3126/nje.v10i3.31543
3. Banerjee I, Mohabeer P, Shukla A, Kashyap A, Robinson J. COVID-19: Recent advances in epidemiology, virology, etiopathogenesis, clinical trials and vaccine development. J Biomed Sci, 2020; 7(1), 18-27. https://doi.org/10.3126/jbs.v7i1.29849
4. Million M, Lagier JC, Gautret P, Colson P, Fournier PE, Amrane S, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis. 2020 May-Jun;35:101738. https://doi.org/10.1016/j.tmaid.2020.101738
5. Ohe M, Shida H, Jodo S, Kusunoki Y, Seki M, Furuya K, Goudarzi H. Macrolide treatment for COVID-19: Will this be the way forward? Biosci Trends. 2020 May 21;14(2):159-160. https://doi.org/10.5582/bst.2020.03058
6. Damle B, Vourvahis M, Wang E, Leaney J, Corrigan B. Clinical Pharmacology Perspectives on the Antiviral Activity of Azithromycin and Use in COVID-19. Clin Pharmacol Ther. 2020;108(2):201-211. https://doi.org/10.1002/cpt.1857
7. Gbinigie K, Frie K. Should azithromycin be used to treat COVID-19? A rapid review. BJGP Open. 2020;4(2):bjgpopen20X101094. https://doi.org/10.3399/bjgpopen20X101094
8. Touret F, Gilles M, Barral K, Nougairède A, van Helden J, Decroly E, et al. In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. Sci Rep. 2020 Aug 4;10(1):13093 https://doi.org/10.1038/s41598-020-70143-6
9. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb 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 Jul;56(1):105949. https://doi.org/10.1016/j.ijantimicag.2020.105949
10. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Med Infect Dis 2020; 101663. https://doi.org/10.1016/j.tmaid.2020.101663
11. Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020;50(4):384. https://doi.org/10.1016/j.medmal.2020.03.006
12. Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. CMAJ. 2020;192(17):E450-E453. https://doi.org/10.1503/cmaj.200528
13. Alizargar J. Dangers of the use of hydroxychloroquine and azithromycin combination in COVID-19 patients. Travel Med Infect Dis. 2020;38:101881. https://doi.org/10.1016/j.tmaid.2020.101881
14. Lighter J, Raabe V. Azithromycin Should Not Be Used to Treat COVID-19. Open Forum Infect Dis. 2020;7(6):ofaa207. https://doi.org/10.1093/ofid/ofaa207