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Article

Azithromycin and the Outcome of Treated COVID-19 Patients: A Hospital-Based Study

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A B S T R A C T

COVID-19 is an infectious disease that has been declared a pandemic. Currently, there is no validated pharmacological treatment for use in COVID-19 disease and is still in the clinical trial stage. The aim of this study to determine the association of azithromycin and the outcome of treated COVID-19 patients. This study used a retrospective cohort. The number of samples in this study were 40 subjects in each group of azithromycin and non-azithromycin. The research sample was all COVID-19 patients who were treated at Dr. M Djamil Hospital Padang with moderate and severe grades receiving treatment with azithromycin and non-azithromycin. The inclusion criteria in this study were moderate and severe COVID-19 patients and data related to research variables were complete and well-documented. Sampling technique with convenience sampling. Data analysis was performed using the Chi-square test. $P < 0.05$ was significant, and the data were analyzed using the SPSS version 21.0 program. The mortality of COVID-19 patients in patients receiving azithromycin therapy (80.0%) compared to non-azithromycin (85.0%). The results of the statistical test showed that there was no relationship of azithromycin administration with the outcome of COVID-19 patients ($p>0.05$), with OR (0.71, 95% CI 0.22-2.26). In this study, it is hoped that the decision on the use of azithromycin should consider the potential benefits and risks, evaluated that the possibility of the drug being effective is greater than the risk to the patient.

I. INTRODUCTION

The COVID-19 pandemic has entered its second year and is still ongoing. The total number of confirmed positive COVID-19 cases in the world as of May 20, 2021 is almost close to 165 million. However, until now there is no approved drug to treat the corona virus in humans. Several options can be considered to control or prevent the emergence of COVID-19 infection, including vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides and interferon therapy. New interventions may take months to years to develop. Given the urgency of the COVID-19 outbreak, research is focusing on the potential to reuse existing, approved or under development antiviral agents to treat infections caused by HIV, hepatitis B virus (HBV), hepatitis C virus (HCV) and influenza, based on therapeutic experience. with two other infections caused by the corona virus, namely Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (Molina et al., 2020). COVID-19 can cause inflammation and tissue damage in the lungs in moderate to severe cases, the use of immunomodulating drugs could provide benefits in the treatment of COVID-19 (Ye *et al*., 2020).

Azithromycin is a macrolide antibiotic that can prevent severe respiratory infections in patients with pneumonia (Bacharier et al., 2015). In vitro studies have shown that azithromycin can prevent replication of the H1N1 influenza virus and zika virus and has immunomodulatory and anti-inflammatory effects in respiratory diseases (Bosseboeuf et al., 2018; Tran et al., 2019; Zhang et al., 2019). Previous study proved the effectiveness of therapy in a total of 36 patients (6 patients on combination therapy of hydroxychloroquine and azithromycin 500 mg on the first day followed by 250 mg per day for the next four days, 16 control patients and 14 patients on hydroxychloroquine therapy alone). On day 6 patients on combination therapy 100% (6/6) were confirmed negative for the COVID-19 virus, 12.5% (2/16) control patients were confirmed negative and 57.1% (8/14) were confirmed on hydroxychloroquine therapy alone negative. Despite the small sample size, the survey showed that hydroxychloroquine treatment significantly reduced or lost viral load in COVID-19 patients and the effect was amplified with azithromycin.

Administering a combination of hydroxychloroquine and azithromycin before complications of COVID-19 is safe with a very low mortality rate in patients. The combination of the two also has a beneficial effect in reducing early transmission. Given the urgent therapeutic need to treat this disease with effective and safe drugs, further evaluation is needed, both in treating patients at an early stage before respiratory complications occur and avoiding the spread of the disease (Gautret et al., 2020).

Azithromycin in combination with hydroxychloroquine is currently in clinical trials for the treatment of COVID-19. In addition, it is important to assess the safety profile of the therapy. A side effect of azithromycin for the current indication is a prolongation of the QT interval so it is necessary to pay attention to the patient's condition (Nguyen et al., 2020).

II. METHODS

The research design in this study was a retrospective cohort in which to determine the role of azithromycin on the outcome of COVID-19 patients treated. The research was conducted at Dr. RSUP. M Djamil Padang from January-June 2021. This study passed the ethical review by the ethics commiittee of Dr M Djamil General Hospital, Padang, Indonesia (No. 17/ KEPK/ 2021). The number of samples in this study were 40 subjects in each group of azithromycin and non-azithromycin. The research sample was all COVID-19 patients who were treated at Dr. M Djamil Hospital Padang with moderate and severe grades receiving treatment with azithromycin

and non-azithromycin. The inclusion criteria in this study were moderate and severe COVID-19 patients and data related to research variables were complete and well-documented. The exclusion criteria in this study were pediatric COVID-19 patients. Sampling technique with convenience sampling. Data analysis in this study used the Chi-square test. P<0.05 was significant. Data were analyzed using SPSS version 21.0.

III. RESULTS

Patient characteristics (Table 1)

Table 1. Patient characteristics

Characteristics	Group		p-value
	Azithromycin (f/%) (n=40)	Non-azithromycin (f/%) (n=40)	
Age (years)			0.382[a]
<50	7 (17.5)	10 (25.0)	
50-59	16 (40.0)	9 (22.5)	
60-69	12 (30.0)	16 (40.0)	
≥ 70	5 (12.5)	5 (12.5)	
Sex			0.071[a]
Male	27 (67.5)	18 (45.0)	
Female	13 (32.5)	22 (55.0)	
Comorbidities			
Cerebrovascular	2 (5.0)	1 (2.5)	1.000[a]
Hypertension	16 (40.0)	13 (32.5)	0.642[a]
Cardiovascular	8 (20.0)	2 (5.0)	0.091[a]
Chronic lung disease	2 (5.0)	1 (2.5)	1.000[a]
Cancer	1 (2.5)	1 (2.5)	1.000[a]
Chronic kidney disease	9 (22.5)	5 (12.5)	0.377[a]
Immunodeficiency	1 (2.5)	0	1.000[a]
Diabetes mellitus	14 (35.0)	11 (27.5)	0.630[a]
Obesity	3 (7.5)	6 (15.0)	0.481[a]
Number of comorbidities			0.038*[a]
None	7 (17.5)	16 (40.0)	
1 comorbidity	15 (37.5)	15 (37.5)	
>1 comorbidity	18 (45.0)	9 (22.5)	

*p<0.05 considered significant; a, Chi-square test

Table 1 shows that there were no differences in age, sex and type of comorbidity in patients receiving azithromycin and non-azithromycin therapy (p>0.05). However, there were differences in the number of comorbidities in patients receiving azithromycin and non-azithromycin therapy (p<0.05).

The association of azithromycin administration with the outcome of COVID-19 patients (Table 2).

Table 2. The association of azithromycin administration with the outcome of COVID-19 patients

Variable	Outcome		p-value	OR (95% CI)
	Death (f/%) (n=40)	Life (f/%) (n=40)		
Azithromycin	32 (80.0)	8 (20.0)	0.769[a]	0.71 (0.22-2.26)
Non-azithromycin	34 (85.0)	6 (15.0)		

OR, odds ratio

Table 2 shows that the mortality of COVID-19 patients in patients receiving azithromycin therapy (80.0%) compared to non-azithromycin (85.0%). The results of the statistical test showed that there was no relationship of azithromycin administration with the outcome of COVID-19 patients (p>0.05), with OR (0.71, 95% CI 0.22-2.26).

IV. DISCUSSION

This results found that there was no relationship of azithromycin administration with the outcome of COVID-19 patients. Azithromycin is a macrolide antibiotic that can act on gram-positive and gram-negative bacteria. Azithromycin works by binding to the 50s sub-unit of the bacterial ribosome, so that it can inhibit the translational activity of mRNA. Thus, protein synthesis will be disrupted and bacterial growth can be inhibited. In general, Azithromycin is given for the treatment of bacterial infections caused by *H. influenza*, *M. catarrhalis*, *S. pneumonia*, *C. pneumonia*, *Streptococcus pyogenes*, *Staphylococcus aureus*, or *Staphylococcus agalactiae* (Fiolet et al., 2021; O'Connel et al., 2021).

By looking at the brief description of Azithromycin, it is clear that Azithromycin is a class of antibiotics used in the treatment of diseases caused by bacterial infections. In fact, COVID-19 is a disease caused by infection with the SARS-CoV-2 virus, so, of course, it can be understood that the use of Azithromycin in the treatment of COVID-19 is not appropriate if the patient with COVID-19 does not have a secondary bacterial infection (Ayerbe et al., 2022).

Based on the observations that have been made, all patients who have received Azithromycin as an adjunct treatment did not experience a faster recovery, when compared to patients who did not receive Azithromycin. In addition, there was no difference in length of stay between patients who received Azithromycin and those who did not. The study findings prove the hypothesis of the experts, that the use of Azithromycin does not have a positive effect on the treatment of COVID-19 patients who do not experience secondary bacterial infections (Gautret et al., 2020).

Apart from the insignificant effect of Azithromycin in COVID-19 patients, the administration of Azithromycin that is not properly indicated is also feared to have the potential to trigger the potential for bacterial resistance in the future. If the consumption of Azithromycin is done carelessly, with inappropriate indications, and in too many doses, resistance to bacteria will appear. Bacteria that get Azithromycin too often will become resistant to the drug, so the infection they cause will be more difficult to treat (Nguyen et al., 2020; Gautret et al., 2020).

Apart from the potential for bacterial resistance, what is no less important is the potential side effects that may arise from the consumption of Azithromycin. Some of the possible side effects include nausea, vomiting, headache, cardiac arrhythmias, swelling of the skin and body, respiratory problems, severe fatigue, and muscle weakness. Therefore, the administration of Azithromycin must indeed be given by and under the supervision of a doctor, which of course is

expected to have considered the risk and benefit aspects of prescribing Azithromycin (Fiolet et al., 2021; O'Connel et al., 2021).

In this study, it is hoped that the decision on the use of azithromycin should consider the potential benefits and risks, evaluated that the possibility of the drug being effective is greater than the risk to the patient (Fiolet et al., 2021; O'Connel et al., 2021; Gautret et al., 2020).

V. CONCLUSION

This study confirmed that there was no relationship of azithromycin administration with the outcome of COVID-19 patients. In this study, it is hoped that the decision on the use of azithromycin should consider the potential benefits and risks, evaluated that the possibility of the drug being effective is greater than the risk to the patient.

REFERENCES

D.H. Tran, R. Sugamata, T. Hirose, S. Suzuki, Y. Noguchi, A. Sugawara, et al, "Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with virus internalization process", J Antibiot (Tokyo), 2019, 72(10), pp. 759-768.

E. Bosseboeuf, M. Aubry, T. Nhan, J.J. de Pina, J.M. Rolain, D. Raoult, D. Musso, "Azithromycin inhibits the replication of zika virus", J Antivir Antiretrovir, 2018, 10(1), pp. 6-11.

J.M. Molina, C. Delaugerre, J. Le Goff, B. Mela-Lima, D. Ponscarme, L. Goldwirt, N. de Castro, "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, pp. 384.

L. Ayerbe, C. Risco-Risco, I. Forgnone, M. Pérez-Piñar, S. Ayis S, "Azithromycin in patients with COVID-19: a systematic review and meta-analysis", J Antimicrob Chemother, 2022, 77(2), pp. 303-309.

L.B. Bacharier, T.W. Guilbert, D.T. Mauger, et al, "Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial", JAMA, 2016, 315(4), pp. 419.

L.S. Nguyen, C. Dolladille, M.D. Drici, C. Fenioux, J. Alexandre, J.P. Mira, et al, "Cardiovascular toxicities associated with hydroxychloroquine and azithromycin: An analysis of the world health organization pharmacovigilance database", Circulation, 2020, 142, pp. 303–305.

P. Gautret, J.C. Lagier, P. Parola, V.T. Hoang, L. Meddeb, M. Mailhe, 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, 105949, pp. 1-6.

Q. Ye, B. Wang, J. Mao, "The pathogenesis and treatment of the `Cytokine Storm' in COVID-19", J Infect, 2020, 80(6), pp. 607–613.

T. Fiolet, A. Guihur, M. Rebeaud, "Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis", Clin Microbiol Infect, 2021, 27, pp. 19–27.

T.F. O'Connell, C.J. Bradley, A.E. Abbas et al, "Hydroxychloroquine/azithromycin therapy and QT prolongation in hospitalized patients with COVID-19", JACC Clin Electrophysiol, 2021, 7, pp. 16–25.

Y. Zhang, J. Dai, H. Jian, J. Lin, "Effects of macrolides on airway microbiome and cytokine of children with bronchiolitis: A systematic review and meta-analysis of randomized controlled trials", Microbiol Immunol, 2019, 63, pp. 343–349.

BIOGRAPHY

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