The effectivity of single and combined dose of oseltamivir therapy on length of stay of COVID-19 patients in Mataram General Hospital, Indonesia

Risky Irawan, Halia Wanadiatri*, Musyarrafah, Fahriana Azmi, Dian Rahadianti

ABSTRACT

Background: Oseltamivir is an antivirus for the corona virus which is currently used as part of the therapy regimen for COVID-19 patients. This is because the definite antivirus of choice for COVID-19 is yet to be found. The combined administration of oseltamivir and antibiotics compared with oseltamivir alone is known to shorten the hospitalization length of patients with severe respiratory infections in the ICU. However, there is no solid data explaining the effectiveness of oseltamivir, both alone or as part of a combination therapy, in the prevention and treatment of COVID-19 patients. The success of treating confirmed COVID-19 patients who are hospitalized can be seen from the length of patient hospitalization. This study aimed compare the length of hospitalization between patients with confirmed COVID-19 cases receiving oseltamivir alone or in combination with antibiotics.

Methods: This study was conducted using an analytical observational design with a cross sectional approach. The samples were 238 people hospitalized at the Mataram General Hospital who were sampled using a total sampling technique according to the inclusion and exclusion criteria.

Results: Amongst the 238 confirmed COVID-19 patients hospitalized at the Mataram General Hospital, 52.5 % received oseltamivir alone, while 47.5% received a combination of oseltamivir and azithromycin. Analysis showed that there was a significant difference in the length of hospitalization between both groups (p<0.001).

Conclusion: The hospitalization period of patients given oseltamivir-azithromycin combination therapy was relatively shorter than that of patients given oseltamivir alone.

Keywords: Azithromycin, COVID-19, oseltamivir.


INTRODUCTION

Coronavirus disease-19 (COVID-19) is a contagious disease caused by a new type of coronavirus. Confirmed COVID-19 cases in Indonesia reached 32,033 cases. The number of confirmed COVID-19 cases in West Nusa Tenggara (WNT) is 380 cases, while Mataram has 312 cases as of 8 June 2020.

The mechanism of infection from SARS-CoV-2 is the attachment of S protein on the viral envelope with its receptor, which is angiotensin-converting enzyme 2 (ACE-2) found in alveolar cells. Therefore, the virus can easily enter type II pneumocytes in the human lung. This S protein is responsible for the transmission of coronavirus in the human body. The pathogenesis of SARS-CoV-2 is not yet known but presumably not much different from well-known SARS-CoV-2. SARS-CoV-2 in humans especially infects the cells in the respiratory tract that lines the alveoli. SARS-CoV-2 will bind to receptors and enter the cells. Glycoprotein contained in the spike of the viral envelope that binds with the cellular receptor is ACE2. SARS-CoV-2 in alveolar cells will duplicate genetic materials and synthesize the needed proteins and make new virions that appear on the cell surface. When the virus enters the cells, its antigen will be presented to the Antigen Presenting Cells (APC). This presentation depends on class I Major Histocompatibility Complex (MHC) molecules. However, class II MHC also contributes. Antigen presentation then simulates the response of humoral and cellular immune response mediated by virus-specific T cells and B cells. The humoral immune response forms IgM and IgG on SARS-CoV-2. The IgM on SARS-CoV-2 disappears at the end of week 12 while IgG can survive long term.

Oseltamivir is one of the most used antiviruses in the regimen. Oseltamivir is a drug used for influenza A and influenza B therapy. However, oseltamivir is used as one of the regimens for COVID-19 because a special antivirus has not been found for COVID-19. Oseltamivir is an analog to sialic acid that works to inhibit the neuraminidase enzyme important for viral replication. Chloroquine and azithromycin are also used as a regimen for COVID-19.
Confirmed COVID-19 patients with moderate-severe symptoms are treated in the hospital. The average length of stay of COVID-19 patients in Wuhan is 19 days, with a range of 3-41 days. This can be the baseline for the length of stay in Indonesia, especially in WNT. Hospitalized patients have a potential of 26-32% to enter ICU, which can increase the mortality rate to 39-72%. With this regimen, COVID-19 patients are expected to recover quickly. Mataram is included in the red zone and has the highest confirmed Covid-19 cases in WNT.

Non-pharmacological treatment includes isolation to prevent transmission to another patient, family, and paramedics. Sufficient hydration and nutrition are also needed to maintain good immunity. Pharmacological treatment includes antivirus, anti-inflammatory drugs, and immunomodulators. Cell and antioxidant therapy can also be considered. There is no specific therapy found that can cure patients diagnosed with COVID-19. The provided treatment includes supportive and symptomatic therapy to prevent respiratory failure.

Oseltamivir is an antivirus used for the therapy of diseases caused by Influenza A virus, Influenza B virus, Parainfluenza virus, picornavirus, and coronavirus. Oseltamivir works by inhibiting viral replication. The administration of combined oseltamivir compared to a single or combined dose of oseltamivir still needs to be studied in the treatment of COVID-19. Successful treatment of confirmed COVID-19 patients is assessed by the length of stay. Therefore, a comparative analysis between a single and combined dose of oseltamivir on the length of stay to increase treatment success of COVID-19 in Mataram Hospital is needed.

**METHODS**

This study is an observational study with a cross-sectional design based on medical records of Covid-19 patients from April-June 2020. The total population was 330 people. This study was conducted in Mataram Regional Hospital. Samples were chosen through total sampling with inclusion and exclusion criteria.

The inclusion criteria included confirmed COVID-19 positive patients with mild symptoms that were hospitalized within the last three months who received single oseltamivir therapy, combined oseltamivir therapy (azithromycin), and had complete medical record data.

Meanwhile, the exclusion criteria included confirmed COVID-19 positive patients aged 0-17 years old with moderate to severe symptoms, had comorbidity (DM, hypertension, cardiac disease, immunocompromised, pulmonay TB, malignancy), and patients who died.

Data analysis performed in this study included univariate and bivariate analysis. Kolmogorov-Smirnov test was used for univariate analysis because the sample was univariate to observe the frequency and distribution of COVID-19 patients with mean and standard deviation and the determination of 95% Confidence Interval (95% CI). Mann-Whitney test was used for bivariate analysis because the data were not normally distributed. The obtained data were processed and analyzed using computer software, which was Statistic Product and Service Solution (SPSS) with a significance of p<0.05.

**RESULTS**

The subjects in this study were confirmed COVID-19 patients with mild symptoms treated in Mataram Hospital from April to June 2020, with the highest number of patients in May with 106 people. The population in this study was 330 people and some subjects dropped out because younger than 17 years old. Therefore, the total sample used was 238 with 128 of them being women, which is shown in Table 1.

The subjects in this study were mostly 28-37 years old with 54 people (22.7%), and the least was between 88-97 years old with 1 person (0.4%), which is shown in Table 2.

There were 52.5% of subjects who received a single dose of oseltamivir, and 47.5% received combined therapy of oseltamivir and azithromycin, which is shown in Table 3.

### Table 1. Description of Gender.

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>110</td>
<td>46.2</td>
</tr>
<tr>
<td>Women</td>
<td>128</td>
<td>53.8</td>
</tr>
<tr>
<td>Total</td>
<td>238</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 2. Description of Age.

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>N</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-27</td>
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<td>15.5</td>
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<tr>
<td>28-37</td>
<td>54</td>
<td>22.7</td>
</tr>
<tr>
<td>38-47</td>
<td>49</td>
<td>20.6</td>
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<td>48-57</td>
<td>51</td>
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<tr>
<td>58-67</td>
<td>37</td>
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<td>68-77</td>
<td>5</td>
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<tr>
<td>78-87</td>
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<td>1.7</td>
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<tr>
<td>88-97</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Total</td>
<td>238</td>
<td>100</td>
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</tbody>
</table>
Based on the Kolmogorov-Smirnov normality test, the variables of the length of stay and single and combined oseltamivir therapy were not normally distributed (p<0.05). Therefore, a non-parametric test with Mann-Whitney U was used to determine the correlation between the administration of single and combined oseltamivir therapy on length of stay. The p-value was 0.00 (p<0.05) and is shown in Table 4.

**DISCUSSION**

Patients with mild symptoms are defined as patients with upper respiratory tract infection without complication with non-specific symptoms, such as fever, fatigue, cough, loss of appetite, malaise, muscle pain, sore throat, difficulty breathing, nasal congestion, or headache and probably accompanied by uncommon symptoms such as diarrhea, nausea or vomiting.18

Patients with mild symptoms were given antivirus at the beginning of therapy. However, antivirus is not as effective in moderate to severe symptoms. This was due to the important role of the body’s inflammatory reaction on disease severity. Oseltamivir is an analog of sialic acid that works as a neuraminidase inhibitor and has activity toward influenza A and B virus. Oseltamivir disrupts the release of influenza virus progeny from infected host cells. Therefore, the spread of infection in the respiratory tract can be prevented. Early administration is important because the replication of the influenza virus peaked at 24-72 hours after the disease onset.7,8,16,18 Atypical pneumonia caused by acute respiratory syndrome coronavirus (SARS-CoV-2) that caused a pandemic in Guangzhou in 2003 made oseltamivir a coronavirus treatment. Active site spike (S)1 protein of SARS is similar to neuraminidase. Thus, neuraminidase inhibitors can be effective in treating SARS-CoV-2. The current COVID-19 pandemic caused by SARS-CoV-2 made oseltamivir reappear as an interesting topic to discuss.7-9,20

Oseltamivir is used as an antivirus in Wuhan with an administration duration of 3-14 days, with an average of 3-6 days.7,8,19 Meanwhile, the administration duration in Mataram Hospital was 5-6 days, with a dose of 75 mg given twice per oral. Other than antivirus, vitamin C was also administered and a combination with a macrolide class antibiotic, azithromycin. Most patients (70%) received antibiotics in a single dose or combined dose with a duration of 3-17 days.8,9,17,19 Azithromycin is usually used in pneumonia cases with the initial dose of 500 mg, followed by 250 mg once a day for 4 days. Azithromycin has 15 atom lactone rings, thus it does not inactivate P450 cytochrome enzymes. Therefore, azithromycin is free from drug interaction.11,15,16

The length of stay in this study was obtained by looking at the result of two negative swabs in hospitalized patients because swab result is a gold standard to determine a patient’s recovery. The length of stay in patients with single oseltamivir therapy ranged from 8-56 days with an average of 27.48 days. Meanwhile, the length of stay in patients with combined oseltamivir therapy ranged from 8-46 days with an average of 20.80 days. This duration of stay was in line with Wang (2020) who stated that the interval length of stay in Covid-19 patients in Wuhan was around 3-41 days.7,21

Kolmogorov-Smirnov test showed abnormal data distribution (p<0.05). Thus, Mann-Whitney was used for bivariate analysis. The result showed a significant difference in length of stay in COVID-19 patients between the administration of single oseltamivir and combined oseltamivir in Mataram Hospital (p<0.05), which can be seen in Table 4. This significant result showed that oseltamivir therapy with azithromycin can shorten the length of stay in confirmed COVID-19 patients in Mataram Hospital. The reason may be this drug is effective to reduce the virulence of SARS-CoV-2 and prevent pneumonia.

The limitation of this study includes many influences from other variables that may cause bias, such as comorbid and other therapy. In the future, these variables need to be controlled and multivariate analysis is required to observe the effect of independent variables on the dependent variable and determine which variable has the most effect.

**CONCLUSION**

This study involved 238 confirmed COVID-19 patients hospitalized in Mataram Hospital. The results found that patients who received combined therapy of oseltamivir with azithromycin tend to have a shorter length of stay compared to patients who received single oseltamivir therapy. Further studies are needed concerning the combination of oseltamivir and a single dose of oseltamivir for COVID-19 patients with consideration to other variables.

**CONFLICT OF INTEREST**

None declared.

**FUNDING**

This research has been approved and received a grant for research publication from the Government of Indonesia.

**AUTHORS CONTRIBUTION**

Author M, DZ, and DR contributed in data collection and literature review. Author RI and HW contributed in manuscript...
preparation, data analysis, and establish cooperation to obtain research and publication grant.

ETHIC IN PUBLICATION

This research was approved by Research Ethic Commission of Medical Faculty of Universitas Islam Al-Azhar, Mataram, West Nusa Tenggara, Indonesia with the ethical clearance number 28/EC/FK-06/UNIZAR/VII/2020.

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