COVID-19 THERAPY: COMPARISON EFFECTIVITY BETWEEN REMDESIVIR AND FAVIPIRAVIR

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ABSTRACT

Introduction: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) is the virus that causes Coronavirus Disease 2019 (COVID-19), a disease of global concern(1). Remdesivir and favipiravir are antiviral drugs that are considered COVID19 therapy, as described in Indonesia's 3rd COVID-19 Management Guidelines. They have a similar mechanism, specifically by inhibiting RNA dependent RNA polymerase of the virus (3). Several studies have reported that patients who were treated with these antivirals had a shorter hospital stays (4–6). However, the comparison of efficacy between remdesivir and favipiravir is still unknown.
Methods: An observational analytic study was done using a retrospective cohort design. Eighty-eight medical records of COVID-19 patients between January 2021 to August 2021 are collected by consecutive sampling techniques, and this research was carried out at Gotong Royong Hospital Surabaya.
Results: Based on the statistical analysis test, there was no clinical improvement difference found, neither patients received remdesivir nor favipiravir based on their clinical manifestations, such as ventilation support and chest X-ray, measured by WHO ordinal scale ($p=0,486$; $p>0,05$ on the first week and $p=0,942$; $p>0,05$ on the second week).
Conclusions: Improved clinical manifestations were seen in the second week of therapy, either in patients who received remdesivir or favipiravir, but there was no significant effectivity difference between those drugs.

Keywords: *COVID-19; Remdesivir; Favipiravir; clinical manifestation*

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease that mainly affects the respiratory system and is caused by a new virus identified in China on December 31st, 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) (1). COVID-19 has already been a pandemic since March 11th, 2019, declared by WHO. Everyone is at risk of being infected, but certain populations have a greater risk of experiencing more severe manifestations— the elderly and people who have comorbidities (7).

The pathogenesis of COVID-19 is divided into two stages: the viral replication phase and the hyperinflammatory phase (8). Based on this understanding, one of the therapies that need to be considered is antiviral which inhibits viral replication. Remdesivir and favipiravir are antivirals that bind to RNA dependent RNA polymerase (RdRp) and prevent the virus from replicating. Several studies have shown positive results when patients were treated with remdesivir or favipiravir, which shortens hospital stays(4–6).

Acute Respiratory Distress Syndrome (ARDS) is a COVID-19 complication that leads to death(1). This is related to the hyperinflammatory response in the later phase of the disease. The risk of developing ARDS is associated with viral load. The patient is more likely to develop ARDS if their viral load is higher(9). Therefore, viral replication should be inhibited as early as possible by administering antivirals, so that the viral load remains at a low level.

We are interested to learn more about the comparison of the effectivity between remdesivir and favipiravir on the development of clinical manifestations of moderate and severe COVID-19 patients at Gotong Royong Hospital Surabaya, assessed based on the WHO ordinal scale.

METHODS

The health research ethics committee approved this research (No.148/WM12/KEPK/MHSW/T/2021)NCT05202548. This research design is an analytic observational and uses retrospective cohort study. Inclusion criteria for this study: 1. Patients over the age of 17 with moderate to severe COVID-19 (10), 2. Patients who were admitted to the hospital between January 2021 to August 2021, 3. The female patient is not in pregnancy and lactating, 4. The patient received remdesivir or favipiravir for a minimum of five days of treatment. Populations that do not match these criteria will be excluded. Among 125 medical records analyzed, 88 were included in this study and 37 were excluded. Forty-six of the 88 samples were treated with favipiravir, whereas 42 were treated with remdesivir. We did not collect data from April 2021 to May 2021 since remdesivir was rarely used during those months. We assess patients' clinical improvement in the first and second weeks using the WHO ordinal scale. If a patient's score decreases by at least two points, they are presumed to have improved clinically. These two things will be analyzed by the Chi-Square test. If the p value <0.05, the difference is considered significant.

RESULTS

From January 2021 to August 2021, 567 patients were admitted to the Gotong Royong Hospital in Surabaya due to COVID-19 and required hospitalization. A total of 483 (85.19%) patients were discharged, while 79 (13.93%) patients passed away. We collected 125 records from 567 patients, but only 88 of them matched the inclusion criteria, while the rest were excluded.

Table I summarizes the characteristics of 88 patients. Male patients outnumbered female patients in this study (47 vs 41), with the largest patients in the range of 48 to 57 years old (25%). The majority of the

patients (85,2%) were admitted to Gotong Royong Hospital Surabaya within a week of the onset of symptoms and a total of 95,5% of patients were admitted with moderate COVID-19 and according to the WHO ordinal scale, 69,4% of patients are categorized as score 4—need hospitalized and required supplemental oxygen. Patients are also treated with immunomodulators, antibiotics, and vitamin supplementation in addition to antivirals. Hypertension, diabetes mellitus, and cardiovascular disease are the three comorbidities commonly found in this study, respectively. Patients with heart disease had the greatest mortality rate (RR= 2,8), as shown in Table II.

The comparative study findings of therapeutic efficacy on the patients' clinical manifestations improvement (Table III) did not show any significant differences, neither in the first (p=0.486; p0.05) nor second (p=0.942; p>0.05) weeks. The length of stay median in the remdesivir and favipiravir groups (Table IV) were nine and eight days, respectively.

In this study, 29 patients treated with remdesivir were discharged from the hospital and 13 (31.0%) passed away, whereas 34 patients treated with favipiravir were discharged from the hospital and 12 (26.1%) , as shown in Table V.

According to chest X-Ray improvement which was analyzed in the first and second weeks, as shown in Table V, the proportion of patients treated with remdesivir was greater than those treated with favipiravir (41% vs 39,1% and 60% vs 45,5%). However, there was no significant difference found in the improvement of the chest X-Ray (p=0,859 ; p>0,05 on the first week and p=0,505 ; p>0,05 on the second week).

DISCUSSIONS

Male patients outnumbered female patients in this study. According to several research, this is because males interact with other people more frequently than women, and men are less conscientious about following health protocols(11–13). Furthermore, studies show that males are more vulnerable to infection due to the effect of chromosomes and inflammatory mediator-activating genes(12).

In this study, 84 (95.5%) patients were admitted to the hospital with moderate severity. According to the WHO ordinal scale, the majority of patients were categorized on a scale of 4—requiring hospitalization and oxygen supplementation (nasal cannula, face mask, and non-rebreathing mask), as many as 61 (6.94%). According to research by Max T. Wayne, *et al.* our findings are similar. Because the majority of the patients in this study were between 48 and 87 years old and had comorbidities, it's possible that they're classed on a scale of four(14).

The morbidity and mortality of COVID-19 patients are influenced by their comorbidity(s) (15). These three comorbidities, diabetes mellitus, hypertension, and cardiovascular disease are also the most common diseases found among COVID-19 patients, according to Bianca de Almeida-Pitotto, et al., Xingsheng Hu, et al., Christoph D. Spinner, et al(5,16,17). Eight of 15 patients (53,3%) who had a history of cardiovascular disease passed away in this study. Patients with cardiovascular disease have a relative risk (RR) of 2.8, which implies they have a 2.8 times greater chance of dying than patients without cardiovascular disease. Some studies shown that patients with cardiovascular disease comorbidity have the worst prognosis (16,18).

Patients' clinical manifestations progress, especially assistive breathing devices, was measured by the WHO ordinal scale and considered to have improved clinically if the score decreases at least two points(19). The number of patients with clinical improvement was higher in patients who were treated with

favipiravir, in the first and second weeks, but no significant difference was found (p = 0.486; p>0,05 in the first week and p = 0.942; p>0,05 in the second week). This study found that the median of hospitalization for patients treated with remdesivir was nine days, compared to eight days for patients treated with favipiravir. This finding is similar to the J.H. Beigel, et al. study, who found that the median of patients treated with remdesivir was ten days, and Z.F. Udwadia, et al., who evaluated the therapeutic efficacy of favipiravir on COVID-19 patients, found that the median of hospitalization was nine days(4,20).

The effects of the two antiviral medications are similar for some reasons. First, both remdesivirand favipiravir work by binding to RdRp and suppressing viral replication(21–23). Second, as many as 85.2% of patients admitted to the hospital during the first week of the onset, according to research by Fujii S., et al., showed that the patient's prognosis will be better if the earlier a patient is treated with antivirals(24). Third, favipiravir is considered for mild-moderate COVID-19 patients while remdesivir is considered for moderate-severe patients(2).

If the interval between the onset of symptoms and the start of the antiviral medication gets longer, it is likely that this is connected to the level of inflammatory response that develops. According to research by Hasan K. Siddiqi et al., the hyperinflammatory response begins in the middle of the viral replication phase (8). The viral burden in the body is minimal if early replication of the virus is avoided. A low viral load causes a less severe inflammatory reaction than a high viral load(9).

The sample of this study are hospitalized COVID-19 patients between January 2021 to August 2021, while the community-wide COVID-19 vaccination program began in March 2021 with the elderly and subsequently expanded to the rest of the population, so this study has not been able to analyze patients' vaccination status. Although the COVID-19 vaccine does not completely.protect a person from infection, research shows that it reduces the number of COVID-19 patients who visit the emergency room for immediate treatment, reduces the likelihood of being hospitalized, and reduces the likelihood of being admitted to the intensive care unit(25). So, we suggest that further studies include the COVID-19 patients' vaccination status in the improvement of patients' clinical manifestations.

The necessity of the breathing device, according to the British Thoracic Society, depends on the severity of the patient's condition and oxygen demand. The nasal cannula is the lowest grade of the three, and patients who require a higher oxygen flow than a face mask are given a nonrebreathing mask(26). In addition, the results of this study have been confounded by the limitations of health facilities (drugs, assistive breathing devices) and rooms for hospitalized patients because there was a domination of delta variant of SARS CoV-2 infection in Indonesia between June 2021 and July 2021.

The conclusion from this study, either remdesivir or favipiravir could be used to treat moderate and severe COVID-19 patients because there was no significant difference in treatment effectiveness when measured by the WHO ordinal scale. While clinically, switching the breathing device from a non-rebreathing mask to a nasal cannula is considered a significant improvement for the patients, so we need a more sensitive parameter to assess clinical manifestations changes in the patients.

CONCLUSIONS

In this study, we found: 1. There was no difference in the effectiveness of remdesivir or favipiravir therapy in improving clinical manifestations of moderate and severe COVID-19 patients, according to the WHO ordinal scale, 2. Both using remdesivir and favipiravir as

antivirals for COVID-19 patients, patients will experience improvement in the second week after the first antiviral administration.

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