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Comparison of the Effectiveness of Remdesivir and Favipiravir in Moderate to Critical COVID-19 Patients

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Abstract

Introduction: COVID-19 is a respiratory disease outbreak that caused a pandemic in late 2019. COVID-19 causes infected patients to experience mild, moderate, severe to critical respiratory diseases that cause death. However, until now there has been no specific therapy for COVID-19. The most currently used therapy is using antivirals, such as remdesivir and favipiravir. This study aims to analyze the effectiveness of antivirals remdesivir and favipiravir in improving symptoms and duration of treatment of moderate to critical COVID-19 patients at Airlangga University Hospital in May-June 2021.

Methods: Observational analytic study with retrospective cohort method obtained from the medical records of moderate to critical COVID-19 patients who used remdesivir and favipiravir antivirals at Universitas Airlangga Hospital. Data were collected using total sampling technique and tested with Mann-Whitney. The parameters used in this study were age, gender, comorbidities, severity, antiviral drugs, and duration of treatment.

Results: Of the 130 study subjects, 27 patients used remdesivir and 103 patients used favipiravir. The test results obtained as follows, the test between antivirals and symptom improvement time found $p = 0.015$ ($p < 0.05$) which means significant, the test between antivirals and length of treatment found $p = 0.018$ ($p < 0.05$) which means significant.

Conclusion: There is a significant difference in effectiveness between the use of remdesivir and favipiravir on symptom improvement time and length of treatment for moderate to critical COVID-19 patients at Airlangga University Hospital.

***Keywords**: COVID-19, Infectious Disease, Remdesivir, Favipiravir, Treatment outcome*

INDTRODUCTION

In December 2019, the world was shocked by the emergence of a pneumonia outbreak in Wuhan, China with no known cause (Hui et al., 2020). In just 3 days, the number of infected patients reached 44 and continues to grow until now there are millions of cases (Burhan, 2020). On January 7, 2020, China has successfully identified the cause of this pneumonia is a new type of coronavirus (Levani et al., 2021).

On February 11, 2020, WHO officially announced the name of this disease as Coronavirus Disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. As the virus continues to spread around the world,

on March 12, 2020 WHO declared COVID-19 a pandemic (Susilo et al., 2020).

COVID-19 is transmitted through small fluid particles or droplets that come out of the mouth or nose of someone infected with the virus (Kumar & Lee, 2020). Based on the severity of the case, COVID-19 is classified into 5 degrees of severity, namely asymptomatic, mild, moderate, severe, and critical (Sipahutar et al., 2023).

Until now, no definite management or therapy has been found for COVID-19 patients, so the management given to patients is only therapy for symptoms that appear and given oxygen therapy (Aditia, 2021). Some studies say there are antivirals that are considered effective as management for COVID-19 such as remdesivir and favipiravir (Maharianingsih et al., 2022).

Remdesivir is a nucleoside analog prodrug that is a broad-spectrum antiviral that can inhibit the SARS-CoV-2 pathogen in vitro, which inhibits SARS-CoV-2 replication in animal models (Awdisma et al., 2021). Dae-Gyun Ahn, *et al.* (2020) said in his research that the first COVID-19 patient in the United States successfully recovered after being treated with remdesivir. The recovery time of patients treated with remdesivir was shorter than that of patients treated with placebo (Alhilal et al., 2022).

In addition to remdesivir, favipiravir can also be an alternative treatment for COVID-19 patients. Favipiravir is a broad-spectrum antiviral that shows in vitro activity against SARS-CoV-2 (Amalia & Insan, 2021). In a previous study, a comparison of remdesivir and favipiravir antiviral therapy in severe COVID-19 patients based on outcomes conducted at RSUD dr. Doris Sylvanus Central Kalimantan showed that subjects treated with favipiravir experienced improved clinical conditions and better outcomes than subjects treated with remdesivir (Riptasari et al., 2022). RSUD dr. Doris Sylvanus Central Kalimantan showed that subjects treated with favipiravir experienced improved clinical conditions and better outcomes than subjects treated with remdesivir (Riptasari et al., 2022).

Based on medical record data from COVID-19 patients treated at Airlangga University Hospital, there are still many patients with severe to critical degrees who are given favipiravir antivirals which should be based on the covid-19 guidebook given remdesivir (Burhan, 2022), this can be influenced by several things such as the availability of antiviral stocks and patient conditions that do not allow if given remdesivir so that favipiravir is given. To find out the benefits of favipiravir in severe to critical COVID-19 patients, it is necessary to conduct research to determine the difference in the effectiveness of remdesivir and favipiravir in moderate to critical COVID-19 patients.

Until now, there has been no similar research data at Airlangga University Hospital, therefore it is necessary to conduct a study regarding the difference in the effectiveness of remdesivir and favipiravir antivirals on the time to improvement of symptoms and the length of treatment of moderate to critical COVID-19 patients in order to obtain information that can be used as input in COVID-19 treatment efforts.

Methods

This study is an observational analytic study with a retrospective cohort method using data obtained from the medical records of moderate to critical COVID-19 patients at Airlangga University Hospital for the period May-June 2021 (Nurfahmayati, 2022). This study was conducted to determine the effectiveness of remdesivir and favipiravir antivirals on improving symptoms and length of treatment of moderate to critical COVID-19 patients. The sample of this study was taken using the total sampling technique, namely all patients who met the inclusion and exclusion criteria

(Bhardwaj, 2019). The inclusion criteria for patients included in this study were patients aged 18 years and over, patients diagnosed with COVID-19 by PCR in May-June 2021, and COVID-19 patients who received remdesivir or favipiravir antiviral therapy, as well as complete medical records, while the exclusion criteria were patients who received more than 1 antivirus.

Therefore, the sample collection obtained 130 samples that met the inclusion and exclusion criteria. The dependent variables of this study are symptom improvement time and length of treatment while the independent variables are remdesivir antiviral and favipiravir antiviral. The data that has been processed will then be analyzed using he IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N. Y., USA) with the Mann-Whitney test. This study has been approved by the Health Research Ethics Committee of Airlangga University Hospital with certificate number 04/KEP/2022 on October 20, 2022.

RESULTS

There were 285 patients diagnosed with moderate to critical degrees of COVID-19 at Airlangga University Hospital in the May-June 2021 period. Of these 285 patients, there were 45 patients who were excluded from age and 110 patients who were excluded because they used antivirals other than remdesivir and favipiravir, so that 130 samples were obtained that met the inclusion and exclusion criteria which were then analyzed.

Table 1. Characteristics of patient profile

	Antiviral	
	Remdesivir n (%)	**Favipiravir n (%)**
Total Patients	27 (20,76%)	103 (79,23%)
Gender		
Male	14 (51,85%)	56 (54,36%)
Female	13 (48,14%)	47 (45,63%)
Age (Years old)		
18-25	0 (0%)	2 (1,94%)
26-35	2 (7,40%)	16 (16,53%)
36-45	4 (14,81%)	19 (18,44%)
46-55	8 (29,62%)	17 (16,50%)
56-65	7 (25,92%)	25 (24,27%)
>65	6 (22,22%)	24 (23,30%)
Degree of severity		
Moderate	4 (14,81%)	64 (62,13%)
Severe	13 (48,14%)	20 (19,41%)
Critical	10 (37,03%)	19 (18,44%)
Comorbidity		
Diabetes Mellitus	7 (25,92%)	25 (24,27%)
Hypertension	4 (14,81%)	19 (18,44%)
Coronary heart disease	0 (0%)	3 (2,91%)
Tuberculosis	0 (0%)	2 (1,94%)
Chronic kidney failure	1 (3,70%)	0 (0%)
Acute kidney failure	0 (0%)	1 (0,97%)
Hepatitis B	0 (0%)	1 (0,97%)
Without comorbidities	15 (55,55%)	52 (50,48%)

The number of COVID-19 patients in May-June 2021 at Airlangga University Hospital who met the inclusion criteria was 130 people who were divided into two antiviral groups, namely 27 patients with remdesivir and 103 patients with favipiravir. Based on gender, patients were grouped into 70 men and 60 women and based on the type of antiviral, 14 men and 13 women used the antiviral remdesivir while 56 men and 47 women used the antiviral favipiravir.

The majority of the severity of COVID-19 patients treated with remdesivir was severe (48.14%), while those treated with favipiravir were mostly moderate (64.13%). In the patients studied, most did not have comorbidities, but the most common comorbidities found in this study were diabetes mellitus and hypertension.

In this study, patient outcomes were assessed based on 2 indicators, namely symptom improvement time and length of treatment.

Differences in the Result of Antivirus Usage against Symptom improvement Time

Table 2. Symptom improvement time by antiviral

		Antiviral			
		Remdesivir n (%)		Favipiravir n (%)	
Total patients		27 (20,76%)		103 (79,23%)	
Symptom improvement time (day)					
	<3	1 (3,70%)	Hospital discharge: 1	9 (8,73%)	Hospital discharge: 4
			Died: 0		Died: 5
	3-7	18 (66,66%)	Hospital discharge: 11	77 (74.75%)	Hospital discharge: 66
			Died: 7		Died: 11
	8-14	8 (29,62%)	Hospital discharge: 6	17 (16,50%)	Hospital discharge: 15
			Died: 2		Died: 2
	>14	0 (0%)	Hospital discharge:0	0 (0%)	Hospital discharge: 0
			Died: 0		Died: 0

The table above shows that most patients in both groups experienced improvement in symptoms within 3–7 days. However, there was a difference in the number of patients who died, with the Remdesivir group having 9 deaths and the Favipiravir group having 13 deaths.

The effectiveness of remdesivir and favipiravir antivirals on the time to symptom improvement of COVID-19 patients can be seen in table 3.

Table 3. Differences in symptom improvement time result based on antiviral

Antiviral	Percentage (%)	Mean (min – max) symptom improvement time	*P-Value*
Remdesivir	27 (20,76%)	6 days (2 – 13)	0,015
Favipiravir	103 (79,23%)	5 days (1 – 13)	

From the results of the Mann-Whitney test in table 3, there is a difference in the effectiveness of antiviral use on the time to improve the symptoms of moderate to critical COVID-19 patients because the result p = 0.015 (p <0.05) which means significant.

Differences in the Results of Antivirus Usage Against Length of Treatment

Table 4. Length of treatment by antiviral

		Antiviral			
		Remdesivir		Favipiravir	
Total Patients		27 (20,76%)		103 (79,23%)	
Length of treatment (day)					
	<7	4 (14,81%)	Hospital discharge: 2	36 (34,95%)	Hospital discharge: 29
			died: 2		Died: 7
	7-14	15 (55,55%)	Hospital discharge: 11	54 (52,42%)	Hospital discharge: 45
			died: 4		Died: 9
	>14	8 (29,62%)	Hospital discharge: 5	13 (12,62%)	Hospital discharge: 9
			Died: 3		Died: 4

Most patients in both groups received treatment for 7–14 days. The Remdesivir group had a higher proportion of patients treated for more than 14 days than the Favipiravir group. However, the difference in the number of patients who died between the two groups was not very significant.

A comparison of the effectiveness of remdesivir and favipiravir on the length of treatment of COVID-19 patients can be seen in table 5.

Table 5. Differences in length of treatment result based on antiviral

Antivirus	Percentage (%)	Mean (min – max) Length of treatment	*P-Value*
Remdesivir	27 (20,76%)	11 days (4 – 20)	0,018
Favipiravir	103 (79,23%)	9 days (2 – 30)	

From the test results in table 5, the significance value obtained p=0.018 which means p<0.05, so there is a significance of the difference in length of treatment based on the use of remdesivir and favipiravir antivirals.

DISCUSSION

Characteristics of patient profile

Patients who were treated with remdesivir were mostly male (54.36%). The results of this study are in line with research conducted by (Nawangsari, 2021 ; Cai, 2020) that 60% of patients exposed to COVID-19 are male and more susceptible to contracting than women. Several factors can cause men to be more susceptible to COVID-19, namely: higher expression of ACE 2 receptors in men compared to women, the concept of immunological differences based on gender based on sex hormones and the X chromosome where the hormone estrogen in women can increase the immune response so that it is more resistant to infection, and poor lifestyles in men, such as smoking and drinking alcohol so that male patients have a higher risk of being infected with COVID-19 than women (Bwire, 2020).

Most patients given remdesivir were 46-55 years old (29.62%) and favipiravir patients were predominantly 56-65 years old (24.27%). However, in a study conducted by (Daud et al., 2022) it was found that there was no correlation between age characteristics and the incidence of COVID-19. This means that all ages have the same risk of being infected with COVID-19, but the most at risk is productive age because it has high mobility and activity (Elviani et al., 2021).

Most patients who were given remdesivir were included in the severe severity degree (48.14%). This result is in accordance with (Alhilal et al., 2022) research that most patients given remdesivir have severe disease severity in accordance with WHO guidelines. Most favipiravir patients fall into moderate severity (62.13%). This result is in line with (Udwadia et al*.,* 2021) research which suggests that favipiravir is widely used and beneficial in mild to moderate COVID-19 patients. However, in this study there were 19 patients out of 29 critical degree patients who were treated using favipiravir, even though the 4th edition of the COVID-19 management guidebook recommends that critical patients be treated using remdesivir. This is in line with research conducted by (Damayanti et al., 2021) that favipiravir can still be effective in severe and critical COVID-19 patients.

Differences in the results of antivirus use on symptom improvement time

Patients in the remdesivir and favipiravir groups did not have prominent symptoms. The results obtained can occur because the majority of favipiravir is a moderate degree (62.13%) and most have a symptom improvement time of 4 days, while the majority of the remdesivir group is a severe degree with the most symptom improvement time is 6 days. The results of this study are in line with research conducted by (Amalia & Insan*,* 2021) which states that favipiravir shows efficacy in improving general clinical symptoms significantly compared to other antivirals. Rezkita et al., (2022) also stated the same research results because favipiravir was considered to increase viral clearance in 7 days and clinical symptom improvement in 14 days. According to the results of Alhilal et al., (2022) research, the results of the remdesivir effectiveness test did not provide results in improving clinical symptoms and reducing mortality.

The same results were also obtained in another study that there were differences between clinical improvements in the remdesivir and favipiravir therapy groups, namely more patients in the favipiravir therapy group who showed clinical symptom improvement compared to the remdesivir therapy group (Riptasari et al., 2022).

Differences in the results of antivirus use on the length of treatment

In this study, there was a difference in the results of the length of treatment of 2 days, namely the remdesivir group had a length of treatment of 11 days and the favipiravir group 9 days. The results obtained can occur because the majority of favipiravir group patients have moderate degrees compared to the remdesivir group which is dominated by severe degrees and based on comorbidities, remdesivir has more comorbid patients (62.96%) than the favipiravir group (60.19%). Based on this, it is possible that favipiravir patients are treated in the hospital faster than remdesivir patients who take COVID-19 treatment together with comorbid treatment. The recommended administration time for remdesivir is 5 to 10 days. Usually patients cannot go home before fulfilling the antiviral administration time because remdesivir does not have an oral drug preparation and the severity of the patient is severe so that patients treated with remdesivir have a longer length of treatment than patients treated with favipiravir (Alhilal et al, 2022).

The results of this study are in line with the results of research conducted by (Khairi et al., 2022) which states that there is a relationship between the administration of remdesivir and the length of treatment. The results of this study are inversely proportional to (Alhilal et al., 2022) research which states that there is no relationship between the use of remdesivir and favipiravir antivirals on the length of treatment of hospitalized patients even though there is a difference in the results of the duration of hospitalization of the favipiravir group longer by 1 day, but this is considered not statistically significant.

The advantage of this research is that the variables studied can be measured more precisely, because they were processed using the SPSS application with a high level of confidence. The limitations are the lack of research sample size because there are no computerized records of patient medical records based on the antiviral used, the number of samples for each group is not homogeneous, this research does not assess patient outcomes and deterioration, does not examine the direct effect of antivirals on improving patient symptoms, does not assess history. treatment of referred patients.

CONCLUSION

Based on a comparative study of the effectiveness of remdesivir and favipiravir antivirals on symptom improvement time and length of treatment for moderate to critical COVID-19 patients at Airlangga University Hospital, favipiravir is considered quite effective for improving symptoms and accelerating the length of treatment in moderate to critical COVID-19 patients.

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