RESEARCH ARTICLE

TREATMENT OUTCOME OF REMDESIVIR COMPARED TO FAVIPIRAVIR ON MODERATE SYMPTOMS COVID-19

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ABSTRACT

Background : Remdesivir and Favipiravir have been widely used as antiviral agents in treating COVID-19. However, studies providing head on comparison of treatment outcomes between the two antiviruses are rare. The aim of this study is to compare the treatment outcome of Remdesivir and Favipiravir in moderate symptoms COVID-19. Subjects were divided into two groups based on received antivirus during COVID-19 treatment in the hospital, Remdesivir group and Favipiravir group. Post-treatment outcome was measured with three indicators: symptom improvement, negative conversion of RT-PCR, and radiological improvement.

Methods : Outcomes of both groups were compared with chi square test with Remdesivir serves as a risk factor and Favipiravir as control. Out of a total of 130 subjects, 65 received Remdesivir, and 65 received Favipiravir. Post-treatment RT-PCR and radiologic examination were performed on a median of Day-10 hospitalization. RT-PCR conversion to negative was significantly more likely in Remdesivir group (RR: 1,917, 95% Cl 1,044 – 3,518, p = 0.047, chi square test).

Results: There was no significant difference between Remdesivir group and Favipiravir group in symptom improvement on Day-5 (RR 0.941, 95% Cl 0.776 – 1,141), nor Day-7 (RR 1.020, 95% Cl 0.855 – 1.216). There was also no significant difference in radiological improvement (RR 0.855, 95% Cl 0.712 – 1.026).

Conclusion: Administering remdesivir to COVID-19 patients significantly increased the occurrence of negative RT-PCR conversion after therapy compared to standard favipiravir therapy.

Keywords: Remdesivir, Favipiravir, COVID-19.

INTRODUCTION

SARS-CoV-2 infection, namely Coronavirus Disease 2019 (COVID-19), is a pandemic situation with more than 186 million detected cases and 4 million deaths reported globally per 11 July 2021.[1] Many different approaches for treating COVID-19 patients have been proposed and used in practice: antiviral agent, supporting antibiotics, anti-IL6, convalescent plasma, corticosteroid, anticoagulant. Among them, the antiviral agent has been routinely used as an integral part of the treatment regime for symptomatic patients. However, the rationale of choosing a particular antiviral agent is often vague due to varying conclusions from multiple trials studying the efficacy of the same drug.[2,3]

Remdesivir is broadly used antiviral agent for COVID-19. Results from a randomized controlled trial of the Adaptive COVID-19 Treatment Trial (ACTT) involving 1062 patients stated that patients treated with Remdesivir showed faster recovery time compared to placebo (median 10 days vs. 15 days; rate of recovery, 1.29; 95% Cl 1.12 - 1.49, p = 0.001).[4] Contrastingly, a study by Wang et al. involving 237 patients with severe COVID-19 found that Remdesivir did not provide significant clinical improvement compared to placebo (HR 1.23, 95% CI 0.87-1.75). However, although not statistically significant, the study mentions that patients with symptom onset of fewer than ten days who received Remdesivir showed faster clinical improvement (HR 1.52, 95% Cl 0.95-2.43).[5]

Favipiravir also appears with favourable treatment outcomes in numerous reports. A meta-analysis including nine clinical trials revealed that Favipiravir group had significantly more significant clinical improvement compared to the control group during seven days of hospitalization.[6] In addition, requiring supplemental oxygen

therapy in Favipiravir group was 7% less than the control group.[6] The mortality rate in Favipiravir group was approximately 30% less than the control group, although not statistically significant.[6]

Indonesia's recent national guidance for COVID-19 management recommended some antiviral agents for use in accordance with disease severity.[7] Remdesivir and Favipiravir are recommended for patients with moderate to severe illness. The recommended dose for Remdesivir is 200 mg intravenous drip for the first day followed by 100 mg intravenous drip once daily to fifth day or up to tenth day, whereas the recommended dose for Favipiravir is a loading dose of 1600 mg every 12 hours orally for the first day followed by 600 mg twice daily for the second to fifth day.[7] Both antiviruses are currently colloquially used for treating symptomatic COVID-19 patients in hospitals across Indonesia. In Abdul Radjak Salemba Hospital, Favipiravir was once the standard care for moderate COVID-19 and is now joined by Remdesivir for the moderate to severely ill. However, choosing one over the other is often based on the physician's preference, as limited studies compare the drugs' efficacy. Concerning the need for data to support a rational decision, this study compared the treatment outcome of Remdesivir and Favipiravir in moderate COVID-19.

METHODS

Cohort retrospective methods was used in this study. The study was conducted in Abdul Radjak Salemba Hospital, Jakarta, from November 2020 to December 2020. Secondary data is used by obtained from patients' medical records.

Subjects were patients hospitalized with COVID-19 in November to December 2020 who met the criteria of moderate severity according to Indonesian guidance for management of COVID-19 3rd edition: 1) showing clinical signs of pneumonia such as fever, cough, shortness of breath, rapid breathing (>20x/min) and blood oxygen saturation ≥ 93%, or 2) radiological features of pneumonia without signs of severe pneumonia.[7] Subjects were recruited with consecutive sampling method.

Inclusion criteria were: 1) Inpatients with moderate COVID-19 confirmed by RT-PCR, 2) Age >19 years old, 3) Treated with either Remdesivir or Favipiravir 4) Results of laboratory tests, RT-PCR, and chest x-ray examinations are well documented. There should be at least two chest x-ray results, one taken initially on admission to hospital (Day-1) and one on evaluation. Exclusion criteria were as follows: 1) Patient who did not undergo either RT-PCR, laboratory tests and/or twice chest x-ray examinations during hospitalization, 2) Discharge from the hospital was done upon patient's request instead of doctor's approval. Since all data was taken from the medical record, subjects whose medical record has missing or incomplete documentation of any form of history of care during hospitalization such as the absence of x-ray result, missing laboratory results, were dropped out of the study.

Eligible subjects were divided into two groups based on achieved antiviral agents, which are Remdesivir group and Favipiravir group. Subjects in Remdesivir group received intravenous Remdesivir 200 mg on the first day followed by 100 mg once daily. The duration varied between 5-7 days according to clinical judgment of the physician in charge. Subjects in Favipiravir group received a loading dose of Favipiravir 1600 mg every 12 hours on the first day, followed by 600 mg twice daily for 5 to 7 days.

Three indicators measured the treatment outcome: 1) Symptom improvement, 2) Negative conversion of RT-PCR, and 3) Radiological improvement. Symptom improvement is the percentage of subjects with improving symptoms on Day-5 and Day-7 of hospitalization compared to Day-1. Negative conversion of RT-PCR is defined as the percentage of subjects obtaining negative results on RT-PCR evaluation. Radiological improvement is defined as the percentage of subjects showing improvement in chest x-ray evaluation compared to the initial chest x-ray performed on the day of admission (Day-1). A lower score in chest x-ray evaluation compared to Day-1, or if the initial finding was normal and consistently showed 0 scores, will be defined as a radiological improvement. Subject's lung image on chest x-ray was reported as a score: score zero – normal finding, no consolidation found; one – unilobar consolidation; two – multilobar consolidation; three - bilateral consolidation.

Outcomes of both groups were compared with chisquare test with, Remdesivir serves as a risk factor and Favipiravir as control, whereas symptom improvement, negative conversion of RT-PCR, and radiological improvement serve as consequences of risk factor.

ETHICAL CLEARANCE

Faculty of medicine and health, University of Muhammadiyah, Jakarta ethical clearance committee has approved research protocol. The ethic number were No.023/PE/KE/FKK-UMJ/2021

RESULTS

Patient Characteristics

Between November 2020 and December 2020, 164 patients met inclusion criteria. Fifteen were dropped out due to incomplete records of laboratory results, and nineteen were dropped due to incomplete records of baseline symptoms. Finally, there were 130 eligible subjects. Half of them were in Remdesivir group, while the other half were in Favipiravir group. All subjects started antiviral agents on Day-1 of hospitalization.

The median age in Remdesivir group is 56 years old, whereas the median age in Favipiravir group is 50 years old. Subjects in Remdesivir group are predominantly male, while in Favipiravir group predominantly female. All subjects had COVID-19 with moderate severity confirmed with RT-PCR. In both groups, most subjects (52.3%) had no comorbidities. The main comorbidities found in Remdesivir group are type II diabetes (13.8%) and hypertension (7.7%). And the comorbidities found in favipiravir group are type II diabetes (9.2%) and chronic kidney disease (7.7%). (Table 1)

Table 1. Comparison of demographic and clinical characteristics between Remdesivir and Favipiravir group

	Remdesivir (n = 65)	Favipiravir (n = 65)
Age [median]	56 (17-85)	50 (20-84)
Gender		
Male	43 (66.2%)	31 (47.7%)
Female	22 (33.8%)	34 (52.3%)
Clinical Symptoms		
Cough	42 (64.6%)	41 (63.1%)
Fever	21 (32.3%)	24 (36.9%)
Shortness of Breath	49 (75.4%)	43 (66.2%)
Sore Throat	6 (9.2%)	8 (12.3%)
Flu Like Symptoms	8 (12.3%)	7 (10.8%)
Anosmia	3 (4.6%)	6 (9.2%)
Diarrhea	2 (3.1%)	3 (4.6%)
Fatigue	16 (24.6%)	14 (21.5%)
Co-morbidities Status		
No Comorbid	34 (52.3%)	43 (66.2%)
Hypertension	5 (7.7%)	4 (6.2%)
Diabetes Mellitus	9 (13.8%)	6 (9.2%)
Cardiovascular Disease	6 (9.2%)	3 (4.6%)
Chronic Renal Failure	1 (1.5%)	5 (7.7%)
Asthma	2 (3.1%)	0 (0%)
Tuberculosis	0 (0%)	1 (1.5%)
Hypertension and Diabetes Mellitus	8 (12.3%)	2 (3.1%)
Anemia	0 (0%)	1 (1.5%)

The most common symptoms in Remdesivir group were shortness of breath (75.4%), cough (64.6%), and fever (32.3%) with the same symptoms appeared as most symptoms in Favipiravir group (66.2%, 63.1%, and 36.9%, respectively) (Table 1). The most common initial chest x-ray (Day-1) finding in Remdesivir group was bilateral consolidation (53.8%), while in Favipiravir group are normal findings (43.1%) (Table 2). No subject in either group showed severe pneumonia. The median time on which chest x-ray evaluation was performed was Day-10 of hospitalization, while RT-PCR evaluation was performed on a median Day-10 of hospitalization.

Table 2. Comparison of laboratory and radilog characteristics between Remdesivir and Favipiravir group

	Remdesivir (n = 65)	Favipiravir (n = 65)
Laboratory findings		
Hemoglobin (g/dl) [median]	13.6 (5.7 – 16.2)	12.9 (7.10 – 16.40)
Leukocytes (10^3/µl) [median]	8.52 (3.5 – 20.7)	7.46 (3.67 – 42.20)
Platelets (10^3/µl) [median]	267 (28.9– 512)	251 (22 – 532)
Hematocrit % [median]	39.4 (18.5 – 50)	43.7 (20.3 – 64)
Erythrocytes 10^6/µl [median]	4.7 (2.29–6.4)	4.03 (2.47– 6.5)
Radiological Findings		
Normal	16 (24.6%)	28 (43.1%)
Unilobar Consolidation	12 (18.5%)	8 (12.3%)
Multilobar Consolidation	2 (3.1%)	6 (9.2%)
Bilateral Consolidation	35 (53.8%)	23 (35.4%)

There is no significant difference between Remdesivir group and Favipiravir group, in symptom improvement on Day-5 of treatment with antiviral agent (RR 0.941, 95% Cl 0.776 – 1,141, p = 0.681), nor is there on Day-7 (RR 1.020, 95% Cl 0.855 – 1.216, p = 1000). Subjects treated with Remdesivir are more likely to achieve RT-PCR conversion to negative significantly, with relative risk of 1,9 (RR: 1,917, 95% Cl 1,044 – 3,518, p = 0.047). There is no significant difference between the two groups in achievement of post-treatment radiological improvement (RR 0.855, 95% Cl 0.712 – 1.026, p = 0.134) (Table 3).

Table 3. Research outcome between Remdesivir and Favipiravir group

	Yes	No	P-value
Symptoms Improvement on Day 5			
Remdesivir	48 (73.8%)	17 (26.2%)	0.681
Favipiravir	51 (78.5%)	14 (21.5%)	
Symptoms Improvement on Day 7			
Remdesivir	52 (80%)	13 (20%)	1.000
Favipiravir	51 (78.5%)	14 (21.5%)	
Negative Conversion of RT-PCR			
Remdesivir	23 (35,4%)	12 (18.5%)	0.047*
Favipiravir	42 (64.6%)	53 (81.5%)	
	Consistently normal or Radiological Improvement	No Radiological Improvement or Deterioration	
Radiological Improvement			
Remdesivir	47 (72.3%)	18 (27.7%)	0.134
Favipiravir	55 (84.6%)	10 (15.4%)	

*(p<0.05 indicates significant finding)

DISCUSSION

Remdesivir is an adenosine analog that inhibits viral replication by preventing its RNA dependent RNA polymerase (RdRp)–mediated RNA translocation.[8-10] Remdesivir shows were promising inhibitory activity on SARS-CoV-1 and MERS-CoV in vitro.[8-10] An experiment in mice infected with chimeric SARS-CoV encoding the RdRp of SARS-CoV-2 was conducted to evaluate in vivo efficacy of Remdesivir.[11] The experiment yielded satisfactory results as Remdesivir diminishes lung viral load and improves pulmonary function in experimental animals. Altogether, these data indicate Remdesivir's potent activity against SARS-CoV-2 both in vitro and in vivo and supports onward testing as well as the usage for treatment.

Favipiravir is also a purine analogue. It is incorporated in guanine or adenine of the viral RNA, thereby inhibiting RdRp and consequently viral replication According to a meta-analysis by Manabe et al., the drug contributes to clinical improvement within 14 days and accelerates viral clearance after seven days of treatment.[12] The study then concludes that Favipiravir has a strong possibility of treating COVID-19, especially in mild to moderate illnesses. Another meta-analysis by Hassanipour et al. found that viral clearance in 14 days after hospitalization was more in Favipiravir group than the control group and requiring supplemental oxygen therapy was 7% less in Favipiravir group.[6] However, it is essential to note that in the study, both findings boding well for Favipiravir was not statistically significant.[6] Favipiravir administration also did not significantly differ in patients transferred to ICU and adverse events .[6] The drug's efficacy remains questionable despite its high utilization for COVID-19.

Rationally choosing an antiviral agent for treating COVID-19 is essential to effectively cut down patients' burden of viral load. A study conducted by researchers in the United Kingdom and Spain during the initial outbreak in 2020 found that high SARS-CoV-2 viral load was strongly associated with the risk of developing symptoms.[13] The viral load may also be a determinant of transmission risk. The study found that viral load among their studied index cases was the main factor determining infection among contacts. For each increase of log10 in index cases' viral load, the odd of onward virus transmission increase by 30%.[13]

Another study reported that a higher prevalence of detectable plasma viral load is associated with worse respiratory severity and increased inflammatory markers.[14] In advanced disease progression, a severe disease usually presents with significant lung involvement on radiologic examination. Considering all these earlier findings, this

study compares the efficacy of antiviral agents based on patients' symptom improvement, negative conversion to RT-PCR in approach to viral load, and radiological improvement.

Symptom Improvement

Between Remdesivir group and Favipiravir group, there is no significant difference in symptom improvement on Day-5 (RR 0.941, 95% Cl 0.776–1,141, p = 0.681) and Day-7 (RR 1.020, 95% Cl 0.855–1.216, p = 1000) of antivirus administration. In a study involving patients with severe COVID-19 by Wang et al., the time of clinical improvement in patients treated with Remdesivir is not significantly different from the placebo group.[5] These findings contradict the result from a clinical trial of Remdesivir by Spinner et al. in which Remdesivir showed promising results in moderate COVID-19 patients compared to placebo.[15] Adaptive COVID-19 Treatment Trial (ACTT-1) also found that administration of Remdesivir for ten days was superior to placebo in accelerating patients' clinical improvement.[4]

Negative Conversion of RT-PCR

This study found that RT-PCR conversion to negative is significantly higher in patients treated with Remdesivir compared to Favipiravir (RR: 1,917, 95% Cl 1,044–3,518, p = 0.047). Administration of 20 µM (12.1 µg/mL) Remdesivir has been reported to decrease titter of SARS-CoV-2 intracellular virus in nasal and bronchial epithelial cells by 7.3 logs10 – 7.9 logs10 in the first 48 hours.[16] Thus, this study's finding supports the implication that Remdesivir may have the potential to reduce viral load in patients with moderate COVID-19. Lower or undetected viral load is a good feature as it is associated with better patient outcomes. High levels of viral load are related to the severity of disease, length of stay in the intensive care unit, and usage of mechanical ventilators and mortality.[17-19]

However, some studies report contradictory results. Goldberd et al. found that administration of Remdesivir did not significantly reduce viral load in the nasopharynx.[20] In another study involving patients with severe COVID-19, administration of Remdesivir did not make a significant difference in the decrease of subjects' viral load compared to placebo.[5] The study then emphasized that the pharmacokinetic aspects of Remdesivir in critically ill patients remained unknown.[5]

Radiological Improvement

Achievement of radiological improvement is not significantly different between Remdesivir and Favipiravir group (RR 0.855, 95% Cl 0.712 – 1.026, p = 0.134). There is minimal research discussing the effect of either drug on lung improvement measured with a radiologic examination. Radiological improvement after treatment is expected in this study, considering that several radiographic features are correlated to deterioration into severe or critical status.[21] Chest x-ray severity index and other clinical information are also predictive factors of in-hospital mortality.[22] However, chest x-ray alone may be difficult to provide thorough information of presenting lung abnormalities as it is not as sensitive as computed tomography scan (CT-scan).

The findings in this study have several limitations. All data is collected retrospectively, hence treatments received by subjects during hospitalization are nonuniform. The time on which evaluations are performed and the types of the examination itself varied since they are based on the physician's decision in a clinical setting rather than an experimental setting. This study also mentions that Remdesivir group has a significantly higher percentage of subjects achieving negative RT-PCR results on a median Day-10. Researchers took RT-PCR evaluation to understand that lower Cycle threshold value (Ct value), therefore positive RT-PCR, is associated with higher viral load and disease severity.[23] In severe and critical COVID-19, the viral load remains consistently high over the disease course, accompanied by the persistence of a low Ct value.[24] However, the persistence of detectable viral genetic material has also been observed during the convalescent phase of COVID-19 when the viral load is diminished. Positive RT-PCR may persist for weeks despite the patient's symptoms resolution.[25] Additional study is needed to confirm the efficacy of Remdesivir compared to Favipiravir in moderate COVID-19 patients, preferably prospective observation or experimental study involving a more significant number of subjects.

CONCLUSION

This study found that administering remdesivir to COVID-19 patients significantly increased the occurrence of negative RT-PCR conversion after therapy compared to standard favipiravir therapy. However, no significant difference was found in terms of clinical and radiological improvement of the patients. Further studies are needed to reveal the efficacy of remdesivir as the management for moderate COVID-19 patients, especially longitudinal studies with prospective methods, involving more subjects and more strict study protocols to eliminate confounding outcomes.

CONFLICT OF INTEREST
There is no conflict of interest.

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