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The effectively of favipiravir as antiviral therapy in the treatment of covid-19 in the several hospital in Blora, Indonesia

Abstract

The outbreak of Corona virus Disease 2019 (COVID-19) in December 2019 in China, has become a pandemic in March 2020. A clinical study in China on the effectiveness of favipiravir involving 320 COVID-19 patients stated that favipiravir was safe and efficacious in the treatment of COVID-19. However, in Indonesia, the clinical studies on the effectiveness and the toxicity of the antiviral are so lacking that the further research will be needed.

The objective of the study is to analize the effectiveness of favipiravir as an antiviral therapy in the treatment of COVID-19 in several hospital in the district of Blora, Central Java, Indonesia. In this study as many as 266 samples of the patient's medical record which met the inclusion criteria were devided into group 1 which given favipiravir and group 2 which not given favipirafir. Data were then analized by using chi-square with continuity correction to evaluate the difference in proportion of those who were given the antiviral and those who were not, in relation to the outcome.

The result showed that as many as 92.5% of the patient given favipiravir showed an improved outcome and 7.5% of those were reported dead. As many as 80.5% of those not given favipiravir showed an improved outcome and 19.5% of those were reported dead. Based on the chi square with continuity correction, it revealed that there was significant difference in the proportion among the groups in relation to the outcome ($p<0,05$). Based on the results and discussions, it is concluded that favipiravir is effective to be used as an antiviral drug in the treatment of COVID-19.

Keywords: antiviral, covid-19, favipiravir

Volume 9 Issue 6 - 2021

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Received: October 15, 2021 | **Published:** November 05, 2021

Introduction

In the end of 2019, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS – CoV-2) caused by a previously unknown coronavirus had just started. The symptoms found in the disease which is also known as the coronavirus disease 2019 (COVID-19) are fever, cough, dyspnea and pneumonia. The global prevalence of COVID-19 as of 7 March 2021 is as follows : 2 734 381 new cases in last seven days, 116 166 652 cumulative cases, 60 323 new death cases in last seven days and 2 582 528 cumulative deaths (WHO). The rate of increase in COVID-19 cases in Indonesia is quite high. According to the data reported by Reseach Center of the Indonesian House of Representative Expertise Board, the increase of the case has reached the peak on January 31 2021 (36.18%). The case fatality rate (CFR) has reached 2.8%, slighty higher than the global CFR (2.3%).[1]

COVID-19 or SARS-CoV-2 is a betacoronavirus which is also included in the Coronaviridae family of the order Nidovirales. COVID-19 is a virus with genetic material in the form of single-stranded RNA wrapped by a lipid bilayer membrane. On the surface of the membrane there is a spike-like structure, called a spike (S). It is used by the virus to bind to its receptor, namely Angiotensin-converting enzyme 2 (ACE2). After that, the virus can enter the host cell and replicate. This happens in an acidic environment.[2]

The main cause of mortality in patients with Covid-19 is acute respiratory distress syndrome (ARDS). This occurs when fluid from the blood vessels fills the air pockets/alveoli thereby inhibiting the absorption of oxygen. The patient will experience shortness of breath, due to lack of oxygen. If not treated immediately, there will be damage to vital organs that always require oxygen such as the kidneys, heart and brain.[3]

Risk factors of the disease may include the presence of comorbid diseases such as hypertension and diabetes mellitus, smoking, cancer and male gender. In addition, it was stated that of the 261 Covid-19 patients with comorbidities, 10 of them were HIV patients and 23 of them were hepatitis B sufferers.[4]

The use of antivirals in the management of COVID-19 is still limited to small-scale clinical studies, so it is difficult to evaluate their effectiveness and safety globally. Antiviral therapies that have been used in several countries during the pandemic are favipirafir, rendesivir and oseltamivir. Favipiravir is an antiviral that was first produced in Japan under the trade name Avigan® and is used to treat influenza that is not cured by conventional therapy. As a prodrug, favipiravir is ribosylated and phosphorylated to form the active metabolite of ribufunanosyl-5'-triphosphate (favipiravir RTP).[6]

Favipiravir is taken orally. If given with food, there will be a 1.5 hour delay in reaching peak levels. Favipirafir is 54% bound to plasma proteins and is distributed externally in body compartments, including the trachea and lungs. The average half-life is 6 hours. Metabolites are excreted in the urine. The side effects of favipiravir include increased uric acid levels, indigestion, diarrhea, and serum ALT and AST. Favipiravir is contraindicated for pregnant women.[6]

Clinical research related to the use of favipiravir in Indonesia is still limited, but in a number of countries it has been or is in progress. In China there was a clinical study involving 320 COVID-19 patients and it was claimed that favipiravir was safe and efficacious in the treatment of COVID-19. The normal adult dose used to treat influenza is 1200 mg as an initial dose, followed by 400 mg on day 1, then 400 mg twice daily on day two up to day five. In the treatment of COVID-19, favipiravir is given for 7-10 days, the maximum use is up to 14 days. Initial dose of 1600 mg followed by 600 mg twice daily from day 2 to day 7 or 10.[6]

The objective of the study is to analize the effectiveness of favipiravir as an antiviral therapy in the treatment of COVID-19 in several hospital in the district of Blora, Central Java, Indonesia. The hyphotesis of the research was that there was a significant difference in the proportion of improved patient given favipiravir over those who were not given favipirafir.

Methods

This was a treatment trial research using the purposive sampling technique. According to the preliminary study in several hospitals in Blora, it was known that the number of patients who were suffering from COVID-19 was around 794 patients. The number of participants enrolled in this study was calculated by using slovin's formula as follow:[3]

$$n = \frac{N}{1 + Ne^2}$$

$$n = \frac{794}{1 + \left(794 \times 0.05^2\right)}$$

$$n = 266$$

Data were collected from January-April 2021 using medical record dated from December 2019 to December 2020. As many as 266 samples were then equally divided into 2 groups. Group 1 was those who were given favipiravir and group 2 was those who were not. The treatments given to the patients consist of NaCl or ringer lactate infusion, 750 mg levofloxacin infusion, 40 mg omeprazole injection, 20 mg furosemide injection, insulin injection, 500 mg azithromycin, 200 mg avigan or favipiravir, 500 mg paracetamol, multivitamins, 200 mg acetylcysteine and 0.5 mg alprazolam, depended on the severity of the disease and the comorbidity. The comorbidities also found in the patients were hipertension, diabetes and other cardiovascular diseases. The inclusion criteria of the study were complete medical record data and patients given favipiravir as antiviral treatment. Incomplete data of the medical record and patients given antiviral other than favipirafir or those give favipiravir in combination with other antivirals were excluded of the study. Data were then analized by using chi-square with continuity correction to evaluate the difference in proportion of those who were given the antiviral and those who were not, in relation to the outcome. This research met the ethical clearance requirement number 071/079/IV/2021.

Results and discussions

Table 1 shows that the percentage of female patient is greater than that of male patient, either in the group of those given favipirafir or without favipiravir. According to the data released by Indonesian Ministry of Health, the amount of women confirmed positive was 49.98%, while men was 50.02%. The percentage of women who were hospitalized or under self-isolation was 51.44%. This amount was slightly higher than that of men (48.56%). In addition the amount of men reported dead was 55.45% and women was 43.55%.[5]

Table 1 Characteristics of the subject

groups		Favipiravir		Without	
		amount	%	Amount	%
gender	male	55	41.35	53	39.84
	female	78	58.65	80	60.15
age (year)	<20	3	2.26	11	8.27
	20-65	116	87.21	112	84.21
	>65	14	10.53	10	7.52
n		133	100	133	100

Table 2 The outcome difference among the treatment groups

Groups	improved		reported dead		P-value
	amount	%	amount	%	
Favipirafir	123	92.5	10	7.5	
without favipiravir	107	80.5	26	19.5	0.05
N	133		133		

Continuity correction 0,007

According to the study conducted by Gebhard et al.,[7] it suggessted that there was no major sex difference in the number of confirmed COVID-19 cases in those countries where sex-disaggregated data were available. Other data show that men are more 50% hospitalized than women. There are several factors which reveal why men are susceptible to COVID-19. A study at the molecular level revealed that circulating level of ACE2 was higher not only in healthy but also in diabetic and men with renal disease, when compared to women.[8,9] ACE2 is a receptor for the SARS-CoV-2 to bind and then enter the human cells. However the connection between circulating ACE2 and COVID-19 is not clear.[7] In addition there was an evidence that sex hormones also play a role in the modulation of RAAS (renin angiotensin aldosteron system). Estrogens downregulate the angiotensin II receptor type I as well as regulate the renin activity.[10]

The ability of the imune system to respond the infection in females and males is different. The number and activity of the immune cells such as monocytes, macrophages and dendritic cells are higher in females than in males. According to the social living, women tend to have a hygiene and healthy living compared to men. Beside that smoking and drinking rates are higher among men than women.[11] These factors above explain why men are more subceptible to the COVID-19 than women. This keeps in line with the data released by the Indonesian Minister of Health. However it was difficult to determine that sex also played a role in the subceptibility of COVID-19 in this research as the data only represented one region in Indonesia.

Table 2 shows that as many as 92.5% of the patient given favipiravir showed an improved outcome and 7.5% of those were reported dead. As many as 80.5% of those not given favipiravir showed an improved outcome and 19.5% of those were reported dead. Based on the chi square with continuity correction, it revealed that there was significant difference in the proportion among the groups in relation to the outcome ($P<0.05$).

Favipiravir is considered save to be used for the treatment of Covid-19. A study suggested that the risk of QT interval prolongation of favipiravir was considered to be not high. The effect of favipiravir in a single dose 1200 and 2400 mg on the QT interval prolongation did not differ from placebo.[5] Another study regarding the effectiveness

Citation: Novembrina M, Ati AA. The effectively of favipiravir as antiviral therapy in the treatment of covid-19 in the several hospital in Blora, Indonesia. *Pharm Pharmacol Int J.* 2021;9(6):227–229. DOI: 10.15406/ppij.2021.09.00349

of favipiravir over lopiravir and ritonavir suggested that lopiravir or ritonavir was lower than favipiravir in viral clearance and improvement of computed tomography scan images. A case study regarding the treatment of favipiravir among patient in critical or severe condition revealed that 3 days after being treated with favipiravir, steroid dan nafamostad, the respiratory condition was improved, the RT-PCR was negative on day 23 and the oxygen administration was diacharged on day 36.[12]

According to the study conducted by cai et al.,[13] the median time of viral clearance for those treated by favipiravir was estimated to ne 4 days. This was significantly shorter than control. The multivariate analysis using antiviral treatment and T. Lymphocyte count as independent factor, showed that favipiravir had a greater effect regarding the viral clearance.

In the molecular level, the lethal mutagenesis has been a promising therapeutic method to manage viral infection. A number of studies have revealed that elevations in the great mutation rates found in RNA viruses have led to viral death in the cell culture. A study conducted by Arias et al [14] has demonstrated that favipiravir can cause norovirus mutagenesis in vivo, which can also lead to virus elimination. Another research carried out by Baranovich and Furuta et al.,[15,16] has also demonstrated the effectiveness of favipiravir against Influenza A virus (H1N1). T-705 (favipiravir) causes a big rate of viral mutation in H1N1 viruses that creates an abortive viral phenotype. It also has also suggested that lethal mutagenesis is a prime antiviral mechanism of T-705 or favipiravir.

A study carried out by Caroline et al.,[17] has showed that T-705 (favipiravir) had an incredible efficacy in a highly lethal rat model of Rift Valley Fever which was given the pathogenic ZH501 strain. This research has also suggested that T-705 or favipiravir has capacity to be a wide-ranging antiviral drug.

Conclusion

Based on the results and discussions, it is concluded that favipiravir is effective to be used as an antiviral drug in the treatment of COVID-19.

Acknowledgments

We are grateful to The Regional Public Hospital dr. R. Soetidjono, Blora, Permata Blora Hospital, DKT Blora Hospital and PKU Muhammadiyah Cepu Hospital for the medical record data of the COVID-19 patients. We are highly appreciative of the advices and suggestions provided by the reviewers which help us to implove the quality of our research article. This research met the ethical clearance requirement number 071/079/IV/2021.

Conflicts of interest

Authors declare that there is no conflict of interest.

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