STUDY OF EFFECTIVENESS AND SIDE EFFECTS OF FAVIPIRAVIR THERAPY ON MILD AND MODERATE COVID-19 PATIENTS

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ABSTRACT

Introduction*: Corona Virus Disease-2019 (COVID-19) is divided into five degrees that are asymptomatic, mild, moderate, severe and critical. Recently, Favipiravir known as off-label antivirals for COVID-19 that inhibits RNA-dependent RNA polymerase (RdRp) and is administered orally 2x1600 mg as loading dose and 2x600 mg as a maintenance dose.* ***Methods****: This observational retrospective study aims to determine effectiveness (PCR/Rapid Ag, temperature, respiratory rate, oxygen saturation, and chest X-ray) and side effects (digestive, uric acid, liver, blood, glucose, and lipids profile) of Favipiravir in mild and moderate COVID-19; which inclusion criteria were Favipiravir (5-10 days); a group of antibacterials: Azithromycin (therapy A), Levofloxacin (therapy B), and combination (therapy C); vitamins, minerals, symptomatic and comorbid therapy; and Fondaparinux used in moderate degree then described quantitatively.* ***Results****: This study obtained 47 HMR dominated by males (55%), aged 19-30 years (36%), cough symptoms (72,3%), and no comorbid status (70.2%). Favipiravir (6-7 days) is effective for mild and moderate degree in all effectiveness parameters with average length in mild degree was 6-12 days and moderate degree was 8-13 days. Possible interaction with Paracetamol was found. Most side effects were diarrhea and no significant side effects were found on liver profile (AST and ALT), glucose profile, and blood profile (leukocytes and erythrocytes).* ***Conclusions****: This result suggests that increasing collaboration of pharmacists with other healthcare in monitoring the use of Favipiravir related to interactions, uric acid, and lipid profiles, also effects in patients under 18 years, men, and elderly is important.*

ARTICLE INFO

Keywords:
Favipiravir; COVID-19; Effectiveness and Side Effects

STUDI EFEKTIFITAS DAN EFEK SAMPING TERAPI FAVIPIRAVIR PADA PASIEN COVID-19 RINGAN DAN SEDANG

ABSTRAK

Pendahuluan: Infeksi Corona Virus Disease-2019 (COVID-19) dibagi menjadi lima kriteria gejala yaitu asimtomatik, ringan, sedang, berat dan kritis. Baru-baru ini, Favipiravir dikenal sebagai antivirus off-label untuk COVID-19 yang menghambat RNA-dependent RNA polymerase (RdRp) dan diberikan secara oral 2x1600 mg sebagai dosis muatan dan 2x600 mg sebagai dosis pemeliharaan. **Metode**: Penelitian ini bersifat observasional retrospektif bertujuan untuk mengetahui efektivitas (PCR/Rapid Ag, suhu, laju pernapasan, saturasi oksigen, dan rontgen dada) dan efek samping (profil pencernaan, asam urat, hati, darah, glukosa, dan lipid) Favipiravir pada COVID-19 ringan dan sedang; yang kriteria inklusinya adalah Favipiravir (5-10 hari); kelompok antibakteri: Azitromisin (terapi A), Levofloxacin (terapi B), dan kombinasi (terapi C); vitamin, mineral, terapi simtomatik dan komorbiditas; dan Fondaparinux digunakan dalam derajat sedang kemudian dideskripsikan secara kuantitatif. **Hasil**: Pada penelitian ini didapatkan 47 RMK didominasi oleh laki-laki (55%), berusia 19-30

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tahun (36%), gejala batuk (72,3%), dan tidak ada status komorbiditas (70,2%). Favipiravir (6-7 hari) efektif untuk gejala ringan dan sedang pada semua parameter efektivitas dengan lama rata-rata gejala ringan 6-12 hari dan gejala sedang 8-13 hari. Kemungkinan interaksi dengan Parasetamol ditemukan. Efek samping terbanyak adalah diare dan tidak ditemukan efek samping yang bermakna pada profil hati (AST dan ALT), profil glukosa, dan profil darah (leukosit dan eritrosit). **Kesimpulan**: Hasil ini menunjukkan bahwa peningkatan kolaborasi apoteker dengan layanan kesehatan lain dalam memantau penggunaan Favipiravir terkait interaksi, asam urat, dan profil lipid, serta efek pada pasien di bawah 18 tahun, pria, dan lanjut usia adalah penting.

Kata kunci:
Favipiravir; COVID-19; Efektivitas dan Efek Samping

Introduction

Coronavirus infection is caused by a *Severe Acute Respiratory Syndrome Coronavirus-2* (SARS-CoV-2) transmitted through direct and indirect contact (KEMENKES, 2020). The pathogenesis of COVID-19 begins with the viral spike envelope glycoprotein binding to the *Angiotensin Converting Enzyme-2* (ACE-2) receptor (Zhang et al., 2020). According to the there (KEMENKES, 2020) are five criteria for COVID-19 symptoms: asymptomatic, mild, moderate, severe, and critical. Mild clinical manifestations include fever, cough, sore throat, nasal congestion, malaise, headache, muscle aches, immunocompromised; moderate i.e., mild pneumonia; severe i.e., severe pneumonia; Critical conditions, such as ARDS, sepsis, and septic shock.

Favipiravir is one of the effective antivirals given to mild and moderate degrees of COVID-19 to inhibit RNA-dependent RNA-polymerase (RdRp) from SARS-CoV-2 (Shannon et al., 2020). According to (Perhimpunan Dokter Paru Indonesia, 2020) Favipiravir (Avigan) was given a loading dose (2 x 1600 mg, p.o.) on day 1 and was followed by a maintenance dose (2 x 600 mg, p.o.) until day 5. According to (World Health Organization, 2020), the maximum maintenance dose is up to 14 days.

The effectiveness of Favipiravir in patients with mild and moderate COVID-19 was confirmed in a study from China conducted by (Cai, 2020) as seen by shorter viral clearance time, and better chest CT scan, and lower incidence of side effects than Lopinavir/Ritonavir. According to (James, 2020), the decrease in Favipiravir's effectiveness and the increase in its side effects are associated with the severity of COVID-19 increases. The administration of Favipiravir raises the side effects of increased uric acid, diarrhea, decreased neutrophil amount, increased transaminitis, teratogenic potential, psychoneurotic symptoms, increased triglycerides, and the presence of glucose in the urine. Favipiravir is contraindicated in use in male and elderly patients (Badan pengawas Obat dan Makanan, 2021; James, 2020). Therefore, this research was conducted by formulating a problem on the effectiveness and side effects of using Favipiravir therapy.

Which aims to determine the effectiveness of Favipiravir (PCR/Rapid Ag, temperature, respiratory rate, oxygen saturation, and chest X-ray) and the side effects of Favipiravir (digestive disorders, uric acid profile, liver, blood, glucose, and lipids) in patients with mild and moderate COVID-19 at Bhayangkara H.S Samsoeri Mertojoso Hospital, Surabaya.

Method

Design and Population

This research is an observational study. The data were obtained from medical records of COVID-19 patients at the inpatient installation of Bhayangkara H.S. Samsoeri Mertojoso Hospital, Surabaya from March 2020 to February 2021. The population of patients consisted of all patients with COVID-19 who had received Favipiravir therapy at the Inpatient Installation of Bhayangkara H.S. Samsoeri Mertojoso Hospital, Surabaya. The sampling

technique used in this research was the Time Limited Sampling method with inclusion criteria, namely patients with mild and moderate COVID-19 with or without comorbidities who had received Favipiravir for 5-10 days with the same therapy, i.e., at mild degrees, namely antiviral (Favipiravir), antibiotics 63 (Azithromycin therapy group, therapy group B (Levofloxacin), and therapy group C (a combination of Azithromycin and Levofloxacin), vitamins and minerals as well as symptomatic therapy. Whereas the patients at moderate levels were added with anticoagulants (Fondaparinux). Moreover, the exclusion criteria for medical records of patients with severe and critical-degree COVID-19 and the outpatients that had been insisted to go home were also included.

Research Instrument

The instruments include patient pharmaceutical documents, master tables, clinical data sheets, and laboratory and radiology data.

Ethical Approval

The ethical approval of this research was given by the health research ethics committee of Bhayangkara H.S Samsoeri Mertojoso Hospital, Surabaya No.04/IV/2021/KEPK/RUMKIT.

Operational Definition

1. The therapeutic group is a therapy group that was deliberately created by the researchers for data homogenizing so that the findings of the study are not biased. The therapy group is described as follows:

Mild Degree

Group therapy A	Group therapy B	Group therapy C
- Favipiravir	- Favipiravir	- Favipiravir
- Azithromycin	- Levofloxacin	-Azithromycin dan Levofloxacin
- Vitamin dan Mineral	- Vitamin dan Mineral	- Vitamin dan Mineral
- Therapy Symtomatic	- Therapy Symtomatic	- Therapy Symtomatic
- Therapy comorbid	- Therapy comorbid	- Therapy comorbid

Moderate Degree

Group therapy A	Group therapy B	Group therapy C
- Favipiravir	- Favipiravir	- Favipiravir
-Azithromycin	- Levofloxacin	-Azithromycin dan Levofloxacin
- Vitamin dan Mineral	- Vitamin dan Mineral	- Vitamin dan Mineral
- Fondaparinux	- Fondaparinux	- Fondaparinux
- Therapy Symtomatic	- Therapy Symtomatic	- Therapy Symtomatic
- Therapy comorbid	- Therapy comorbid	- Therapy comorbid

2. The profile of Favipiravir administration includes the dose, route, frequency, and duration of administration.

3. The clinical data include data related to vital signs such as blood pressure, pulse, body temperature, respiratory rate, and oxygen saturation. The laboratory data are routine laboratory data for COVID 19, such as peripheral blood, random blood sugar, SGOT/SGPT, uric acid, triglycerides, and PCR swabs. The radiological data is supporting data, including chest X-rays, while the radiological data is supporting data, including chest X-rays

Data Analysis

a. The profile of Favipiravir therapy includes dose, route, frequency, and duration of administration in patients with mild and moderate COVID-19.

b. The effectiveness of Favipiravir administration through PCR/Rapid Ag parameters, temperature, respiratory rate, oxygen saturation, and chest X-rays.

c. The side effects of Favipiravir administration through parameters of digestive disorders, uric acid profile, liver profile, complete blood profile, glucose profile, and lipid profile.

Result and Discussion

The results of the study using a retrospective method from Health Medical Record (RMK) data of COVID-19 patients at the inpatient installation of Bhayangkara Mertojoso Hospital Surabaya for the period December 2020 to February 2021 indicated that there were 174 patients with medical records and a diagnosis of COVID-19 administered with mild-moderate Favipiravir through Hospital Information System (SIRS) tracing. Of the 174 RMK patients, 47 patients met the inclusion criteria, and patients with both mild and moderate levels were divided into three therapy groups (A, B, and C).

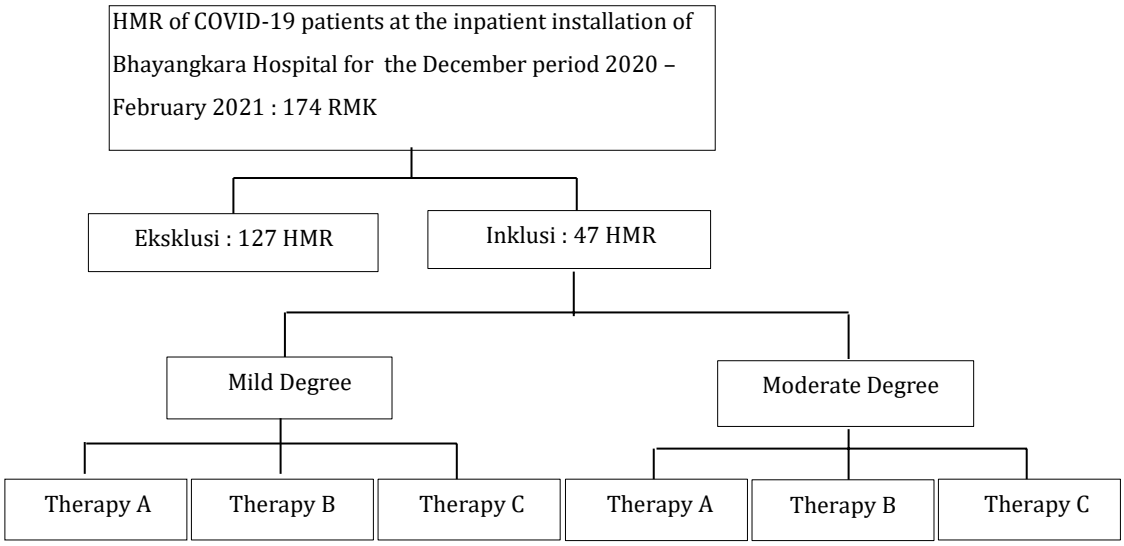

Figure 1. Schematic of Research Inclusion and Exclusion in COVID-19 Patients

Table 1. Distribution of Therapeutic Group Profiles in COVID-19 Patients

Mild degree		Moderate degree	
Therapy group	Total patients (%)	Therapy group	Total patients (%)
A	12 (50%)	A	10 (43,5%)
B	9 (35,7%)	B	7 (30,4%)
C	3 (12,5%)	C	6 (26,1%)

Table 1. Shows the difference in the number of patients in the treatment group, where the Azithromycin treatment group with antibiotics had a higher percentage than the other groups in both mild and moderate degrees. (Perhimpunan Dokter Paru Indonesia, 2020) have established therapeutic recommendations for COVID-19 from several drug classes, but in this paper, the researchers focused on the use of Favipiravir with the antibiotic group. Two antibiotics were chosen, namely Azithromycin and Levofloxacin because, according to the study conducted by (Perhimpunan Dokter Paru Indonesia, 2020)), for mild degrees, Azithromycin (1x500 mg, p.o.) is given for 5 days, while at moderate levels, Azithromycin (1x500 mg, p.o.) or iv 5-7 days or alternatively given Levofloxacin (1x750 mg, p.o.) or iv 5-7. According to the study conducted by (Poschet & Perkett, 2020) and (Scroggs et al., 2021) Azithromycin and Levofloxacin have an antiviral effect, so they were created as a therapeutic group to find out the effectiveness of their use together with Favipiravir against COVID-19 in this research

Table 2. Profile of Duration of Favipiravir Administration in Mild and Moderate COVID-19 Patients

Dose, Route, Frequency	Time of Giving (Days)	**Mild Degree**		
		Therapy A Total patients (Persentase)	**Therapy B Total patients (Persentase)**	**Therapy C Total patients (Persentase)**
loading dose (2 x 1600 mg) po H-1, *maintenance dose* (2 x 600 mg) po H2-Hn	5	3 (25%)	0 (0%)	1 (33,33%)
	6	8 (66,67%)	6 (66,67%)	2 (66,67%)
	7	1 (8,33%)	1 (11,11%)	0 (0%)
	10	0 (0%)	2 (22,22%)	0 (0%)
Dose, Route, Frequency	Time of Giving (Days)	**Moderate Degree**		
		Therapy A Total patients (Persentase)	**Therapy B Total patients (Persentase)**	**Therapy C Total patients (Persentase)**
loading dose (2 x 1600 mg) po H-1, *maintenance dose* (2 x 600 mg) po H2-Hn	5	2 (20%)	2 (28,57%)	2 (33,33%)
	6	7 (70%)	1 (14,29%)	2 (33,33%)
	7	1 (10%)	1 (14,29%)	0 (0%)
	8	0 (0%)	1 (14,29%)	0 (0%)
	9	0 (0%)	0 (0%)	1 (16,67%)
	10	0 (0%)	2 (28,57%)	1 (16,67%)

Favipiravir is a prodrug that needs to be activated first through phosphoribosylation and phosphorylation to form Favipiravir Ribufuranosyl Triphosphate which will then activate RNA-Dependent RNA-Polymerase (RDRP). Therefore, a loading dose is needed so that the desired drug concentration in the blood can be achieved and then given a maintenance dose. Recommendations for Favipiravir administration are loading dose (2 x 1600 mg, p.o.) H-1, maintenance dose (2 x 600 mg, p.o.) H2-Hn (Perhimpunan Dokter Paru Indonesia, 2020). It can be seen in both mild and moderate degrees, offering Favipiravir with a duration of administration of six days. This is in line with the rules for using Favipiavir written on the

(Clinical Practice Book Preparation, 2020) while the length of serving is up to seven days. According to (World Health Organization, 2020) the Favipiavir can be used for a maximum of 14 days in the maintenance dose, and thus, the use of Favipiravir does not exceed the WHO's recommendation. Favipiravir is safe to be administered to both comorbid and non-comorbid patients, but the use of Favipiravir in gout patients and male patients needs to have a serious caution and is not recommended for pregnant women, nursing mothers, and patients under 18 years.

In this research, inclusion criteria were taken with a maximum duration of 10 days based on a prospective, open-labeled, pilot-scale randomized study in Russia in COVID-19 patients with 60 moderate-grade where Favipiravir (2 x 1600 mg, p.o.) on the first day continued with 2 x 600 mg until day 14 or (2 x 1800 mg, p.o.) on day 1 continued with 2 x 800 mg until day 14 had a high viral clearance on day 5 (62.5% vs. 30.0 %) (p = 0.018) on day 10 (92.5 vs 80.0%) (p = 0.155) versus standard of care, i.e., Hydroxycycloroquine/Chloroquine, Lopinavir+Ritonavir, without etiotropic therapy (Ivashchenko et al., 2020). The administration of up to day 10 has a high percentage of viral clearance of 92.5% at a moderate level which describes the inclusion criteria for the duration of Favipiravir administration of 5-10 days. Also, according to the study conducted by (Murai et al., 2021), there was a report on Favipiravir induced fever in the administration of more than 10 days, indicating an allergic reaction in some cases.

The selection of inclusion criteria for up to 10 days is also supported by the study of (Chen et al., 2020) showing that Favipiravir was effective in an open-label, prospective, randomized, multicenter study in 236 adults with COVID-19 pneumonia in China, Favipiravir (2x1600 mg, p.o.) at H1, then (2x600 mg, p.o.) H2 to H7-10 days showed a greater clinical recovery rate at 7 days (61 vs. 52%) compared to umifenovir (3x200 mg, p.o.) to H7-10 days. Whereas in moderate-degree COVID-19 with pneumonia after 7 days (71% vs 56%); at a critical level after 7 days (6% vs 0%), which indicates the higher the severity of the disease, the lower the effectiveness of Favipiravir, as what has been found in the study conducted by (James, 2020).

In a study on meta-analysis conducted by (Shrestha et al., 2020) demonstrating the effectiveness and side effects of using Favipiravir in the treatment of COVID-19, the clinical deterioration of Favipiravir was less with other antivirals, although the difference was not statistically significant, and treatment with Favipiravir had substantial clinical and radiological improvement over standard therapy. Viral clearance, non-invasive oxygen or ventilation requirements, and side effects of Favipiravir were the same as that of the standard therapy group. Therefore, there have been many studies that show the effectiveness of Favipiravir, especially in patients with mild and moderate-degree COVID-19. However, the studies have not considered the role of the use of other therapies that are also used together with Favipiravir such as antibiotics, antioxidants, vitamins, and minerals which also support the effectiveness of Favipiravir in improving patient's health status, so this research specifically examines the effectiveness of Favipiravir in three groups of antibiotic therapy in accordance with The Indonesian Society of Respirology (ISR) recommendations as well as supporting therapy which also plays a key role in patient's recovery which made the results of the study unbiased and actual since it was widely applied in the field.

Table 3. Parameter Profile of Favipiravir Effectiveness in COVID-19 Patients Mild and Moderate Degrees

Parameter	Mild Degree					
	Therapy A		Therapy B		Therapy C	
	C	NC	C	NC	C	NC
PCR/ *Rapid* Ag	50% (5D)	75% (5-11 D)	100% (10 D)	100% (5-15 D)	-	100% (5-15 D)

Temperatur e	100%	100%	100%	100%	-	100%
Breathing Frequency	100%	100%	100%	100%	-	100%
Oxygen Saturation	100%	100%	100%	100%	-	100%
Thoracic Photos	50% (7 D)	77,8% (7-11 D)	100% (10 D)	100% (9-10 D)	-	100% (9-10 D)
Average Length of Treatment	Comorbid: 6-10 Day Non-Comorbid : 9-12 Day Conclusion: 6-12 Day					
Parameter	**Moderate Degree**					
	Therapy A		**Therapy B**		**Therapy C**	
	C	**NC**	**C**	**NC**	**C**	**NC**
PCR/ *Rapid* Ag	40% (8 D)	100% (5-10 D)	75% (7-11 D)	100% (7-11 D)	100% (8-17 D)	100% (9-14 D)
Temperatur e	100%	100%	100%	100%	100%	100%
Breathing Frequency	100%	100%	100%	100%	100%	100%
Oxygen Saturation	60%	60%	25%	100%	0%	75%
Thoracic Photos	40% (7-10 D)	100% (5-10 D)	67% (8-13 D)	100% (10 D)	100% (8-17 D)	75% (6-10 D)
Average Length of Treatment	Comorbid: 8-13 Day Non-Comorbid : 9-12 Day Conclusion: 8-13 Day					

Information: C (Comorbid), NC (Non-Comorbid), and D (Day: Length of Treatment)

Based on the research findings, Favipiravir provides a negative PCR/Rapid Ag change, normalization of temperature and respiratory rate, improvement of oxygen saturation, and improvement of chest X-rays in both patients with mild and moderate-degree COVID-19. This is following several studies showing that the administration of Favipiravir is effective at mild and moderate degrees so that it is used as an *Emergency Use Authorization* (EUA) in adult patients (over 18 years) with mild and moderate-degree COVID-19, as combined with supporting therapy (Badan Pengawas Obat dan Makanan, 2020). James' study (2020) also showed the effectiveness of Favipiravir decreased with increasing severity of COVID-19, which was conducted in 90% of 2158 cases in Japan, Favipiravir was used (1x1800 mg, p.o.) on the first day followed by (2x800 mg, p.o.) on the next day with a median duration of 11 days. The speed of increase in clinical effect on day 7 and day 14 in mild cases were respectively 73.8% and 87.8%, 66.6%; 84.5% in moderate cases; and 40.1% and 60.3% in severe cases. Therefore, this research is following James' study (2020) which can be seen at a mild degree of normalization of oxygen saturation reaching 100% in all therapy groups, while at a moderate degree the oxygen saturation parameter worsens, especially in patients with comorbid. Besides, if this is seen from the length of treatment (including all parameters) at mild degrees, the length of treatment ranges from 6-12 days and 8-13 days in moderate degrees.

Based on the effectiveness of Favipiravir in patients with comorbid and non-comorbid related to the average length of treatment, the effect seems faster in the former than that of the latter. This does not make Favipiravir more effective to be administered to patients with comorbid, because in this research, the comparison of the number between the patients with comorbid and the patients with non-comorbid was very high (with the probability of 3:7). It

could lead to bias to conclude, and the sample depicting comorbid patients was mostly only one patient, so they could not represent the overall results, as well as providing appropriate comorbid therapy to patients and monitoring the patients' condition. It can, in general, make the patients with comorbid have a fast recovery period since the controlled patients' condition does not worsen the COVID-19 condition even though comorbidities are one of the factors in increasing the risk of COVID-19. Also, the pharmacogenetic differences that make Favipiravir activity different in each person also show differences in the effectiveness of Favipiravir in each person as seen from the vital sign parameters, PCR/Rapid Ag, and patient chest X-rays, and differences in psychological conditions also affect the effectiveness of Favipiravir.

Each parameter in patients with comorbid and noncomorbid in table 3 indicating the mild-degree PCR/Rapid Ag parameters and the percentage of improvement in patients with non-comorbid shows the treatment group B < A < C with a length of treatment in the therapeutic group A < B < C, while the percentage of comorbid improvement in the therapy group A is less than that of the therapy group B (A < B) with a length of treatment in the therapy group A < B. The comparison between moderate PCR/Rapid Ag and the percentage of improvement in patients with non-comorbid shows that therapeutic group A = B = C with the length of stay in therapeutic group A < B < C, while the percentage improvement in comorbid shows the therapeutic group A < B < C with the length of treatment of Therapeutic group A < B < C.

The parameters of temperature and respiratory rate were normal in all treatment groups. The parameters of mild oxygen saturation show normal condition during therapy, while in the moderate degree, the percentage of improvement in patients with non-comorbid shows the treatment group A < C < B, while patients with comorbid in the treatment group C < B < A. Mild-degree chest X-ray parameters shows the percentage of improvement in patients with non-comorbid (Therapeutic group A < B = C) with the length of treatment (Therapeutic group A < C < B), while the percentage of improvement in patients with comorbid show the Therapeutic group A < B with the length of treatment in the Therapeutic group A < B. The moderate-degree chest X-rays show a percentage of improvement in patients with non-comorbid (Therapeutic group C < A = B) with the length of treatment (Therapeutic group A < C < B), while the percentage improvement in patients with comorbid (Therapeutic group A < B < C) with the length of treatment (Therapeutic group A < B < C).

Table 4. Overview of the Effectiveness Parameter Profile of Favipiravir on Mild and Moderate COVID-19 Patients

Parameter	Mild Degree			Moderate Degree		
	Therapy A	**Therapy B**	**Therapy C**	**Therapy A**	**Therapy B**	**Therapy C**
PCR/*Rapid* Ag	66,7%	66,7%	100%	70%	85,7%	100%
Temperature	100%	100%	100%	100%	100%	100%
Breathing Frequency	100%	100%	100%	100%	100%	100%
Oxygen Saturation	100%	100%	100%	66,7%	57,1%	50%
Thoracic Photos	72,7%	100%	100%	70%	80%	83,3%

The comparison of the effectiveness between the patients with mild and moderate degrees, as presented in Table 4, shows the PCR/Rapid Ag parameters, temperature, respiratory rate, oxygen saturation and chest X-ray at mild degrees respectively as follows: therapy A (66.7%, 100 %, 100%, 100%, and 72.7%), therapy B (66.7%, 100%, 100%, 100%, and 100%), and

therapy C (100%, 100%, 100%, 100%, and 100%) with the average length of parameter of 6-12 days, while at moderate levels respectively as follows: therapy A (70%, 100%, 100%, 66.7%, and 70%), therapy B (85.7%, 100%, 100%, 57.1%, and 80%), and therapy C (100%, 100%, 100%, 50%, and 83.3%) with the average length of parameter 8-13 days. Therefore, Favipiravir is effective for patients with mild and moderate COVID-19, with or without comorbidities, and the effectiveness of Favipiravir decreases as the severity of COVID-19 increases, with the duration of effectiveness of each individual varies due to pharmacogenetic differences.

Side Effects Profile on the Use of Favipiravir

(1) Uric Acid Profile, Lipid Profile, and Male Fertility

Favipiravir has a side effect of increasing the uric acid profile with an incidence of 4.79%, while Favipiravir and Favipiravir hydroxide (M1) affect the absorption from standard substrates through the action of *Human Organic Anion Transporter-1* (hOAT1), *Human Organic Anion Transporter-3* (hOAT3), and *Human Urate Transporter-1* (hURAT1). Favipiravir inhibits the absorption of uric acid through the expression mechanism of hURAT1 (concentration-dependent manner), while M1 will practically increase its absorption (BPOM, 2020 and Toyama Chemical, 2014). Favipiravir has a side effect of increasing triglycerides with an incidence of 1%. In animal testing, there was an effect of urinary retention in the bladder which causes edema, which then causes circulatory disorders resulting in death. The side effects of increased triglycerides were also found in living animals given a dose of 200 mg/kg/day (Badan pengawas Obat dan Makanan, 2021; Toyama, 2014). However, in this research, both the side effects of increasing uric acid and triglycerides could not be seen since the patients did not have laboratory data regarding uric acid and triglyceride profiles.

The Favipiravir should carefully be administered in men because it is distributed in sperm and affects male fertility, so it is recommended to use the most effective contraceptive method in sexual intercourse during treatment and for seven days after treatment (condoms) and not to have sex with pregnant women (Badan pengawas Obat dan Makanan, 2021). The effect of Favipiravir on male reproductive function is generally indicated by a decrease in sperm motility rate, a decrease in sperm vitality, and an increase in the incidence of morphological defects at doses of 60 mg/kg/day where this effect is reversible. Also, the dose of Favipiravir that did not cause these side effects was 20 mg/kg/day (Toyama, 2014)

(1) Gastrointestinal Profile

Table 5. Profile of Gastrointestinal Effects on the Use of Favipiravir

Profile Gastrointestinal	
Health Status	**Total Pasients (Persentase)**
• Normal	30 (63,8%)
• Abnomal	17 (36,2%)
- Nausea	3 (6,4%)
- Nausea and vomiting	2 (4,3%)
- Abdomen pain	1 (2,1%)
- Heart burn	1 (2,1%)
(3)Diarrhea	7 (14,9%)
(4)Nausea + Heart burn	1 (2,1%)
(5) Nausea + Abdomen Pain	2 (4,3%)

Table 5. Shows the gastrointestinal profile of patients administered with Favipiravir with the percentage of effects that mostly occur, namely diarrhea. However, the side effects of

gastrointestinal disturbances only come from Favipiravir could be confirmed in this research. It might also be due to other drugs (polypharmacy use), but to minimize the bias, side effect analysis was not differentiated by treatment group to generalize that all patients receiving Favipiravir experience gastrointestinal side effects. Meanwhile, to distinguish whether the side effects are caused by COVID-19 or not, it was then analyzed if the patients had gastrointestinal disturbances at the beginning of the symptom and if there were no complaints during the therapy. The patients were given a therapeutic agent according to the indication with the duration of administration for or exceeding the administration of Favipiravir for overcoming the gastrointestinal side effects that may be caused by the administration of Favipiravir. This finding is in line with what has been written by the (Badan Pengawas Obat dan Makanan, 2020) that Favipiravir has gastrointestinal side effects, namely diarrhea, with an incidence of 4.79%; nausea, vomiting, and abdominal pain with an incidence of 0.5 - <1% as well as based on the clinical trial phase III on Favipiravir for influenza versus Oseltamivir. Favipiravir was administered orally for five days at a dose of 1200 mg (first dose) and 400 mg (second dose). On day 1, and then from day 2 to day 5 at 400 mg BID, the clinical trials were conducted on 762 Japanese (540 subjects, 140 Taiwanese subjects, and 82 Korean subjects) with the following findings: (Toyama, 2014)

Adverse events and/or adverse drug reactions reported by ≥2% of subjects in either group

System organ class	Preferred term	Adverse events		Adverse drug reactions	
		Favipiravir group (n = 378)	Oseltamivir phosphate group (n = 380)	Favipiravir group (n = 378)	Oseltamivir phosphate group (n = 380)
Gastrointestinal disorders	Diarrhoea	24 (6.3)	23 (6.1)	16 (4.2)	20 (5.3)
	Vomiting	2 (0.5)	10 (2.6)	1 (0.3)	7 (1.8)
	Nausea	3 (0.8)	9 (2.4)	3 (0.8)	8 (2.1)

Number of subjects with the event/reaction (%)

Figure 2. Side Effects of Gastrointestinal Disorders from the Results of Favipiravir Clinical Trial Phase III – Influenza (Toyama Chemical, 2014)

Based on the findings from the (Badan pengawas Obat dan Makanan, 2021) about the side effects, adverse events, and adverse drug reactions as shown by the study conducted by (Toyama, 2014) Favipiravir has a significant effect on potential gastrointestinal disturbances, such as diarrhea, nausea, and vomiting. The effect of Favipiravir on the gastrointestinal tract in this research was not significant and had been addressed by administering therapy to the patients.

Table 6. Liver, Glucose and Blood Profile Using Favipiravir

Side Effect Profile (Liver Profile, Glucose Profile, Blood Profile)				
The Side Effects	**Parameter**	**Total pasient**	**Total presentase**	**Increase/ Decrease Parameter (%)**
Peningkatan Enzim hati (Transaminase)	SGOT	8	19%	90%
	SGPT	16	38,1%	88,37%
Profile Glucose Abnormalities	RBS	3	8,1%	69,1%
Decreasing Number of Profiles Blood	Leukosit	0	0%	0%
	Eritrosit	0	0%	0%

Description: Increase and decrease in side parameters compared to the value of normal limits for each parameter (SGOT: 5-40 U/L, SGPT: 5-35 U/L, RBS : < 180 mg/dL, Leukocytes : 4000-1000/uL, and Erythrocytes : (L) 4.5-6 x 106 /uL and (P) 4.0-5.5 x 106 /uL)

Table 6. Shows the liver, glucose, and blood profiles in patients administered with Favipiravir. However, in this research, it was not confirmed that the side effects of increased transaminase enzymes, abnormal glucose profiles, and the decreased amount of leukocyte and erythrocyte only come from Favipiravir. Still, it might also be caused by other drugs (polypharmacy use). However, to minimize the bias, the side effect analysis was not differentiated by the treatment group to generalize that all patients receiving Favipiravir experienced adverse effects on the liver profile, glucose profile, and complete blood profile.

The side effects of Favipiravir on the liver profile can be indicated from the increase in the enzyme parameters of SGOT and SGPT above normal limits with incidence rates of 19% and 38.1%, respectively, and the percentage increased in SGOT by 90% and the percentage increased in SGPT by 8.37%. The side effects on the liver profile are not only caused by the use of Favipiravir but also due to the use of polypharmacy (the effects of other drugs that also cause an increase in SGOT and SGPT), or maybe possible due to interactions with the use of other drugs. This finding is in line with has been written in the (Badan Pengawas Obat dan Makanan, 2020) that Favipiravir has a side effect of increasing SGOT and SGPT with an incidence of 1%, and based on oral testing on cynomolgus monkeys at a dose of 0 (solvent, 0.5% methylcellulose solution), 100, 200, or 300 mg/kg/day BID for two weeks. The finding in the 300 mg/kg/day group showed an increase in AST and ALT and a decrease in albumin as well as an increase in liver weight and vacuolization (Toyama, 2014).

The side effects of Favipiravir on the glucose profile can be seen from the increase in Random Blood Sugar (RBS) parameters above normal limits with an incidence rate of 8.1%, and the percentage increase in RBS by 69.1%. The side effects on the glucose profile are not only caused by the use of Favipiravir but also due to the use of polypharmacy (the effect of other drugs that also cause an increase in glucose), or maybe due to interactions with the use of other drugs. This finding is in line with what has been written in the (Badan Pengawas Obat dan Makanan, 2020) that Favipiravir has a side effect in the form of the presence of glucose in urine with an incidence of 0.5 - 1%. This is possible due to high blood sugar levels which can be indicated by RBS parameters. Meanwhile, oral testing in cynomolgus monkeys given a dose of 0 (solvent, 0.5% methylcellulose solution), 100, 200, or 300 mg/kg/day BID for 2 weeks at 300 mg/kg/day group, shows a decrease in blood sugar, in another study in adolescent beagles (8 weeks of age) administered with oral BID Favipiravir at a dose of 0 (gelatin capsule), 15, 30, 60, or 100 mg/kg/ day for 1 month. The findings in the 60 mg/kg/day group at the end of the treatment period showed an increase in blood glucose (Toyama, 2014). Based on the findings of this research and the findings of side effects at the (Badan Pengawas Obat dan Makanan, 2020) and (Toyama, 2014) Favipiravir affects glucose abnormalities, especially increasing blood glucose. While the literature related to the percentage increase in RBS has not been found.

Favipiravir did not show significant side effects on the leukocyte and erythrocyte profiles. Moreover, there was no decrease in leukocytes and erythrocytes beyond normal limits on the blood profile and there was only a slight decrease in the value of leukocytes and erythrocytes in the patients, but it was still within normal limits. This finding is in line with what has been written by the (Badan Pengawas Obat dan Makanan, 2020) that Favipiravir has side effects, such that is a decrease in leukocytes and neutrophils with a small incidence of 1%. Therefore, it is in line with the results of this research which did not find any side effects of reducing leukocytes since this research used few samples. Meanwhile, clinical testing phase II of Favipiravir-Influenza in a parallel, active-controlled, double-blind group was conducted in 75 locations in Japan with a sample of 144 subjects (n = 40 per group with an age range of 45-64 years). The Favipiravir was administered p.o. five days in the high-dose group, 600 mg BID on Day 1 and then 600 mg QD from day 2 to day 5; and low-dose group, 400 mg BID on Days 1 and 2 and then 400 mg QD from Days 3 to 5. In the oseltamivir phosphate group, the

oseltamivir should have been administered in the form of an oral drug at 75 mg BID for five days and the findings were obtained (Toyama, 2014) as follows:

Adverse events and/or adverse drug reactions reported by ≥2% of subjects in any group

System organ class	Preferred term	Adverse events			Adverse drug reactions		
		High-dose group (n = 55)	Low-dose group (n = 52)	Oseltamivir phosphate group (n = 53)	High-dose group (n = 55)	Low-dose group (n = 52)	Oseltamivir phosphate group (n = 53)
Investigations	Neutrophil count decreased	3 (5.5)	4 (7.7)	2 (3.8)	3 (5.5)	1 (1.9)	0 (0.0)
	AST increased	2 (3.6)	0 (0.0)	1 (1.9)	2 (3.6)	0 (0.0)	1 (1.9)

Number of subjects with the event/reaction (%)

Figure 3. Side Effects of Neutrophil Decrease in Phase II Clinical Trials Favipiravir – Influenza (Toyama, 2014)

The decrease in RBC, Ht, Hb, or reticulocyte amount or decrease in myelopoiesis observed in repeated dose toxicity studies do not reflect the direct effect of Favipiravir on hematopoietic tissue, but there may be secondary changes associated with worsening clinical conditions.

Conclusion: Favipiravir (loading dose of 2 x 1600 mg, p.o.) of H-1 followed by a maintenance dose (2 x 600 mg, p.o.) of H2-Hn in therapy groups A, B, and C for 6-7 days effectively showed improvement in parameters PCR/Rapid Ag, temperature, respiratory rate, oxygen saturation and chest X-rays in patients with mild COVID-19 (6-12 days of treatment) and moderate degrees (8-13 days of treatment). Most of the side effects of Favipiravir on the gastrointestinal tract were diarrhea and no significant side effects were found on the parameters of the liver profile (SGOT and SGPT), glucose profile (RBS), and blood profile (leukocytes and erythrocytes).

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