Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
Pharmacy and Pharmaceutical Sciences Journal
Published by Faculty of Pharmacy Universitas Airlangga
OPEN ACCESS
E-ISSN 2580-8303
P-ISSN 2406-9388

Jurnal Farmasi dan Ilmu Kefarmasian Indonesia Vol. 9 No. 3 December 2022, 209-219
DOI: 10.20473/jfiki.v9i32022.209-219
Available online at https://e-journal.unair.ac.id/JFIKI/

Isoprinosine along with Favipiravir or Oseltamivir in Patients with Moderate Covid-19 at RSD Dr. Soebandi Jember

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Submitted: 12 February 2022
Accepted: 23 March 2022
Published: 9 December 2022

Abstract

Background*: Isoprinosine is an immunomodulator that is now being used to treat Covid-19 patients.* ***Objectives****: To evaluate Isoprinosine with Favipiravir or Oseltamivir in moderate Covid-19.* ***Methods****: In a retrospective observational analysis, in-hospital moderate Covid-19 patients treated between June 2020 and June 2021 were included.* ***Results****: Inclusion criteria for 364 patients were met, with 135 receiving Favipiravir-Isoprinosine (Group 1) and 229 receiving Oseltamivir-Isoprinosine (Group 2). In group 1, the majority of patients (58.50%) were female (35.60%), had no comorbidities (71.60%), were discharged with a positive PCR (74.80%), did not require a breathing apparatus (99.26%), had leukocyte levels between 4,5-11,0 (82.22%), lymphocyte levels between 25-33 (34.07%), and were discharged with no ground-glass opacity (34.07%) (54.10%), LOS was 9-13 days (50.37%), while the mortality rate was 0.70%. In group 2, the majority of patients were male (54.10%), with the highest age range being 42-56 years (35.80%), without comorbidities (69.0%), discharged with a positive PCR (72.50 %), and without the need for a breathing apparatus (99.13%), with leukocyte levels ranging from 4.5 – 11.0 (81.22 %), with lymphocyte levels ranging from 25.0 – 33.0 (26.20 %), and were discharged with no ground-glass opacity (49.34 %), LOS was 9 - 13 days (34.06 %), and the mortality rate was 0.87%.****Conclusion****: In this trial, it was determined that combining isoprinosine with antivirals favipiravir or Oseltamivir could produce significant clinical improvement.*

Keywords*: isoprinosine, covid-19, moderate, immunomodulator*

How to cite this article:
Maryska, C., Hasmono, D., Baisuni, S. D., Hidayatiningsih, A. N., Puspitasari, A. D., Puspitarini, R. D. & Suprapti, B. (2022). Isoprinosine along with Favipiravir or Oseltamivir in Patients with Moderate Covid-19 at RSD Dr. Soebandi Jember. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, 9(3), 209-219. http://doi.org/10.20473/jfiki.v9i32022.209-219

P-ISSN: 2406-9388
E-ISSN: 2580-8303

INTRODUCTION

From March 2020 to the present, a virus has caused a global pandemic. SARS-CoV-2 is the virus, and the World Health Organization has named the disease coronavirus disease 2019 (Covid-19) (WHO) (Yuki *et al*., 2020). The first case in Indonesia was discovered in March 2020, consisting of two individuals, and the second case was discovered on March 6, 2020, consisting of two individuals. Thus far, Covid-19 cases have continued to rise (Burhan *et al.*, 2020). Coronavirus is a virus with a single-stranded RNA genome isolated from various animal species. The number of cases continues to grow over time, confirming that this virus can be transmitted from human to human (Burhan *et al.*, 2020).

Covid-19 is an infectious disease that primarily affects respiratory and other organs. Covid-19's clinical manifestations and severity vary considerably. Asymptomatic, mild, moderate, severe, and critical were used to classify the severity. As is the case with infectious diseases in general, the immune system plays a crucial role in the fight against viruses (Yazdanpanah *et al*., 2020). SARS-CoV-2 can suppress the host immune system by inducing programmed cell death (apoptosis) (Mortaz *et al.*, 2020).

Numerous drugs, including lopinavir-ritonavir, remdesivir, hydroxychloroquine, and Azithromycin, have been tested in clinical trials to treat Covid-19 and be curative. Additional numerous medicines are undergoing clinical trials to determine whether they can be used as a definitive or adjunctive therapy (Yuki *et al*., 2020). PDPI (Perhimpunan Dokter Paru Indonesia-Indonesian pulmonary doctors association) has established guidelines for managing Covid-19 patients with varying degrees of severity in Indonesia. It has been updated several times in response to scientific advances (Burhan *et al.*, 2020). Favipiravir, Oseltamivir, and remdesivir are currently available and widely used antivirals for Covid-19 patients. However, this study is limited to favipiravir and Oseltamivir.

Favipiravir is an antiviral prodrug. Intracellularly, favipiravir is ribosylated and phosphorylated to form the active form, favipiravir ribofuranosyl-5-triphosphate (favipiravirRTP) (Instiaty *et al.*, 2020). Favipiravir's mechanism of action as a selective inhibitor of RNA-dependent RNA polymerase (RdRp) from SARS-CoV-2, where the RdRp in SARS-CoV-2 is tenfold more active than that in other viruses (Shannon *et al.*, 2020). FavipiravirRTP inhibits the RdRp virus by binding to it and inhibiting viral genome transcription and replication (Instiaty *et al.*, 2020). Thus, favipiravir can be used as an antiviral in treating Covid-19.

Oseltamivir is available in oseltamivir phosphate, a prodrug metabolized by plasma and hepatic esterase to oseltamivir carboxylate, the active form. Oseltamivir is approved for influenza A and B treatment and prevention and is available in oral formulations. After the replication cycle, influenza viruses require the enzyme neuraminidase to generate new viruses from infected cells. The active metabolite of Oseltamivir, oseltamivir carboxylate, interacts with neuraminidase, altering its conformation and inhibiting its activity. Inhibiting neuraminidase causes viral aggregation on the cell surface, reducing virus spread in the respiratory tract. Oseltamivir is in vitro activity against SARS-CoV-2 is unknown. In contrast to influenza, coronavirus lacks neuraminidase. Oseltamivir was used as an empirical therapy during the Covid-19 pandemic in China before the identification of a causative agent of the SARS-CoV-2 virus and because the pandemic occurred during the influenza season in China (Instiaty *et al.*, 2020)

Immunomodulators are also used in patients with Covid-19. Isoprinosine is an immunomodulator used in patients with Covid-19 (Dluholucky, 2020). Isoprinosine, also known as Inosine Pranobex or Methisoprinol, is a synthetic purine derivative with immunomodulatory and antiviral properties. Based on in vivo studies, it is known that the use of isoprinosine results in an increase in immunity or immunityIsoprinosine enhances immunity by stimulating T lymphocyte differentiation into cytotoxic T cells and T helper cells and increasing lymphokine production. Additionally, isoprinosine enhances the natural killer function of cells. Isoprinosine boosts humoral immunity by stimulating B lymphocyte differentiation into plasma cells, increasing antibody production. It increases the IgG and complement surface markers, and enhances the chemotaxis and phagocytosis of neutrophils, monocytes, and macrophages (Petrova *et al.*, 2010). Numerous studies have demonstrated that administering isoprinosine as adjuvant therapy may benefit specific subgroups of patients, particularly those who frequently experience immune dysfunction due to viral infections (Lasek *et al.*, 2015). According to a study conducted in nursing homes in the Czech Republic, the case fatality rate was significantly reduced by up to 11.9 percent, with an odds ratio (OR) of 2.8 (Beran *et al.*, 2020)

There is a dearth of research on the antiviral and Isoprinosine effects of Covid-19. Hence, this study

P-ISSN: 2406-9388
E-ISSN: 2580-8303

evaluates Isoprinosine with Favipiravir or Oseltamivir in moderate Covid-19.

MATERIALS AND METHODS

Materials

Study design

This retrospective observational study used medical records from patients with moderate Covid-19 at the RSD dr. Soebandi Teaching Hospital in Jember. It took place between June 2020 and June 2021.

Study population and setting

This study enrolled adolescent (12 years), adult, and elderly patients with a moderate diagnosis of Covid-19 who were hospitalized at RSD dr. Soebandi.

Data source and data extraction

This study analyzed data from 13 months of medical records (June 2020 – June 2021) with a time-limited sampling. The Faculty of Pharmacy at Universitas Airlangga has approved this study ethically. The demographic information about the patient, the medication, the laboratory data, the clinical data, the PCR test, the Photo Thorax, the length of stay, and the death rate were all collected. Gender, age, residence, and comorbidities are all included in demographic profiles. Medication data are records of medications prescribed to patients while undergoing treatment at the hospital. Laboratories data includes leukocyte and lymphocyte counts. Clinical data are records of patients' oxygen demand levels, which are classified as mild (1 – 6 lpm), moderate (7 – 10 lpm), or severe (11 – 15 lpm). Patients receiving isoprinosine therapy, the standard treatment for moderate Covid-19 patients, adolescent patients, adult patients, and older adults, were included in this study.

Tools

The data collection process was documented in Microsoft Excel spreadsheets. Patient identifiers have been used in place of initials to maintain patient confidentiality. A total of 364 patients were sampled. The data analysis was then presented in a table.

Statistical examination

In this study, both parametric and non-parametric statistical tests were used.

RESULTS AND DISCUSSION

Descriptive analysis

All data were subjected to descriptive analysis. A therapy group then classified the data. Group 1 comprises patients who are receiving treatment with Favipiravir – Isoprinosine. While Group 2 contains patients who received Oseltamivir – Isoprinosine therapy. The analysis of the description yielded the conclusions that can be seen in Table 1.

Based on the data in Table 1, It is known that the majority of members of group 1 are female (58.50%), the majority are between the ages of 18-60 years (88.89%), and the majority are free of comorbidities (71.60%). Meanwhile, in group 2, the majority of participants were male (54.10%), the median age range was 18-60 years (85.59%), and the majority did not have any comorbidities (69.00%).

A descriptive analysis of clinical data, laboratory data, supporting examination data, LOS data, and patient mortality rates were also carried out. Table 2 summarizes the analysis's findings.

As shown in Table 2, KRS patients with clinical conditions in groups 1 and 2 do not require oxygen. Prior to receiving combination therapy, most patients in both groups had an oxygen demand of 1-6 lpm.

Table 1. The use of isoprinosine in combination with antivirals in the treatment of patients with moderate Covid-19

Characteristics		Favipiravir-Isoprinosine Combination	Oseltamivir-Isoprinosine Combination
Gender	Man	56 (41.50%)	124 (54.10%)
	Woman	79 (58.50%)	105 (45.90%)
Age	12 - 17	5 (3.70%)	4 (1.75%)
	18 - 60	120 (88.89%)	196 (85.59%)
	> 60	10 (7.41%)	29 (12.66%)
	Mean ± SD	39.6 ± 12.92	42.00 ± 14.14
Comorbid	No Comorbid	91 (71.60%)	147 (69.00%)
	Hypertension	25 (19.70%)	34 (16.00%)
	Diabetes Mellitus	11 (8.70%)	32 (15.00%)

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Table 2. Clinical data on isoprinosine in combination with favipiravir or oseltamivir

Characteristics			Favipiravir-Isoprinosine Combination	Oseltamivir-Isoprinosine Combination
Oxygen Consumption Level	Pre	Mild	69 (51.10%)	151 (66.00%)
		Moderate	49 (36.30%)	55 (24.00%)
		Severe	17 (12.60%)	23 (10.00%)
	Post	No Requirement for Oxygen	134 (99.26%)	227 (99.13%)

Table 3. Laboratory data on isoprinosine in combination with favipiravir or oseltamivir

Characteristics			Favipiravir-Isoprinosine Combination	Oseltamivir-Isoprinosine Combination
Leukocytes	Pre	< 4.5	13 (9.63%)	18 (7.86%)
		4.5 – 11.0	104 (77.04%)	177 (77.29%)
		>11.0	18 (13.33%)	34 (14.58%)
		mean ± SD	mean 7.50 ± 3.35	mean 7.85 ± 3.69
	Post	< 4.5	6 (4.45%)	4 (1.75%)
		4.5 – 11.0	111 (82.22%)	186 (81.22%)
		>11.0	18 (13.33%)	39 (17.03%)
		mean ± SD	mean 8.52 ± 3.66	mean 8.90 ± 3.75
Lymphocytes	Pre	< 25.00	86 (63.70%)	141 (61.57%)
		25.00 – 33.00	25 (18.52%)	50 (21.83%)
		>33.00	24 (17.78%)	38 (16.60%)
		mean ± SD	mean 22.72 ± 11.51	mean 22.19 ± 10.76
	Post	< 25.00	52 (38.52%)	109 (47.60%)
		25.00 – 33.00	46 (34.07%)	60 (26.20%)
		>33.00	37 (27.41%)	60 (26.20%)
		mean ± SD	mean 27.10 ± 9.84	mean 25.79 ± 11.34

According to Table 3, leukocyte levels in group 1 were between 4.5 -11.0 (82.22%), and lymphocyte levels were between 25.0-33.0. (34.07%). Meanwhile, in group 2, the leukocyte count was between 4.5 - 11.0 (81.22%), and the lymphocyte count was between 25.0 - 33.0 (26.2%). Normal leukocytes and lymphocytes levels increased in both combinations before and after the patient received therapy.

According to Table 4, the LOS for group 1 was between 9 and 13 days (50.3%), and the percentage of patients who died was 0.70%. While in group 2, the median LOS was 9 - 13 days (34.0%), and the mortality rate was 0.87%.

In Table 5, it is stated that in group 1, patients discharged with positive PCR (74.80%) and no infiltrates on chest X-rays were included (54.10%). In group 2, patients discharged with a positive PCR (72.50%) and no infiltrates on chest X-rays were included (49.34%). Following treatment, the number of patients developing pneumonia decreased significantly in the two combination groups. Similarly, the number of patients with positive PCR results decreased in both combination groups.

Parametric difference tests were performed on data with interval or ratio types, such as leukocyte counts, lymphocyte counts, and patient length of stay. The parametric difference test was also performed on normally distributed and homogeneous data. The Paired t-test was used to determine the parametric difference in this study. The non-parametric difference test can be used with data that are not normally distributed or homogeneous; it can also be used with ordinal or interval/ratio scales. The Wilcoxon test is used to determine non-parametric differences in this study. If the p-value for the paired t-test or Wilcoxon test is less than 0.05, the test is considered significant. Because there is no data prior to and following the procedure, the LOS variable and the patient's mortality rate cannot be tested independently. Table 6 contains the results of statistical tests conducted in this study.

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Table 4. Characteristics of LOS data and mortality rates in isoprinosine-favipiravir- or oseltamivir-combination

Characteristics		Favipiravir-Isoprinosine Combination	Oseltamivir-Isoprinosine Combination
Length of Stay	< 9 hari	3 (2.22%)	10 (4.37%)
	9 - 13 hari	68 (50.37%)	78 (34.06%)
	> 13 hari	64 (47.41%)	141 (61.57%)
	mean ± SD	mean 13.0 ± 3.27	mean 17.22 ± 11.45
Death		1 (0.70%)	2 (0.87%)

Table 5. Other test data characteristics of isoprinosine in combination with favipiravir or oseltamivir

Characteristics			Favipiravir-Isoprinosine Combination	Oseltamivir-Isoprinosine Combination
PCR	Pre	Positive	135 (100%)	229 (100%)
	Post	Positive	101 (74.80%)	166 (72.50%)
		Negative	34 (25.50%)	63 (27.50%)
chest photograph	Pre	Pneumonia	87 (64.40%)	159 (69.43%)
		No Ground Glass Opacity	48 (35.60%)	70 (30.57%)
	Post	Pneumonia	62 (45.90%)	116 (50.66%)
		No Ground Glass Opacity	73 (54.10%)	113 (49.34%)

When a patient is hospitalized for a suspected infection, isoprinosine is given. After confirming the diagnosis of Covid-19 with two PCR tests, isoprinosine was discontinued, and standard Covid-19 therapy was initiated according to the applicable Clinical Pathway at RSD dr. Soebandi. The standard therapy is Azithromycin iv 1 x 500 mg, Oseltamivir po 2 x 75 mg (for 7-14 days)/Lopinavir 400 mg-Ritonavir 100 mg p.o 2 x 2 tabs for 7-14 days/Favipiravir p.o loading dose of 2 x 1600 mg (first day) and then 2 x 600 mg on days 2 - 5, Vitamin C p.o 1 x 500 mg, and other medications as indicated by the patients. After antiviral therapy was completed, Isoprinosine was continued; it was given on day six following favipiravir in group 1 and on day eight following favipiravir in group 2. There was no group of patients receiving Lopinavir/Ritonavir in this study. Lopinavir/Ritonavir was used in several Covid-19 patients at dr. Soebandi, but the government has made the case that the antiviral should be reserved for HIV patients only.

As is the case with infectious diseases in general, the immune system plays a critical role in the fight against viruses (Yazdanpanah *et al*., 2020). SARS-CoV-2, on the other hand, can impair the host immune system by suppressing T cell function and inducing programmed cell death (apoptosis) (Mortaz *et al.*, 2020). Thus, immunomodulatory agents may be considered in the treatment of Covid-19 patients. Isoprinosine is one of the immunomodulators currently being used in Covid-19 patients.

The study included 760 medical records of moderate Covid-19 patients as a total sample. Nevertheless, only 364 medical records met the criteria for inclusion. The following parameters were examined in this study: supporting data in the form of PCR and thorax photograph; laboratory data in the form of leukocyte and lymphocyte; clinical data from patients in the form of oxygen demand level; length of stay patient mortality.

Gender is recognized as a significant factor in the epidemiology of various diseases. This also holds for Covid-19. According to studies conducted in China and Europe, men die at a higher rate from Covid-19 infection than women and are independently associated with poor Covid-19 disease progression. This is because women and men have different immune responses. Additionally, male-specific behaviours such as smoking, drinking alcohol, or consuming alcoholic beverages increase the risk of death from Covid-19 (Vahidy *et al.*, 2021). Women are predisposed to autoimmune diseases, whereas men are predisposed to infectious diseases. Acceptable explanations include the X chromosome's protection and the female hormone estrogen. Estrogen is known to have the potential to mitigate the severity of SARS-CoV-2 infection. Several studies indicated that women had superior anti-inflammatory, antiviral, and humoral system responses during the infection process compared to men. It is well-established that testosterone can impair a man's response to vaccines (Ciarambino *et al.*, 2021). The majority of sexes in group 1 were female, while most in group 2 were male.

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Table 6. Analysis of variables with dependent variables

No.	Variable	Different Test	Test Type	Significance	Sig. of Favipiravir and Isoprinosine in Combination	Sig. of Oseltamivir and Isoprinosine in Combination
1.	PCR	Non-Parametric	Wilcoxon	p-value < 0.05	0.000	0.000
2.	Oxygen Consumption Level	Non-Parametric	Wilcoxon	p-value < 0.05	0.000	0.000
3.	Leukocytes	Non-Parametric	Wilcoxon	p-value < 0.05	0.010	0.000
4.	Lymphocytes correlation coefficient	Parametric	Paired t-test	p-value < 0.05	0.000 0.318	0.000 0.520
5.	chest photograph	Non-Parametric	Wilcoxon	p-value < 0.05	0.000	0.000
6.	LOS	-	-	-	-	
7.	Death	-	-	-	-	

In contrast to numerous previous studies, the number of male patients infected with Covid-19 is significantly greater than that of female patients. This could have occurred due to the study's focus on moderate Covid-19 patients. Consequences of men's vulnerability to disease worsening severe or critical disease. This, however, requires additional research.

In this study, the average age of patients with moderate COVID-19 infection was 42 years, with a range of 12-81 years and a standard deviation of 14. In general, increasing age is associated with increasing the severity of Covid-19. Children are generally less susceptible to Covid-19 due to the still-functioning general system and lack of exposure to the surrounding environment during the Pandemic (Davies *et al.*, 2020). A study conducted in Italy shows that higher age is one of the independent factors associated with the risk of death (Aksel *et al.*, 2021). Another study confirmed that Covid-19 patients aged 50 years were 15.4 times more likely to die than confirmed Covid-19 patients aged 50 years (Biswas *et al.*, 2021).

Comorbidity is a predictor of Covid-19 patient progression. The percentage of samples without comorbidities was highest in both groups, namely group 1 (71.60%) and group 2 (69.00%). In group 1, hypertension was the most prevalent comorbidity (19.70%), while in group 2, hypertension was the least prevalent (16.00%). Diabetes Mellitus is the most common comorbid condition, with a percentage of 8.70% in group 1 in group 2 15.00%. Age and pre-existing comorbidities such as hypertension, diabetes, obesity, heart disease, chronic kidney disease, and liver disease worsen Covid-19 progression. According to studies conducted in China, North America, and Europe, the patient's age and comorbidities influence the mortality rates associated with worsening Covid-19 progression (Surendra *et al.*, 2021). This is based on existing research data, which indicates that group 1 has a mortality rate of 0.7% and group 2 has a mortality rate of 0.87%. According to a study, the mortality rate at age 15 is 0.6%, at age 50 is 39.5%, and at all age groups is 6% (Beran *et al.*, 2021).

All patients in this study had been discharge in a non-oxygen-requiring state, with the highest percentages in group 1 (96.26%) and group 2 (96.26 percent) (99.13%). No studies demonstrate Oseltamivir's efficacy in reducing the need for breathing apparatus in Covid-19 patients. According to one systematic review study, there is no evidence that favipiravir can reduce patients' need for breathing apparatus (Özlüşen *et al.*, 2021). However, Hassanipour et al. found a clinically significant improvement in oxygen demand between the favipiravir and the control groups 7 days after hospitalization (RR = 1.24, 95 percent CI = 1.09-1.41; P = 0.001). After 14 days of hospitalization, viral clearance occurred in the favipiravir group but was not statistically significant (RR = 1.11, 95 percent CI = 0.98-1.25; P = 0.0094). The favipiravir group had a 7% lower oxygen demand than the control group (RR = 0.93, 95% CI = 0.67-1.28; P = 0.664). The WHO recommends oxygen therapy for patients with respiratory distress, hypoxemia, or shock with a target SpO2 of greater than 94%. The favipiravir group had a 7% lower oxygen demand than the control group (RR = 0.93, 95% CI = 0.67-1.28; P = 0.664). Appropriate oxygen therapy allows for increased oxygenation of thickened and inflamed lung tissue, effectively treating hypoxemia (Long *et al.*, 2021). Shortness of breath is caused by SARS-CoV-2-mediated mitochondrial

P-ISSN: 2406-9388
E-ISSN: 2580-8303

damage in smooth muscle cells of the pulmonary arteries, resulting in impaired pulmonary hypoxic vasoconstriction (Shianata *et al*., 2021). Isoprinosine is administered following antiviral therapy, hoping the virus-cleansing process will be accelerated by boosting the body's immune system. Although there is no literature directly related to the level of patient oxygen demand, the KRS profile of patients who no longer require oxygen is one of the clinical conditions that can describe a patient's lung function improvement.

The significance of groups 1 (0.010) and 2 (0.000) is well established. On this basis, it can be concluded that each combination results in a difference in leukocyte levels prior to and following therapy, both in group 1 and group 2. The normal leukocyte count ranges from 4.5 to 11.0 in RSD dr. Soebandi. According to existing clinical reports, there are changes in the leukocyte portion of the circulation in patients with mild and severe degrees. These changes can take the form of values falling below or exceeding normal levels (Wang *et al.,* 2020). Between before and after therapy, the percentage of patients with normal leukocyte counts increases.

The combination of Isoprinosine Favipiravir and Isoprinosine Oseltamivir is known to have a significant value of 0.000. Thus, it can be concluded that each combination results in differences in lymphocyte levels prior to and following treatment with Isoprinosine Favipiravir and Isoprinosine Oseltamivir. The correlation values for each combination must be compared to determine which combination has a greater effect on the patient's lymphocyte levels. The correlation coefficient between isoprinosine and favipiravir is 0.318, while the correlation coefficient between isoprinosine and Oseltamivir is 0.520. The greater the correlation coefficient, the greater the impact on the patient's lymphocyte count..

However, additional research using a control group with and without isoprinosine is necessary to determine which drug affects lymphocyte levels. Quantitative and functional lymphocyte changes can impair the immune response to the virus and may develop an immunopathological response. Lymphopenia is a prevalent immunological disorder in severe Covid-19 patients, accounting for 96.1% of cases. The percentage of lymphocytes in the blood is a laboratory measurement significantly associated with the development of Covid-19 disease (Jafarzadeh *et al.*, 2021). Yusra and Natasha report that common 2020 laboratory data abnormalities in Covid-19 include a decrease in absolute lymphocyte and albumin counts, as well as an increase in lactate dehydrogenase (LDH) and c-reactive protein (CRP), but normal procalcitonin (PCT). COVID-19 is classified as severe when LDH, CRP, D-dimer, and IL6 levels increase while platelets and lymphocytes decrease. The percentage of lymphocytes in the blood can be considered a reliable and accurate indicator for grading Covid-19 patients. Low lymphocytes can express the primary SARS-CoV-2 receptor, the enzyme angiotensin II (ACE2). SARS-CoV-2 can also enter lymphocytes via an ACE2-independent pathway. Both SARS-CoV-2 and immune-mediated immunity have mechanisms that can result in lymphopenia by impairing lymphocyte production, survival, and redistribution of lymphocytes. In Covid-19 patients, metabolic and biochemical changes may also affect lymphocyte production and survival. Lymphopenia can result in immunosuppression and initiate a cytokine storm; these factors contribute significantly to viral persistence, replication, multi-organ failure, and death (Beran *et al.*, 2021).

There is a bias in the LOS variable due to the Covid-19 management guidelines in Indonesia, according to PDPI. At the pandemic's start, patients were permitted to KRS if their PCR results were negative for two consecutive days. Then, in PDPI ed 2, the criteria changed to allow patients to KRS if they have been free of symptoms (requiring treatment for both Covid-19 and comorbid diseases) for three days even though the PCR results remain positive (Burhan *et al.*, 2020). A different test cannot be conducted on the LOS variable because there is no prior and subsequent data.

Given that groups 1 and 2 produced statistically significant results, it can be concluded that there is a difference or influence between the two combinations on the PCR variable. The expected PCR result is negative. The Favipiravir Isoprinosine combination had a negative PCR result rate of 25.29%, while the Oseltamivir Isoprinosine combination had a negative PCR result rate of 27.50%. By examining this percentage, it is clear that Oseltamivir Isoprinosine provides superior results. Oseltamivir is no longer recommended for Covid-19 patients who do not exhibit flu-like symptoms. This may have occurred because the study's findings indicated that the data obtained were more favuorable to Oseltamivir Isoprinosine than to the use of Favipiravir Isoprinosine.

Additionally, the criteria for patient discharge in managing Covid-19 patients who change affect. Covid-19 patient management PDPI ed.1, valid from April

P-ISSN: 2406-9388
E-ISSN: 2580-8303

2020 to July 2020, states that patients may be discharged home if their two-time polymerase chain reaction (PCR) results are negative. As of August 2020, it is known that patients with PDPI ed.2 Covid-19 can be discharged with several requirements even if the PCR results remain positive. If the PCR follow-up reveals a positive result after clinical improvement and a three-day fever-free period, a persistent positive condition caused by detecting inactivated virus fragments or particles may exist. The Cycle Threshold (CT) value can be used to determine whether or not a patient's condition is infectious, as the cut-off value varies according to the reagents and tools used. According to several hypotheses, persistent positive results result from the device detecting inactivated virus components. Numerous studies have discovered that asymptomatic patients can still have positive RT-PCR results a few weeks after symptoms have resolved (Burhan *et al.*, 2020). According to PDPI edition 3 of 2020, patients may be discharged from hospital care if they meet the criteria for isolation completion and clinical criteria, namely the results of a thorough clinical study, including radiological images demonstrating improvement and blood tests demonstrating improvement, conducted by a physician stating the patient is allowed to go home. Whether related or unrelated, the patient requires no further action/treatment (Burhan *et al.*, 2020).

Because favipiravir will not be available at RSD dr. Soebandi Jember until November 2020, the magnitudes of the two percentages in the PCR results cannot be compared to determine which combination is superior. Oseltamivir lacks sufficient empirical evidence to recommend it as a treatment for Covid-19 infection associated with dyspnea or hypoxia in Wuhan. However, Oseltamivir may be used in Covid-19 patients to prevent further deterioration of the senses of taste and smell (Chiba, 2021). Favipiravir therapy resulted in a more rapid viral clearance, as indicated by a more rapid negative PCR result, compared to the group that did not receive Favipiravir (Finberg *et al.*, 2021). Isoprinosine has been shown to enhance the immune system by increasing the number of Th1 cells and the activity of natural killer cells (Sliva *et al*., 2019). With an enhanced immune system, it is hoped that the process of virus clearance in patients will be accelerated.

X-ray of the chest Each combination has a Sig value of 0.000. Thus, isoprinosine Favipiravir or isoprinosine Oseltamivir provides a significant difference in the patient's chest X-ray results. The combination of isoprinosine and favipiravir has a 54.10 percent success rate in preventing infiltrates on chest x-rays, while isoprinosine Oseltamivir has a 49.34 % success rate. In a study of the efficacy of Favipiravir therapy in Covid-19 patients, it was discovered that administering Favipiravir increased the improvement in chest X-rays by 91.43 %t in patients with negative PCR results following seven days of Favipiravir administration (Özlüşen *et al.*, 2021). This could also be related to the antibiotic Azithromycin administered to patients with moderate-grade Covid-19 at the RSD dr. Soebandi Jember.Azithromycin 5 days or Levofloxacin seven days daily is equally effective and safe for acute bacterial bronchitis exacerbations (ABECB). Although macrolide agents continue to be an effective treatment option for patients with acute bacterial exacerbations of ABECB and other community-acquired respiratory tract infections (Amsden *et al.*, 2003).

Along with patients discharged from the hospital with no visible infiltrate on the chest X-ray, there were also patients discharged with pneumonia. In Covid-19 patients who do not experience severe respiratory distress during hospitalization, abnormal lung examinations will occur ten days after the first Covid-19 symptoms appear. After two weeks, the lung lesions are absorbed, leaving behind ground-glass opacities (GGO) and subpleural parenchymal bands. Clinically cured patients of Covid-19 can still be found to have GGO (Pan *et al.*, 2020). The improvement of the immune system can also be seen in the patient's lung function, and the addition of isoprinosine to the treatment regimen is expected to aid in the immune system's improvement so that it can fight existing viruses.

Isoprinosine has long been recognized for its ability to treat various viral infections, including influenza and other influenza-like illnesses. Isoprinosine contains an immunomodulatory mechanism that promises an overall therapeutic effect against various viral pathogenic variants. While immunomodulators are unlikely to result in complete recovery, early intervention can alter the course of the disease. Clinical and immunological analytical studies conducted over the last six years have established that isoprinosine can treat most viral infections via natural killer cells and cytotoxicity; this efficacy is expected to be transferred to the acute respiratory infection caused by the Covid-19 virus that is currently spreading. Early isoprinosine therapy has been shown to reduce early viral immunosuppression and lymphopenia, which are

P-ISSN: 2406-9388
E-ISSN: 2580-8303

strongly associated with the progression of Covid-19, hospitalization, and death.

However, retrospective studies and studies conducted in Ecuador and India indicate that isoprinosine may be beneficial in the treatment of Covid-19 patients. Since the summer of 2020, two multicenter randomized clinical trials with IP in patients with moderate COVID-19 have been ongoing in India. The first was a 60-patient open-label proof-of-concept study. It examined the effect of IP in COVID-19 patients when used in conjunction with standard of care versus when used alone. Subgroup analysis of patients in this study revealed that when inosine pranobex was added to standard of care containing Azithromycin and Hydroxychloroquine with or without Ivermectin, it resulted in a significantly higher clinical response at Day-14 (100.00 percent vs. 69.23 percent; p = 0.03). At Day 7, 14, and 21, there was a trend toward a (numerically) greater clinical response in the IP + standard of care group compared to the Standard of care group; however, statistical significance was not reached. This could be due to the study's small sample size or to variation in the current standard of care across sites. IP was generally well-tolerated. According to a randomized controlled trial conducted in Ecuador from March to April 2020, 60 Covid-19 patients were randomly assigned to one of two groups, with 30 patients receiving Isopsinosine therapy and the remaining 30 patients receiving placebo. From the start of the study, it was known that patients in the Isoprinosine group improved clinically within 15 days, as measured by swab PCR being negative faster, reaching the SaO2 target > 90 percent faster, and chest x-rays showing a greater number of no lesions in patients in the Isoprinosine group. Additionally, isoprinosine is used in the Czech Republic and possibly elsewhere. The analysis of healthcare reimbursement data for patients treated with Isoprinosine in combination with other standard therapies and mortality data reveals essential information about Isoprinosine's effectiveness in Covid-19 patients (Beran *et al.*, 2021).

CONCLUSION

RSD dr. Soebandi Jember obtained the results from a study evaluating the combination of isoprinosine and antiviral Favipiravir or Oseltamivir in treating moderate-grade Covid-19 patients with RSD. The two of varieties improved clinical conditions as measured by PCR parameters, oxygen demand levels, leukocyte counts, lymphocyte counts, and thorax photos. Both combinations have a mortality rate of less than 1%.

STUDY LIMITATION

This study is limited to the availability of antivirus in RSD dr. Soebandi, causing an imbalance in the number of participants between the two groups. Additional research with a control group devoid of isoprinosine is required.

ACKNOWLEDGMENT

This study involves many authors who have an essential role in realizing this journal. Each author has expertise that is very useful in the research process from beginning to end. All authors declare that this study was accomplished without any funding or support.

AUTHOR CONTRIBUTIONS

Conceptualization, C. M., D. H., B. S., R. D. P.; Methodology, C. M., D. H., B. S., R. D. P.; Software, C. M., S. D. B., A. N. H.; Validation, D. H., B. S., R. D. P., A. D. P.; Formal Analysis, C. M., D. H., B. S.; Investigation, C. M., D. H., B. S., R. D. P.; Resources, C. M., D. H., B. S., R. D. P.; Data Curation, C. M., D. H., B. S.; Writing - Original Draft, C. M., D. H., B. S., R. D. P.; Writing - Review & Editing, C. M., D. H., B. S., R. D. P.; Visualization, C. M.; Supervision, D. H., B. S., R. D. P.; Project Administration, D. H., B. S., R. D. P., Funding Acquisition, C. M.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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P-ISSN: 2406-9388
E-ISSN: 2580-8303