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Use of Favipiravir in Covid-19 Patients: A Narrative Review

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Abstract
COVID-19 is an acute respiratory disease resulting from the infection of SARS-COV-2 viruses and causes high morbidity, which requires appropriate treatment targets. Favipiravir is an antiviral that selectively inhibits RNA-dependent RNA polymerase (RdRp) of virus. This review aimed to identify several studies that prove the effectiveness and safety of using Favipiravir for COVID-19 patients. The search method used the electronic media PubMed and ScienceDirect with the keywords "Efficacy", "Favipiravir", "Treatment", "Safety", SARS-COV-2", and "Favipiravir induced", accompanied by the addition of the affixes "AND" and "OR" and selection by the publication date starting December 2019. The literature search resulted in eight (8) published articles that met the exclusion and inclusion criteria. The results of the review showed that concurrent administration of Favipiravir and Lopinavir/Ritonavir or Chloroquine, with a dosage of Favipiravir of 3200 mg/day followed by 1200 mg/day each in 2 divided doses, was considered adequate for improving the clinical symptoms of COVID-19 patients with mild-moderate symptoms in early administration. Meanwhile, administering Favipiravir with anti-IL-6 Tocilizumab for patients with severe symptoms showed a fairly good effect. The most frequently reported ADE (adverse drug events) in the use of Favipiravir were hyperuricemia and elevated alanine aminotransferase (ALT) levels. This review concluded that the best clinical response to Favipiravir is shown in COVID-19 patients with mild-to-moderate early symptoms.

Keywords: COVID-19; Favipiravir; Treatment

1. INTRODUCTION

COVID-19 is a disease caused by the SARS-COV-2 viral infection, which can produce several symptoms of severe acute respiratory syndrome. This viral infection is deemed to cause high morbidity and, therefore, requires prompt treatment. COVID-19 first appeared in Wuhan, China, in December 2019. It can disrupt the respiratory system by causing severe symptoms and fatality, especially in elderly patients aged 70-80 years (Onder et al., 2020). The existence of SARS-COV-2 began with the emergence of the Severe Acute Respiratory Syndrome Coronavirus (SARS-COV) in 2002 and the Middle East Respiratory Syndrome Coronavirus (MERS-COV) in 2012. The incidence of SARS-COV and MERS-COV has triggered the emergence of the SARS-COV-2 virus, which is more dangerous than its two predecessors. It has also been known that most of the genome sequence of the SARS-COV-2 virus is

homologous with the genome of the SARS-COV virus, whereas some others are homologous with the genome of the MERS-COV virus (Lu et al., 2020; Zhou et al., 2020).

The treatment for COVID-19 focuses on two targets, which include reducing the number of viruses in the body and improving the health status of the patients (Inoue et al., 2020). Previous research shows that several antiviral agents are deemed effective against COVID-19 in the general population. Among these antiviral groups, Favipiravir acts as an antiviral agent previously developed to treat influenza (Koshi et al., 2021).

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a selective, powerful antiviral agent inhibiting the RNA-dependent RNA polymerase (RdRp) found in viruses. Favipiravir was discovered through a chemical screening based on a specific antiviral activity against influenza viruses conducted by Toyama Chemical Co., Ltd. Favipiravir goes through intracellular phosphoribosylation to obtain its active form, Favipiravir-RTP (Favipiravir ribofuranosyl-5B-triphosphate), which is known as a substrate for RNA-dependent RNA polymerase (RdRp) that inhibits the activity of RNA polymerase (Udwadia et al., 2021a). Favipiravir has a broad antiviral spectrum against other RNA viruses, such as bunyavirus, influenza, and filovirus. It is identified as having in-vitro activities against SARS-COV-2, although it requires higher concentrations compared to such other drugs as Chloroquine or Remdesivir, with a value of EC50 of 61.88 μM (Wang et al., 2020).

The initial clinical experience of Favipiravir against SARS-COV-2 shows promising results, but it remains necessary to further study its effectiveness and safety, especially in specific patient groups, such as geriatrics and pediatrics. Although the WHO only authorizes emergency use and clinical trials of Favipiravir exclusively for COVID-19 patients, several studies have reported that their trial results effectively improve the clinical symptoms of COVID-19 patients. In this review, the effectiveness of Favipiravir is discussed according to the patient's symptoms, including those with mild and moderate to severe symptoms, through a narrative review presented in a narrative study.

2. MATERIALS AND METHODS

The data collection from 2020-2021 was conducted through literature searches using the electronic media, PubMed and ScienceDirect, with the search keywords "Efficacy", "Favipiravir", "Treatment", "Safety", "SARS-COV-2", and "Favipiravir induced" supported by the addition of "AND" and "OR" affixes. The specified eligibility criteria were articles published in English, presenting research, case reports, as well as prospective and retrospective observational studies, and addressing a research topic of the treatment of Favipiravir in COVID-19 patients. The exclusion criteria were review articles and articles that discussed Favipiravir for non-COVID-19 patients.

The quality of the article selection was evaluated using the indicator parameters for effectiveness and safety studies, and the content integrity of each article with the RCT method was evaluated using the Consort 2010. In contrast, articles with case reports were assessed using the Care Checklist 2013. Based on the search results, a total of 86 articles were obtained, 43

articles were selected based on an assessment of the abstracts and titles, 35 articles discussed Favipiravir for non-COVID-19 patients, and the result was eight articles to be reviewed.

3. RESULTS AND DISCUSSION

3.1. Favipiravir mechanism of action

SARS-COV-2 is a type of positive-sense single-stranded RNA virus belonging to the subfamily "coronavirinae" in the family "coronaviridae" which is part of the order "nidovirales" and has four main structural proteins, including the spike, envelope, membrane, and nucleocapsid. The spike protein plays a crucial role in the binding of the virus to the host cell membrane (Tortorici & Veesler, 2019). Transmission of SARS-COV-2 can occur through a patient's droplets/cough, and the virus will then infect healthy cells through a direct interaction with a specific receptor, or the ACE2 receptor, found on the SARS-COV-2 host-cell surface (Hoffmann et al., 2020). SARS-COV-2 typically infects body organs with many ACE2 cells, including the pulmonary epithelial cells (Cevik et al., 2020). The detailed pathogenesis of SARS-COV-2 remains to be known, but it is estimated to be similar to its predecessor, SARS-COV (Cevik et al., 2020).

SARS-COV-2 initially enters the body and moves toward the pulmonary epithelial cells, and then the spike protein of the virus will bind itself to the primary receptor ACE2. In the cells, the virus structure will be cleaved with the aid of the enzyme TMPRSS2 to allow fusion between the cell membrane and the virus envelope, followed by the formation of a genome ready to release into the cytoplasm. In the cytoplasm, the ribosome will translate the viral RNA into proteins. The viral RNA is propagated by the enzyme RNA-dependent RNA polymerase (RdRp), after which the constituent proteins and RNA combine to form virions in the Golgi apparatus and prepare for exocytosis and replication in other cells (Allen et al., 2020).

The mechanism of action of Favipiravir against SARS-COV-2 is known to play a role in terminating the viral RNA chain (Shannon et al., 2020). Favipiravir acts as a guanosine analog to prevent viral RNA synthesis (Figure 1). Favipiravir is an antiviral therapy since its guanosine analog resembles the natural structure of the body's nucleoside or nucleotide. As a result, the RNA polymerase of the virus will mistakenly recognize Favipiravir-RTP as a purine nucleotide (Furuta et al., 2013). Like other positive-strand RNA viruses, the nucleus of the viral replication is present in RNA-dependent RNA polymerase (RdRp).

It has been known that SARS-COV-2 utilizes the viral RNA-dependent RNA polymerase (RdRp) to replicate and express its genome, and RdRp will join the non-structural proteins (NSPs) to form a replication-transcription complex that plays a role in the synthesis up to the extension of RNA strands (Hillen, 2021). The RNA-dependent RNA polymerase (RdRp) of SARS-COV-2 is known to be 10-fold more active than that of any other virus. It has an extraordinarily high nucleotide incorporation rate, allowing Favipiravir or other nucleotide analogs to be inserted easily into viral RNA (Shannon et al., 2020). Therefore, RNA-dependent RNA polymerase (RdRp) becomes one of the antiviral targets which is considered promising to overcome COVID-19 (Subissi et al., 2014).

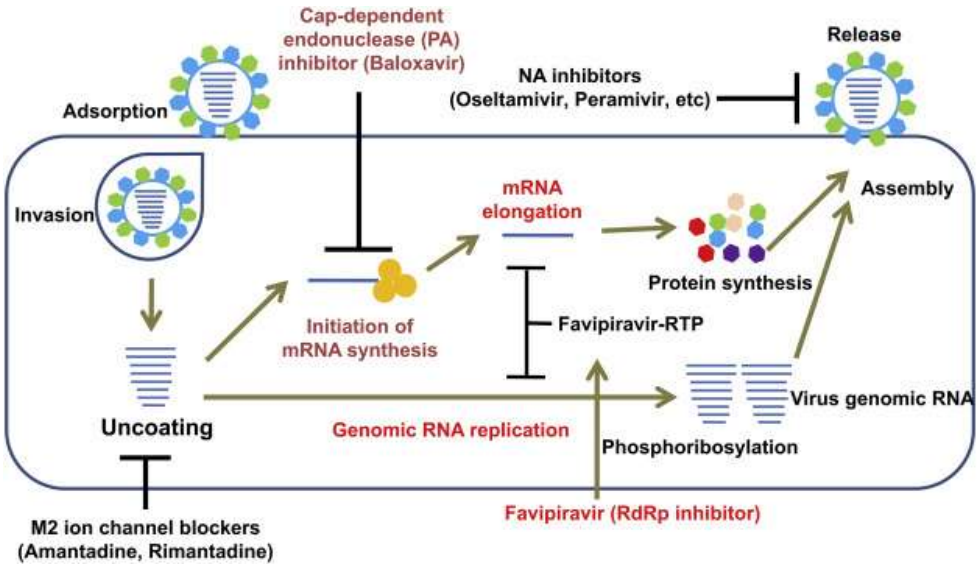

Figure 1. Mechanism action of favipiravir (modified from (Fang and Wang, 2020)).

Favipiravir is among the antivirals targeting the inhibition of RNA-dependent RNA polymerase (RdRp) in viruses. Favipiravir is a prodrug that will undergo an intracellular metabolic process to convert into its active form. First, Favipiravir enters the body and has active phosphoribosylation catalyzed by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) to form an active compound called Favipiravir-ribofuranosyl-50-triphosphate (Favipiravir-RTP). Favipiravir-RTP will then bind to the active site of RdRp (RNA-dependent RNA polymerase) when the viral replication process occurs to inhibit RNA replication (Allen et al., 2020).

3.2. Effectiveness of Favipiravir

A total of 8 articles are to be reviewed for the effectiveness of favipiravir (Table 1 and Table 2). In the articles to date, there have been no specifically approved drugs for the treatment of COVID-19. However, some antiviral agents, including Favipiravir, are considered effective in improving the clinical symptoms of COVID-19 patients. Favipiravir is currently used in the treatment of COVID-19 by some countries, including Indonesia, and in various trials as a promising clinical intervention to combat SARS-COV-2 infection. Favipiravir was initially used to treat influenza RNA viruses (Guo et al., 2020). Reports on the effectiveness of Favipiravir in COVID-19 still need to be made. In an in-vitro clinical trial conducted on Vero E6 cells, it was found that the EC50 of Favipiravir was 61.88 mM (Wang et al., 2020). The absorption time of Favipiravir in the body is approximately 0.5 to 1 hour (Nguyen et al., 2017). The dose of Favipiravir used in the treatment of COVID-19 remains unspecified. However, some studies have determined that it is adjusted to the initial administration for the influenza virus, in which on the first day of treatment, patients are given 3200-3600 mg Favipiravir orally followed by a dosage of 1200-1600 mg divided into two doses per day until day 10 or day 14 (Ivashchenko et al., 2021; Udwadia et al., 2021b).

The main characteristic of the patients in this study is COVID-19 patients who were confirmed positive by the result of the RT-PCR method in a laboratory and had varied symptoms from mild-moderate to severe. Mild symptoms are characterized by a fever of < 38ºC and a respiratory rate of 12 to ≤ 20 breaths/minute (Cai et al., 2020). Moderate symptoms include cough, sore throat, body aches, and nasal congestion (Ivashchenko et al., 2021; Udwadia et al., 2021b). Meanwhile, severe symptoms include lung conditions showing pneumonia positive from a chest CT scan, cough, difficulty breathing, and infections in the lower respiratory tract (Khamis et al., 2021; Lou et al., 2021). The patients' average age in all the literature discussed in the study was 18-89 years in both groups with mild-moderate and severe symptoms. The comorbidities commonly experienced by the patients with mild-moderate to severe symptoms were diabetes mellitus (22.7%), hypertension (34.9%), liver disorder (16%), pulmonary disease (6.8%), mild-severe chronic kidney disease (25.1%), and conjunctivitis (5.17%).

At the early treatment stage, the patients had a variety of symptoms from mild-moderate to severe, and a drug combination was therefore administered comprising antivirals and such other drugs as analgesics-antipyretics, antibiotics, and vitamins (Chen et al., 2021; Udwadia et al., 2021b). Many studies have been conducted to assess the effectiveness of Favipiravir for COVID-19 patients. Studies of COVID-19 patients with initial symptoms show that the administration of Lopinavir/Ritonavir and anti-malarial Chloroquine together with Favipiravir improved lung conditions based on the observation of average chest CT scan results on day 10-15 with 91.43% vs. 62.22% (P = 0.004) as well as a relatively faster viral clearance (4 days with IQR 2.5-9 vs. 11 days with IQR 8-13; P < 0.001). In addition, the combination of Favipiravir and Chloroquine was also studied in groups of patients with severe symptoms. However, the findings reported that Favipiravir and Chloroquine did not significantly improve patients' inflammatory response (P= 0.785) (Cai et al., 2020; Ivashchenko et al., 2021; Udwadia et al., 2021b).

Other studies were also conducted to examine the effects of Favipiravir administration on patients during initial treatment and when the symptoms deteriorated. They also investigated the effects of adding a combination of Favipiravir and Baloxavir for patients given standard care. The results showed no significant differences in the two treatment groups (initial treatment and deteriorated symptoms) since the hazard ratio [aHR] was 1.42 with a 95% confidence interval [95% CI] of 0.76 to 2.62, and the time to reduce fever was relatively similar in both groups, which was three days (aHR = 1.88, 95% CI = 0.81 to 4.35). Meanwhile, adding Baloxavir and Favipiravir is perceived as providing insignificant clinical benefits to patients (Doi et al., 2020; Lou et al., 2021).

Of all the articles reviewed, administering Favipiravir in COVID-19 patients with mild-moderate symptoms is considered acceptable to reduce clinical symptoms, accelerate viral clearance time, and improve lung conditions, as evidenced by the chest CT scan if administered for early symptoms. However, administering Favipiravir to COVID-19 patients immediately after the onset of symptoms or approximately around the sixth day after the first onset of

symptoms is deemed less effective in improving the clinical symptoms. This is likely caused by the growing number of viruses, the concentration of the administered drug, and the duration of Favipiravir administration. Meanwhile, in patients with severe symptoms, the administration of Favipiravir in combination with Arbidol does not improve the patient's clinical symptoms, nor does the administration of other drugs, such as Baloxavir marboxil and Chloroquine. However, the administration of Favipiravir and Anti-IL-6 Tocilizumab is considered effective in improving patients' lung inflammation, although their use for COVID-19 patients should be reevaluated since they are considered to carry the risk of cytokine storm response (Zhou et al., 2020).

Furthermore, inadequate improvement of COVID-19 patients with severe clinical symptoms is likely due to the disease severity characterized by the viral load, comorbidity, age, and early clinical symptoms that are too severe to treat with an only standard of care (Gonçalves et al., 2020).

Meanwhile, the viral clearance and clinical symptom improvement in patients with mild-moderate symptoms do not differ much from those with severe symptoms. On average, Viral clearance occurred from day 4 to day 10 (Cai et al., 2020; Ivashchenko et al., 2021). Improvement in the lung conditions observed from the chest CT scan results was typically noticed starting from day 14 and day 15 (Ivashchenko et al., 2021; Zhao et al., 2021). In addition, patients' fever was reduced on the third day of the drug administration (Udwadia et al., 2021b). In essence, evaluating the effectiveness of Favipiravir requires further clinical research with a larger population of patients. Various clinical characteristics, ages, physical conditions, and comorbidities are some of the factors that influence such evaluation. In addition, drug concentration and pharmacology of drugs also affect their effectiveness (Lou et al., 2021).

3.3. Favipiravir safety treatment

Adverse drug events (ADE) are also frequently found in COVID-19 treatment. Physiological and pathological factors can influence adverse reactions. As indicated in this study, each patient has different clinical characteristics. The main characteristic is that COVID-19 patients were confirmed positive by the laboratory using the RT-PCR method, with mild-moderate to severe early symptoms. The average age of the patients was 18-89 years, combined with all patients with mild-moderate to severe symptoms. Some patients had one or more comorbidities, with the most common being diabetes mellitus (22.7%), hypertension (34.9%), liver disorder (16%), pulmonary disease (6.8%), mild-severe CKD/chronic kidney disease (25.1%), and conjunctivitis (5.17%). These comorbidities were generally found in patients aged 50-80 years or above.

According to the articles collected in this study, the most frequent incidence of ADE (adverse drug event) was hyperuricemia (Table 3), affecting almost half of the patient population (48.9%) (Chen et al., 2021; Doi et al., 2020). Favipiravir is likely to decrease the excretion of uric acid into the urine and, therefore, result in elevated uric acid concentration in the blood.

Table 1. Effectiveness of Favipiravir in patients with mild-moderate symptoms.

Reference	Country	Study Design	Patient Population	Dosage and Route of Administration		Clinical Outcome	Information
Favipiravir (FVP) vs. Lopinavir/Ritonavir (LPV/RTV)							
(Cai et al., 2020).	China	Non-randomized control trial	Non-critical COVID-19 patients FVP (n=35) vs. LPV/RTV (n=45)	FVP, peroral Day 1 = 1600 mg, 2x1 day Day 2-14 = 600 mg, 2x1 day	LPV/RTV, peroral Day 1-14 = 400mg/100 mg, 2x1day	Improved chest CT scan on day 14: FVP = 32/35 (91.4%) LPV/RTV = 28/45 (62.2%) Viral load drop: FVP = 4 days LPV/RTV = 11 days FVP showed an excellent clinical response to COVID-19 for viral load drop and improved chest CT scan.	All patients were given 5 million IU Interferon, 2x1 day via inhalation
Favipiravir (FVP) vs. Hydroxychloroquine (HCQ) and Lopinavir/Ritonavir (LPV/RTV)							
(Ivashchenko et al., 2021)	Russia	Multicenter randomized control trial phase II/III	COVID-19 patients with mild-moderate symptoms FVP = 1600 mg, n=20 FVP = 1800 mg, n=20	FVP peroral Day 1 = 1600 mg Day 2-14 = 600 mg FVP n=20 Day 1 = 1800 mg Day 2-14 = 800 mg FVP n = 20	Standard of Care (SOC): HCQ and LPV/RTV followed the COVID-19 treatment guidelines in Russia	Viral clearance: FVP = 37/40 (92.5%) SOC = 16/20 (80.0%) Improved chest CT scan: FVP = 36/40 (90%) SOC = 16/20 (80.0%) On days 10 and 15, Favipiravir showed a quite good response for viral clearance and an improved chest CT scan.	Standard of Care: Hydroxychloroquine for 15/20 patients (75%), Lopinavir/Ritonavir for 1/20 patients (5%), no etiotropic therapy for 4/20 patients (20%)

Table 1. Effectiveness of Favipiravir in patients with mild-moderate symptoms (*Continued*).

Reference	Country	Study Design	Patient Population	Dosage and Route of Administration	Clinical Outcome	Information
Favipiravir (FVP)						
(Doi et al., 2020).	Japan	Prospective, Randomized, Open-label Trial of Early vs. Late Favipiravir	Inpatients with confirmed COVID-19 were given Favipiravir in the early treatment and late treatment of the symptom stage Early treatment group, n=36 Late treatment group, n=33	FVP peroral Day 1 = 1800mg 2x1 day followed by 800 mg 2x1 day with a total of 19 doses for 10 days	N/A	Viral clearance on day 6: Early treatment group = 66.7% Late treatment group = 56.1% The average time to reduce fever was 3 days. Administration of Favipiravir did not significantly improve the viral clearance in the first six days of the administration.	N/A
Favipiravir (FVP) vs. Control							
(Udwadia et al., 2021b).	India	Randomized, Comparative, Open-label, Multicenter Phase 3 Clinical Trial	COVID-19 patients with mild-moderate symptoms Favipiravir n=70 Control n = 68	FVP peroral Day 1 = 1800mg 2x1 day Day 2-14 = 800 mg 2x1 day	N/A	Improved clinical outcome was indicated by a decreased body temperature, higher oxygen saturation, and reduced respiratory rate on day 3 (FVP) and day 5 (control group). Favipiravir might reduce the duration of clinical signs and symptoms in patients with mild-moderate COVID-19 symptoms, as indicated by the shorter clinical recovery time.	The control group was administered with antipyretics, cough suppressants, antibiotics, and vitamins.

Table 2. Effectiveness of Favipiravir in patients with severe symptoms.

Ref.	Country	Study Design	Patient population	Dosage and Route of Administration		Clinical Outcome	Information
Favipiravir (FVP) vs. Arbidol				Dosage of Compared Drug			
(Chen et al., 2021)	China	Multicenter Randomized Control Trial	COVID-19 pneumonia patients FVP n = 116 Arbidol n=120	FVP, peroral Day 1 = 1600 mg, 2x1day Day 2-14 = 600 mg 2x1 day for 10 days	Arbidol, peroral = 200 mg 3x1 day	Clinical recovery on day 7 = 62/120 patients (51.67%) in the Arbidol group and 71/116 patients (61.21%) in the Favipiravir group Favipiravir showed no superior efficacy compared to Arbidol in improving patients' clinical recovery until day 7.	The administration of Arbidol was combined with standard of care by using traditional Chinese medicine, antibiotics, supplementary antivirals, immunomodulatory drugs, steroids, psychotic drugs, nutritional support, cardiovascular drugs, and oxygen support.
Favipiravir (FVP) vs. Baloxavir marboxil (BAL)							
(Lou et al., 2021).	China	Open control trial	COVID-19 patients FVP n=9 BAL n=10 Control group n = 10	FVP, peroral = 1600 mg 2x1 day followed by 600 mg 3x1 day, duration of administration = no more than 14 days	BAL, peroral = Day 1 and day 4 = 480 mg 1x1 day readministered on day 7 if the test result remained positive	Viral shedding time of 14 days FVP = 7/9 (77%) BAL = 7/10 (70%) Control group = 10/10 (100%) Adding Favipiravir and Baloxavir marboxil to the standard of care did not provide significant clinical benefits.	FVP and BAL were followed by administration of previous antivirals = Lopinavir/Ritonavir (400mg/100mg, BID, peroral) or Darunavir/Cobicistat and Arbidol (200mg, TID, peroral); all with Interferon-α inhalation (100,000 IU, TID or QID)

Table 2. Effectiveness of Favipiravir in patients with severe symptoms (*Continued*).

Ref.	Country	Study Design	Patient population	Dosage and Route of Administration		Clinical Outcome	Information
Favipiravir (FVP) vs Hydroxychloroquine (HCQ)							
(Khamis et al., 2021).	Oman	Randomized, open-label controlled trial	COVID-19 patients FVP n = 44 HCQ n = 45	FVP, peroral Day 1 = 1600 mg followed by 600 mg 2x1 day for a maximum of 10 days FVP combined with 8 million IU (0.25mg) Interferon beta-1b 2x1 day for 5 days	HCQ, peroral Day 1 = 400 mg 2x1 day followed by 200 mg 2x1 day for 7 days	Clinical recovery was assessed based on the patient's clinical outcome: **Transferred to ICU** FVP = 8/44 (18.2%) HCQ = 8/45 (17.8%) **Discharged** FVP = 29/44 (65.9%) HCQ = 31/45 (68.9%) **O2 saturation when discharged** FVP = 94 HCQ = 95 **Died** FVP = 5/44 (11.4%) HCQ = 6/45 (13.3%) Favipiravir + IFN1B and hydroxychloroquine showed no significant differences in the inflammatory markers/clinical outcomes in COVID-19 patients with moderate to severe pneumonia.	N/A
Favipiravir (FVP) vs. Tocilizumab							
(Zhao et al., 2021).	China	Multicenter random trial (3:1:1)	Combined COVID-19 adult patients (FVP vs. Tocilizumab) N = 14 FVP n = 7 Tocilizumab n = 5	FVP peroral Day 1 = 1600 mg, 2x1 day Day 2-7 = 600 mg 2x1 day	Tocilizumab, I.V = 4-8 mg/kg (400 mg) Tocilizumab was administered into 100 ml of 0.9% normal saline	On day 14, FVP vs. Tocilizumab significantly reduced lung lesions compared to the FVP group. In the FVP vs. Tocilizumab group, nearly all patients experienced clinical recovery of fever, muscle pain, shortness of breath, and diarrhea (14/14 or 100%). The number of deaths/ventilators in the FVP group was higher (2/7 or 28.5%) as opposed to the combination group and Tocilizumab monotherapy group (0/14 and 0/5 or 0%). Tocilizumab vs. Favipiravir and Tocilizumab monotherapy improved pneumonia in COVID-19 patients and inhibited the symptom severity.	N/A

This is because Favipiravir is metabolized into inactive M1 metabolites by aldehyde oxidase and xanthine oxidase and excreted into the urine. In the kidneys, uric acid treatment is regulated by the balance between tubule reabsorption and secretion in the proximal tubules. Favipiravir and M1 act as moderate inhibitors of organic anion transporters 1 and 3 (OAT1 and OAT3), which are involved in the excretion of uric acid in the kidneys. M1 increases the reabsorption of uric acid through urate transporter 1 (URAT1) in the proximal tubules of the kidneys (Mishima et al., 2020). There was a case report on a COVID-19 male patient aged 42 years who had a history of hyperuricemia without recurring gout for more than one year, diabetes, or hypertension. The patient was administered with Favipiravir at a dosage of 3600 mg/day followed by 1600 mg/day, each in two divided doses until day 14. On the 13th day, it was reported that the patient's uric acid level increased by 2.3 mg/dl, and the patient was then given NSAID treatment until the complaint declined. The patient recovered on day 20 and was discharged two days later (Hase et al., 2020). This report suggests that a patient's medical history can affect the incidence of hyperuricemia in Favipiravir administration (Hase et al., 2020). The second ADE (adverse drug event) widely reported in several articles was elevated ALT (Alanine Transaminase) levels in the liver experienced by approximately 22 patients or 16.38% of the patient population in all the articles (Chen et al., 2021; Doi et al., 2020).

A case report on Favipiravir for COVID-19 treatment revealed that some patients in the 50-80 age range (11.4%) experienced a significant increase in liver enzymes after 12 days to 2 weeks of treatment. Several patients were then treated with ursodeoxycholic acid (15mg/kg), after which the symptoms and results of laboratory examinations of liver enzyme levels gradually improved within 4 up to 10 weeks (Kumar et al., 2021; Wu and McGoogan, 2020). Another incidence has also been reported as respiratory failure in 2/7 (28.5%) in the Favipiravir group, which was higher than the findings (0/14 and 0/5 patients) in other study groups (Zhao et al., 2021). The other study on Remdesivir also reported a similar finding, which needs careful monitoring of adverse reactions in patients with comorbid conditions and pregnancy (Siada et al., 2022; Kurniawan et al., 2022).

Table 3. Adverse drug events associated with Favipiravir (FVP).

Reference and Year	Study Design	Patient Category	Findings
(Kumar et al., 2021)	Case report	3 COVID-19 patients aged 70 years, 52 years, and 50 years	Elevated liver enzymes or ALT after using Favipiravir
(Magpie et al., 2021)	Case report	1 COVID-19 patient aged 64 years	Hypersensitivity in the form of fever after 14 days of Favipiravir administration
(Doi et al., 2020)	Prospective, Randomized, Open-Label Trial	82 COVID-19 patients in the safety group	• Hyperuricemia in 69/82 (84.1%) • Elevated triglycerides in 9/82 (11%) Increased Alanine aminotransferase in 7/82 (8.5%)

Table 3. Adverse drug events associated with Favipiravir (FVP) (*Continued*).

Reference and Year	Study Design	Patient Category	Findings
(Chen et al., 2021)	RCT multicenter trial	240 COVID-19 patients randomized for FVP administration (120) and control group (120)	• ADE was reported in 37% of the Favipiravir group and 28% of the control group • The most common ADE of Favipiravir were abnormal LFT/liver function tests (10 or 10%), elevated serum uric acid (16 or 13.79%), psychiatric symptoms (5 or 4.31%), and gastrointestinal reactions (16 or 13.79%).
(Cai et al., 2020)	Open control trial nonrandomized, before- after controlled study	80 patients tested COVID-19 positive by RT-PCR = 35 patients given FVP, 45 patients in the control group	• Four (4) patients given FVP (11.43%) reported ADE: • 2 (5.71%) with diarrhea • 1 (2.86%) with liver injury • 1 with poor diet
(Doi et al., 2020)	Prospective, Randomized, Open-Label Trial	82 COVID-19 patients in the safety group	• Hyperuricemia in 69/82 (84.1%) • Elevated triglycerides in 9/82 (11%) • Increased Alanine aminotransferase in 7/82 (8.5%)
(Ivashchenko et al., 2021)	Multicenter Randomized Control Trial Phase II/III	60 COVID-19 patients with moderate pneumonia, randomized with different dose regimens of Favipiravir versus standard of care	• 7/40 (17.5%) in the Favipiravir group experienced adverse drug reactions, including diarrhea, nausea, vomiting, chest pain, and elevated levels of liver transaminase. • Mild-moderate adverse drug reactions leading to drug discontinuation occurred in 2/40 patients (5%).
(Lou et al., 2021)	Open control trial	29 COVID-19 patients confirmed positive by RT-PCR randomized for 1:1:1	• Some patients in the Favipiravir group experienced more than one side effect, including: • Respiratory failure and elevated alanine aminotransferase (4 or 44%), lymphopenia and lower hemoglobin (7 or 77%), increased lactate dehydrogenase and D-dimer (5 or 55%), decreased albumin (8 or 88%), and higher triglycerides (6 or 66%).

Table 3. Adverse drug events associated with Favipiravir (FVP) (*Continued*).

Reference and Year	Study Design	Patient Category	Findings
(Doi et al., 2020)	Prospective, Randomized, Open-Label Trial	82 COVID-19 patients in the safety group	• Hyperuricemia in 69/82 (84.1%) • Elevated triglycerides in 9/82 (11%) • Increased Alanine aminotransferase in 7/82 (8.5%)
(Khamis et al., 2021)	Randomized, open-label controlled trial	Covid-19 patients with moderate-severe symptoms randomized for Favipiravir (45) and standard of care (45)	• No significant side effects, such as hyperuricemia, liver enzyme disorder, or QTc prolongation, were reported from using Favipiravir in this study.

4. CONCLUSION

A limitation was noted in the included studies. The standard of care varied across studies, and other antiviral therapies were or have not been included during treatment. Based on this case, analyzing the result of the treatment effect of a specific drug can be difficult. The use of Favipiravir for COVID-19 patients has a noticeable effect on clinical improvement only among patients with mild-moderate symptoms when administered early at a dosage of 3200 mg/day followed by 2400 mg/day, each in two divided doses up to day 14, in combination with Lopinavir/Ritonavir antivirals or with Chloroquine. In the group of patients with severe symptoms, Favipiravir was administered at the same dose as that for the previous group and, in some studies, was given in combination with Arbidol, Chloroquine, and Interferon beta-1b. However, its combination with anti-IL-6 Tocilizumab was regarded as having a good response. The frequent ADE (adverse drug events) due to Favipiravir use reported in some studies were hyperuricemia and elevated alanine aminotransferase (ALT).

CONFLICT OF INTEREST

All authors declared that there was no conflict of interest.

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