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Efficacy of Favipiravir in the Treatment of Moderate COVID-19 Patients: A Randomized, Open-label, Controlled Clinical Trial

Orta Şiddette COVID-19'lu Hastaların Tedavisinde Favipiravirin Etkinliği: Randomize, Açık Etiketli, Kontrollü Bir Klinik Çalışma

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Abstract

Introduction: Since the beginning of the Coronavirus disease-2019 (COVID-19) pandemic, scientists have studied many drugs to treat it, but none of them have been approved as a complete cure. Favipiravir is one of those drugs that effectively clears the body from the virus by interfering with the process of replication. This study aimed to determine the efficacy of favipiravir compared with supportive medication to treat moderate COVID-19 patients.

Materials and Methods: In this randomized, open-label, controlled clinical trial, we examined the efficacy of favipiravir to treat moderate COVID-19 patients. The study was conducted in Labbafinejad Hospital (Tehran, Iran) from April to September 2021. A 1:1 ratio of eligible patients were assigned to the intervention and control groups. The control group received supportive medication. In addition to supportive medication, the intervention group received favipiravir. The primary endpoint was the hospitalization rate during the seven-day follow-up. And the secondary endpoints were symptoms, signs, and laboratory tests of the patients.

Results: Out of 78 patients who were included in the study, 40 patients were assigned to the control group and 38 patients were assigned to the intervention group. At the beginning of treatment, the respiratory rate was higher in the intervention group (p=0.001), however, on the fifth (p=0.001) and seventh (p<0.001) days, it was significantly lower in the intervention group. In addition, oxygen saturation at the beginning of treatment was lower in the intervention group (p<0.001); however, on the fifth (p=0.016) and seventh (p<0.001) days, it was significantly higher in the intervention group. Furthermore, the consumption of favipiravir was not associated with the hospitalization rate (p=0.200).

Conclusion: Favipiravir enhances respiratory manifestations in patients with moderate COVID-19 when compared to supportive medication alone.

Keywords: Antiviral agents, COVID-19, favipiravir, SARS-CoV-2

Öz

Giriş: Koronavirüs hastalığı-2019 (COVID-19) pandemisinin başlangıcından bu yana, bilim adamları COVID-19'u tedavi etmek için pek çok ilaç üzerinde çalıştılar ve bunların hiçbiri kesin tedavi olarak kabul edilmedi. Favipiravir, replikasyon sürecine müdahale ederek vücudu virüsten etkili bir şekilde temizleyen ilaçlardan biridir. Bu çalışma, orta şiddette COVID-19'lu hastaları tedavi etmek için destekleyici ilaçlarla karşılaştırıldığında favipiravirin etkinliğini belirlemeyi amaçladı.

Gereç ve Yöntem: Bu randomize, açık etiketli, kontrollü klinik çalışmada, orta şiddette COVID-19'lu hastaları tedavi etmek için favipiravirin etkinliğini inceledik. Çalışma, Nisan-Eylül 2021 tarihleri arasında İran'ın Tahran kentindeki Labbafinejad Hastanesi'nde gerçekleştirildi. Uygun hastalar müdahale ve kontrol gruplarına 1:1 oranında atandı. Kontrol grubu destekleyici ilaç aldı. Destekleyici ilaçlara ek olarak, müdahale grubuna favipiravir verildi. Birincil sonlanım noktası, yedi günlük takip sırasında hastaneye yatış oranıydı. İkincil sonlanım noktaları ise hastaların semptomları, bulguları ve laboratuvar testleriydi.

Bulgular: Çalışmaya dahil edilen 78 hastadan 40'ı kontrol grubuna, 38'i müdahale grubuna alındı. Tedavinin başlangıcında solunum hızı müdahale grubunda daha yüksekti (p=0,001), ancak beşinci (p=0,001) ve yedinci (p<0,001) günlerde müdahale grubunda anlamlı olarak daha düşüktü. Ayrıca

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Öz

müdahale grubunda tedavinin başlangıcında oksijen satürasyonu daha düşüktü (p<0,001), ancak beşinci (p=0,016) ve yedinci (p<0,001) günlerde müdahale grubunda anlamlı olarak daha yüksekti. Bununla birlikte, favipiravir kullanımı hastaneye yatış oranı ile ilişkili değildi (p=0,200).
Sonuç: Orta şiddette COVID-19'lu hastalarda favipiravir, tek başına destekleyici ilaçlara kıyasla solunumsal göstergeleri iyileştirmektedir.
Anahtar Kelimeler: Antiviral ajanlar, COVID-19, favipiravir, SARS-CoV-2

Introduction

The epidemic of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) was first reported in Wuhan, China, in December 2019. The disease caused by this virus, Coronavirus disease-2019 (COVID-19), spread quickly around the world until on March 11, 2020, the World Health Organization declared it a pandemic. So far, there have been millions of confirmed cases and thousands of deaths due to COVID-19. Accordingly, it is a priority of global health to control this disease[1,2].

Severe acute respiratory syndrome-Coronavirus-2 is an RNA virus that multiplies through the replication system of host cells[3]. The main target of SARS-CoV-2 is often the epithelial cells of the lung's alveoli, which eventually lead to atypical pneumonia[4]. Most COVID-19 patients have nonspecific symptoms and recover only with supportive therapies (fluid therapy, supplemental oxygen, antipyretics, analgesics, and antiemetics)[5]. However, considering the mechanisms of infectivity and pathogenicity of SARS-CoV-2, scientists have proposed antiviral drugs to treat COVID-19[6]. Some of them interfere with the replication, membrane fusion, and assembly of the virus, such as remdesivir, lopinavir/ritonavir, umifenovir, and favipiravir[7].

Favipiravir is a nucleoside analog oral antiviral drug developed by the Japanese Toyama Chemical company. It selectively inhibits RNA-dependent RNA polymerase and causes lethal mutations in the replication process that produce nonviable viruses. The efficacy of favipiravir on a large number of viruses such as influenza A, yellow fever, Ebola, Lassa virus, and West Nile virus has been previously reported[8,9]. Additionally, a previous meta-analysis study has shown that virus clearance [Odds ratio (OR)=0.40, 95% CI=0.19-0.84, p=0.02] and clinical improvement (OR=1.60, 95% CI=1.03-2.40, p=0.04) of patients were significantly higher in the group treated with favipiravir compared to control group on day 7[10].

This study aimed to determine the efficacy of favipiravir compared with supportive medication to treat moderate COVID-19 patients.

Materials and Methods

Study Design

This randomized, open-label, parallel-group clinical trial was conducted to assess the efficacy of favipiravir compared with supportive medication in patients with moderate COVID-19. The present clinical trial protocol has been approved by the Iranian Registry of Clinical Trials (IRCT ID: IRCT20211004052664N1).

Participants

The study population included all COVID-19 patients referred to the infectious diseases clinic of Labbafinejad hospital. This study was performed at Labbafinejad hospital, Tehran, Iran, between April and September 2021.

The following were the inclusion criteria for our study: (1) laboratory confirmation of SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) or imaging findings highly suggestive of COVID-19; (2) outpatients with moderate severity (respiratory rate <30/min, oxygen saturation >94%, or pulmonary infiltration <50% in both lungs)[11]; (3) age of at least 18 y; (4) agreed to participate in this study; (5) oral tolerance to the medication. The PCR kits are made by the Pishtazteb company in Iran. Additionally, an expert radiologist read the lung computed tomography (CT) scan of the patients. Unilateral and bilateral multilobular infiltrations, especially peripheral, and ground-glass opacities in lung CT scan were considered highly suggestive of COVID-19.

Additionally, the exclusion criteria were: (1) immunocompromised patients defined as receiving immunosuppressive medications, solid organ transplant, hematopoietic stem cell transplant, infection with human immunodeficiency virus, and active cancer[12]; (2) pregnancy; (3) consumption of other antiviral therapies from symptom onset; (4) severe hypersensitivity or anaphylactic shock after taking favipiravir.

Randomization and Blinding

First, we obtained written informed consent from eligible patients. Then, patients within 3-9 d of COVID-19 symptoms onset were randomized at a 1:1 ratio into two groups of control and intervention (simple randomization using a random

numbers table). Random concealment is also performed using sequentially numbered sealed opaque envelopes. This study was an open-label, nonblinded study.

Interventions

Patients in the control group received supportive therapy. According to the national guideline for COVID-19 management at the time of the study, outpatients with moderate severity received the following oral drugs: acetaminophen (500 mg every 6 h, until fever stops), diphenhydramine (10-15 ml every 6-8 h, in cases of coughing), vitamin D_3 (50000 IU, weekly, if there was no history of vitamin D consumption), zinc and selenium supplements (daily)[13]. Patients in the intervention group, in addition to supportive therapy, received oral favipiravir (Cytovex, made by Abidi company in Iran) at a dose of 1600 mg every 12 h for the first day and 600 mg every 12 h for the next 4 d. Additionally, the patients in both groups did not receive corticosteroids and anticoagulant drugs.

Outcomes

The primary endpoint was the hospitalization rate during the seven-days follow-up period. The secondary endpoints were symptoms and signs of the patients and laboratory tests. Patient symptoms were fever, sore throat, myalgia, cough, dyspnea, headache, gastrointestinal symptoms, and anorexia, which were assessed by an expert physician on days one (start of treatment), three, five, and seven. Patient signs were blood pressure (systolic and diastolic), pulse rate, respiratory rate, body temperature, and peripheral blood O_2 saturation, which were assessed by an expert physician on days one (start of treatment), three, five, and seven. Also, laboratory tests included a complete blood count (CBC) and a serum level of C-reactive protein (CRP), which were obtained on days one (start of treatment) and seven.

Statistical Analysis

Statistical Package for the Social Sciences version 18.0 was used to analyze the data. We described the obtained data as frequency, percentage, mean, and standard deviation. We also analyzed variables using independent-samples t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test as required. Also, in this study, the $p<0.05$ was considered significant.

The Ethics Committee of the School of Medicine, of Shahid Beheshti University of Medical Sciences, approved this study on March 3, 2021 (approval ID: IR.SBMU.MSP.REC.1399.750). The study was performed in accordance with the Helsinki Declaration.

Results

Baseline Characteristics of the Patients

According to the study's flow chart, 78 patients were randomized, of which 40 patients were assigned to the control group and 38 patients were assigned to the intervention group (Figure 1). In this study, the mean age of patients was 52.50±12.55 y (range: 18-78 y), and 43 (55.12%) were male. The time from the symptom

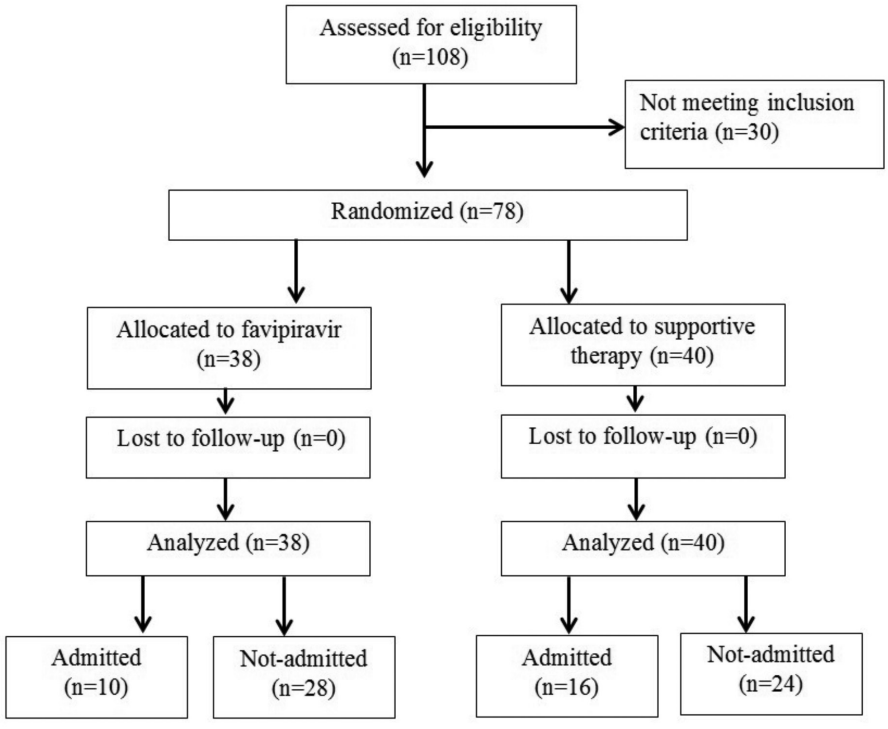

Figure 1. Flow chart of the study

onset to randomization of the intervention group (5.29±1.39) was significantly shorter than the control group (5.90±1.15) (t=2.115, p=0.038). However, there was no distinction between the two groups in terms of other basic characteristics. The detailed basic characteristics of the patients in both groups are shown in Table 1. In the control and intervention groups, respectively, the RT-PCR results of 23 (57.50%) and 21 (55.26%) patients were both positive. Additionally, all patients had imaging results that were COVID-19 suggestive.

The clinical symptoms of patients in the intervention and control groups at various time points are shown in Table 2. Although there was no difference in the two groups cough frequency at the beginning of treatment, on day seven, the intervention group's frequency was considerably lower than the control group's (χ^2=9.531, p=0.002). At the beginning of the course of treatment, the frequency of dyspnea was higher in the intervention group (χ^2=10.535, p=0.001); however, on the fifth day, it was much lower in the intervention group compared with the control group (χ^2=8.232, p=0.004).

The physical examination of the patients at different time points is shown in Table 3. At the beginning of treatment, the respiratory rate was higher in the intervention group compared with the control group (t=-3.626, p=0.001); however, it was significantly lower on the fifth (t=3.463, p=0.001) and seventh (t=2.815, p<0.001) days in the intervention group. Additionally, oxygen saturation was lower in the intervention group compared with the control group (t=4.232, p<0.001); however, it was significantly higher on the fifth (t=-2.480, p=0.016) and seventh (t=-2.317, p<0.001) days in the intervention group.

The laboratory results of patients at the start of treatment and on day seven are shown in Table 4. On the seventh day, there was no significant difference between the intervention and control groups in any of the laboratory variables.

Figure 2 shows that there was no significant difference (χ^2=1.642, p=0.200) between the intervention and control groups' (26.3% vs. 40.0%) overall hospitalization rates (26.3% vs. 40.0%) up until the end of the follow-up (χ^2=1.642, p=0.200). Additionally, we did not see any side effects in the patients.

Discussion

We performed this study to evaluate the efficacy of favipiravir in the treatment of patients with moderate COVID-19. Based on our results, favipiravir was effective in improving the respiratory demonstrations of the patients; however, it was not associated with the hospitalization rate. As shown in Table 5, our findings were consistent with some previous studies[14-17] and inconsistent with others[18-20].

The study by Szabo et al.[18] has revealed that the consumption of favipiravir did not affect the clinical course and progression of the disease. The contradiction between our findings and this

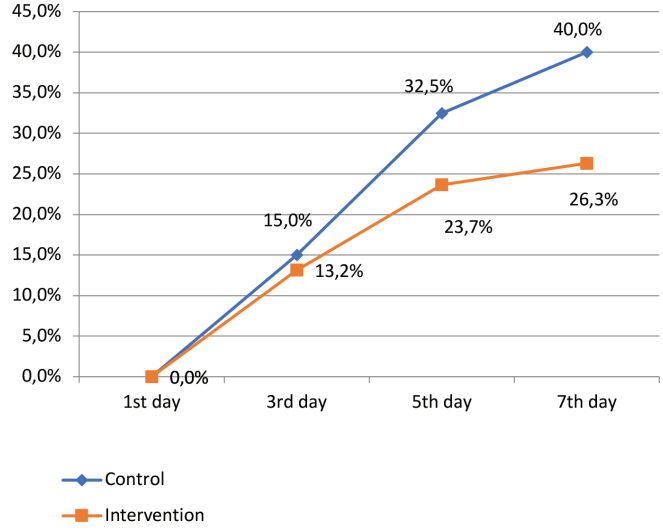

Figure 2. Hospitalization rate of the patients

Table 1. Comparison of baseline characteristics of the patients

		Control (n=40)	Intervention (n=38)	All (n=78)	Values	d.f.	p value
Age		51.95±13.34	53.08±11.80	52.50±12.55	-0.395	76	0.694[a]
Gender	Male	23 (57.5)	20 (52.63)	43 (55.12)	0.187	1	0.666[b]
	Female	17 (42.5)	18 (47.36)	35 (44.87)			
Diabetes mellitus		14 (35.0)	10 (26.3)	24 (30.8)	0.690	1	0.406[b]
Hypertension		12 (30.0)	16 (42.1)	28 (35.9)	1.457	1	0.265[b]
Cardiac disorders		0 (0)	2 (5.3)	2 (2.6)	-	-	0.234[c]
Chronic respiratory disorders		3 (7.5)	3 (7.9)	6 (7.7)	-	-	1.000[c]
Time from symptom onset to randomization		5.90±1.15	5.29±1.39	5.60±1.30	2.115	76	0.038[a]

Values are expressed as n (%) or mean±standard deviation.
[a]Independent-samples t-test.
[b]Chi-square test.
[c]Fisher's exact test.

study can be attributed to several causes. The patients in the above study were moderate to severe, which is distinct from our study. In moderate to severe cases, the patient's condition is usually more complicated, involving several organs. Additionally, the outcomes evaluated in this study included mortality and the need for immunomodulators and mechanical ventilation, which is different from ours.

Additionally, some studies were conducted to compare the therapeutic effects of favipiravir with other antiviral drugs. For example, a study by Solaymani-Dodaran et al.[21] showed that the need for intensive care and intubation, length of hospitalization and recovery, and mortality rate in the favipiravir-treated group were not different from those in the lopinavir/ritonavir-treated group. In a study conducted by Chen et al.[22] to compare the therapeutic effects of favipiravir with umifenovir, the rate of clinical recovery did not differ during the seven-day follow-up. Nevertheless, the time to improve fever and cough was shorter in the group treated with favipiravir. Generally, all of these drugs improve clinical symptoms by interfering with the replication and pathogenicity mechanisms of the virus.

Moreover, consumption of favipiravir significantly reduces pulmonary infiltration and decreases serum levels of erythrocyte sedimentation rate, CRP, and lactate dehydrogenase. However, it did not affect the concentration of inflammatory cytokines such as interleukin (IL)-8, IL-6, and interferons[23]. As shown in our study, the use of favipiravir did not affect all organs and improved respiratory symptoms alone. However, the duration of virus clearance from respiratory secretions and the proportion of viral shedding decreased following favipiravir consumption[24].

In terms of safety, most of the side effects of favipiravir are mild, such as increased uric acid and liver enzymes, gastrointestinal symptoms, and neutropenia. However, it should be used with

Table 2. Comparison of symptoms of the patients over time

		1st day	3rd day	5th day	7th day
Fever	Control	30 (75.0)	33 (82.5)	10 (29.4)	2 (7.7)
	Intervention	33 (86.6)	28 (73.7)	5 (15.2)	1 (3.4)
	p value	0.185	0.346	0.162	0.598*
Sore throat	Control	19 (47.5)	6 (15.0)	4 (11.8)	1 (3.8)
	Intervention	11 (28.9)	4 (10.5)	2 (6.1)	0 (0)
	p value	0.092	0.738*	0.673*	0.473*
Myalgia	Control	29 (72.5)	28 (70.0)	17 (50.0)	8 (30.8)
	Intervention	23 (60.5)	22 (57.9)	10 (30.3)	6 (20.7)
	p value	0.262	0.265	0.100	0.392
Cough	Control	39 (97.5)	40 (100.0)	34 (100.0)	24 (92.3)
	Intervention	37 (97.4)	37 (97.4)	30 (90.9)	16 (55.2)
	p value	1.000*	0.487*	0.114*	0.002
Dyspnea	Control	4 (10.0)	28 (70.0)	20 (58.8)	2 (7.7)
	Intervention	16 (42.1)	20 (52.6)	8 (24.2)	0 (0)
	p value	0.001	0.115	0.004	0.219*
Headache	Control	22 (55.0)	7 (17.5)	4 (11.8)	1 (3.8)
	Intervention	15 (39.5)	2 (5.3)	1 (3.0)	0 (0)
	p value	0.170	0.155*	0.356*	0.473*
Gastrointestinal symptoms	Control	21 (52.5)	1 (2.5)	34 (100)	26 (100)
	Intervention	12 (31.6)	1 (2.6)	33 (100)	29 (100)
	p value	0.062	1.000	-	-
Anorexia	Control	30 (75.0)	28 (70.0)	12 (35.3)	5 (19.2)
	Intervention	31 (81.6)	22 (75.9)	11 (33.3)	8 (27.6)
	p value	0.482	0.265	0.866	0.467
Missing data	Control	0	0	1	2
	Intervention	0	0	1	1

Values are expressed as n (%). *Fisher's exact test, the other statistical tests were chi-square test.

Table 3. Comparison of vital signs of the patients over time

		1st day	3rd day	5th day	7th day
Systolic blood pressure	Control	114.00±12.36	111.79±11.44	115.29±13.75	111.54±7.31
	Intervention	117.37±13.29	114.47±14.46	111.97±8.83	111.72±6.58
	p value	0.250	0.371	0.243	0.753*
Diastolic blood pressure	Control	72.25±6.78	72.56±8.26	72.65±9.71	72.69±4.53
	Intervention	74.87±8.50	74.08±9.28	71.97±8.83	71.72±5.86
	p value	0.136	0.452	0.733	0.805*
Pulse rate	Control	90.88±3.68	89.83±6.23	86.71±7.29	81.58±4.11
	Intervention	93.68±5.69	89.30±5.85	84.36±6.89	81.69±3.09
	p value	0.012	0.703	0.182	0.604
Respiratory rate	Control	25.35±0.83	26.08±2.36	25.00±3.08	21.08±2.92
	Intervention	26.08±0.94	25.03±2.64	22.45±2.92	19.3±1.60
	p value	0.001	0.069	0.001	0.000*
Body temperature	Control	38.14±0.60	38.04±0.60	37.35±0.72	36.96±0.40
	Intervention	38.51±0.56	37.90±0.62	36.80±1.87	36.86±0.35
	p value	0.007	0.312	0.118	0.123*
O_2 saturation	Control	95.97±0.86	94.10±1.91	93.76±2.52	95.53±1.60
	Intervention	95.10±0.95	94.42±1.98	95.15±2.01	96.51±1.52
	p value	0.000	0.469	0.016	0.000*
Missing data	Control	0	1	1	2
	Intervention	0	0	1	1

Values are expressed as mean±standard deviation. *Mann-Whitney U test, the other statistical tests were independent-samples t-test.

Table 4. Comparison of laboratory findings of the patients

	1st day					7th day				
	Control	Intervention	Values	d.f.	p value	Control	Intervention	Values	d.f.	p value
White blood cells (×cells/L)	5937.50±1195.4	5586.84±1460.3	1.163	76	0.248	5825.81±1143.9	5682.35±954.2	0.551	63	0.584
Neutrophil: lymphocyte ratio	5.67±2.7	6.49±2.5	−1.358	76	0.178	4.69±2.5	4.70±1.9	−0.015	63	0.988
Hemoglobin (g/dl)	14.08±1.3	14.11±1.1	−0.117	76	0.907	13.99±1.2	14.15±1.2	−0.535	63	0.594
Platelet count (×cells/L)	277025.00±83934.1	261421.05±81064.7	0.834	76	0.407	287161.29±98455.4	293264.71±82321.7	−0.272	63	0.787
Serum CRP level (mg/L)	12.80±4.0	15.89±3.7	−3.503	76	0.001	16.21±16.6	13.61±11.1	0.746	63	0.459
Missing data	0	0	–	–	–	4	9	–	–	–

Values are expressed as mean±standard deviation.
All comparisons were performed using an independent-samples t-test.

caution in pregnant women, as cases of teratogenicity have been reported[25]. Favipiravir is also metabolized in the liver and excreted by the kidneys. Consequently, it should be prescribed with caution in patients with liver or kidney disorders[26].

Study Limitations

Our study had several limitations. This study was an open-label study without blinding and a placebo group. To remove the placebo effect, it is necessary to design a blinded controlled study. Some patients on days fifth and seventh had missing values in outcomes. Besides, we followed the patients for up to seven d. If we followed longer, we would have a more complete judgment of the effect of the intervention. The control PCR was not done after treatment. Additionally, we only considered CBC and CRP as laboratory tests. While additional enzymes

Table 5. A review of previous studies on favipiravir effectiveness on COVID-19 patients

Study	Country	Study type	Results
Favipiravir consumption was beneficial.			
Alamer et al.[14]	Saudi Arabia	Retrospective study	The median time to discharge of the favipiravir group was shorter than the group treated with standard therapy (10 vs. 15 days, p<0.001).
Shinkai et al.[15]	Japan	Randomized clinical trial	The recovery time of the favipiravir group was shorter than the placebo group (11.9 vs. 14.7 days, p=0.0136).
Udwadia et al.[16]	India	Randomized clinical trial	The median time to clinical improvement of the favipiravir group was shorter than the supportive care group (3 vs. 5 days, p=0.030).
Ivashchenko et al.[17]	Russia	Randomized clinical trial	The median time to clinical improvement of the favipiravir group was shorter than the standard of care group (2 vs. 4 days, p=0.007).
Favipiravir consumption was not beneficial.			
Szabo et al.[18]	Hungary	Prospective sequential cohort study	Favipiravir consumption did not affect the progression of the disease (22.7% vs. 13.3%, p=0.13)
Lou et al.[19]	China	Randomized controlled trial	The median time to clinical improvement of the favipiravir group was not different from the control group (14 vs. 15 days).
Al-Muhsen et al.[20]	Saudi Arabia	Prospective observational study	Treatment with favipiravir was associated with more extended hospital stay (14 vs. 10 days, p=0.034) and a higher mortality rate (adjusted hazard ratio=3.63, p=0.034).

COVID-19: Coronavirus disease-2019

like aspartate transaminase and alanine transaminase could be evaluated.

Conclusion

This study suggests that the consumption of favipiravir in moderate COVID-19 patients was associated with increased oxygen saturation and decreased respiratory rate. In the other words, taking favipiravir can suppress the respiratory demonstrations in moderate cases of COVID-19, and it can be used as an outpatient treatment.

Ethics

Ethics Committee Approval: The Ethics Committee of the School of Medicine, of Shahid Beheshti University of Medical Sciences, approved this study on March 3, 2021 (approval ID: IR.SBMU.MSP.REC.1399.750).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.T., D.Y., Design: S.T., D.Y., A.B., L.G., Data Collection or Processing: S.T., A.B., Analysis or Interpretation: L.G., A.K., Literature Search: A.K., Writing: S.T., A.B., A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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