THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2021.35902
Med Bull Sisli Etfal Hosp 2022;56(2):189–195

Original Research

Favipiravir Experience in COVID-19 Patients at a Tertiary Center Intensive Care Unit

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Abstract

Objectives: The aim of this study was to compare intensive care unit (ICU) and overall hospital mortality in patients treated with favipiravir and lopinavir-ritonavir for COVID-19.

Methods: Data were collected retrospectively between March 10 and May 10, 2020, from patients' records admitted to ICU due to COVID-19. Laboratory data, clinical characteristics, ICU and hospital mortality, ICU and hospital length of stay were compared in patients treated with favipiravir and lopinavir-ritonavir.

Results: A total of 100 patients' data were investigated. Favipiravir was used as the treatment for 85% of patients, with the rest treated with lopinavir-ritonavir. Clinical and laboratory data of both antiviral treatment groups were similar. Length of hospital stay was 16 (9–24) days with favipiravir and 8.5 (5–12.5) days with lopinavir-ritonavir (p=0.002). Length of ICU stay for favipiravir and lopinavir-ritonavir groups were 8 (5–15) days and 4 (3–9) days, respectively (p=0.011). ICU mortality was 65.9% for the favipiravir and 80% for lopinavir-ritonavir (p=0.002). Hospital mortality for favipiravir and lopinavir-ritonavir was 67.1% and 80%, respectively (p=0.001).

Conclusion: The mortality in patients treated with favipiravir was less than patients treated with lopinavir-ritonavir. Favipiravir needs more attention and trials for its effect to be confirmed.

Keywords: COVID-19, intensive care unit, favipiravir, lopinavir-ritonavir, mortality

Please cite this article as "Acar Sevinc S, Surhan Cinar A, Balta Basi N, Metin S, Yucel T, Islamoglu S, et al. Favipiravir Experience in COVID-19 Patients at a Tertiary Center Intensive Care Unit. Med Bull Sisli Etfal Hosp 2022;56(2):189–195".

COVID-19 is the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and may present in different clinical scenarios: About 80% of patients present with mild, 13.8% present with severe disease, and 6.1% with critical disease.[1] According to the guidelines published by the Ministry of Health in Turkey, patients with severe and critical disease were advised to be admitted to intensive care unit (ICU).[2] Turkey diagnosed

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Submitted Date: July 13, 2021 **Accepted Date:** September 18, 2021 **Available Online Date:** June 28, 2022

its first COVID-19 case on March 11, 2020. A detailed treatment algorithm was published on April 14, 2020,[2] defining critical illness and treatment agents.

Many agents have been given for treatment of SARS-CoV-2 infection. "COVID-19 Diagnosis and Treatment Guideline" by the Ministry of Health advised nationwide use of favipiravir or lopinavir-ritonavir[2] although evidence was scarce this at the time of the publication.[3] Lopinavir-ritonavir is an HIV protease inhibitor shown to have activity against SARS-CoV-2 in Vero E6 cells.[4] Favipiravir is an RNA dependent RNA polymerase inhibitor and approved for the treatment of influenza in Japan at 2014.[5,6]

The aim of this study was to compare ICU and hospital mortality in patients with favipiravir and lopinavir-ritonavir treatment and compare other laboratory parameters in patients treated with these two antiviral agents.

Methods

Type of the Study

This is a retrospective cross-sectional study performed in accordance with the ethical standards of the Declaration of Helsinki. Local Ethical Committee approval number is 1574 at July 30, 2020, (NCT04645433). Informed consent was taken from patients or legally acceptable representatives for the use of their medical data.

Population and the Place

Patients admitted to ICU in our institution between March 10 and May 10, 2020, due to SARS-CoV-2 infection were included to the study. Admissions to ICU because of reasons other than COVID-19, patients younger than 18 years old and patients who received a full course of both lopinavir-ritonavir and favipiravir sequentially were excluded from the study.

Data Collection

Data were collected retrospectively from hospital records. Patients' age, sex, weight and height, comorbid illnesses including diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, and smoking habits were noted. The department that patients transferred from (e.g., emergency service or inpatient services), symptoms at admission to ICU were noted. Oxygen saturation, partial oxygen pressure, pH, partial carbon dioxide pressure, bicarbonate level, and paO_2/FIO_2 from the first arterial blood gas analysis at ICU were added to the investigated parameters.

Detailed laboratory values at the time of ICU admission were noted. Lymphopenia was accepted an absolute lymphocyte count <1.5 × 109/L. Acute renal failure frequency was calculated and diagnosed by Acute Kidney Injury Network criterion.[7]

COVID-19 Diagnosis

COVID-19 was diagnosed with either chest computed tomography findings and/or nasopharyngeal reverse-transcription polymerase chain reaction (RT-PCR) swab test results.[2] Tomography findings related to COVID-19 were classified as positive or negative. Nasopharyngeal RT-PCR swab test results for COVID-19 were also recorded.

Treatment

Admission criteria for ICU were based on national guideline.[2] They were severe pneumonia, dyspnea, respiratory distress, respiratory rate more than 30/min, PaO_2/FiO_2 <300, increasing need for oxygen on follow-up, hypotension, heart rate more than 100 per minute, acute organ dysfunction, increase in troponin level and arrhythmia, lactate more than 2 mmol/L, and capillary refill disorder. Severe pneumonia was defined with three criteria: (i) Tachypnea (≥30/min), and SpO_2 level <90% at room air together with classical COVID-19 symptoms; (ii) presence of bad prognostic measures such as lymphocyte count <0.8 × 109/L or CRP >40 mg/L or ferritin >500 ng/ml or D-dimer >1000 ng/ml; III. Bilateral diffuse pneumonia in chest computed tomography or X-ray.[2]

Respiratory support therapy was classified as nasal oxygen, nasal high flow oxygen, non-invasive mechanical ventilation (NIMV), and invasive mechanical ventilation (IMV). Type of respiratory support at ICU was investigated for the first admission day and during whole stay. Patients were classified according to whether they had sedatives, neuromuscular blockers, vasopressors, or not and frequency of prone position or self-prone position were calculated during ICU stay. IMV was performed if respiratory workload was increased, such as dyspnea, tachypnea (≥30/min), use of extra respiratory muscles, paradoxical respiration, and respiratory alkalosis was present ($PaCO_2$ <35 mmHg, pH>7.45). In other cases, NIMV may be tried.[2]

Treatment for COVID-19 was also regulated by "COVID-19 Diagnosis and Treatment Guideline."[2] Empirical hydroxychloroquine sulfate was given to all hospitalized patients unless contraindicated. Oseltamivir was advised empirically if the suspicion of influenza was high considering seasonal factors. Azithromycin was given empirically to patients with bilateral diffuse pneumonia. Other antibiotics were given if there was suspicion of bacterial pneumonia as well.

Favipiravir was advised for all patients with severe pneumonia and progressing pneumonia findings or worsening clinical manifestations except pregnant, breast feeding or postpartum women. RT-PCR results were not waited for before starting favipiravir in this group of patients and continued if RT-PCR results were negative but tomography findings were consistent with COVID-19. If the first swab result was negative, the second swab was ordered in the case of high clinical and/or radiologic suspicion.

Loading dose was 1600 mg twice a day. Maintenance dose was 600 mg per 12 h for 4 days. Lopinavir-ritonavir therapy was used in selected ICU patients before widespread availability of favipiravir (March 23, 2020) and/or if favipiravir was contraindicated. Combination of lopinavir 200 mg-ritonavir 50 mg tablet was the given form. It was given as double tablets twice daily for 10–14 days. Patients were accepted as under favipiravir therapy if they had an incomplete course of lopinavir-ritonavir therapy (<5 days) and followed by favipiravir for 5 days.

Mortality and length of stay during ICU and hospital censored for discharges were calculated for all patients and antiviral treatment groups.

Statistical Analysis

Statistical analyses were performed with the Scientific Package for the Social Science (version 21.0; SPSS Inc., Chicago, IL, USA). Continuous variables were given as mean±standard deviation if they distributed normally or as median (interquartile range) if they were distributed abnormally. Qualitative variables were given as a percentage. Comparison of normally distributed data was performed by independent samples t-test. Abnormally distributed data compared with the Mann–Whitney U test. Categorical variables were compared by the Chi-Square test. Differences were considered statistically significant for p values <0.05. Survival analysis was performed by Kaplan–Meier curve.

Results

A total of 114 patients were enrolled to the study. Nine patients were excluded due to admission reasons other than COVID-19. Patients treated with both lopinavir-ritonavir and favipiravir were also excluded (n=5). Final analysis was performed for 100 patients (Table 1). Mean age of patients was 65.6±13.3 years and most of them were male (70%). Detailed demographic characteristics and laboratory values for all patients and antiviral therapy subgroups are given in Table 1.

IMV was the mode of respiratory supportive therapy at 1st day of admission to ICU in 46 % of all cohort. Its frequency was 73 % during whole ICU period.

Hydroxychloroquine and azithromycin were given to all patients. Favipiravir was given to 85% (n=85), lopinavir-ritonavir was given to 15 % (n=15) of patients. Demographic characteristics and laboratory values of the patients with favipiravir and lopinavir-ritonavir therapy were all similar except respiratory rate (p=0.017) and heart rate at admission to ICU (p=0.03) (Table 1). Median ICU stay was 8 (5–15) days in patients treated with favipiravir whereas it was 4 (3–9) days in lopinavir-ritonavir group (p=0.011). Median length of hospital stays in patients treated with favipiravir and lopinavir-ritonavir was 16 (9–24) days and 8.5 (5–12.5) days, respectively (p=0.002). The other treatment details for patients with favipiravir and lopinavir-ritonavir therapy are given in Table 2.

Overall ICU mortality for favipiravir and lopinavir-ritonavir were 65.9% and 80%, respectively (p=0.002) (Fig. 1a). Moreover, overall hospital mortality for favipiravir and lopinavir-ritonavir were 67.1% and 80%, respectively (p=0.001) (Fig. 1b).

Discussion

This retrospective cross-sectional study investigates clinical, laboratory features, and mortality of patients with COVID-19 treated with favipiravir and lopinavir-ritonavir.

Demographic and laboratory data of our cohort was consistent with other published studies.[8-13] The COVID-19 pandemic has been a quite dynamic process. The data changed quickly making previous strategies to treat disease questionable. Apart from the drugs administered, clinical experience and management have also changed during ICU care. The initial policy was to intubate COVID-19 patients if they need more than 6 liters oxygen due to global trends at that time and to prevent COVID-19 spread by means of a closed circle respiratory system. This is the reason for higher frequency of IMV, sedation, neuromuscular blockage, and vasopressor support at first admission day to ICU in patients treated with lopinavir-ritonavir. As time passed, our institution changed strategy for intubation and supported respiratory system by methods other than IMV. Even though the 1st day approach was different in antiviral treatment groups due to the effect of time, overall respiratory support frequencies were similar except for high flow nasal oxygen. The reason for absence of high flow nasal oxygen usage in lopinavir-ritonavir group was due to logistic problems at beginning of pandemic in our institution. Regarding all these factors, it may be speculated that the

Table 1. Demographic, clinic, and laboratory details of all patients

Parameter	All patients n=100	Favipiravir n=85	Lopinavir-ritonavir n=15	p
Age, years, mean±SD*	65.6±13.3	64.9±12.9	69.8±15.1	0.192
Male patients n (%)	70	69.4	73.3	0.76
BMI†, kg/m^2, mean±SD	26.2±2.9	26.2±3.09	26.2±2.01	0.968
Comorbidities				
Diabetes (%)	30	32.9	13.3	0.127
Hypertension (%)	44	44.7	40	0.735
CAD‡ (%)	18	16.5	26.7	0.343
COPD§ (%)	9	9.4	6.7	0.859
Smoking habits				0.229
Never used (%)	48	44.7	66.7	
Ex-smoker (%)	3	3.5	-	
Active user (%)	15	14.1	20	
Unknown (%)	34	37.6	13.3	
ICU‖ admission from				0.631
Emergency department (%)	32	32.9	26.7	
Inpatient services (%)	68	67.1	73.3	
Chest computed tomography, consistent with COVID-19 (%)	99	98.8	100	0.673
Nasopharyngeal swab RT-PCR**, positive (%)	72	71.7	73.3	0.901
Clinical presentation				
Fever (%)	31	29.4	40	0.414
Cough (%)	50	48.2	60	0.401
Dyspnea (%)	81	80	86.7	0.544
Respiratory rate/min, median (IQR††)	24.5 (18-29.5)	26 (18-30)	18 (16-25)	0.017
Heart rate/min, median (IQR)	88.5 (80-99.5)	88 (78-98)	98 (80-115)	0.03
Arterial blood gas				
pH, median (IQR)	7.44 (7.35-7.49)	7.45 (7.36-7.49)	7.41 (7.28-7.50)	0.379
PaO_2, mmHg, median (IQR)	74 (59.2-90.7)	74 (58.5-87.4)	91.7 (61-115)	0.067
spO_2, %, mean±SD	92.4±5.07	92.3±5.06	93.4±5.23	0.454
$PaCO_2$, mmHg, median (IQR)	34.5 (28.3-42)	34.8 (28.4-41.5)	33 (27.6-48)	0.866
HCO_3, mEq/L, mean±SD	22.7±4.3	22.9±4.46	21.6±3.39	0.304
PaO_2/FiO_2, median (IQR)	120 (100-180)	120 (100-180)	120 (100-186)	0.830
Whole blood count				
Leukocyte, $\times10^9$/L, median (IQR)	9.0 (6.1-12.2)	8.88 (6.12-12.11)	10.01 (6.55-13.24)	0.592
Lymphocyte, $\times10^9$/L, median (IQR)	0.76 (0.46-1.05)	0.75 (0.46-1.08)	0.95 (0.44-1.05)	0.813
Neutrophil, $\times10^9$/L, mean±SD	8.5±4.4	8.5±4.6	8.5±3.5	0.955
Lymphopenia, %	95	95.3	93.3	0.748
Other laboratory values				
Glucose, mg/dl, median (IQR)	137 (112-177)	137 (111-178)	146 (112-168)	0.854
Urea, mg/dl, median (IQR)	46 (32-68)	46 (32-68)	46 (27-72)	0.889
Creatinine, mg/dl, median (IQR)	0.93 (0.75-1.32)	0.93 (0.75-1.35)	1.12 (0.76-1.31)	0.806
Aspartate aminotransferase, U/L, median (IQR)	45 (30.2-66.5)	44 (29-67)	47 (40-58)	0.434
Alanine aminotransferase, U/L, median (IQR)	31.5 (20.2-53.7)	32 (20.5-53.5)	28 (19-63)	0.714
Lactate dehydrogenase, U/L, median (IQR)	438 (336-560)	457 (323-612)	418 (321.5-480)	0.219
Albumin, g/dl, mean±SD	3.03±0.50	3.02±0.52	3.06±0.37	0.786
Ferritin, ng/ml, median (IQR)	522 (250-1094)	522 (232.5-1102)	506 (312-841)	0.918
Prothrombin time, seconds, mean±SD	14.7±5.06	14.9±4.99	13.5±5.45	0.301
D-dimer, ng/ml, median (IQR)	1135 (583-2200)	1200 (610-2440)	780 (386-1450)	0.141
Troponin, ng/L, median (IQR)	26.4 (11.0-105.2)	25.2 (9.65-100.5)	72 (20.5-226)	0.101
Lactate, mmol/L, median (IQR)	1.41 (1.20-2.09)	1.41 (1.23-1.99)	1.51 (0.99-2.83)	0.977
C reactive protein, mg/L, mean±SD	178.3±86.1	179.2±86.3	173.0±85.8	0.799
Procalcitonin, ng/ml, median (IQR)	0.48 (0.19-1.27)	0.48 (0.18-1.15)	0.53 (0.26-1.40)	0.802
Acute renal failure (%)	53.7	50.6	71.4	0.149

*SD: Standard deviation; †BMI: Body mass index; ‡CAD: Coronary artery disease; §COPD: Chronic obstructive pulmonary disease; ‖ICU: Intensive care unit; **RT-PCR: Reverse transcriptase polymerase chain reaction; ††IQR: Interquartile range.

Table 2. Respiratory support, treatment details, and length of hospital stay for all patients and subgroups

Parameter	All patients n=100	Favipiravir n=85	Lopinavir-Ritonavir n=15	p
Respiratory support				
Nasal oxygen				
First day (%)	26	27.1	20	0.566
All time (%)	35	37.6	24.7	0.186
High flow nasal oxygen				
First day (%)	21	24.7	0	0.03
All time (%)	35	41.2	0	0.002
NIMV*				
First day (%)	6	7.1	0	0.289
All time (%)	9	10.6	0	0.186
IMV †				
First day (%)	46	41.2	73.3	0.021
All time (%)	73	71.8	80	0.508
Sedation				
First day (%)	49	43.5	80	0.001
All time (%)	78	77.6	85.7	0.494
Neuromuscular blockage				
First day (%)	18	16.5	26.7	0.033
All time (%)	53.5	55.3	42.9	0.387
Vasopressor				
First day (%)	28	27.1	33.3	0.046
All time (%)	68.7	68.2	71.4	0.811
Self-prone position (%)	29.3	30.6	21.4	0.485
Prone position (%)	31.3	28.2	50	0.104
Treatment				
Oseltamivir (%)	41	36.5	66.7	0.028
Other antibiotics (%)	60.6	63.5	42.9	0.142
Prednisolone (%)	25.3	25.9	21.4	0.722
ICU‡ stay, days, median (IQR§)	7 (5–13.75)	8 (5–15)	4 (3–9)	0.011
Hospital stay, days, median (IQR)	15 (8–21)	16 (9–24)	8.5 (5–12.5)	0.002

*NIMV: Non-invasive mechanical ventilation; †IMV: Invasive mechanical ventilation; ‡ICU: Intensive care unit; §IQR: Interquartile range.

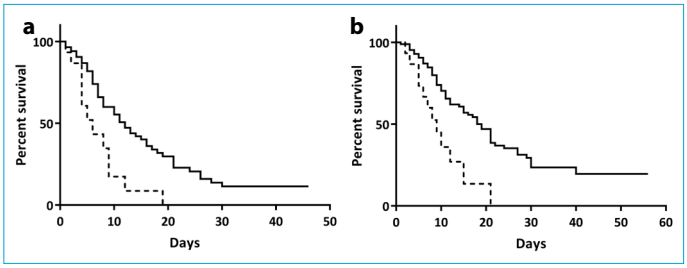

Figure 1. Survival curves for patients treated with favipiravir or lopinavir-ritonavir at **(a)** ICU **(b)** hospital. Solid line represents patients treated with favipiravir and dotted line represents patients treated with lopinavir-ritonavir. Patients treated with favipiravir had better ICU survival (p=0.002) and hospital survival (p=0.001).

reason for the difference in respiratory support therapy between the two antiviral groups was due to logistic problems and change in clinical practice, not due to a medication derived reason.

Median ICU stay was 9 (6–13) days in Italian ICU case series,[9] 9 (4–14) days in Seattle ICU case series.[14] Patients with favipiravir therapy stayed in ICU similar to published literature. Patients treated with lopinavir-ritonavir had shorter stays in ICU compared to favipiravir which could be related to limited number of patients and higher mortality rate in this group.

All patients were treated with hydroxychloroquine in our study. The World Health Organization recommended trials related to hydroxychloroquine to be suspended on July 4, 2020, due to lack of benefit at interim analysis of Solidarity trial.[15] This trial was a randomized study with more than 5500 participants to evaluate effects of hydroxychloroquine, remdesivir, lopinavir-ritonavir, lopinavir-ritonavir, and interferon-beta on survival.[16] Timing of publication was out of our study period making it impossible to change our practice, though our findings led to further question-

ing of hydroxychloroquine's believed effect.

The WHO also declared suspension of trials with lopinavir-ritonavir for COVID-19 at 06 July 2020 due to lack of effectiveness on mortality at solidarity trial.[15] In our study, lopinavir-ritonavir was used in ICU until favipiravir had started to be imported. This is the reason for unequal distribution of antiviral treatment arms. Favipiravir and lopinavir-ritonavir cohorts were almost always in the same laboratory and clinical condition. Even though the groups could not be randomized, this similarity might mean that the effect of medical treatment could not be biased by parameters related to clinical presentation at the time of admission.

Chen et al. randomized 240 patients to either favipiravir or umifenovir.[17] Clinical recovery rate at day 7 in both groups was similar. Cai et al. gave favipiravir and interferon-α by aerosol inhalation in 45 patients as the treatment group, and compared to a control group treated with lopinavir-ritonavir and interferon-α by aerosol inhalation in 35 patients.[18] They found faster viral clearance period and higher improvement rate in chest imaging. In our study, mortality in the favipiravir group was less than the lopinavir-ritonavir group. This might have resulted from the drug itself as the admission parameters between the two groups were similar. The other factor for better survival might have arisen from better care of patients because favipiravir was used later than lopinavir-ritonavir during the pandemic. To test this effect, the need for randomized clinical trials is obvious.

Limitations of the study were its retrospective design precluding randomization, limited number of participants, and the absence of a control group which was due to strict treatment criteria by national guidelines. However, if we consider that lopinavir-ritonavir was ineffective, our patients who had this agent could be accepted as having received maximal symptomatic care like a control group.

Even though we found favipiravir as effective, evidence for the use of favipiravir to treat COVID-19 is not sufficient. It is not in the scope of global trials so more trials with it to be accepted as effective against COVID-19 are needed. Our study may lead to increased focus on favipiravir and stimulate further studies.

Disclosures

Ethics Committee Approval: This is a retrospective cross-sectional study performed in accordance with the ethical standards of the Declaration of Helsinki. Local Ethical Committee approval number is 1574 at July 30, 2020, (NCT04645433).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.A.S, A.S.C.; Design – S.A.S., N.B.B.; Supervision – H.M.O., Materials – S.A.S., S.M., T.Y., S.I.; Data collection and processing – S.A.S., N.B.B., S.M., T. Y., S.I., Analysis and interpretation – S.A.S., A.S.C.; Literarute search – S.A.S.; Writing – S.A.S.; Critical review – A.S.C.

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