Comparison of lopinavir/ritonavir combination and favipiravir in COVID-19 treatment

Abstract

Background/aim: SARS-CoV-2, a ribonucleic acid coronavirus, rapidly spread worldwide within a short timeframe. Although different antiviral, anti-inflammatory, and immunomodulatory drugs are used, current evidence is insufficient as to which drug is more efficient. Our study compared favipiravir and lopinavir/ritonavir (LPV/RTV) therapies in inpatient care for coronavirus disease 2019 (COVID-19) pneumonia.

Materials and Methods: Demographic data, test results, treatments, and latest status of patients receiving inpatient COVID-19 pneumonia therapy were recorded. The initial favipiravir and LPV/RTV receiving groups were compared regarding the need for intensive care units (ICU) and mortality. Logistic regression analysis was performed by including variables showing significant differences as a result of paired comparisons into the model.

Results: Of the 204 patients with COVID-19 pneumonia, 59 (28.9%), 131 (64.2%), and 14 were administered LPV/RTV, favipiravir, and favipiravir with LPV/RTV, respectively. No difference was found in age, sex, presence of comorbidity, and tocilizumab, systemic corticosteroid, and plasma therapy use between patients administered with these three different treatment regimens. The mean mortality age of the patients was 71±14.3 years, which was substantially greater than that of the survivors (54.2±15.5 years). Compared with patients administered with LPV/RTV, ICU admission and mortality rates were lower in patients administered with favipiravir. CK-MB, AST, CRP, LDH, and creatinine levels were higher, whereas lymphocyte counts were lower in patients who died. Age, AST, CRP, LDH, and neutrophil counts were higher in patients

needing ICU, and eosinophil and lymphocyte counts were significantly lower. Logistic regression analysis showed that favipiravir use independently decreased mortality (P=0.006).

Conclusion: The use of favipiravir was more effective than LPV/RTV in reducing mortality in hospitalized patients with COVID-19.

Key Words: COVID-19, pneumonia, favipravir, lopinavir/ritonavir, mortality

1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic that emerged at the end of 2019, caused by the newly detected. SARS-CoV-2 is transmitted through the respiratory tract with droplets and aerosols emitted by an infected person. COVID-19 is characterized by a wide clinical spectrum, ranging from mild flu-like symptoms to severe acute respiratory distress syndrome and death [1]. The COVID-19 virus has infected more than 71 million people worldwide and caused more than one and a half million deaths as of December 14, 2020.

Although many treatments have been tried, no specific drug can currently prevent infection and treat COVID-19 [2]. Most of the available data for pharmacological treatments were derived from drugs used during SARS-CoV or MERS-CoV outbreaks or from in vitro observations. Various clinical and experimental studies on possible treatments for COVID-19, such as antiviral (lopinavir/ritonavir [LPV/RTV], favipiravir, remdesivir, and arbidol), anti-inflammatory (hydroxychloroquine and tocilizumab), and immunomodulatory drugs, stem cell therapy, and antioxidants are ongoing [1, 2]. There are no clear data on their superiority to each other; therefore, drug preferences vary by country. The serious consequences of the SARS-CoV-2 pandemic in terms of global

health and economics are continuing, and therefore, evidence-based clinical research and sharing of experiences are needed to reduce the spread of the disease and to find the most appropriate treatment options.

Our study aimed to compare the results of LPV/RTV combination and favipiravir treatment in hospitalized patients with COVID-19.

2. Materials and Methods

Our study retrospectively evaluated 204 patients with COVID-19 who received inpatient treatment between March 30, 2020 and September 30, 2020 in our hospital. The patients' age, gender, comorbidity, smoking history, length of hospital stay and treatments used, ICU needs, and mortality status were recorded. Besides, complete blood count, biochemistry test results, blood coagulation tests, liver, and kidney function tests, electrolytes, C-reactive protein, procalcitonin, lactate dehydrogenase, d-dimer, and plasma fibrinogen results were evaluated.

COVID-19 patients in our country are managed in line with the national treatment guideline, regularly updated by the scientific committee established by the Ministry of Health. LPV/RTV was used as an antiviral in some patients, and favipiravir was used in others due to changes in the national guideline published for COVID-19 treatment [3,4]. Tocilizumab, systemic corticosteroid, or convalescent plasma was also administered to patients with disease progression despite administration of antiviral treatment. Those administered with these treatments were also included in the study. COVID-19 was diagnosed using PCR or clinical, laboratory, and radiological findings. Patients who are younger than 18 years, pregnant, breastfeeding, and using hydroxychloroquine concurrently were excluded.

The ethics committee approved this study according to the rules of our institute (Ethical approval number: 2020/8/8) and the Ministry of Health.

2.1. Statistical analysis

Data were analyzed using IBM SPSS 25 package program. Continuous measurements were presented as mean ± standard deviation if they were normally distributed or median (with minimum and maximum). However, if the continuous measurements were not normally distributed, categorical variables were presented as counts (%). Independent sample T test was used to compare qualitative variables with two categories and quantitative variables, and chi-squared test was used to compare two categorical variables. Logistic regression analysis was performed by including variables with significant differences as a result of paired comparisons into the model. Type I error rate was taken as 0.05 in the study.

3. Results

The mean age of the patients was 56 ± 16 years, and 142 (69.6%) of them were male. In addition, 124 (60.8%) patients had at least one concomitant chronic disease. LPV/RTV, favipiravir, and favipiravir and LPV/RTV were administered to 59 (28.9%), 131 (64.2%), and 14 patients, respectively. No significant difference was found in terms of age, gender, presence of comorbidity, and use of tocilizumab, systemic corticosteroid, and convalescent plasma therapy between patient groups who were administered different treatment regimens. During their follow-up, 27 (13.2%) patients needed to ICU. The mortality rate was 10.8% (22/204). The duration of hospital stay in the group administered with both drugs was significantly higher than that in groups administered with LPV/RTV and favipiravir alone (Table 1).

The mean age of the patients who died was 71 ± 14.3 years, which was significantly higher than that of survivors (54.2 ± 15.5 years). The laboratory results of the two groups showed that CK-MB, AST, CRP, LDH, and creatinine levels were higher in the patients who died, whereas their lymphocyte count was lower. Although age, AST, CRP, LDH, and neutrophil counts were higher, eosinophil and lymphocyte counts were significantly lower in patients who needed ICU than those who did not (Table 2).

ICU requirement and mortality rates were lower in patients administered with favipiravir compared with those administered with LPV/RTV or LPV/RTV plus favipiravir. When ICU need and mortality rates were compared, no significant difference in presence of comorbidity, gender, and use of tocilizumab, systemic corticosteroid, and convalescent plasma was found between the groups (Table 3-4).

In logistic regression analysis, each one-unit increase in age and AST level increases the risk of ICU need by 1.067 and 1.018 times, respectively. Each one-unit increase in age and CK-MB levels increased the risk of death by 1.137 and 1.036 times, respectively. As a result of the logistic regression analysis, the treatment regimens used were not seen as an independent risk factor for the development of ICU need. Only the use of favipiravir reduced mortality independently (P = 0.006) (Table 5–6). Favipiravir use had an 8.33-fold protective factor for mortality compared with LPV/RTV use.

4. Discussion

In this retrospective observational study that evaluated the difference in efficacy between favipiravir and LPV/RTV in COVID-19 treatment, the mortality rate was found to be lower in patients treated with favipiravir compared with those treated with LPV/RTV. No statistically significant difference in ICU need was found between the two drugs.

Although favipiravir and patients treated with LPV/RTV were analyzed for viral burden and radiological outcomes beforehand, to the best of our knowledge, this is the first investigation to examine the clinical results, such as ICU need and mortality, of the two medications.

LPV and RTV are antiretroviral protease inhibitors used in combination in the treatment of HIV since 2000. LPV is effective against viral 3-chymotrypsin-like protease. RTV is used together to increase the half-life of LPV through cytochrome P450 inhibition and is effective only as a pharmacokinetic enhancer [5]. A randomized, controlled, open-label study for suppression of SARS-CoV-2 in China investigated the efficacy and safety of oral LPV/RTV in 199 adults hospitalized with severe COVID-19. In this study, patients were randomized 1:1 to receive LPV/RTV (400 mg/100 mg) (n = 99) twice daily in addition to standard care (n=100) or standard care for 14 days. The study showed no difference in clinical improvement between the two groups. Mortality at 28 days was also similar in both groups. No benefit beyond standard care was observed with LPV/RTV therapy in adult patients hospitalized with severe COVID-19 [6]. In a retrospective analysis of a small patient group, 75% of patients with COVID-19 treated with arbidol and LPV/RTV (16 patients) had negative SARS-CoV-2 in nasopharyngeal samples on the 7th day after treatment compared with those treated with LPV/RTV alone (35%, 17 patients) [7]. In another phase 2, multi-center, open-label, randomized study, triple antiviral therapy with interferon beta-1b, LPV/RTV, and ribavirin was compared to reduce virus transmission, alleviate symptoms, and facilitate discharge of patients with mild to moderate COVID-19. It has been reported to be safe and superior to LPV/RTV alone [8].

A clinical study involving 80 patients in Shenzhen was conducted to evaluate the safety and efficacy of favipiravir in COVID-19 treatment. In these open-label, nonrandomized, controlled trial results, 35 patients in the favipiravir arm had a significantly shorter viral clearance time (median, 4 vs 11 days; $P < 0.001$) compared with 45 patients in the LPV/RTV arm. Furthermore, radiological improvement was better in the favipiravir arm (recovery rate, 91.43% vs 62%; $p = 0.004$) [9]. In another multi-center randomized clinical study, no statistically significant difference was observed in the seven-day clinical improvement (improvement in body temperature, respiratory rate, oxygen saturation, and cough relief for >72 h after treatment) between favipiravir and umifenovir. However, in the favipiravir treatment group, fever reduction and cough relief time were significantly reduced [10]. In our study, no difference was observed in terms of ICU need between the patient groups treated with favipiravir and LPV/RTV, but favipiravir decreased mortality 8.33 times, independently from other factors affecting mortality.

Studies showed that the mortality rates were higher in patients with advanced age with COVID-19 [11,12]. In our study, advanced age was determined as an independent risk factor for mortality, each unit increment in age increases the mortality risk by 1.137 times. Various laboratory parameters have been studied as predictors of the probable course of the disease and mortality, such as age, lymphopenia, leukocytosis, and elevated ALT, LDH, high-sensitivity cardiac troponin I, creatine kinase, d-dimer, serum ferritin, IL-6, prothrombin time, and creatinine. Procalcitonin levels have been reported to be associated with mortality [12,13]. In our study, although CRP, LDH, creatinine, and CK-MB were elevated, and lymphocyte count was decreased in patients who died, logistic regression analysis revealed that only CK-MB among these laboratory parameters was independently associated with mortality.

Our study has a few limitations. The study was retrospective and had limited number of patients. Furthermore, because LPV/RTV, except pregnant women, is not any more suggested in the national guideline, enrolling more patients from a single referral center seems to be not possible.

In conclusion, the use of favipiravir was more effective in reducing mortality compared with LPV/RTV in hospitalized patients with COVID 19.

References

1. Elsawah HK, Elsokary MA, Abdallah MS, ElShafie AH. Efficacy and safety of remdesivir in hospitalized Covid-19 patients: Systematic review and meta-analysis including network meta-analysis. Reviews in Medical Virology 2020 Oct 31:e2187. doi: 10.1002/rmv.2187

2. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R et al. COVID-19 diagnosis and management: a comprehensive review. Journal of Internal Medicine 2020; 288(2): 192-206. doi: 10.1111/joim.13091

3. T. C. Ministry of Health, General Directorate of Public Health. COVID-19 (SARS-CoV2 Infection) Guide (Science Board Study) March 11, 2020.www.hsgm.saglik.gov.tr

4. T. C. Ministry of Health, General Directorate of Public Health. COVID-19 (SARS-CoV2 Infection) Guide (Science Board Study) Aprıl 2, 2020.www.hsgm.saglik.gov.tr

5. Lu CC, Chen MY, Lee WS, Chang YL. Potential therapeutic agents against COVID-19: What we know so far. Journal of The Chinese Medical Association 2020;83(6):534-536. doi: 10.1097/JCMA.0000000000000318

6. Cao B, Wang Y, Wen D, Liu W, Wang J et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. The New England Journal of Medicine 2020; 382(19): 1787-1799. doi: 10.1056/NEJMoa2001282

7. Deng L, Li C, Zeng Q, Liu X, Li X et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. Journal of Infection 2020; 81(1): 1-5. doi: 10.1016/j.jinf.2020.03.002

8. Hung IF, Lung KC, Tso EY, Liu R, Chung TW et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital

with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020; 395: 1695-1704. doi: 10.1016/S0140-6736(20)31042-4

9. Cai Q, Yang M, Liu D, Chen J, Shu D et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing) 2020; 6(10):1192-1198. doi: 10.1016/j.eng.2020.03.007

10. Chen C, Zhang Y, Huang J, Yin P, Cheng Z et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. bioRxiv preprint. https://doi.org/10.1101/2020.03.17.20037432

11. Shahid Z, Kalayanamitra R, McClafferty B, Kepko D, Ramgobin D et al. COVID-19 and Older Adults: What We Know. Journal of The American Geriatrics Society 2020; 68(5): 926-929. doi: 10.1111/jgs.16472

12. Zhou F, Yu T, Du R, Fan G, Liu Y et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062. doi: 10.1016/S0140-6736(20)30566-3

13. Li L, Zhang B, He B, Gong Z, Chen X. Critical patients with coronavirus disease 2019: Risk factors and outcome nomogram. Journal of Infection 2020; 80(6): 37-38. doi: 10.1016/j.jinf.2020.03.025

239 **Table 1.** Comparison of the clinical characteristics of the patients according to the
240 treatments

	LPV/RTV	Favipravir	LPV/RTV + Favipravir	Total	Chi-Square	P
Age (mean±SD)	54.5±15.8	55.97±16.6	62±13.5			0.302
Male	41(28.9)	90(63.4)	11(7.7)	142(100)	0.480	0.853
Female	18(29)	41(66.1)	3(4.8)	62(100)		
Comorbidities (n, %)						
Absent	23(28.7)	55(68.8)	2(2.5)	80(100)	4.077	0.128
Present	36(29)	76(61.3)	12(9.7)	124(100)		
Tocilizumab Treatment (n, %)						
No	58(29.9)	122(62.9)	14(7.2)	194(100)	2.144	0.282
Yes	1(10)	9(90)	0(0)	10(100)		
Convalescent Plasma Treatment (n, %)						
No	58(29.6)	124(63.3)	14(7.1)	196(100)	1.179	0.581
Yes	1(12.5)	7(87.5)	0(0)	8(100)		
Systemic Corticosteroid Treatment (n, %)						
No	59(30.1)	124(63.3)	13(6.6)	196(100)	4.056	0.084
Yes	0(0)	7(87.5)	1(12.5)	8(100)		
Length of Hospitalization	10.25±4.89	11.67±5.97	18.43±9.4			*<0.001

241

242

243

Table 2. Comparison of patients' hospital admission findings in terms of ICU need and mortality

	No need of ICU	Need of ICU	P	Survived	Dead	P
Age	54.55±16.3	65.1±12.6	0.001*	54.2±15.5	71±14.3	<0.001*
BMI	27.5±6.4	27.5±5.6	0.965	27.6±6	26.2±8.3	0.324
D-Dimer	1.7±3	2.03±4.4	0.610	1.7±3.3	1.9±2.2	0.839
Troponine	93.2±931	324.6±1520	0.465	22.2±109.5	958.2±3045.2	0.174
CK	175.3±212.3	301.9±399.5	0.149	176.1±212.1	307.7±414.3	0.166
CK-MB	23.02±16.3	27.9±11.1	0.148	22.4±15.7	34.1±12.7	0.001*
Fibrinogen	476.43±141.9	475.7±238.5	0.991	476.6±141.3	474±259.4	0.971
Ferritin	360.5±349.7	488.9±364.3	0.124	367.1±357.5	456.9±287.4	0.345
Procalcitonin	0.3±0.82	1.81±7.9	0.362	0.29±0.77	2.41±8.86	0.311
ALT	35.5±25.6	45.7±35.7	0.072	35.8±25.4	45.8±39	0.251
AST	46.8±26.3	68.85±48.1	0.027*	46.8±25.1	73.9±55.2	0.033*
CRP	93.9±112.7	149.6±89.1	0.015*	95±111.7	152.9±95.1	0.021*
LDH	422.6±181.8	575.9±201.8	<0.001*	429.5±191.4	563.3±150.6	0.002*
Na	134.9±9.8	136.8±3.5	0.319	135.1±9.7	135.54±3.9	0.821
K	4.5±1	4.2±0.5	0.142	4.4±0.9	4.5±1.1	0.636
Creatinine	0.9±0.38	0.98±0.3	0.279	0.9±0.37	1.06±0.29	0.046*
Lymphocyte#	1.3±0.6	1.02±0.6	0.036*	1.3±0.6	0.9±0.6	0.011*
Monocyte#	0.7±0.55	0.6±0.5	0.710	0.7±0.55	0.6±0.44	0.366
Neutrophil#	6.04±3.9	8.2±5.02	0.039*	6.13±4.04	7.9±4.66	0.053
Eosinophil#	0.06±0.16	0.009±0.02	<0.001*	0.06±0.15	0.03±0.04	0.258
WBC	8.14±3.93	9.9±5.01	0.089	8.22±4.03	9.62±4.75	0.132
Hemoglobin	13.2±1.9	13.01±1.5	0.633	13.2±1.8	13±2	0.592
Hematocrit	38.8±5.2	38.4±3.8	0.643	38.9±5.05	37.7±5.07	0.304
Platelet#	229.3±81.1	201.5±75.6	0.096	228.7±80.2	200.6±83	0.124

Table 3. Comparison of patient characteristics and treatments in terms of intensive care need

ICU need	Present (%)	Absent (%)	Total (%)	Chi-square	P
Gender					
Male	124(87.3)	18(12.7)	142(100)	0.017	0.895
Female	53(85.5)	9(14.5)	62(100)		
Comorbidity					
Absent	74(92.5)	6(7.5)	80(100)	2.993	0.084
Present	103(83.1)	21(16.9)	124(100)		
Tocilizumab					
No	169(87.1)	25(12.9)	194(100)	0.029	0.866
Yes	8(80)	2(20)	10(100)		
Convalescent Plasma					
No	171(87.2)	25(12.8)	196(100)	0.221	0.639
Yes	6(75)	2(25)	8(100)		
Steroids					
No	171(87.2)	25(12.8)	196(100)	0.221	0.639
Yes	6(75)	2(25)	8(100)		
Medication					
LPV/RTV	122(93.1)	9(6.9)	131(100)	18.257	<0.001*
Favipiravir	48(81.4)	11(18.6)	59(100)		
Favipiravir +LPV/RTV	7(50)	7(50)	14(100)		

252 **Table 4.** Comparison of patient characteristics and treatments in terms of mortality

Mortality	Alive (%)	Dead (%)	Total (%)	Chi-square	P
Gender					
Male	127 (89.4)	15 (10.6)	142 (100)	0.001	0.999
Female	55 (88.7)	7 (11.3)	62 (100)		
Comorbidity					
Absent	76 (95)	4 (5)	80 (100)	3.641	0.056
Present	106 (85.5)	18 (14.5)	124 (100)		
Tocilizumab					
No	173 (89.2)	21 (10.8)	194 (100)	0.001	0.999
Yes	9 (90)	1 (10)	10 (100)		
Convalescent Plasma					
No	175 (89.3)	21 (10.7)	196 (100)	0.001	0.999
Yes	7 (87.5)	1 (12.5)	8 (100)		
Steroids					
No	174 (88.8)	22 (11.2)	196 (100)	0.178	0.673
Yes	8 (100)	0 (0)	8 (100)		
Medication					
LPV/RTV	46 (78)	13 (22)	59 (100)	14.475	0.001*
Favipiravir	125 (95.4)	6 (4.6)	131 (100)		
Favipiravir +LPV/RTV	11 (78.6)	3 (21.4)	14 (100)		

253

254

255

Table 5. Logistic regression analysis on the risk factors associated with ICU in hospitalized patients with COVID-19 pneumonia

	B	S.E.	Wald	P	OR (95% CI)
LPV/RTV			4.48	0.106	
Favipiravir	-1.101	0.579	3.622	0.057	0.332(0.107-1.033)
Favipiravir + LPV/RTV	0.139	0.793	0.031	0.861	1.149(0.243-5.432)
Age	0.065	0.022	9.005	0.003*	1.067(1.023-1.113)
AST	0.018	0.008	5.44	0.020*	1.018(1.003-1.033)
CRP	0.002	0.003	0.373	0.541	1.002(0.997-1.007)
LDH	0.002	0.001	1.71	0.191	1.002(0.999-1.005)
Lymphocyte#	0.42	0.467	0.809	0.368	1.523(0.609-3.805)
Neutrophil	0.104	0.063	2.72	0.099	1.109(0.981-1.255)
Eosinofil	-37.413	14.081	7.059	0.008*	0
Constant	-8.16	2.015	16.392	0	0

Table 6. Logistic regression analysis on the risk factors associated with mortality in hospitalized patients with COVID-19 pneumonia

	B	S.E.	Wald	P	OR (95% CI)
Age	0.129	0.035	13.855	<0.001*	1.137(1.063-1.217)
CK-MB	0.035	0.016	5.006	0.025*	1.036(1.004-1.068)
AST	0.022	0.013	3.102	0.078	1.022(0.997-1.048)
CRP	-0.001	0.004	0.074	0.786	0.999(0.99-1.007)
LDH	0.003	0.002	2.204	0.138	1.003(0.999-1.007)
Creatinine	0.184	0.657	0.078	0.779	1.202(0.332-4.352)
Lymphocyte#	-0.587	0.749	0.616	0.433	0.556(0.128-2.41)
Constant	-13.608	3.46	15.471	0	0
LPV/RTV			7.42	0.024*	
Favipiravir	-2.119	0.778	7.407	0.006*	0.120(0.026-0.553)
Favipiravir + LPV/RTV	-1.332	1.034	1.658	0.198	0.264(0.035-2.004)