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Comparison of non-severe COVID-19 pneumonia patients treated with lopinavir/ritonavir and favipiravir

Lopinavir/ritonavir ve favipiravir ile tedavi edilen ağır olmayan COVID-19 pnömoni hastalarının karşılaştırılması

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Abstract

Aim: There is no proven medical treatment for COVID-19 to date. We aimed to evaluate the effectiveness of LPV/r and FVR treatments in non-severe COVID-19 pneumonia patients and compare the clinical outcomes.

Methods: In this retrospective cohort study, the data of non-severe COVID-19 pneumonia patients treated with lopinavir/ritonavir and FVR were analyzed.

Results: A total of 91 non-severe COVID-19 patients, 33 (36.2%) treated with LPV/r and 58 (63.8%) treated with FVR, were included in the study. The mean ages of the LPV/r group and FVR group were 53.1 (13) years and 57.2 (17.44) years, respectively (P=0.24). There was no statistically significant difference between the two groups in terms of comorbidities (P=0.06). FVR patients had higher radiological weight scores than LPV/r patients, but this was not statistically significant (8.67 (3.7) vs 7.66 (3.22) P=0.2, respectively). While SpO_2 levels of FVR patients at the time of admission were lower than those of LPV/r patients, CRP levels were higher (92.22 (2.8) vs 97.87 (2.05), P<0.001, respectively and 75.42 (62) vs 45.42 (49.92), P=0.02, respectively). FVR patients had a shorter fever regression time than LPV/r patients (2.7 (0.9) vs 4 (1), P<0.001, respectively). Post-treatment neutrophil, lymphocyte, N/L ratio and D-Dimer levels decreased more in FVR group compared to the LPV/r group (P=0.01, <0.001, 0.001, <0.001, respectively).

Conclusion: Although non-severe COVID-19 patients using FVR had lower oxygen saturations, more widespread radiological involvement, and higher CRP levels at admission, we found that FVR was more effective in improving laboratory parameters and controlling fever than LPV/r treatment. The efficacy of lopinavir/ritonavir and FVR warrants further verification by future, larger studies.

Keywords: COVID-19, Non-severe pneumonia, Favipiravir, Lopinavir/ritonavir

Öz

Amaç: Günümüzde COVID-19 için kanıtlanmış bir medikal tedavi yoktur. Çalışmamızda ağır seviyeli olmayan COVID-19 pnömoni hastalarında LPV/r ve FVR tedavilerinin etkinliğini değerlendirerek, LPV/r ile FVR ile tedavi edilen hastalar arasındaki klinik sonuçları karşılaştırmayı amaçladık.

Yöntemler: Bu çalışma retrospektif bir kohort çalışmasıdır. Lopinavir/ritonavir ve FVR ile tedavi edilen ağır seviyeli olmayan COVID-19 pnömoni hastalarının verileri incelendi.

Bulgular: 33'ü (%36,2) LPV/r ve 58'i (%63,8) FVR ile tedavi edilen, toplam 91 ağır seviyeli olmayan COVID-19 pnömoni hastası çalışmaya dahil edildi. LPV/r grubunun yaş ortalaması 53,1 (13), FVR grubunun yaş ortalaması 57,2 (17,4) idi (P=0,24). Her iki grup arasında komorbidite varlığı açısından istatiksel olarak anlamlı fark yoktu (P=0,06). FVR hastalarının LPV/r hastalarına göre radyolojik ağırlık skoru daha yüksekti ancak bu istatistiksel olarak anlamlı değildi (sırasıyla 8,67 (3,7) ve 7,66 (3,22), P=0,2). FVR hastalarının başvuru esnasındaki SpO_2 seviyeleri LPV/r hastalarına göre daha düşük, CRP seviyeleri daha yüksekti (sırasıyla 92,22 (2,8) ve 97,87 (2,05), P<0,001, 75,42 (62) ve 45,42 (49,92), P=0,02). FVR hastalarında LPV /r hastalarına göre ateşin düşme süresi daha kısa idi (sırasıyla 2,7 (0,9) ve 4 (1), P<0,001). FVR kullanan hastalarda tedavi sonrasında LPV/r kullanan hastalara göre Nötrofil, Lenfosit, N/L oranı ve D-Dimer seviyelerinin daha fazla düştüğü saptandı (sırasıyla P=0,01, <0,001, 0,001, <0,001).

Sonuç: FVR kullanan hastaların, başvuru esnasında daha düşük oksijen saturasyonlarına, daha yaygın radyolojik tutulumlarına ve daha yüksek CRP seviyelerine sahip olmasına rağmen LPV/r kullanan hastalara göre laboratuvar parametrelerinin düzelmesinde ve ateşin kontrol altına alınmasında daha etkili olduğunu saptadık. COVID-19 hastalarında LPV/r ve FVR tedavilerinin etkinliği üzerine daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: COVID-19, Ağır olmayan pnomoni, Favipiravir, Lopinavir/ritonavir

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Introduction

Starting from Wuhan/China in December 2019, COVID-19 turned into a pandemic that affected the entire world. As of the end of June 2020, the number of people infected with SARS-CoV-2 has exceeded 10 million and the number of COVID-19 related deaths has exceeded 500 thousand worldwide. In the same period, more than 190 thousand of infected people were reported in Turkey, while the death toll exceeded 5000 [1].

There is currently no proven treatment for COVID-19. Treatment is planned experimentally, considering the clinical experience in SARS and MERS outbreaks and the antiviral activity of some drugs. However, there is not enough data about the effectiveness of the antiviral drugs and at which stage we should use them. Therefore, treatment guidelines and used antiviral agents differ among countries [2]. Although antiviral therapy is generally used in patients with severe and critical COVID-19, there are no studies in the literature regarding the use of antiviral therapy in non-severe (mild and moderate) COVID-19 patients.

Lopinavir/ritonavir (LPV/r) is a proteinase inhibitor in coronaviruses that acts by inhibiting the 3CLpro proteinase, which is responsible for processing the polypeptide product into protein components in the RNA genome [3]. Early LPV/r usage in SARS has been shown to reduce intubation rates, ARDS development and mortality [4-5]. However, this positive effect has not yet been demonstrated in COVID-19 patients [6].

Favipravir (FVR) is a purine analogue that is an RNA-dependent RNA polymerase inhibitor (RDRI) [7]. It has been used in the treatment of COVID-19, considering that it can also be effective in the SARS-CoV-2 virus, an RNA virus known to contain RDRI. Limited number of studies have demonstrated that the use of FVR in COVID-19 patients controls symptoms such as cough and fever in a shorter time and reduces the time for radiological recovery and virus removal [8-9].

In this study, we aimed to evaluate the effectiveness of LPV/r and FVR treatments in non-severe COVID-19 pneumonia patients and compare the clinical outcomes.

Materials and methods

Study population

Ninety-one moderate-level COVID-19 patients, who were followed between 10 March 2020 and 1 May 2020 in Istanbul Sultan Abdülhamid Education and Research Hospital, were included in the study. The patients were divided into two groups as those using FVR (Group 1, n=58) or LPV/r (Group 2, n=33). Ethics committee approval was obtained from the ethics committee of Ümraniye Training and Research Hospital. Inclusion criteria were as follows: 1. Being over 18 years old 2. Having a positive PCR test for COVID-19 3. Despite being COVID PCR negative, being clinically, laboratory and radiologically diagnosed with COVID-19 4. Having newly emerged infiltration compatible with COVID-19 pneumonia in computed tomography 5. SpO_2 level at room air $\geq$ 90% and respiratory rate <30/min 6. Being followed up in an inpatient clinic and using Lpv/r for at least 7 days and FVR for at least 5 days. Exclusion criteria were as follows: 1. Being under the age of 18 2. Being pregnant or breastfeeding 3. Having no findings compatible with COVID-19 pneumonia in computed tomography 4. SpO_2 level in the room air <90% and respiratory rate >30 /min 5. Using LPV/R less than 7 days or FVR less than 5 days. SARS-CoV-2 was detected by next-generation sequencing or real-time RT-PCR method.

Lopinavir/ritonavir and Favipiravir treatment protocol

In the LPV/r group, 2 x 2 200/50 mg LPV/r was used for at least 7 days. In the FVR group, 2x 600 mg FVR was used for the next 4 days after a loading dose of 2x1600 mg for the first day (5 days in total).

Collection of data and evaluation of treatment effectiveness

The demographic and clinical features, laboratory findings and treatment parameters of the patients were obtained from the hospital information system. Demographic features, patient symptoms and comorbidities, progression rates to intensive care unit, laboratory parameters during and after treatment (WBC, neutrophil, lymphocyte, neutrophil/lymphocyte ratio, lactate dehydrogenase (LDH), D-dimer, C-reactive protein (CRP)) were all recorded. Computed tomography was performed to all patients. The severity of radiological findings was evaluated by scoring between 0-20 according criteria described by Chang et al [10]. Based on this classification system, severity of lung involvement was scored as none (0%) (0 points), minimal (1-25%) (1 point), mild (26-50%) (2 points), moderate (51-75%) (3 points) and severe (76-100%) (4 points) by evaluating the percentage of involvement for each lobe. Total radiological weight score was obtained by summing the scores of 5 lobes (0-20).

Statistical analysis

Because of the suitability of the Central Limit Theorem, parametric tests were used without normality testing [11]. In the analysis of the data, mean and standard deviation, minimum and maximum values were used for scales, and frequency and percentage values were used for defining categorical variables. Non-parametric tests were used for LDH and D-Dimer measurements, because of the high deviations from the mean. Student's t and Mann-Whitney U tests were used to compare the means of the two independent groups, and Paired t test was used to compare the means of two dependent groups. Chi-square test statistics were used to evaluate the relationship between categorical variables. Exposure ratio (odds ratio) of the variables that were related to the treatment status are given. $P<0.05$ was considered statistically significant. In the evaluation of the data, www.e-picos.com New York software and MedCalc statistics package program were used.

Results

Ninety-one patients who were hospitalized with the diagnosis of non-severe COVID-19 pneumonia were included in the study. Their mean age was 55.7 ± 16 years. The patients were divided into two groups as those using LPV/r (n=33) and FVR (n=58). While the mean age of patients using LPV/r was 53.1 (13) years, that of patients using FVR was 57.2 (17.44) years ($P=0.24$) (Table 1). At least one comorbid disease was present in 45 patients (49.5%). There was no statistically significant difference between the two groups in terms of presence of

comorbidities (P=0.06) (Table 1). The frequency of coronary artery disease was higher in the FVR (P=0.04) group. A total of 3 patients (3.3%) (2 patients (6.1%) in the LPV/r group and 1 (1.7%) in the FVR group) were transferred from the in-patient clinic to the intensive care unit. There were no deaths in either group. FVR patients had insignificantly higher radiological weight scores than LPV/r patients (8.67 (3.7) vs 7.66 (3.22), P=0.2, respectively). SpO_2 levels of FVR patients at admission were lower than those of LPV/r patients (92.22 (2.8) vs 97.87 (2.05), P<0.001, respectively). FVR patients had a shorter fever regression time compared to LPV/r patients (2.7 (0.9) vs 4 (1), P<0.001, respectively) (Table 1).

Table 1: Demographics, baseline and clinical characteristics of patients treated with LPV/r and FVR

Variables		Total (n=91) n (%)	LPV/r (n=33) N (%)	FVR (n=58) n (%)	*P*-value*
Gender	Male	59 (64.8)	20 (60.6)	39 (67.2)	0.52
	Female	32 (35.2)	13 (39.4)	19 (32.8)	
Age	Mean (SD) (years)	55.7(16)	53.1(13.1)	57.2(17.4)	0.24
Comorbidities	Yes	45 (49.5)	12 (36.4)	33 (56.9)	0.06
	No	46 (50.5)	21 (63.6)	25 (43.1)	
Hypertension	Yes	32 (35.2)	11 (33.3)	21 (36.2)	0.78
	No	59 (64.8)	22 (66.7)	37 (63.8)	
Diabetes	Yes	13 (14.3)	3 (9.1)	10 (17.2)	0.28
	No	78 (85.7)	30 (90.9)	48 (82.8)	
Arrhythmia	Yes	6 (6.6)	-	6 (10.3)	0.06
	No	85 (93.4)	33 (100)	48 (89.7)	
CAD	Yes	7 (7.7)	-	7 (12.1)	0.04
	No	84 (92.3)	33 (100)	51 (87.9)	
CRAD (COPD/ Asthma)	Yes	6 (6.6)	1 (3)	5 (8.6)	0.41
	No	85 (93.4)	32 (97)	53 (91.4)	
Signs and symptoms					
Fever	Yes	77 (84.6)	26 (78.8)	51 (87.9)	0.24
	No	14 (15.4)	7 (21.2)	7 (12.1)	
Cough	Yes	59 (64.8)	19 (57.6)	40 (69)	0.27
	No	32 (35.2)	14 (42.4)	18 (31)	
Dyspnea	Yes	22 (24.2)	8 (24.2)	14 (24.1)	0.99
	No	69 (75.8)	25 (75.8)	44 (75.9)	
Diarrhea and nausea	Yes	21 (23.1)	4 (12.1)	17 (29.3)	0.06
	No	70 (76.9)	29 (87.9)	41 (70.7)	
Headache	Yes	8 (8.8)	1 (3)	7 (12.1)	0.14
	No	83 (91.2)	32 (97)	51 (87.9)	
Transfer to ICU	Yes	3 (3.3)	2 (6.1)	1 (1.7)	0.26
	No	88 (96.7)	31 (93.9)	57 (98.3)	
Radiological weight score	Mean (SD)	9.3 (3.55)	7.66 (3.22)	8.67 (3.7)	0.2
SpO_2 level (room air)	Mean (SD)	93.18 (2.85)	97.87 (2.05)	92.22 (2.8)	<0.001
Clinical length of stay (day)	Mean (SD)	11.1 (3.7)	11.5 (3)	10.9 (4)	0.51
Fever response time (day)	Mean (SD)	3.2 (1.18)	4 (1)	2.7 (0.9)	<0.001

N: number, SD: standard deviation, Min: minimum, Max: maximum, CAD: coronary artery disease, CRAD: chronic respiratory airway disease, COPD: chronic obstructive pulmonary disease, GIS: gastrointestinal system, ICU: intensive care unit. *P is significant at the level of <0.05. (Chi-square test, Student's t test)

Prognostic laboratory parameters at the time of hospital admission were compared between the two groups (Table 2). CRP values were higher in FVR patients compared to the LPV/r group (75.42 (62) vs 45.42 (49.92), P=0.02, respectively). There was no statistical difference between WBC, Neutrophil, Lymphocyte, N/L ratio, LDH and D-Dimer levels (Table 2).

Clinical and prognostic laboratory parameters before and after Lpv/r and FVR treatments were also compared (Table 3). After the treatment, N/L ratio and LDH significantly decreased and WBC significantly increased in the LPV/r group (P=0.01, P=0.01, P=0.05, respectively), and neutrophil, lymphocyte, N/L ratio, CRP and LDH levels significantly decreased and SpO_2 levels significantly increased (P<0.02, <0.001, <0.001, <0.001, <0.001, respectively) in the FVR group (Table 3). Post-treatment neutrophil, lymphocyte, N/L ratio and D-Dimer levels were significantly decreased in patients using FVR when compared to patients using LPV/r (0.01, <0.001, 0.001, <0.001, respectively) (Table 3).

Table 2: Comparison of laboratory parameters at presentation of patients treated with LPV/r and FVR

Variables	Total (n=91)	LPV/r (n=33) x̄ (SD)	FVR (n=58) x̄ (SD)	*P*-value*
WBC (K/mm3)	5.95 (1.95)	5.67 (1.91)	6.11(1.97)	0.3
Neutrophil (K/mm3)	3.4 (2.3)	4.06 (1.82)	4.53 (1.99)	0.27
Lymphocyte (K/mm3)	2.2 (1.82)	1.33 (0.94)	1.14 (0.46)	0.22
N/L ratio	2.97 (2.7)	3.78 (2.57)	4.44 (2.43)	0.23
CRP (mg/L)	64.54 (59.68)	45.42 (49.92)	75.42 (62.39)	0.02
LDH (U/L)	613.86 (745.35)	527.03 (284.98)	663.27 (908.15)	0.4
D-Dimer (µg/L)	809.41(1329.75)	666.23(715.01)	873.6(1528.74)	0.6

N: number, SD: standard deviation, WBC: white blood cell, N/L ratio: neutrophil/lymphocyte ratio, CRP: C-reactive protein, LDH: lactate dehydrogenase. *P is significant at the level of <0.05. (Student's t test/Mann-Whitney U)

Table 3: Comparison of prognostic laboratory and clinical parameters before and after LPV/r and FVR treatment

	LPV/r (n=33)			FVR (n=58)			*P*-value *
Variables	Before treatment x̄ (SD)	After treatment x̄ (SD)	*P*-value	Before treatment x̄ (SD)	After treatment x̄ (SD)	*P*-value	
WBC (K/mm3)	5.67 (1.91)	6.4 (2.7)	0.05	6.11 (1.97)	6.2 (1.9)	0.77	0.17
Neutrophil (K/mm3)	4.06 (1.82)	3.81 (1.67)	0.35	4.53 (1.99)	3.86 (1.65)	<0.02	0.01
Lymphocyte (K/mm3)	1.33 (0.94)	1.52 (0.48)	0.29	1.14 (0.45)	1.75 (0.64)	<0.001	<0.001
N/L ratio	3.78 (2.57)	2.69 (.35)	0.01	4.44 (2.43)	2.4 (1.11)	<0.001	0.0001
CRP (mg/L)	45.42 (49.92)	49.11 (65.39)	0.79	75.42 (62.39)	19.41 (30.63)	<0.001	0.39
LDH (U/L)	527.03 (284.98)	400.15 (91.52)	0.01	663.27(908.15)	399.2 (104.9)	<0.001	0.49
D-Dimer (µg/L)	686.33 (737.86)	936.41 (959.97)	0.54	873.6 (1528.74)	557.7 (580.39)	0.39	<0.001
SpO_2	94.87 (2.05)	94.72 (1.82)	0.72	92.22 (2.8)	95.37 (2.6)	<0.001	0.13

N: number, SD: standard deviation, WBC: white blood cell, N/L ratio: neutrophil/lymphocyte ratio CRP: C-reactive protein, LDH: lactate dehydrogenase. *P is significant at the level of <0.05. (Paired t test/Wilcoxon test/Student's t test)

Discussion

There are limited data regarding the effectiveness of LPV/r and FVR treatments in patients with non-severe COVID-19 pneumonia. This retrospective study is the first to evaluate the effects of LPV/r and FVR treatments on clinical and laboratory parameters in that patient group.

In our study, we found that FVR was more effective in improving laboratory parameters and controlling fever when compared to LPV/r in non-severe COVID-19 patients, despite lower oxygen saturation, more widespread radiological involvement, and higher CRP levels. In their study, Cai et al. [8] showed that in COVID-19 patients with SpO_2 >93% and respiratory rate <30 /minute who received FVR, viral clearance was faster compared to those who received LPV/r (4 vs. 11 days). They also showed that radiological recovery (91.43% vs. 62.22%) was better. No comparison of clinical and laboratory parameters was made in this study.

Approximately 20% of COVID-19 patients progress to multi-organ dysfunction, including respiratory failure, septic shock, acute cardiac injury, or acute renal failure [12-13]. In our study, only 3 patients were transferred to the intensive care unit due to respiratory failure. None of them died. Although the number of patients using FVR was higher than patients using LPV/r (n=58 vs n=33), the proportion of patients transferred to the intensive care unit was insignificantly lower (1.7% vs 6.1%).

High AST, ALT, total bilirubin, LDH, D-Dimer, CRP, WBC levels and low lymphocyte values were shown to be associated with progression in COVID-19 patients [14]. A recent meta-analysis also states that patients with severe COVID-19 have higher levels of neutrophils, LDH, D-Dimer, CRP, WBC levels and lower lymphocyte counts than patients with non-

severe COVID-19 [15]. In our study, Neutrophil, Lymphocyte, N/L ratio and D-Dimer levels were significantly decreased after FVR treatment when compared to LPV/r.

In their study, Cao et al. [7] compared standard treatment with Lpv/r in 199 severe COVID-19 patients. They found no significant differences in clinical improvement (hazard ratio for clinical improvement: 1.31, 95% confidence interval [CI], 0.95 to 1.80) and mortality (9.2% vs. 25.0%, respectively, difference: -5.8 percentage points; 95% CI, -17.3 to 5.7). In our study, a decrease in N/L ratio and LDH levels, and a significant increase in WBC values were observed after LPV/r treatment. Two patients were transferred to the intensive care unit despite receiving treatment, but there were no deaths. It can be easily concluded that the major reason for the absence of mortality was the study being conducted among non-severe patients.

Although the use of FVR in COVID-19 has been approved in China, the use of favipiravir has not been mentioned in the treatment guidelines [16]. There are limited publications on the use of FVR in the treatment of COVID-19. In a study comparing FVR with arbidol in COVID-19 patients, it was shown that cough and fever reduction time was shorter in the favipiravir group, although there was no difference between the two groups in terms of clinical recovery on the 7th day of treatment (1.75 days vs 1.70 days, respectively, P<0.001) [9]. In our study, the fever decline time was shorter in FVR patients compared to LPV/r patients (2.7 (0.9) vs 4 (1)).

Limitations

The most important limitation of our study is its retrospective cohort design, which is why the side effects associated with the use of Lpv/r and FVR could not be evaluated in this study. However, none of the patients had to stop taking the drug due to side effects.

Conclusion

Although non-severe COVID-19 patients using FVR had lower oxygen saturations, more widespread radiological involvement, and higher CRP levels at admission, we found that FVR treatment was more effective in improving laboratory parameters and controlling fever than LPV/r. The efficacy of lopinavir/ritonavir and FVR warrants further verification in future study.

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