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Coronavirus Pandemic

Favipiravir for the treatment of COVID-19 pneumonia: Can we predict the response to treatment?

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Abstract

Introduction: Early experience with favipiravir in the treatment of COVID-19 is promising, but no clinical data have been published in medical journals. This study aimed to review the experience with favipiravir treatment for COVID-19 pneumonia and to examine whether there are any predictors of treatment response.

Methodology: Fifty-six patients with severe or progressive pneumonia associated with COVID-19 who were treated with favipiravir monotherapy for at least five days were included in this retrospective study. Treatment response was defined as clinical recovery without any need for admission into the intensive care unit and/or anti-cytokine therapy. The demographic, clinical, laboratory and radiographic features of the patients were compared between favipiravir-responders and non-responders.

Results: Of the 56 patients, 34 patients (60.7%) responded to treatment and recovered. There was no difference in the demographic, clinical, and radiographic findings between the responders and non-responders. The inflammatory biomarkers were also similar except for the CRP levels on the day favipiravir was started [74 (36-111) vs. 118.5 (46.5-203) mg/L, respectively, $p = 0.043$]. There was also a significant difference in the median time to defervescence [1 (1-2) vs. 3.5 (1.75-9.25) days, respectively]. Of clinical interest, 27 (79.4%) and 31 (91.2%) of the responders became afebrile within two and four days, respectively. The response rate was lower in patients who presented severe pneumonia associated with respiratory failure.

Conclusions: Patients with non-severe pneumonia at admission and whose fever resolved within two days of treatment are more likely to improve with favipiravir.

Key words: COVID-19; treatment; favipiravir.

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Introduction

COVID-19 is caused by a virus, SARS-CoV-2, and its major symptoms are fever, cough, and dyspnoea, and minor symptoms are alteration of the smell and taste, gastrointestinal symptoms, headache, and cutaneous manifestations [1,2]. Despite the global toll of pandemic, remdesivir is the only antiviral drug approved by the Food and Drug Administration for the treatment of COVID-19 [3]. However, it is expensive and unavailable in most of the developing countries.

Favipiravir is an RNA polymerase inhibitor [4-6], which has been shown in molecular docking and quantitative structure-activity relationships (QSAR) studies to have favorable binding affinity to and interact with RNA-dependent RNA polymerase [7]. Following early clinical reports [8,9], it has been approved and manufactured in Turkey. It has been recommended by the national guideline as a treatment option for COVID-19 and distributed free of charge by the Turkish government [10,11]. Two recent meta-analyses have reported that favipiravir treatment is associated with better viral clearance and better clinical improvement, but the studies had relatively small populations and most were observational [12,13]. Besides, none of the studies investigated whether there is any patient subgroup or clinical condition which may show a better response to favipiravir treatment. This study aimed to determine the rate of treatment success with favipiravir and to examine whether there are any predictors of treatment response.

Methodology

This study was a retrospective analysis of the records of all patients with SARS-CoV-2 related

pneumonia (n = 601) admitted to Ege University Hospital, Izmir, Turkey between March 11 and May 31, 2020. As per the national guideline [6], favipiravir was given if the patients met either of the following criteria: severe pneumonia at admission [oxygen saturation (SpO2) ≤ 90%] without any previous treatment or non-severe but progressive pneumonia which failed to respond to an initial regimen of hydroxychloroquine (HCQ), given as first-line treatment. Failure was defined as persistence of fever with worsening in symptoms and oxygenation despite HCQ treatment. Severe pneumonia was defined as the presence of either respiratory failure (SpO2 < 90%) necessitating oxygen support or of evidence of acute organ (renal, hepatic, cardiac) dysfunction.

Favipiravir was given to 81 patients with a loading dose of 1600 mg twice daily (BID), followed by 600 mg BID daily for 5 to 7 days. Of these, 25 patients received favipiravir in combination with other drugs (including hydroxychloroquine, systemic steroids) that might affect the clinical course and were excluded from analysis. Thus, 56 patients who received favipiravir monotherapy were included in this study.

Demographic, clinical, laboratory, radiographic findings, and data on the clinical outcome were recorded. High resolution computerized tomography (HRCT) was performed in all patients on admission.

The patients were evaluated for treatment response, defined as recovery following favipiravir treatment without any need for mechanical ventilation or for the use of anti-cytokine (tocilizumab) treatment and/or convalescent plasma. Treatment responders and non-responders (those who progressed and necessitated mechanical ventilation or the use of additional treatment or who died) were compared for the presenting features to determine whether there are any predictors of treatment response.

The study was approved by the local ethics committee (approval number: 20-5T/48). Statistical analysis was performed using SPSS 20.0 for Windows software. Means for continuous variables were compared using t-test for independent groups when the data were normally distributed; otherwise, the Mann-Whitney U test was used. Chi-square test or Fisher's Exact test was used for categorical variables.

Results

All 56 patients had a temperature of 38 ºC or higher, 10 patients had severe pneumonia with respiratory failure at admission, 46 patients had worsening oxygenation despite previous HCQ treatment (Table 1). Thirty-four patients (60.7%) responded to treatment; i.e., they did not require any other treatment or respiratory support. The remaining 22 patients had progressive disease and received mechanical ventilation (n = 19) and/or convalescent plasma (n = 6) and/or tocilizumab (n = 14). Four patients (7.1%) died during hospital stay.

There was no difference in age, gender, presence of comorbidities, biomarkers of infection or inflammation, HRCT findings and the time elapsed since the onset of symptoms between patients who responded to favipiravir treatment and those who did not (Table 2). The only exception was the CRP level on the day favipiravir was started; it was lower in patients who recovered following favipiravir [median levels were 74 (36-111) vs. 118.5 (46.5-203) mg/L, $p = 0.043$]. A receiver operating characteristics (ROC) curve for CRP level showed that it had poor discriminating performance (AUC = 0.663, $p = 0.04$). A cut-off CRP level of 86 mg/L had a sensitivity of 63.6% and a specificity of 63.6% in predicting treatment response.

The SpO_2/FiO_2 levels tended to be higher in the favipiravir-responder group [338 (245-439) vs. 260 (183-386)], but the difference did not reach statistical significance ($p = 0.08$). On the other hand, there was a lower rate of treatment response in patients who had respiratory failure at admission (30%) compared with those with non-severe pneumonia who progressively worsened despite HCQ treatment (67.4%) ($p = 0.04$) (Table 1).

There was a significant difference in the time to defervescence between the responders and non-responders to favipiravir (Table 1). Of the 34 patients who responded, 27 (79.4%) and 31 (91.2%) became afebrile within two and four days, respectively.

Table 1. Oxygenation levels and response rates of the two groups of patients treated with favipiravir according to the national guideline.

	Severe pneumonia at admission (n = 10)	Non-severe progressive pneumonia despite HCQ treatment (n = 46)
SpO_2 / FiO_2 level at admission	231 (151-279)*	457 (438-461)
SpO_2 / FiO_2 level on the day favipiravir was started	231 (151-279)*	343 (250-439)
Treatment responders, n (%)	3 (30%)	31 (67.4)†

* As these patients had severe pneumonia and favipiravir was started at admission, the two SpO_2/FiO_2 levels are the same; † Significantly different than patients with severe pneumonia ($p = 0.04$); Abbreviations: HCQ, Hydroxychloroquine; SpO_2, Oxygen saturation measured by pulse oximetry; FiO_2, Fraction of inspired oxygen.

Treatment responders had shorter median hospital stays [7 (5-10) vs. 13.5 (10-18) days, $p < 0.001$].

Adverse events developed in 6 patients (10.7%), consisting of mild (less than 3-fold) elevation in hepatic enzymes (n = 6), accompanied with nausea in two and neutropenia in one patient. None of these events required withdrawal of the drug. All of them resolved after favipiravir treatment end.

Discussion

This study showed that favipiravir treatment is associated with clinical improvement in 60.7% of the COVID-19 patients who either had severe pneumonia at admission or worsening pneumonia despite previous treatment with hydroxychloroquine. None of the investigated parameters, including demographics, duration of symptoms and biomarkers of inflammation, were found to be of clinical use in discriminating potential responders to favipiravir. Although lower levels of CRP were associated with treatment success, the sensitivity and specificity were too low for clinical use. On the other hand, there was a significant difference in the time to defervescence between the responders and non-responders to favipiravir treatment. Thus, physicians caring for these patients may expect the fever to subside within two to four days if the patient is to recover.

The findings of this study cannot be accepted as proof of the effectiveness of the drug as there was no control group. It may be argued that these patients might have improved with supportive treatment only. However, all patients were febrile when favipiravir was initiated and 79.4% of the treatment responders defervesced within two days, which may be considered as consequential evidence of effectiveness. This is in accordance with the report that viral clearance was documented within four days of treatment in 62.5% of COVID-19 patients [14]. The mean duration of fever in a general cohort of COVID-19 patients has been reported to be 5.6 ± 8.8 days [15]. Thus, assessing the response to favipiravir treatment with the resolution of fever on the fourth day of treatment may be useful to the clinicians.

An antiviral drug could be more effective if given earlier in the disease course or to patients with less severe disease. However, we did not find any relationship between treatment success and the duration of symptoms (any combination of fever, cough, malaise, myalgia, dyspnoea, alterations in the sense of smell and taste etc). Of the two groups of patients included in the study, patients who had severe disease at admission (admission median SpO_2/FiO_2 231 (151-279) were less likely to improve with favipiravir as compared to patients who initially had non-severe but progressive pneumonia (admission median SpO2/FiO2 457 (438-461). This suggests that an excessive inflammatory response had already started in the former group of patients and was relatively unresponsive to antiviral treatment.

Two meta-analyses of 11 and nine clinical studies investigating the efficacy and safety of favipiravir have been recently published [12,13]. Both reported that

Table 2. Characteristics of the favipiravir responders and non-responders on the day favipiravir treatment was started and their clinical outcome.

	All patients (n = 56)	**Responders (n = 34)**	**Non-responders (n = 22)**	***p* value**
Age*	57.2 ± 16.4	57.8 ± 17.9	56.4 ± 14.3	0.75
Gender (F/M)	25/31	15/19	15/7	0.10
Comorbidities *(n, %)*	34 (60.7)	20 (58.8)	14 (63.6)	0.78
Leukocyte ($\times 10^9$/L)	6.65 (4.77-10.3)	6.46 (4.96-8.70)	7.58 (4.18-10.17)	0.81
Neutrophil ($\times 10^9$/L)	4.96 (3.22-7.73)	4.54 (3.23-6.62)	6.19 (3.16-8.97)	0.34
Lymphocyte ($\times 10^9$/L)	1.09- (0.77-1.61)	1.30 (0.82-1.75)	1.06 (0.69-1.33)	0.20
CRP (mg/L)	83 (38-143)	74 (36-111)	118.5 (46.5-203)	**0.043**
Ferritin (µg/L)	601 (244-949)	544 (209-735)	724 (279-1251)	0.27
D-dimer (µg/L)	852 (529-1539)	781 (476-1539)	908 (728-1539)	0.47
SpO_2/FiO_2	290 (230-433)	338 (245-439)	260 (183-386)	0.08
HRCT findings *(n, %)*				
Bilateral involvement	52 (92.9)	30 (88.2)	22 (100)	0.14
Ground glass opacities	51 (91.1)	30 (88.2)	21 (95.5)	0.58
Consolidation	29 (51.8)	19 (55.9)	10 (45.5)	0.44
Temperature (°C)	38 (38-39)	38 (38-39)	38 (38-39)	0.23
Time from onset of symptoms to start of favipiravir (day)	7.5 (6-11)	7.5 (6-13.25)	7.5 (5-10.25)	0.23
Time to defervescence† (day)	1.5 (1-4)	1 (1-2)	3.5 (1.75-9.25)	**< 0.001**
Time to discharge‡ (day)	9.5 (6-14)	7 (5-10)	13.5 (10-18)	**< 0.001**

* Data for age are shown as mean ± SD. All other parameters are presented as median (IQR); † Signifies the number of days from the start of favipiravir treatment to day the patient defervesced; ‡ Signifies the number of days from the start of favipiravir treatment to day the patient was discharged; Abbreviations: CRP, C-reactive protein; SpO_2, Oxygen saturation measured by pulse oximetry; FiO_2, Fraction of inspired oxygen; HRCT, High-resolution computerized tomography.

favipiravir treatment resulted in higher rates of clinical improvement in the first and second week of hospitalization. One of the meta-analyses also showed that there was a higher rate of viral clearance at the first week of treatment with favipiravir [13]. However, there was no difference in the requirement for intensive care and in mortality between favipiravir and comparator groups. Interestingly, none of the studies examined whether there was any predictor of clinical response; i.e., whether there was any subgroup of patients or any clinical condition which may be associated with a better response to favipiravir treatment.

The study had certain limitations. One was the relatively small number of patients. However, the study population only received favipiravir for treatment and were closely followed up for clinical outcomes and laboratory parameters, which provided reliable information. Thus, the findings should be of value and relevance to the clinicians. Another limitation was that, because of its retrospective nature, the clinical outcome, but not the virologic outcome (i.e., the follow-up cycle threshold values) were considered as the primary endpoint. On the other hand, in the real-world setting, the relevance of follow-up PCR tests is debatable.

Conclusions

The findings in this study confirm that favipiravir treatment is safe and associated with a fast-clinical response in COVID-19 patients who do not present with respiratory failure. Clinicians should consider alternative therapies in patients who do not defervesce within four days. There is a need for controlled trials and these should include mild-to-moderate pneumonia and monitor time to defervescence.

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References

1. De Vito A, Geremia N, Fiore V, Princic E, Babudieri S, Madeddu G (2020) Clinical features, laboratory findings and predictors of death in hospitalized patients with COVID-19 in Sardinia, Italy. Eur Rev Med Pharmacol Sci 24: 7861-7868.
2. Vaira LA, Hopkins Salzano CG, Petrocelli M, Melis MA, Cucurullo M, Ferrari MM, Gagliardini L, Pipolo C, Deiana G, Fiore V, De Vito A, Turra N, Canu S, Maglio A, Serra A, Bussu F, Madeddu G, Babudieri S, Fois AF, Pirina P, Salzano FA, De Riu P, Biglioli F, De Riu G (2020) Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study. Head and Neck 42: 1560-1569.
3. Food and Drug Administration (2020) FDA approves first treatment for COVID-19. Available: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19. Accessed: 25 September 2020.
4. Shannon A, Selisko B, Le N, Huchting J, Touret F, Piorkowski G, Fattorini V, Ferron F, Decroly E, Meier C, Coutard B, Peersen O, Canard B (2020) Rapid incorporation of Favipiravir by the fast and permissive viral RNA polymerase complex results in SARS-CoV-2 lethal mutagenesis. Nat Commun 11: 4682.
5. Shiraki K, Daikoku T (2020) Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther 209: 107512.
6. Coomes EA, Haghbayan H (2020) Favipiravir, an antiviral for COVID-19? J Antimicrob Chemother 75: 2013-2014.
7. Rafi O, Bhattacharje G, Al-Khafaji K, Taskin-Tok T, Alfasane A, Das AK, Parvez AK, Rahman S (2020) Combination of QSAR, molecular docking, molecular dynamic simulation and MM-PBSA: Analogues of lopinavir and favipiravir as potential drug candidates against COVID-19. J Biomol Struct Dyn 1-20.
8. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, Shen C, Li X, Peng L, Huang D, Zhang J, Zhang S, Wang F, Liu J, Chen L, Chen S, Wang Z, Zhang Z, Cao R, Zhong W, Liu Y, Liu L (2020) Experimental treatment with favipiravir for COVID-19: An open-label control study. Engineering (Beijing) 6: 1192-1198.
9. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, Luo Y, Ju L, Zhang J, Wang X (2020) Favipiravir versus arbidol for COVID-19: A randomized clinical trial. medRxiv 2020.03.17.20037432; doi: https://doi.org/10.1101/2020.03.17.20037432.
10. Turkish Ministry of Health, Department of Public Health. Guideline for COVID-19 [in Turkish] (2020) Available: https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf. Accessed: 20 July 2020.
11. Simsek Yavuz S, Unal S (2020) Antiviral treatment of COVID-19. Turk J Med Sci 50 Suppl 1: 611-619.
12. Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo, R (2021) The efficacy and safety of Favipiravir in treatment of COVID-19: a systematic review and meta-analysis of clinical trials. Sci Rep 11: 11022.
13. Manabe T, Kambayashi D, Akatsu H, Kudo K (2021) Favipiravir for the treatment of patients with COVID-19: A systematic review and meta-analysis. BMC Infect Dis 21: 489.
14. Ivaschenko AA, Dmitriev KA, Vostokova NV, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, Gordeev IG, Ilin A, Karapetian RN, Kravchenko DV, Lomakin NV, Merkulova EA, Papazova NA, Pavlikova EP, Savchuk NP, Simakina EN, Sitdekov TA, Smolyarchuk EA, Tikhomolova EG, Yakubova EV, Ivachtchenko AV (2020) AVIFAVIR for treatment of

patients with moderate COVID-19: Interim results of a phase II/III multicenter clinical trial. Clin Infect Dis 73: 531-534.
15. Klein H, Asseo K, Karni N, Benjamini Y, Nir-Paz R, Muszkat M, Israel S, Niv MY (2021) Onset, duration and unresolved symptoms, including smell and taste changes, in mild COVID-19 infection: A cohort study in Israeli patients. Clin Microbiol Infect 27:769-774.

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