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Original Research

Assessment of the efficacy and safety of favipiravir in patients with SARS-CoV-2 infection in United Arab Emirates: A single-center study

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Abstract

Background: Anti-viral medications are among the treatment options for coronavirus infectious disease 2019 (COVID-19) management although they are still not FDA approved for coronavirus treatment. We conducted the study to assess the efficacy, and safety of favipiravir versus symptomatic management in patients with COVID-19. **Methods:** A cross-sectional study included 476 participants, divided into two groups. All patients received symptomatic management, and 300 received favipiravir 1,600 mg/day on day 1 and 600 mg/day on days 2 to 5. **Results:** The mean age of the patients was 44.18 ± 12.24 years (49.2% females). The most described COVID-19 symptoms was cough, followed by sore throat, headache, and fever. Each side effect of favipiravir was experienced by almost 38% of the patients. The average days for symptoms relief was 4.73 ± 2.25 days. The results of the linear regression showed that the intake of favipiravir vs symptomatic management only was significantly associated with a higher mean number of days until symptoms relief. **Conclusion:** The results highlight that efficacy of favipiravir is not supported yet for the treatment of COVID-19 as it was associated with higher mean number of days until symptoms relief. However, no remarkable issues with safety associated with Favipiravir were observed.

Keywords: COVID-19; favipiravir; symptomatic management; safety; efficacy

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INTRODUCTION

Coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, was initially reported in late December 2019 in Wuhan city, China and declared a pandemic in March 11, 2020.[1]The infection rapidly spreads worldwide critically impacting public health systems and encompasses a spectrum of clinical symptoms including fever, dry cough, and fatigue, often occurring with pulmonary involvement. Wildlife hosts and infected patients are currently the primary sources of the disease, which is transmitted indirectly via infected air droplets when person-to-person close contact happens [2]. COVID-19 infection was not only an epidemic condition but also progressed to be classified as a pandemic disorder. Various efforts as intense public health efforts, preventive measures, tailored treatment strategies, and vaccine administration were implemented to contain the epidemic worldwide.[3]

There are different stages of COVID-19 infection based upon symptom severity, lung involvement, and the manifestation of hypoxemia. The symptoms range from upper respiratory tract infection, dyspnea, mild to severe pneumonia, and followed by death.[4] Overall various strategies as ensuring appropriate fluid management, controlling inflammation, implementing ventilation, and prescribing antiviral medications are widely used to treat the clinical symptoms of COVID -19. The outpatient treatment options aimed to minimize the need for hospital admission, shorten infection duration, decrease severity, and prevent post-COVID-19 syndrome.[5] Although there is advancement with the use of mechanical ventilation

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and extracorporeal oxygen supplementation, there was a delay in the approval of anti-viral targeted against COVID-19.[6] The choice of investigational drugs is based upon in-vitro efficacy data and pharmacokinetic simulations to predict lung tissue drug concentrations.[7] The development of simple and effective oral medications are highly preferable cornerstone medications for the treatment of COVID-19 infection among elderly and patients living at homes.[8] Thus, oral anti-viral agents play a role in treating breakthrough infection in COVID-19 patients as vaccine administration is an effective measure for preventing COVID-19. Some antiviral drugs have been approved for the treatment of COVID-19.[9] Favipiravir, an antiviral medication belonging to RNA-dependent RNA polymerase inhibitor, is FDA approved for the treatment of novel strains of influenza but not COVID-19 infection.[10] Its therapeutic efficacy has been established for the treatment of some life-threatening infections as Ebola, Lassa fever, and rabies.[11,12] Favipiravir has received increasing attention and showed promising results in patients with mild to moderate COVID-19.[3,13-15] Two clinical studies conducted on hospitalized COVID-19 patients treated with Favipiravir showed reduction in the time for viral clearance, improvement in the chest CT scan finding [16], and a significantly reduction in the time to relief from pyrexia and cough compared to patients given the symptomatic management only.[17] Favipiravir has been included in various regimen protocols as a potential treatment for mild to moderate COVID-19 by various health authorities and regulators.[18,19]

During COVID-19 pandemic, supplementation with Zinc, Vitamin C, and Vitamin D are widely used in the management of COVID-19 infection since deficiencies in certain minerals as Zinc is associated with serious complications and linked with the development of acute respiratory distress syndrome and increased mortality.[20] However, the National Institutes of Health guidelines also stated that there are insufficient data regarding the use of supplements for the treatment of COVID-19.[21]

The protocol of using antiviral therapy in The Department of Health - Abu Dhabi (DOH) depends on the patient's health conditions and comorbidities. Thus, if COVID-19 is confirmed in asymptomatic patients, no treatment is required but Favipiravir is prescribed as a loading dose of 1600 mg orally every 12 hours in the first day, then 600 mg orally every 12 hours as a maintenance dose for 4 days in patients with non-communicable disorders and auto-immune diseases. Furthermore, in COVID -19 patients with pneumonia accompanied with radiological evidence, the dose of Favipiravir should be 1600 mg orally every 12 hours as a loading dose on the first day, then 600 mg orally every 12 hours as a maintenance dose for 6 days.[22,23] There have been many international trials and observational studies that report the efficacy and adverse events of Favipiravir in the management of patients with COVID-19 but data about its efficacy and safety is lacking in the United Arab Emirates.[14,24,25] The aim of our study was to assess the efficacy of Favipiravir versus symptomatic management only in COVID-19 infected patients in the United Arab Emirates.

MATERIALS AND METHODS

Study Design

A cross-sectional study performed from October 2022 through January 2023 and enrolled 476 participants from one COVID-19 center located in United Arab Emirates (UAE). Patients with confirmed laboratory COVID-19 infection were screened for possible enrollment in the study. Eligibility criteria included adult patients residing in the UAE with confirmed COVID-19 infection through Polymerase Chain Reaction (PCR) and did not require hospitalization. Excluded were pregnant, breastfeeding women, participants with severe or critical COVID-19 as defined by World Health Organization.[26] All patients received symptomatic management (vitamin C, vitamin D, Zinc, etc.) alone or in combination with favipiravir at the following dose regimen 1,600 mg/day on day 1, then 600 mg/day on days 2 to 5. Patients were treated in accordance with the UAE government guidelines.[27]

Sample size calculation

Using the G-power software, a minimum sample of 439 was deemed necessary, based on a R^2 deviation of 5%, an alpha error of 5%, a power of 80% and a maximum of 23 variables to be entered in the final model.

Questionnaire and variables

Data collection was performed by registered pharmacists through identification of patients from medical records who were diagnosed with COVID-19 infection. Patients were contacted by phone. Data was collected through licensed and registered pharmacists using a questionnaire developed based upon other studies.[3,5,6,15,28] The questionnaire included two sections; the first section gathered the socio-demographic and socio-economic characteristics: age, gender, marital status, weight, height, employment status, and educational level. Data about COVID-19 symptoms (fever, headache, cough, runny nose, congestion, and sore throat), baseline lab values (hematocrit, serum creatinine, liver enzymes, and platelets) was collected. It assessed previous comorbidities, surgery, and medication history including the medications given during COVID-19 infection, and the number of administered COVID-19 vaccinations. Furthermore, the questionnaire assessed the number of days until symptoms relief after being infected (from day 1 to day 10). Patients who received favipiravir were asked about the side effects of the medication. The questionnaire also included the following scales:

Doctor-patient communication scale (DPC): the scale includes 15 items scored on a Likert scale from 1 to 4 (1 = No, 2= Possibly No, 3 = Possibly Yes, 4 = Yes).[29]Higher scores indicate better communication between the patient and the doctor (Cronbach's alpha in this study= 0.92).

Lebanese medication adherence scale (LMAS-14): a validated scale with 14 questions assessing medication adherence and used to measure the compliance to medications.[30] Higher scores reflect lower degree of adherence (Cronbach's alpha in this study= 0.94).

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Statistical analysis

IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used to perform the data analysis. The number of days until symptoms relief variable was considered normally distributed, with its skewness and kurtosis values varying between -1 and +1.[31] The Student t test was used to compare two means, whereas Pearson test was used to correlate two continuous variables. Bonferroni correction was applied for multiple analysis; significance in the bivariate analysis was estimated at p = .002; it was calculated by dividing 0.05 by the total number of variables entered in the analysis (=23). A linear regression was then conducted, taking the number of days until symptoms relief as the dependent variable. All factors that showed significance in the bivariate analysis were entered as independent variable. P <0.05 was deemed statistically significant in the final model.

RESULTS

A total of 476 patients was included in this study where 300 patients were prescribed favipiravir and 176 patients given the symptomatic management. Their mean age was 44.18 ± 12.24 years (49.2% females). Other characteristics of the participants are available in Table 1.

Table 1. Sociodemographic and other characteristics of the patients (n= 476)

	n (%)
Gender	
Male	242 (50.8%)
Female	234 (49.2%)
Marital status	
Single	110 (23.1%)
Married	366 (76.9%)
Employment status	
Unemployed	132 (27.7%)
Employed in the medical field	333 (70.0%)
Employed outside the medical field	11 (2.3%)
Education	
Secondary or less	161 (33.9%)
University	314 (66.1%)
Cigarette smoking	
No	422 (88.7%)
Yes	54 (11.3%)
Hematocrit	
Normal	457 (96.0%)
Lower than normal	18 (3.8%)
Higher than normal	1 (0.2%)
Oxygen saturation	
Normal	472 (99.2%)
Lower than normal	4 (0.8%)
Serum creatinine	
Normal	448 (94.1%)
Lower than normal	1 (0.2%)
Higher than normal	27 (5.7%)
Liver enzymes- AST/ALT	
Normal	427 (89.7%)
Higher than normal	49 (10.3%)
Platelets	
Normal	464 (97.7%)
Higher than normal	11 (2.3%)
Cardiovascular disease	
Normal	460 (96.6%)
Lower than normal	16 (3.4%)
Hypertension (yes)	143 (30.0%)
Asthma (yes)	32 (6.7%)
Diabetes (yes)	106 (22.3%)
Dyslipidemia (yes)	55 (11.6%)
Other diseases	68 (14.3%)
	Mean ± SD
Age, years	44.18 ± 12.24
Body Mass Index, kg/m2	30.17 ± 17.17
Lebanese Medication Adherence Scale	49.75 ± 9.57
Doctor patient communication	54.79 ± 5.79

The most commonly described COVID-19 symptoms experienced by the patients were cough, followed by sore throat, headache and fever. The average days for symptoms relief was 4.73 ± 2.25 days. Moreover, 63% of the patients took Favipiravir. Other characteristics of the symptoms, treatments and side effects of Favipiravir are displayed in Table 2.

Bivariate analysis

Having hypertension, as well as the intake of one of the following: Antihistamines, nasal spray, vitamin C and D, zinc and favipravir was significantly associated with a higher mean number of days until symptoms relief (Table 3). Older age (r= 0.15; p= 0.001) and lower medication adherence (higher l scores) (r= 0.28; p <0.001) were significantly associated with a higher mean number of days until symptoms relief. BMI (r= 0.11; p= 0.016) and DPC scores (r= 0.014; p= 0.768) were not associated with the number of days until symptoms relief.

Multivariable analysis

The results of the linear regression taking the number of days until symptoms relief as the dependent variable, showed that the intake of favipiravir vs symptomatic management only was significantly associated with a higher mean number of days until symptoms relief (Table 4).

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Table 2. COVID-19 symptoms experienced by the patients	
Fever	208 (43.7%)
Headache	222 (46.6%)
Fatigue	43 (9.0%)
Runny nose/ congestion	188 (39.5%)
Cough	401 (84.2%)
Body, muscle or joint pain	137 (28.8%)
Diarrhea	9 (1.9%)
Sore throat	287 (60.3%)
Nausea/ vomiting	12 (2.5%)
Loss of smell or taste	7 (1.5%)
Shortness of breath	6 (1.3%)
COVID-19 vaccine intake	463 (97.3%)
Average number of days until symptoms relief	4.73 ± 2.25
Pain killers	466 (97.9%)
Cough syrup	58 (12.2%)
Antihistamine	409 (85.9%)
Antibiotics	22 (4.6%)
Nasal spray	392 (82.4%)
Vitamin C	470 (98.7%)
Vitamin D	468 (98.3%)
Zinc	457 (96.0%)
Favipiravir intake	300 (63.0%)
Side effects of favipiravir	
Nausea/vomiting	179 (37.6%)
Chest pain	176 (37.0%)
Mood disturbances	178 (37.4%)
Diarrhea	180 (37.8%)
Headache	183 (38.4%)
Stomach acidity	178 (37.4%)
Body pain	183 (38.4%)
Increase in liver enzymes	178 (37.4%)
Hyperuricemia	176 (37.0%)
Other	199 (41.8%)

Table 3. Bivariate analysis of factors associated with the number of days until symptoms relief		
	Mean ± SD	***p***
Gender		.010
Male	4.47 ± 2.16	
Female	5.00 ± 2.32	
Education		.923
Secondary or less	4.70 ± 2.31	
University	4.72 ± 2.21	
Cigarette smoking		.241
No	4.77 ± 2.32	
Yes	4.39 ± 1.56	
Platelets		.014
Normal	4.68 ± 2.25	
Higher than normal	6.36 ± 1.86	
Cardiovascular disease		.199
Normal	4.70 ± 2.24	
Lower than normal	5.44 ± 2.53	
Hypertension		**.001**
No	4.48 ± 2.11	
Yes	5.31 ± 2.46	
Asthma		.006
No	4.65 ± 2.26	
Yes	5.78 ± 1.91	
Diabetes		.204
No	4.66 ± 2.24	
Yes	4.97 ± 2.29	
Dyslipidemia		.181
No	4.68 ± 2.27	
Yes	5.11 ± 2.11	
COVID-19 vaccine intake		.667
No	4.46 ± 2.22	
Yes	4.73 ± 2.25	
Pain killers		.003
No	3.50 ± .97	
Yes	4.75 ± 2.26	
Cough syrup		.003
No	4.81 ± 2.32	
Yes	4.10 ± 1.56	
Antihistamine		**<.001**
No	3.87 ± 1.59	
Yes	4.87 ± 2.31	
Antibiotics		.699
No	4.74 ± 2.27	
Yes	4.55 ± 1.87	
Nasal spray		**<.001**
No	3.32 ± 1.18	
Yes	5.03 ± 2.31	
Vitamin C		**.001**
No	3.50 ± .55	
Yes	4.74 ± 2.26	
Vitamin D		**.002**
No	3.00 ± 1.07	
Yes	4.76 ± 2.25	
Zinc		**<.001**
No	3.53 ± .96	
Yes	4.78 ± 2.28	

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Favipiravir		**<.001**
No	3.37 ± 1.08	
Yes	5.52 ± 2.37	

Numbers in bold indicate significant *p* values after Bonferroni correction.

Table 4. Linear regression taking the number of days until symptoms relief as the dependent variable

	Unstandardized Beta	Standardized Beta	*p*	95% CI
Hypertension (yes vs no*)	.02	.003	.942	-.43; .46
Antihistamine (yes vs no*)	.08	.01	.778	-.47; .63
Nasal spray (yes vs no*)	.33	.06	.263	-.25; .90
Vitamin C (yes vs no*)	-.41	-.02	.659	-2.23; 1.41
Vitamin D (yes vs no*)	.88	.05	.345	-.95; 2.70
Zinc (yes vs no*)	-.41	-.04	.484	-1.56; .74
Favipiravir (yes vs no*)	2.09	.45	**<.001**	1.50; 2.68
Age	-.003	-.02	.738	-.02; .01
Medication adherence	-.004	-.02	.735	-.03; .02

Numbers in bold indicate significant *p* values.

DISCUSSION

Each side effect of favipiravir (nausea/vomiting, chest pain, mood disturbance, diarrhea, stomach acidity, body pain, increase in liver enzymes, hyperuricemia) was experienced by almost 38% of the patients. The results of the linear regression showed that the intake of favipiravir vs symptomatic management was significantly associated with a higher mean number of days until symptoms relief.

Efficacy of Favipiravir

Our results showed that favipiravir intake was associated with a higher mean number of days until symptoms relief which is not consistent with the results of a study conducted in Japan where patients receiving favipiravir demonstrated a statistically significant improvement in their clinical condition three days earlier than those receiving placebo.[32] Despite this, there was no evidence of survival benefit for patients treated with favipiravir compared to those receiving oxygen and dexamethasone.[33] This lack of effect on survival is consistent with the findings of a recent meta-analysis.[15] Most of the studies lack evidence on the survival benefits mainly because the study population in the clinical trials was primarily composed of patients with non-severe COVID-19 who were able to tolerate the oral formulation and thus, may have had a lower risk of mortality compared to other populations. The discrepancy between the findings of the present study and the meta-analysis conducted by Shrestha et al.[34] might be due to the limited number of studies and small sample size included in the later. According to a randomized study conducted by Adolfo Pérez-García et al. on patients with mild COVID-19, the group receiving favipiravir demonstrated a 50% reduction in virus clearance time compared to the group receiving Lopinavir/Ritonavir.[35] According to other studies.[36-39] patients who are prescribed favipiravir for 7-14 days show a notable improvement in their clinical condition compared to patients receiving other drugs. However, in our study proving the effectiveness of Favipiravir was challenging, given the wide spectrum of clinical presentation in patients with COVID-19 ranging from mild to severe.

Safety of Favipiravir

In our study, Favipiravir was considered a safe drug with favorable side effect profile, consistent with the results from another study and meta-analysis.[6,34,40] However, in our study side effects occurrence was around 38%, higher than the side effects reported by Erdem et al. (13%).[41] The most commonly documented side effects in this study were gastrointestinal, elevation of liver enzymes, and hyperuricemia consistent with the adverse events profile in other studies.[13,15]

Limitations

There are some limitations to our study. First, information bias may be present due to the problems in question understanding, recall deficiency and over or under evaluation of the symptoms. Besides, due to the retrospective nature of our study, a recall bias might be possible. A selection bias can also be considered since the sample was recruited from one institution and was represented more by people with university education and employed in the medical field. Thus, results cannot be extrapolated to the general population. Residual confounding bias is also possible, since there could be factors such as such as natural herbal supplements used, that were not measured in this study.

CONCLUSION

Favipiravir was associated with higher mean days of symptoms relief in patients with mild to moderate COVID-19 infection. Awareness about early identification of symptoms and appropriate timely prescription of antivirals is integral to

promote better prognosis and ensure optimal outcome. In addition, this study can open the gate for future research that should focus on the precise documentation of symptom onset and early antivirals prescription. Finally, this study has a profound implication on the minimization of the use of anti-viral medications as the sole medications in COVID-19 infections as it was not associated with better clinical outcome. Thus, health care professionals should focus on the preventive strategies to minimize infectious cases rather than treatment. We should consider probably that the late initiation of antivirals once the patient has advanced symptoms is too late and this would explain their low efficacy in the clinical setting. The findings of this study raise the need for more clinical trials with a larger sample size and utilization of different anti-viral medications. Caution should be exercised in the widespread use of Favipiravir for the COVID-19 epidemic due to limited evidence and specific safety concerns.

DECLARATIONS

Ethical statement: The study was approved by Abu Dhabi health research and technology ethics committee (Ref: DOH/CVDC/2022/1630). All objectives were explained to each patient; oral informed consent was obtained over the phone from all patients prior to enrolling the study.

DATA AVAILABILITY STATEMENT: The database cannot be shared publicly but is available upon a reasonable request from the corresponding author.

DECLARATION OF INTERESTS: The authors declare no conflicts of interest.

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ABBREVIATIONS: FDA: food and drug administration; RNA: Ribonucleic acid; COVID-19: Coronavirus Disease 2019; CT: Computed tomography; DOH: Department of Health; PCR: Polymerase Chain Reaction; UAE: United Arab Emirates; DPC: Doctor patient communication; LMAS: Lebanese Medication Adherence Scale; SD: Standard deviation; CI: confidence interval; AST: Aspartate aminotransferase; ALT: Alanine transaminase; SPSS: Statistical Package for the Social Sciences.

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