BRIEF REPORT

Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study

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Abstract

No specific antiviral drugs have been approved for the treatment of COVID-19. This study aimed to evaluate the efficacy of favipiravir in treatment of COVID-19. This was a multicenter randomized controlled study including 96 patients with COVID-19 who were randomly assigned into a chloroquine (CQ) group and a favipiravir group. None of the patients in the favipiravir group needed mechanical ventilation ($p = 0.129$). One patient (2.3%) in the favipiravir group and two patients (4.2%) in the CQ group died ($p = 1.00$). Favipiravir is a promising drug for COVID-19 that decreases the hospital stay and the need for mechanical ventilation.

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Introduction

COVID-19 has led to a major worldwide health and economic crisis, with more than 27 million people having contracted the disease and more than 800,000 deaths [1, 2]. No

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specific antiviral drugs have been approved for the treatment of COVID-19 [3].

The food and drug administration (FDA) granted emergency approval to allow hospitals to use chloroquine and hydroxychloroquine for treatment of COVID-19, and these drugs have been used as standard of care in some countries [4–24]. However, many questions remain about the efficacy of chloroquine in treatment of COVID-19 [6–16]

Other antiviral drugs have been suggested to be repurposed for the treatment of COVID-19, such as interferon-α, lopinavir/ritonavir, ribavirin, and remdesivir [5, 6]. Some clinical trials concentrating on viral RNA-dependent RNA polymerase (RdRp) inhibitors have been registered and started [6–11]. Favipiravir, a purine analogue and a potent RdRp inhibitor that has been approved for use in influenza treatment, is also being considered for treatment of COVID-19 [7–11].

Favipiravir acts as a purine analogue and is incorporated in place of guanine or adenine [7–10] and thereby inhibits viral replication. It has been used for treatment of some life-threatening infections such as Ebola, Lassa fever, and rabies, and its therapeutic usefulness has been established in these diseases [8–11].

Data about the efficacy of favipiravir in the treatment of COVID-19 are very scarce. Therefore, the aim of the study was to evaluate the efficacy of favipiravir in treatment COVID-19.

Methods

This was a multi-center, randomized, interventional phase2/phase3 study that included 96 patients with confirmed SARS-CoV-2 infection. This study was performed at the Ain-Shams University and Tanta University hospitals in the period from April to August 2020. Ethical approval was obtained from the Tanta University Faculty of Medicine Ethics Committee, and the approval number was 34035/20. The study was registered on clinicaltrials.gov under the registration number NCT 4351295.

Patients who met the criteria to be included in the study were enrolled. The criteria for inclusion included being an adult 18 to 80 years of age with confirmed SARS-CoV-2 infection with mild or moderate symptoms and having been admitted to the hospital three days after the onset of symptoms. All of the patients agreed to participate in the study and signed an informed consent statement.

Patients who had allergy or contraindication to the drug, pregnant and lactating mothers, and patients with cardiac problems, liver or renal failure, or other organ failure were excluded from the study.

Ninety-eight patients were eligible to participate in the study. After exclusion of patients who refused to participate,

96 patients were randomly assigned into two groups. The chloroquine (CQ) group included 48 patients who received chloroquine 600 mg tablets twice daily added to the standard-of-care therapy for 10 days. The favipiravir group included 48 patients who received 1600 mg of favipiravir twice a day on the first day and 600 mg twice a day from the second to tenth day, added to the standard-of-care therapy for 10 days. Four patients in this group quit after the beginning of the study, and the final number in this group was 44 patients. The four patients who left the study referred to complete their treatment and be transferred to military hospitals, after which we lost contact with them (Fig. 1).

All participants in the study were interviewed and their demographic and basal data were recorded, including age, sex, weight, height, and body mass index (BMI). All of the patients were subjected to a thorough clinical examination, and blood samples were taken for biochemical analysis, including a complete blood count (CBC), liver function tests, renal function tests, chest X-ray, chest CT scan, and ECG. The principal outcomes of the study were the mortality rate and the need for mechanical ventilation.

Sample size calculation was done using G*power software. A study done by Cai et al. [17] showed that antiviral therapy with favipiravir was able to reduce the time of viral clearance from 11 days to 4 days (about 63%). Based on that study, with a sample power of 80%, an α error of 0.05, and an allocation ratio of 1, the sample size was at least 43 patients in each group [18].

Statistical analysis: The normality of the different variables was tested by Shapero Wilks test. Continuous variables were expressed as the mean, SD and median, while the categorical variables were expressed as numbers and percentages. Student's t-test was used for normally distributed quantitative variables, while the Mann-Whitney test was used for non-normally distributed ones. The chi-square test (χ^2) was used for categorical variables and whenever any of the expected cells were less than five, Fischer's exact test was used. Univariate binary logistic regression was used to ascertain the effect of possible risk factors on the overall mortality of the patients. A two-sided P-value less than 0.05 was considered statistically significant. The analysis was done with SPSS Statistical Package version 23 (SPSS Inc. Released 2015. IBM SPSS Statistics for Windows, version 23.0, Armnok, NY, IBM Corp.).

Results

The two groups were matched for gender and age ($p = 0.525$ and 0.717, respectively). There was no significant difference regarding laboratory parameters, including hemoglobin, WBCs, platelets, CRP, ferritin, D dimer, ALT, AST,

Fig. 1 Flow chart of patient inclusion in the study
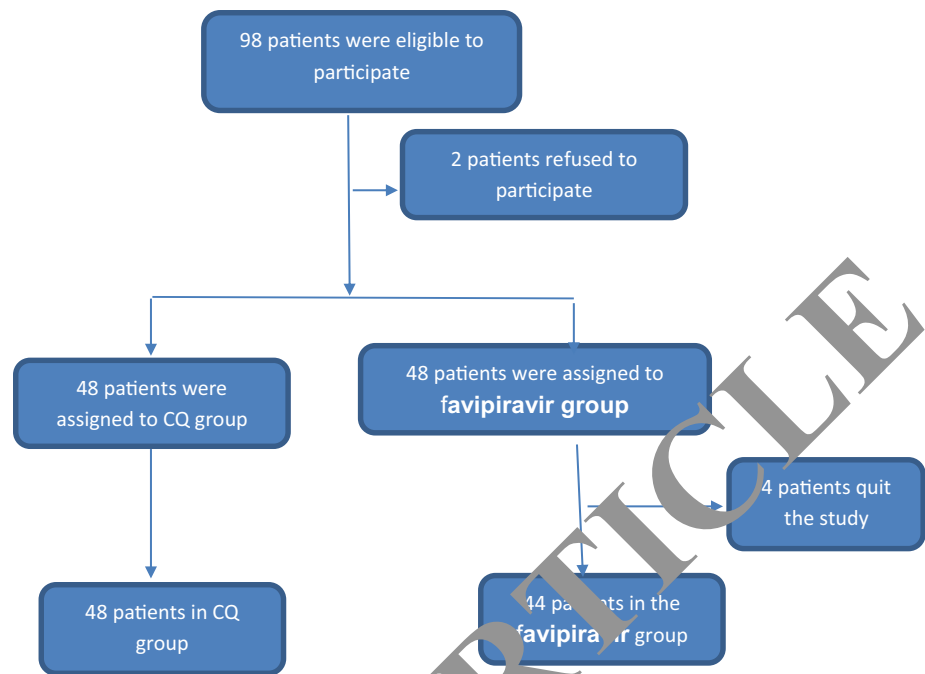
or creatinine. There was also no significance difference between the two groups regarding comorbidities (Table 1).

Although not statistically significant ($p = 0.06$), the favipiravir group had a lower mean duration of hospital stay (13.29 ± 5.86 days) than the CQ group (15.89 ± 4.75 days). None of the patients in the favipiravir group needed mechanical ventilation or had an oxygen saturation lower than 90%, but in comparison to the CQ group, these differences were not significant ($p = 0.118$ and 0.129, respectively). Four patients in the CQ group needed mechanical ventilation and received methylprednisolone after their condition worsened. Two patients (4.2%) in the CQ group and one (2.3%) in the favipiravir group died ($p = 1.00$, Table 2). No significant differences were observed between the groups regarding side effects (Table 2).

Univariate logistic regression of possible risk factors for overall mortality revealed that the patient's age and CRP level were the only factors significantly associated with mortality ($p = 0.043$ and 0.019, respectively). Favipiravir treatment was not significantly associated with COVID-19 mortality in this study ($p = 0.615$).

Discussion

The current epidemic of COVID-19 has reached pandemic proportions, and intense public health efforts are under way to contain the epidemic worldwide. However, as conclusive therapies for proven COVID-19 continue to be a challenge, there is a considerable interest in repurposing existing antiviral agents [19]. Favipiravir (FPV) is a novel RdRp inhibitor

that has been demonstrated to be efficient in treating influenza and Ebola virus infections [20, 21].

Favipiravir is a prodrug that is ribosylated and phosphorylated intracellularly to form the active metabolite favipiravir ribofuranosyl-5′-triphosphate (T-705-RTP). T-705-RTP competes with purine nucleosides and interferes with viral replication by getting incorporated into the viral RNA and thereby inhibiting the RdRp of RNA viruses [24–28].

In this randomized multicenter study, the patients who received FPV had a lower mean duration of hospitalization than the CQ group. None of the patients in the FPV group needed mechanical ventilation, in contrast to the CQ group, but these results were not statistically significant. This is a potentially important observation, as decreasing the need for mechanical ventilation among COVID-19 patients is crucial, especially in developing countries and regions of the world with limited resources.

Two patients (4.2%) in the CQ group and one (2.3%) in the FPV group died. This finding suggests that improvement of the patient's condition may depend on inhibition of SARS-CoV-2 and that FPV controls the disease progression of COVID-19 by inhibiting SARS-CoV-2 polymerase activity [9].

To our knowledge, this is the first randomized study to evaluate the efficacy of favipiravir for treatment of COVID-19.

The positive results of this study are supported by three previous case reports. The first was by Noda et al., who reported the cases of two elderly COVID-19-positive patients, one of whom had hypoxemia, who received favipiravir with a seemingly beneficial effect [22]. The second

Table 1 Baseline clinical and laboratory characteristics of the studied groups

Parameter	CQ (n = 48) Mean± SD Median	Favipiravir (n = 44) Mean ± SD Median	P-value
Age in years	36.15 ± 17.67 34.0	34.86 ± 15.95 29.0	0.717
Hb	13.21 ± 1.90 13.10	13.31 ± 1.63 13.10	0.804
WBCs	5.60 ± 2.61 4.80	6.58 ± 2.99 6.19	0.085
Platelets	271.64 ± 103.77 272.0	242.29 ± 89.08 235.50	0.129
CRP	15.75 ± 18.08 9.0	23.05 ± 54.08 7.20	0.095
Ferritin	151.85 ± 81.80 144.50	145.68 ± 147.44 108.50	0.071
D dimer	67.79 ± 203.46 1.00	61.66 ± 171.52 5.17	0.099
ALT	29.20 ± 19.99 23.50	26.85 ± 19.98 21.0	0.096
AST	25.68 ± 8.11 25.50	26.66 ± 20.25 20.0	0.085
Creatinine	0.97 ± 0.51 0.90 No. (%)	1.40 ± 1.05 0.95 No. (%)	0.107
Gender			
Male	25 (52.1)	20 (45.5)	0.5
Female	23 (47.9)	24 (54.5)	
Co-morbidities	6 (12.5)	11 (25.0)	0.179

*CQ, chloroquine; n, number; SD, standard deviation; HB, hemoglobin; WBCs, white blood cells; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein

case report described a case of COVID-19 pneumonia that did not worsen and was relieved by early administration of favipiravir and ciclesonide [23]. The third report described administration of a combination of FPV with short-course systemic corticosteroid treatment to a patient who was critically ill with COVID-19 pneumonia and COPD who subsequently showed improvement [28]. Although these data support our finding, they are case reports that need to be verified in large randomized controlled studies.

A non-randomized interventional study involving 80 patients with non-severe COVID-19 compared favipiravir with lopinavir/ritonavir and showed increased viral clearance in the favipiravir group on day 7, supporting the possible applicability of favipiravir in treatment of COVID-19 [17].

A positive effect of favipiravir was also suggested in a case series by Doi et al. who used a combination of favipiravir and nafamostat mesylate, which showed promising results in critically ill COVID-19 patients [27].

The dose of FPV to be given to critically ill patients is controversial, especially since the publication of recent data showing lower serum levels of the drug in these patients than in less severely ill patients [26].

The main limitation of this study is that it was based on clinical outcomes, the need for ICU admission, and mortality and that the viremic response was not investigated. This was due to the limited resources available. Also, the study included only COVID-19 patients who were mildly or moderately ill and therefore had a better prognosis than severely or critically ill patients.

In conclusion, favipiravir is a promising drug for treatment of COVID-19 that might decrease the hospital stay and the need for mechanical ventilation.

Table 2 Clinical outcomes of the two groups

Parameter	CQ (n = 48) Mean ± SD Median	Favipiravir (n = 44) Mean ± SD Median	P-value
Duration of hospital stay	15.89 ± 4.75	13.29 ± 5.86	0.060
Need for mechanical ventilation	4 (8.3)	0 (0.0)	0.118
O2 saturation			
100-95%	37 (77.1)	40 (90.9)	0.129
95-90%	9 (18.8)	4 (9.1)	
<90%	2 (4.2)	0 (0.0)	
Mortality	2 (4.2)	1 (2.3)	1.00
Side effects:			
Nausea	2 (4.2)	1 (2.3)	0.938
Headache	3 (6.2)	1 (2.3)	0.672
Diarrhea	2 (4.2)	3 (6.8)	0.920
Elevated liver enzymes	1 (2.1)	3 (6.8)	0.548
Anemia	1 (2.1)	2 (4.5)	0.938
Hyperuricemia	0 (0.0)	2 (4.5)	0.436
Decreased neutrophils	1 (2.1)	2 (4.5)	0.938

*n, number; SD, standard deviation; O2, oxygen

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

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