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Efficacy of Favipiravir in the Treatment of Mild to Moderate COVID-19 Patients in Erbil: A Controlled Clinical Trial

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Abstract

Background and objectives: Favipiravir (FAV) is considered to have potential efficacy against the SARS-CoV-2 virus. We aimed to explore the efficacy of favipiravir in the treatment of mild and moderate cases of COVID-19 pneumonia. **Methods**: 250 patients of mild and moderate COVID-19 patients confirmed by reverse transcription-polymerase chain reaction (RT-PCR) were included from 22nd of June 2020 till 25th of October 2021, aged 18 to 90 years, 125 patients received FAV 3200 mg on day 1 followed by 600 mg twice daily (from day 2 –day 10). In another group, 125 patients did not receive favipiravir (SOC, standard of care group). They received paracetamol, vitamins D, and C plus Zinc, and azithromycin within the first 10 days of symptoms' onset. In both groups, the patients were monitored for clinical recovery on the 5th,10^{th,} 15th days and after one month of receiving the therapeutic trials. Patients were enrolled from Rizgari Teaching Hospital, and from an outpatient respiratory private clinic. Both arms were comparable as regards demographic characteristics, severity, and comorbidities**.** It was a non-randomized –controlled trial. **Results:** On day five, the rate of clinical improvement in the FAV group (74.4%) was significantly ($p < 0.001$) higher than the rate in the SOC group (12.8%). On day 10, the mentioned rate was 88.8% in the FAV group compared with 47.2% in the SOC group ($p < 0.001$). The median time of clinical recovery was 6.5 days in the FAV group vs.

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10.5 days in the SOC group. The rate of hospitalization in the FAV group was 11.2% compared with 28% in the SOC group. ($P < 0.001$). None of the patients of the FAV group died within 30 days, compared with 13.6% of patients in the SOC group.

Conclusions: Favipiravir was superior to the SOC in shortening the time to clinical improvement in patients with mild to moderate COVID-19. As well as in decreasing the hospitalization rate, and mortality rate within the first month post-infection.

Keywords: COVID-19; Favipiravir; Oral antiviral agent; SARS-CoV-2; Treatment efficacy.

1. Introduction

At the end of 2019, the entire world witnessed the first appearance of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1].

By March 11, 2020, it was declared a pandemic by the World Health Organization (WHO). As of February 22, 2022, globally, more than 425, million cases of COVID-19 and more than 5.9 million deaths have been reported so far [2].

The first cases registered in the Kurdistan region of Iraq (on March 1, 2020) were four people of Sulaimani city, including a family of three and another woman, all have been in Iran days ago, [3] since then, the number has been increasing. Favipiravir (FAV) is considered a potential treatment for COVID-19 due to its efficacy against different viral infections [4] considering its past history of efficacy against viral influenza [5]. Favipiravir, a broad-spectrum antiviral agent, acts by inhibiting RNA-dependent RNA polymerase. It is approved in India in the management of mild-moderate COVID-19. It has shown potent in vitro activity against SARS-CoV-2 [6].

Bing a novel RNA-dependent RNA polymerase (RdRp) inhibitor, FAP has also shown efficacy against the Ebola virus [7, 8]. FAV, known as Avigan, is a pyrazine derivative and guanine analogue that acts as a chain termination tool and prevents RNA elongation. Favipiravir demonstrated anti-viral activities against a broad array of RNA viruses, including arenaviruses, bunya viruses, and filoviruses [9]. In Japan, favipiravir has been approved for influenza A resistant to neuraminidase inhibitors [10].

We aimed to explore the efficacy of favipiravir in the treatment of mild and moderate cases of COVID-19 pneumonia The primary objective of the study was to evaluate the efficacy of favipiravir in the treatment of mild and moderate COVID-19 patients regarding the clinical improvement and reduction of disease duration. In addition to evaluating the drug efficacy in decreasing the rate of hospital admission, the need for artificial lung ventilation, and the rate of mortality.

2. Materials and Methods

An interventional controlled clinical trial was carried out in Erbil, Iraq. Two hundred fifty (250) adult patients (aged ≥ 18 years), diagnosed of having mild to moderate COVID-19, with clinical manifestation of COVID-19

pneumonia within the first 10 days, were included in the study. The diagnosis was confirmed by RT-PCR of oro-or nasopharyngeal swabs. Mild clinical condition was defined as having at least three of the following symptoms: fever, cough, anorexia, and malaise for more than two days. Moderate clinical condition was defined as having at least three of these symptoms: fever, cough, malaise/anorexia, and Spo2 of 90-94%. The exclusion criteria were as follows: Pregnant and lactating women, chronic liver disease with ALT/AST increased five times higher than the upper limit of normal, creatinine clearance (Cockcroft-Gault Equation) of < 30 ml/min or having hemodialysis/peritoneal dialysis, known allergy or hypersensitivity to favipiravir, and those receiving remdesivir or any other antiviral drug with potential effect against SARS-CoV-2 virus. Moreover, mild COVID-19 cases who are asymptomatic or had symptoms of two days or less were excluded.

Patients fulfilling the inclusion criteria, who have attended a private clinic and Rizgary teaching hospital (public hospital) during the period of the 22nd of June 2020 through the 25th of October 2021 were included in the study.

Half of them (125 patients) received favipiravir 3200 mg on day one followed by 600 mg twice daily (from day two - day five). The second group (125 patients) did not receive favipiravir (SOC), they received paracetamol, vitamins D, vitamin C plus zinc and azithromycin; they refused to receive favipiravir either due to cost or compliance in the first 10 days of their illnesses. In both groups, the patients were monitored for clinical recovery on the 5th, 10th, 15th days and after 30 days of receiving the therapeutic trials as well as 30 days, mortality and RCU admission were monitored. Both arms were comparable regarding demographic characteristics, severity, and comorbidities.

Efficacy evaluation included clinical status using WHO 8-Category Ordinal Scale 11 and COVID-19 symptoms assessment, oxygen saturation levels, and the body temperature that was performed daily during the first ten days of the study and on days 15, and 30.

The trial protocol was approved by the ethics committee of the Kurdistan Board of medical specialties. All patients (or their relatives) provided written informed consent before the enrollment.

3. Results

Outcomes

The primary endpoint:

Described as reduction of disease duration and the time to clinical improvement (a reduction of patient clinical status on at least 1 score according to WHO 8-Category Ordinal Scale) [11].

Clinical recovery:

Described as the rate of clinical improvement at day 5, 10, 15 and 30, the time to body temperature normalization (<37°.3 C without antipyretics for at least 48 hours), average score according to WHO 8-Category

Ordinal Scale at days 5 and 10, furthermore as the time to resolution of the main disease symptoms such as anorexia and myalgia.

Secondary endpoints:

Are described as the rate of hospitalization for outpatients (respiratory care unit (RCU), admission including the need of use of artificial lung ventilation (ALV), and the mortality rate during the 30 days.

One patient in the FAV group developed a 5-fold increase in the level of liver enzymes and he discontinued the drug and was not included in this study.

Statistical analysis

Data had been entered into the Statistical Package for Social Sciences (SPSS, version 25). A Chi-square test of association was used. A p-value of ≤ 0.05 was considered as statistically significant.

Results

The total number of patients was 250, of whom 125 were allocated to receive favipiravir (n=125), and 125 patients received SOC (n=125).

Table 1 shows that the mean age (SD) of the FAV group was 48.7 (17.2) years, and that of the SOC was 46.3 (16.2) years (p = 0.261). More than half (53.2%) of the whole sample were males, but there was no significant difference in gender distribution of the two groups (p = 0.526). The majority (72.8%) of the cases were mild, and the difference between the groups was not significant (p = 0.203). The table shows that 43.2% of the FAV group had comorbidities compared with 34.4% of the SOC group (p = 0.153).

Table 1: Baseline demographics and disease characteristics.

Baseline characteristics	**Favipiravir**	**SOC**	**Total**	**P-value**
	No. (%)	**No. (%)**	**No. (%)**	
Age (years)				
Mean (SD)	48.7 (17.2)	46.3 (16.2)		0.261†
Range	18-90	18-88	18-90	
Sex				0.526*
Male	64(51.2)	69(55.2)	133(53.2)	
Female	61(48.8)	56(44.8)	117(46.8)	
Disease severity at baseline				0.203*
Mild	86(68.8)	96(76.8)	182(72.8)	
Moderate	39(31.2)	29(23.2)	68(27.2)	
Comorbidities				0.153*
Present	54(43.2)	43(34.4)	97(38.8)	
No comorbidities	71(56.8)	82(65.6)	153(61.2)	
Total	125 (100.0)	125 (100.0)	250 (100.0)	

†By t test. *By Chi square test.

The rates of clinical improvement in the FAV group were significantly ($p < 0.001$) higher than the rates of the SOC group as follows: day 5 (74.4% vs 12.8%), day 10 (88.8% vs 47.2%), day 15 (88.8% vs 61.6%), day 30 (100% vs 86.4%). The rate of hospitalization was 11.2% in the FAV group compared with 28% in the SOC group ($p < 0.001$). None of the FAV group died, while 13.6% of the SOC group died during the 30 days (after the development of symptoms). The median time to clinical recovery was faster in the favipiravir group 5 days vs.10 days in the SOC group as presented in Table 2, Figure 1, Figure 2 and Figure

Table 2: Outcomes of the two study groups.

	Favipiravir N = 125	**SOC N = 125**	**Total N = 250**	**P-value**
Rate of clinical improvement	**No. (%)**	**No. (%)**	**No. (%)**	
Primary endpoints				
Up to day 5	93 (74.4)	16 (12.8)	109 (43.6)	<0.001
Up to day 10	111 (88.8)	59 (47.2)	171 (68.4)	<0.001
Up to day 15	111 (88.8)	77 (61.6)	188 (75.2)	<0.001
Up to day 30	125 (100)	108 (86.4)	233 (93.2)	<0.001
Time to clinical improvement				
Median days **Mean days to recovery**	5 (SD 1.7) **4.9±1.7**	10 (SD 6.5) **11.7±6.5**		p < 0.001
Secondary endpoints				
Hospitalization (admission to RCU) (severe and or critical illness)	14 (11.2)	35 (28.0)	49 (19.6)	<0.001
Mortality	0 (0.0)	17 (13.6)	17 (6.8)	<0.001

Abbreviations: SOC-standard of care; RCU: respiratory care unit.

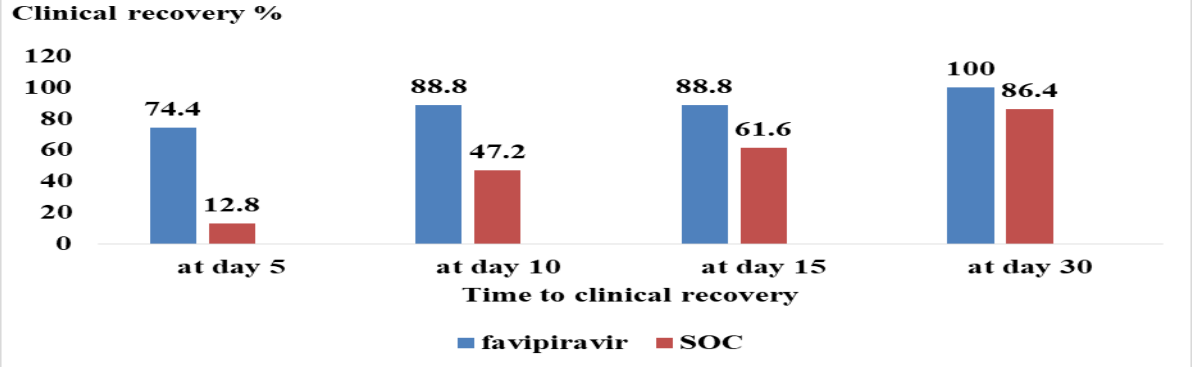

Figure 1: Rates of the clinical recovery of the two groups in different time periods.

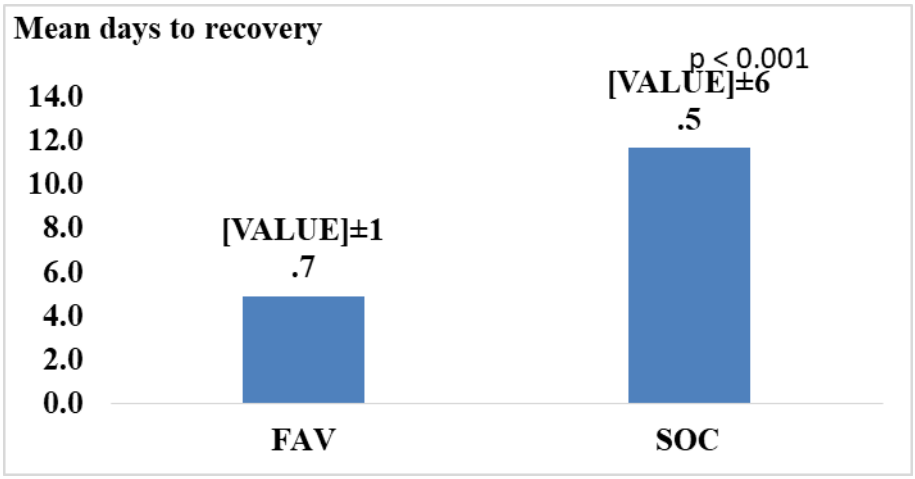

Figure 2: Mean days to recovery.

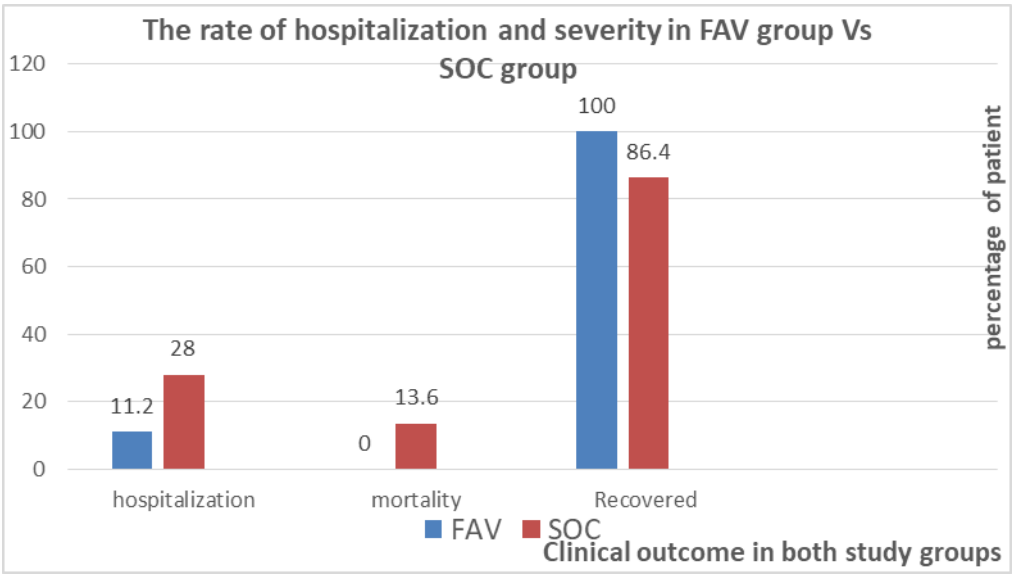

Figure 3: The rate of hospitalization and severity in FAV group Vs SOC group.

4. Discussion

It was found that a 5 to 10-day course of favipiravir was superior to SOC in the treatment of mild to moderate COVID-19. The difference in median time to clinical recovery was 5 days in the favipiravir group and 10 days in the SOC group. This is important from the clinical point of view as, in general, the patient's condition deteriorates to severe in the eight to the twelfth days of their illnesses even with a mild or moderate disease course from the start. This observation was similar to those reported by Ruzhentsova and his colleagues [12] and Cai and his colleagues [5]

There was also a significant difference in the rate of clinical improvement in favor of favipiravir (5.8 fold higher) on Day 5 and 1.8 fold higher on day10 of the favipiravir group compared to the SOC group. Furthermore, the rates of clinical improvement on Days 15 and 30 were 1.4 fold and 1.2 fold higher in the

favipiravir group compared to the SOC group respectively which are statistically significant. Also, the rate of hospitalization, the rate of use of artificial lung ventilation (ALV), the rate of transfer to the respiratory care unit (RCU), and the mortality rate during the 30 days were significantly lower in the FAV group compared to the SOC group. Thus, based on the results it's considered that favipiravir is superior to SOC therapy. As these results were consistent with other several unblinded trials in favor of favipiravir and have become a treatment option in China, India, and Russia [5,16,17].

The time to viral clearance was not compared between the groups. Because the viral clearance is not considered a predictive measure due to a lack of a clear correlation with the clinical condition of the patient [13] difficulty in considering retesting PCR is another reason and refusal by the patients. WHO recommends as a primary endpoint a measure of patients' clinical status at a particular time point after enrollment, while all other biomarkers of illness, including viral clearance, could be considered only as a secondary endpoint [14] Although FDA considers that virological outcomes may be acceptable as a primary endpoint only in Phase 2 studies [15].

5. Conclusion

Favipiravir is shown to shorten the duration of clinical recovery by nearly 5 days in patients with mild and moderate COVID-19 pneumonia when given within 10 days or earlier of symptoms onset, in the form of temperature normalization and improvement of appetites and tiredness. Furthermore, it showed statistically significant higher improvement of 5 to 10 days' treatment in favor of favipiravir therapy as compared to SOC treatment. At the same time, it should be noted that favipiravir treatment resulted in a significantly higher reduction in severity, the rate of hospitalization, the rate of use of artificial lung ventilation (ALV), the rate of transfer to the respiratory care unit (RCU), and the mortality rate during the 30 days.

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