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The effect of Favipiravir on liver enzyme among patients with mild to moderate COVID-19 infection: A prospective cohort study

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ABSTRACT

Teratogenicity and hyperuricemia are considered as the major adverse effects of favipiravir, but less is known about other possible side effects which includes drug-induced liver damage and renal injury. In the current research, assessment of favipiravir-induced liver injury was performed by evaluating liver enzymes among patients with mild to moderate COVID-19 infection. A prospective cohort study was conducted on 66 patients diagnosed with mild to moderate COVID-19 infection who were treated with favipiravir for 5 days. During this period, a baseline assessment of liver enzymes (aspartate aminotransferase – AST, alanine transaminase – ALT and alkaline phosphatase – ALP) in addition to bilirubin before initiation of therapy and after 1 day of completion of therapy were carried out. The comparison of all measured parameters among all patients before and after receiving the treatment showed that non-significant differences were obtained in their levels. It was noticed that COVID-19 patients demonstrated high AST levels in which only 16 patients out of the all-subjected cases (66 patients) had AST levels of less than 45 U/L whereas the majority of patients showed normal ALT, ALP, and bilirubin levels. It was concluded that 5 days administration of favipiravir in mild to moderate COVID-19 patients who had no previous liver diseases did not affect the liver enzymes significantly and only transient elevations were occurred.

Keywords: *ALP; ALT; AST; bilirubin; COVID-19; favipiravir; liver function tests*

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INTRODUCTION

The Chinese Center for Disease Control and Prevention (CDC) found a new coronavirus in a throat swab sample of one patient on January 7, 2020, and the World Health Organization (WHO) named it 2019nCoV.[1,2] The virus was discovered as a coronavirus that had >95% homology with the bat coronavirus and >70% homology with the SARS-CoV. The virus was also discovered in Huanan sea food market environmental samples, implying that it originated there. The number of cases began to rise dramatically, some of which had no connection to the live animal industry, implying that human-to-human transmission was taking place.[3] People with all age groups were at risk of being infected. Infection is spread by big droplets produced by symptomatic individuals coughing and sneezing, although it can also be spread by asymptomatic persons and before the beginning of symptoms.[4] The clinical signs of COVID-19 vary from asymptomatic to acute respiratory distress syndrome and multi-organ failure. Fever (not always), sore throat, myalgia, cough, weariness, headache, and dyspnea are also common clinical signs.[5] Some COVID-19 pneumonia patients have kidney damage, and autopsy results of individuals who died from the disease occasionally reveal renal impairment. The clinical features of kidney-related problems such as hematuria, proteinuria, and AKI, on the other hand, are poorly understood.[6] There has recently been some insight into the impact of COVID-19 on other organs, since some publications have revealed that more than half of COVID-19 patients had varied degrees of liver dysfunction.[7]

The median period from the beginning of symptoms to dyspnea was 5 days, 7 days for hospitalization, and 8 days for acute respiratory distress syndrome (ARDS). In published series, 25%–30% of afflicted patients required intensive care hospitalization. Acute lung damage, acute heart injury, shock, and acute renal injury were among the complications seen. The recovery process began in the second or third week.[8] Various diagnosis methods, such as serological, molecular, and radiological, can aid health centers in detecting SARS-CoV-2. Radiological and serological techniques are the best among the others, and the radiological method is the most preferred one as it could diagnose the infection quickly and accurately with fewer false-negatives.[9] Even if liver damage is not a significant aspect of the disease, it has been documented as a common clinical manifestation in individuals with SARS-CoV infection.[10,11]

Favipiravir is a medicine produced by FUJIFILM Toyama Chemical Co., Ltd., a Japanese pharmaceutical company, and it is approved in Japan for the treatment of very lethal or resistant flu. Only when the government deems it essential in an emergency may the medicine be utilized.[12,13] When COVID-19 first appeared in Japan in February 2020, favipiravir was not licensed for COVID-19, and compassionate use of the medicine required consent from each medical facility's ethical review committee. The Japanese Society of Infectious Diseases originally released favipiravir usage recommendations on February 22, 2020, and they have been updated on a regular basis since then. When we encountered a patient in need of favipiravir treatment, however, these recommendations have not yet been released; therefore, we used the medication based on the JIKI trial of favipiravir for Ebola virus illness.[14] Teratogenicity and hyperuricemia are the most common adverse effects of favipiravir,[15] but less is known about other possible side effects including drug-induced liver damage and renal injury. We examined liver enzymes in individuals with mild to moderate COVID-19 infection to determine favipiravir-induced liver damage.[16]

This study aimed to assess the effect of favipiravir administration in COVID-19 patients on the levels of alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin which are common liver function tests.

MATERIALS AND METHODS

Study design

A prospective cohort study was conducted on 66 patients (36 male and 30 female) age ranging from 30 to 65 years old (mean± SD age of 50.22±10.78) diagnosed with mild to moderate COVID-19 infection who were treated with 1600 mg favipiravir twice on the first day (loading dose), followed by 600 mg twice daily for four consecutive days. During this period, a baseline assessment of liver enzymes (AST, ALT, and ALP) in addition to bilirubin before initiation of therapy and after 1 day of completion of therapy were carried out. All patients were followed up by the investigators during their visit to the clinic and all their data were collected in a structured questionnaire (Supplement A).

Study setting

The study carried out in an outpatient clinic, during the period from March 1, 2021 till the end of April 2021. An informed written consent for participation in the study was signed by all investigated subjects according to the Helsinki principles.

Inclusion criteria

1. Patients with confirmed mild to moderate COVID-19 infection
2. Normal liver function at baseline
3. Negative history of liver diseases
4. Age above or equal to 18 years

Exclusion criteria

1. Abnormal liver enzymes at baseline (≥1 UNL)
2. History of liver diseases
3. Pregnancy and breast feeding
4. Drug allergy

Sample collection and preparation

Samples of about 5 mL of blood were obtained from all subjects before receiving the treatment and the sampling was performed again after 6 days (1 day after the completion of the treatment). The blood samples were put into serum separating tubes (SST) and left at room temperature to clot for 15–30 min and then centrifuged at 4000 rpm (1252 x) g for 10 min. The sera obtained were divided into small aliquots and stored at (-20^{o}C) until the assessment of ALT, AST, ALP, and bilirubin levels according to the manufacturer instructions.

RESULTS

Results obtained in this study revealed that non-significant differences were obtained between male and female patients in the age and all the levels of liver injury markers assisted in the current work and also non-significant differences in these markers' levels between smoker, past smoker, and non-smoker patients before receiving the treatment are illustrated in Table 1. The only exceptions are the significant differences between male and female patients in bilirubin levels and the significant differences in the age among smoking status subgroups. On the other hand, after receiving treatment, all measured parameters showed non-significant differences between male and female patients and also among smoking status subgroups as given in Table 2.

TABLE 1. Ages and liver markers' levels (mean±SD) in patients' subgroups before receiving treatment.

	ALT	AST	ALP	Bilirubin
Initial levels	31.27 ± 8.45	101.67 ± 49.41	68.82 ± 26.93	0.99 ± 0.34
After receiving the treatment	42.72 ± 19.01	111.38 ± 32.95	72.63 ± 21.85	0.87 ± 0.22
p-Values	0.411	0.713	0.894	0.533

TABLE 2. Ages and liver markers' levels (mean±SD) in patients' subgroups after receiving treatment.

Total N=66		**Age**	**ALT**	**AST**	**ALP**	**Bilirubin**
		50.22 ± 10.78	31.27 ± 8.45	101.67 ± 49.41	68.82 ± 26.93	0.99 ± 0.34
Gender	Male (n=36)	47.59 ± 5.68	32.33 ± 9.23	78.61 ± 29.89	69.44 ± 21.39	0.81 ± 0.31
	Female (n=30)	53.2 ± 6.43	30 ± 7.53	129.33 ± 58.38	68.07 ± 34.5	1.2 ± 3.35
	p-Value	0.956	0.508	0.146	0.776	0.021
Smoking status	Smoking (n=22)	52.64 ± 11.38	30.36 ± 6.07	86.46 ± 20.47	46.45 ± 14.47	0.7 ± 0.2
	Non-smoking (n=34)	46.29 ± 9.78	32.06 ± 10.46	109.82 ± 51.97	79.52 ± 27.61	1.16 ± 0.27
	Past smoking (n=10)	60.25 ± 3.86	30.6 ± 6.02	107.4 ± 45.88	81.6 ± 23.38	1.04 ± 0.35
	p-Value	0.038	0.866	0.833	0.71	0.46

TABLE 3. Levels of ALT, AST, ALP, and bilirubin (mean±SD) in COVID-19 patients after receiving favipiravir in comparison with these levels before receiving the treatment.

Total (N=66)		**ALT**	**AST**	**ALP**	**Bilirubin**
		42.72 ± 19.01	111.38 ± 42.95	72.63 ± 21.85	0.87 ± 0.22
Gender	Male (n = 36)	55.59 ± 28.01	96.06 ± 27.06	75.12 ± 31.83	0.79 ± 0.17
	Female (n = 30)	28.13 ± 7.84	128.73 ± 53.04	69.8 ± 14.01	0.94 ± 0.33
	p-Value	0.335	0.419	0.904	0.446
Smoking status	Smoking (n = 22)	67.73 ± 24.88	109.45 ± 28.78	82.73 ± 31.24	0.79 ± 0.2
	Non-smoking (n = 34)	29.76 ± 8.01	108.35 ± 41.82	77 ± 19.01	0.95 ± 0.28
	Past smoking (n = 10)	29 ± 5.48	129.5 ± 53.83	26.25 ± 5.44	0.71 ± 0.14
	p-Value	0.446	0.945	0.726	0.604

The comparison of all measured parameters between all patients before and after receiving the treatment show that non-significant differences were observed in these levels (Table 3). It was noticed that COVID-19 patients demonstrated high AST levels in which only 16 patients out of the all-subjected cases (66 patients) had AST levels of less than 45 U/L whereas the majority of patients showed normal ALT, ALP, and bilirubin levels. Correlation studies in subjected patients before receiving treatment revealed that there was only a significant positive correlation between the levels of AST and bilirubin whereas all other correlations were non-significant. After the end of treatment administration, there was only a significant positive correlation between ALT and ALP and also a positive significant correlation between AST and bilirubin whereas as all other correlations were non-significant.

DISCUSSION

The present study examined the short-term hepatic effect of favipiravir administration in mild to moderate COVID-19 patients in which subjects received the treatment for 5 days and the liver function assessment parameters that include ALT, AST, ALP, and bilirubin were assessed before receiving the treatment and after 1 day of therapy completion. The interval was chosen to be only 6 days in an attempt to eliminate any effects of other drugs that may be used after the completion of favipiravir treatment such as paracetamol (in high doses) that

TABLE 4. Correlations between all studied parameters in patients before receiving the treatment.

		ALT	AST	ALP	Bilirubin
Age	r	0.060	–0.071	–0.083	–0.249
	p	0.745	0.701	0.651	0.177
ALT	r	–	0.277	0.743**	0.290
	p	–	0.125	0.000	0.114
AST	r	–	–	0.050	0.793**
	p	–	–	0.786	0.000
ALP	r	–	–	–	–0.071
	p	–	–	–	0.706

TABLE 5. Correlations between all studied parameters in patients after receiving the treatment.

		ALT	AST	ALP	Bilirubin
Age	r	–0.273	–0.120	–0.115	–0.195
	p	0.131	0.514	0.533	0.285
ALT	r	–	–0.086	0.302	-0.044
	p	–	0.635	0.088	0.809
AST	r	–	–	–0.244	0.419*
	p	–	–	0.171	0.015
ALP	r	–	–	–	–0.051
	p	–	–	–	0.776

may affect liver function test and interfere with the intended results. In agreement with a previous study conducted in Iraq,[8] the current work revealed that the COVID-19 infection rate was slightly higher in male (n= 36) than that in female (n=30) which represent 55% and 45%, respectively. The same authors also demonstrated that the levels of ALT were elevated in only 10% of COVID-19 patients whereas AST levels were elevated in about 40% of patients subjected to their research which is nearly comparable to results obtained in the current work which demonstrated that AST levels were elevated in about 24.24% of COVID-19 patients whereas ALT levels were normal in about 98.5% of patients subjected to the current work (only one patient showed abnormal ALT level).

Results also demonstrated that levels of ALP and bilirubin were normal in the majority of patients subjected to the present research, which is comparable to previously presented literatures, which demonstrated that a mild elevation in ALP and total bilirubin were reported[17] and the majority of cases that presented a high ALP and bilirubin levels were severe cases rather than mild and moderate cases[18] that is subjected to the current work. To assess the effect of gender on levels of studied markers before and after receiving treatment, a comparison was done which revealed that there were non-significant diferences between genders in the levels of the studied markers either before or after receiving favipiravir which is in agreement with previous study that revealed a non-significant differences in liver function test between male and female patients.[18]

The results obtained in the current research revealed that the levels of ALT, AST, ALP, and bilirubin were non-significantly affected by cigarette smoking as it illustrated obviously by the non-significant differences in the comparison among cigarette smoking, non-smoking, and past smoking groups. This partially agree with a study conducted on COVID-19 inpatients who demonstrated that the levels of ALT were non-significantly affected by smoking status whereas a significant change was demonstrated in the levels of AST[19] which is owned to a previous study that subjected only severe cases rather than mild to moderate patients as compared to the current study. On the other hand, no previous studies found for the assessment of the effect of cigarette smoking on the levels of ALP and bilirubin in COVID-19 patients. Furthermore, there is no previous work that relate the liver function test in COVID-19 patients who received favipiravir with the smoking status to assess the effect of cigarette smoking on the levels of ALT, AST, ALP, and bilirubin after receiving the treatment. The main goal of the current study was the short-term evaluation of the effect of favipiravir administration for the

treatment of mild to moderate COVID-19 patients on the liver functions as expressed in the levels of ALT, AST, ALP, and bilirubin only 1 day after the completion of the treatment that might be the cause of non-significant increment in the levels of ALT, AST, and ALP which is consistent with several previous studies reporting an asymptomatic transient increase in liver enzymes as a response to favipiravir-induced liver injury especialy in mild to moderate COVID-19 patients.[20–22]

On the other hand, Erdem et al.[23] reported that there were mild to moderate elevations in hepatic enzymes in only 13% of patients during treatment with favipiravir given that the patients subjected to their research were ranged from mild to severe cases in which about 50% of cases were admitted to intensive care unit (ICU) whereas the current work conducted only on mild to moderate COVID-19 patients which might be the cause of the difference in the results obtained. Additionally, Kumar and his colleagues[24] demonstrated that favipiravir induced a liver injury in three patients who received the treatment for 12–14 days which is consistent with the present work in which patients received the treatment for only 5 days. It was also reported that favipiravir might have caused a cholestatic liver injury especially in patients who received high doses particularly in patients with impaired liver function. This necessitates the monitoring of liver enzymes for COVID-19 patients especially in those who received high doses or having a previous history of liver abnormalities.[16]

Correlation studies revealed that the age of patients did not affect the levels of studied markers either before or after receiving the treatment which indicates that these markers were not affected by favipiravir in correlation with age and ensure the safety of this treatment for almost all ages if the patients are free from any previous history of liver problems and received the treatment in a moderate dose for a shorter period as in the current study. This is in contrast to the above mentioned researches in which high doses were administered for a longer duration that lead to a favipiravir-induced liver injury.[16,24] Moreover, before receiving treatment, all markers were not significantly correlated with each other except the positive significant correlation between AST and bilirubin. The expected explanation of these findings is the difference in the pattern of these markers in COVID-19 patients which was also reported previously by Hwaiz et al.[25] who stated that 60% of COVID-19 patients subjected to their study showed abnormal liver indices with a total bilirubin demonstrated the most common increment and less common ALT and AST and least common ALP abnormality which in turn prevent the parallel increment of these markers. The only correlation that demonstrated in the current study before receiving the treatment may be owned to that bilirubin increased in COVID-19 patients more than other liver markers[25] with the elevation in AST level that may be increases as a response to inflammations occurred in COVID-19. On the other hand, after completion of treatment, the direct significant correlation between bilirubin and AST persist and a new significant correlation was obtained between ALT and ALP which may be due to the transient effect of the treatment used on the levels of these two markers which lead to a parallel elevation.

In general, it was concluded that 5 days administration of favipiravir for patients with mild to moderate COVID-19 who had no previous liver diseases did not affect the liver enzymes significantly and only transient elevation were occurred.

ETHICAL APPROVAL

The study has approved by the Institutional Review Board (IRB) of the Department of Pharmacy, Kut University College, Wasit, Iraq.

CONFLICTS OF INTEREST

There are no conflicts of interest among the authors, and the research was not funded or even supported by any pharmaceutical company.

INFORMED CONSENT

An informed written consent for participation in the study was signed by all investigated subjects according to the Helsinki principles.

AUTHORS' CONTRIBUTION

We certify that this work was completed by the authors listed in this article, and that the authors will be held liable for any claims based on the content of this article. Mohammed Abd Ali Shahadha is responsible for collecting data and also designed the study. Ahmed Hamza Al-Shammari conceived and designed the study in addition to analyzing the data and wrote the manuscript.

DISCLOSURE

No part of this article was presented in any conference or published before. *"This manuscript submitted has not been previously published, nor is it before another journal for consideration"*.

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QUESTIONNAIRE FORM

Name: ID

Age: Gender: Female ( ) Male ( )

Smoking status: Negative ( ) Positive ( ) Past ( )

Baseline

ALT: AST:

ALP:

Bilirubin:

End of Therapy

ALT: AST:

ALP:

Bilirubin:

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