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Case Report

Suspected cholestatic liver injury induced by favipiravir in a patient with COVID-19



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ABSTRACT

Favipiravir is an antiviral drug that is expected to have a therapeutic effect on SARS-CoV2 infection. Teratogenicity and hyperuricemia are known as the main side effects of favipiravir, but little is known about other side effects. This report describes a case of cholestatic liver injury induced by favipiravir. A 73-year-old Japanese with a history of alcoholic hepatitis was infected with SARS-CoV2. Drug therapy was instituted with lopinavir/ritonavir combined with interferon β -1b. However, his condition worsened despite additional support with continuous hemodiafiltration and veno-venous extracorporeal membrane oxygenation. We suspected complications of bacterial pneumonia and started favipiravir in addition to antimicrobial therapy. Favipiravir was administered at 6000 mg/day on the first day and 2400 mg/day for the second and subsequent days for 14 days. After the initiation of antibiotics, transaminase and total bilirubin were elevated, suggesting a transient cholestatic liver dysfunction. The liver dysfunction in this case may have been triggered by antibacterial treatment, and high dose of favipiravir may have promoted the deterioration of liver function. Monitoring of liver function is vital and close attention should be paid when using favipiravir at high doses or in patients with impaired liver function.

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1. Introduction

The novel coronavirus infection (COVID-19) caused by SARS-CoV2 has quickly spread worldwide. As of May 2020, many aspects of the disease are not well understood, such as the infection route, effective treatment modalities, and the clinical course after infection. Research organizations worldwide are urgently conducting numerous investigations and studies to find answers, and many researchers and pharmaceutical companies are rapidly developing therapeutic agents to combat the virus. Favipiravir is a drug developed by the Japanese pharmaceutical company FUJIFILM Toyama Chemical Co., Ltd., and it is approved in Japan for the treatment of highly lethal or resistant flu. The drug can be used only when the government deems it necessary in an emergency [1,2]. In

February 2020, when COVID-19 began to spread in Japan, favipiravir was not approved for COVID-19, and compassionate use of the drug required approval from the ethics review committee in each medical facility. The usage guidelines for favipiravir were first issued by the Japanese Society of Infectious Diseases on February 22, 2020, and there have been regular revisions since then. However, these guidelines had not yet been issued when we encountered a patient in need of favipiravir treatment, so we provided treatment based on the JIKI trial of favipiravir for Ebola virus disease [3].

The major side effects of favipiravir are teratogenicity and hyperuricemia [4], but little is known about other potential side effects, such as drug-induced liver damage and renal injury. Here we describe our experience with favipiravir-induced cholestatic liver injury and discuss implications for clinical practice.

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1.1. Case report

The patient was a 73-year-old Japanese man (height, 166 cm; weight, 71 kg) with COVID-19. He was a member of cruising tour ship and diagnosed infected with SARS-CoV2 in early February. Before diagnosis of COVID-19, he was administered prednisolone because of sudden deafness. He had history of hypertension, hyperlipidemia, gastric ulcer, benign prostatic hyperplasia, and alcoholic hepatitis. He was transferred to our hospital after being admitted to another hospital. On admission, computed tomography showed infiltrative shadows on the lung fields bilaterally and ground-glass opacities extending to the upper part of the middle lobe. Respiratory/ventilatory support parameters were FiO₂ 0.6, positive end-expiratory pressure 10 cmH₂O, minute volume 10 L, PaO₂/FIO₂ ratio 130, and pCO₂ 40 mmHg. Drug therapy was instituted with lopinavir/ritonavir combined with interferon β-1b based on a report by Chan et al. [5]. His condition, however, worsened despite additional support with continuous hemodiafiltration (CHDF) and veno-venous extracorporeal membrane oxygenation (ECMO). In addition, respiratory failure worsened further, so vancomycin and antithrombin III agents were added. Subsequently, we decided to use favipiravir as treatment for the COVID-19 at a dose of 6000 mg on day 1 and 2400 mg/day from day 2 onward, for a total of 14 days. The Figure shows the transition of liver function test values and the course of treatment. Transaminases were elevated until day 4: aspartate aminotransferase (AST) from 70 U/L (day 0) to 112 U/L (day 4) and alanine aminotransferase (ALT) from 37 U/L to 59 U/L, respectively. Total bilirubin (T-Bil) increased until day 3 from 5.2 mg/dL to 12.6 mg/dL. In addition, γ-glutamyl transpeptidase (γ-GTP) increased up to day 4 (32 U/L to 229 U/L), alkaline phosphatase (ALP) up to day 5 (292 U/L to 710 U/L), lactate dehydrogenase (LDH) up to day 8 (692 U/L to 1182 U/L) (see Fig. 1).

Bloody stools appeared from day 3 after the start of favipiravir. On day 6, blood pressure decreased, so we increased the dose of catecholamine and started continuous administration of steroids. Trimethoprim-sulfamethoxazole was added based on the results of sputum culture, and micafungin was added because of elevated serum β-D-glucan level. Blood transfusion was given as needed because of progressing anemia after day 6. Micafungin administration was discontinued when β-D-glucan became undetectable, and on day 13 vancomycin was also discontinued. On day 11, however, transaminases peaked again (AST, 268 U/L; ALT, 115 U/L) and total bilirubin was also rising. Polymerase chain reaction assay results were positive in blood samples until day 4, but remained negative thereafter in both blood and sputum.

2. Discussion

We encountered a case of cholestatic liver injury in the early stages of favipiravir treatment for COVID-19. Based on the CIMOS/RUCAM scoring system, it was classified as a cholestatic liver injury, with a score of 6 (possible) [6]. To our knowledge, there have been no previous reports of acute cholestatic liver injury caused by favipiravir, and possible risk factors are as yet unknown. We consider this a case of acute liver injury for a number of reasons. First is the history of alcoholic hepatitis. The patient had been drinking about 500 mL of Japanese sake for 50 years. The standard alcohol content of sake is around 15% alcohol by volume, that is to say, this patient consumed 75 g of alcohol a day for 50 years. With this history, he started to take favipiravir under conditions of pre-existing compromised liver function from baseline. Although it was difficult to evaluate for encephalopathy and ascites, the Child-Pugh classification was speculated as B from the test values before starting the favipiravir. Second, the favipiravir dose was high in this

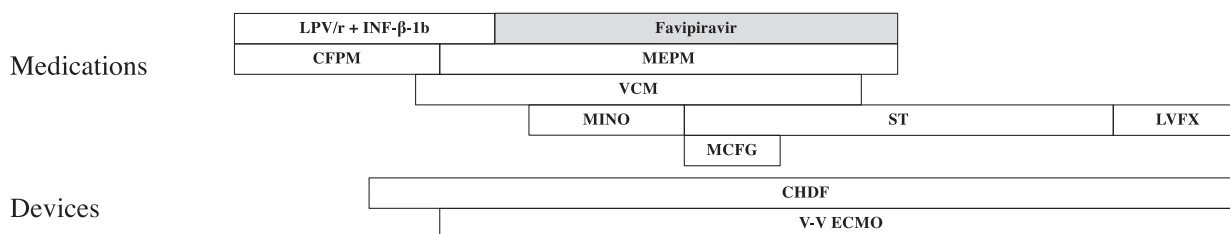
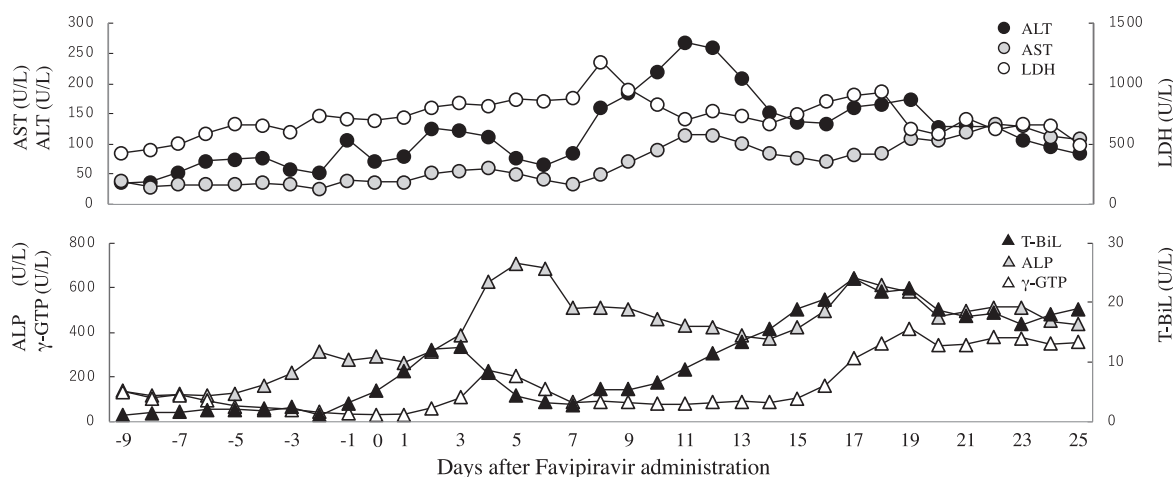


Fig. 1. Changes in liver function test values and usage of antimicrobials and extracorporeal circulation devices over the treatment course. AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase; ALP: alkaline phosphatase; γ-GTP: γ-glutamyl transpeptidase; T-Bil: total bilirubin; LPV/r: lopinavir/ritonavir; INF-β-1b: interferon-beta-1b; CFPM: cefepime; MEPM: meropenem; VCM: vancomycin; MINO: minocycline; ST: trimethoprim-sulfamethoxazole; LVFX: levofloxacin; MCFG: micafungin; CHDF: continuous hemodiafiltration; V-V ECMO: veno-venous extracorporeal membrane oxygenation.

case. Favipiravir dosage is 3200 mg/day on the 1st day and 1200 mg/day on the 2nd day and later as an adapted dose for the new influenza in Japan. However, we determined the dose based on that used in the JIKI trial which was an experimental treatment for Ebola virus disease, in order to gain the maximum effect against an as yet unknown virus. According to the package insert, the AUC of favipiravir increases 1.70–1.79 times in the presence of mild or moderate liver injury. Furthermore, Vincent et al. reported that blood levels of favipiravir in patients with Ebola virus disease were approximately 50% in American patients compared with Japanese patients [7]. We administered a high dose of favipiravir in this case to a Japanese patient with moderate liver damage, and this initial high exposure may have contributed to drug-induced liver injury.

Favipiravir may also be likely cause liver damage from the viewpoint of its chemical structure. Pyrazinamide, an antituberculosis drug, has as a typical side effect hepatotoxicity, although the exact mechanism is unclear [8]. Favipiravir is structurally very similar to pyrazinamide, and it can be regarded as a potentially hepatotoxic drug.

There are three limitations to mention about this case. First, it appears that ALT, AST, and LDH began to increase before favipiravir administration. This may be due to the effects of the vancomycin or meropenem started previously. Although this may have contributed to the liver damage at least in part, the findings of elevated ALP, γ -GTP, and total bilirubin from close to day 0, which suggested cholestatic liver injury, are consistent with a high loading dose of favipiravir. In other words, the possibility of simultaneous liver damage caused by multiple drugs and cholestatic liver damage caused by favipiravir cannot be ruled out. Second, the risk of microthrombosis has been reported in severe cases of COVID-19 [9]. This case is a severe condition, and the possibility that microthrombosis may have caused biliary obstruction cannot be ruled out. Furthermore, SARS-CoV-2 itself may have caused liver damage. Recently, it was reported that the entry gateway for SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2) receptor [9–11]. The ACE2 receptor is not only expressed in the lung but also in the liver, especially in cholangiocyte compared to hepatocyte [9,13]. However, most previous cases of liver injury in COVID-19 patients were characterized by the elevation of ALT and AST, but not by the elevation of T-Bil, ALP and γ -GTP [10,12,13]. In our case, cholestatic liver injury was suspected due to the markedly elevation of T-Bil and ALP, γ -GTP peaked on day 4. However, no findings to date have been reported to characterize liver damage as either COVID-19 or drug-induced. Thus, based on the timing and circumstantial evidence, we cannot rule out an effect of favipiravir. Third, the reason for the liver damage seen after day 7 is unclear. Respiratory and circulatory dynamics worsened in this patient around day 6 after favipiravir administration, possibly due to disruption of tissues in the body. Other medications are also being considered, but there has been no improvement after discontinuation of the medications and the relevance is difficult to determine.

This is the first case of favipiravir-induced cholestatic liver injury to be reported. Severe acute liver injury may occur when high doses of favipiravir are used, particularly in patients with impaired liver function. Monitoring of liver function is vital and close attention

should be paid when using favipiravir at high doses or in patients with impaired liver function.

Authorship statement

All authors meet the ICMJE authorship criteria. All authors have seen and approved the final version of the manuscript, and contributed significantly to the work.

Contributors TS was responsible for the organization and coordination of the trial. SY was the chief investigator. MS, TN, HI and II were responsible for the data analysis. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

None of the authors report any conflict of interest. We have not received any financial support for this report.

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References

- [1] Du YX, Chen XP. Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. *Clin Pharmacol Ther* 2020. <https://doi.org/10.1002/cpt.1844> [Epub ahead of print] Review.
- [2] Nagata T, Lefor AK, Hasegawa M, Ishii M. Favipiravir: a new medication for the Ebola virus disease pandemic. *Disaster Med Public Health Prep* 2015;9:79–81.
- [3] Nguyen TH, Guedj J, Anglaret X, Laouénan C, Madelain V, Taburet AM, et al. Favipiravir pharmacokinetics in Ebola-infected patients of the JIKI trial reveals concentrations lower than targeted. *PLoS Neglected Trop Dis* 2017;11:e0005389.
- [4] Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proc Jpn Acad Ser B Phys Biol Sci* 2017;93:449–63.
- [5] Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, et al. Treatment with lopinavir/ritonavir or interferon- β 1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis* 2015;212:1904–13.
- [6] Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. *Int J Mol Sci* 2015;17:14.
- [7] Madelain V, Nguyen TH, Olivo A, de Lamballerie X, Guedj J, Taburet AM, et al. Ebola virus infection: review of the pharmacokinetic and pharmacodynamic properties of drugs considered for testing in human efficacy trials. *Clin Pharmacokinet* 2016;55:907–23.
- [8] Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol* 2008;23:192–202.
- [9] Morgan K, Samuel K, Vandeputte M, Hayes PC, Plevris JN. SARS-CoV-2 infection and the liver. *Pathogens* 2020;9:430.
- [10] Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020;40:998–1004.
- [11] Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. *J Hepatol* 2020;S0168–8278(20):30377–9.
- [12] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
- [13] Zhang C, Lei Shi L, Wang F. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020;5:428–30.