Case Report

Toxic hepatitis

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Toxic hepatitis case with prolonged jaundice due to Favipiravir

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Abstract

Favipiravir (FPV) is an antiviral drug used in the treatment of severe acute respiratory syndrome coronavirus 2 infection. The main side effects of this drug are teratogenicity and hyperuricemia. Limited information is available on other side effects. Here, we aimed to present our toxic hepatitis case with prolonged jaundice after FPV treatment.

Keywords: COVID-19; favipiravir; jaundice; toxic hepatitis.

Introduction

The new coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 was first detected in Wuhan, China, and soon spread all over the world. Many aspects of the virus, such as the route of infection, its clinical course after infection, and effective treatment methods, are not fully understood. Research organizations conduct many studies to understand these aspects and rapidly develop therapeutic agents to combat the virus. Favipiravir (FPV), a nucleotide analog, is an antiviral agent approved in Japan for influenza treatment. It has been used effectively in the treatment of influenza and Ebola and is effective in many RNA viruses. It stops viral replication by inhibiting viral RNA polymerase.[1,2] The effectiveness of FPV in the treatment of COVID-19 is not fully known. It has been put into use in an emergency in our country, hoping that it would be beneficial due to its use in other fields and the results of *in vitro* studies.[3] There are different doses of FPV depending on the purpose of use. It is used in high doses in the treatment of COVID-19. The main known side effects of this drug, which is excreted by the kidneys and is generally well tolerated, are teratogenicity and hyperuricemia.[4,5] Little is known about other potential side effects such as drug-induced liver and kidney damage.

Case Report

Eight weeks ago, a 35-year-old male patient was diagnosed with COVID-19, and acetylsalicylic acid 100 mg/day (5 days), paracetamol 500 mg tb (he used a total of 10 tablets for 5 days), and FPV 200 mg (2×1600 mg on the first day, followed by four 2×600 mg) treatment was given during the day. The patient, whose laboratory tests before COVID-19 were normal, was referred to our outpatient clinic due to the high levels of liver enzymes and bilirubin in the examinations performed in the hospital, where he had complaints of weakness, sleepiness, and yellowing of the eyes 7 weeks after the COVID-19 treatment. The patient, who had no comorbidity, had no history of other drug use. He had no history of alcohol use and liver or biliary tract disease. On physical examination, the whole body appeared to be icteric. Blood pressure was arterial: 100/65 mmHg, pulse: 82 min^{-1}, respiratory rate: 14 min^{-1}, fever: 36.8°C. In the biochemical examination of the patient, alanine aminotransferase (ALT, 2914 IU/L), aspartate aminotransferase (1514 IU/L), gamma-glutamyl transferase (73 IU/L), alkaline phosphatase (ALP, 136 IU/L), serum total bilirubin (22.6 mg/dL), and conjugated bilirubin (12.6 mg/dL) levels were normal. In complete blood count, WBC was 6.83×10^3 μL^{-1}, hemoglobin was 15.3 g/dL, and platelet was 223×10^3 μL^{-1}. The prothrombin time is 14.2 s and the International normalized ratio was 1.19 s. Viral (hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, Epstein–Barr virus, rubella virus, and herpes virus) and autoimmune markers were negative. Serum ceruloplasmin and 24-h urine copper levels were normal, and there was no Kayser–Fleischer ring on eye examination. Serum ferritin was 3920 ng/mL, serum iron was 263 µL/dL, total iron binding capacity was 77 µL/dL, and alpha-1 antitrypsin was 370 mg/dL (90–200). No vascular or space-occupying pathology was detected in abdominal ultrasonography and computed tomography. The liver biopsy could not be performed because he did not accept it. At this stage, it was thought that hepatotoxicity developed secondary to FPV in the patient. Ursodeoxycholic acid 750 mg/day and NAC infusion (5 days) were started. Two sessions of plasmapheresis were applied to the patient whose serum total bilirubin level increased up to 44.6 mg/dL and increased pruritus. The patient, whose clinical and laboratory findings improved after plasmapheresis, was discharged on the 36th day of hospitalization and was followed up on an outpatient basis. The patient, who had no complaints during follow-up, returned to normal levels of liver enzymes and bilirubin at the end of the fourth month. Biochemistry results during the clinical follow-up of the patient are shown in Table 1.

Discussion

Drug-induced liver injury (DILI) is classified as hepatocellular, cholestatic, and mixed types according to ALT and ALP levels.[6] Most cases of DILI are asymptomatic. Symptomatic patients may present with the usual symptoms of acute liver damage such as fatigue, nausea, abdominal pain, jaundice, itching, and dark urine. Patients may have signs of acute liver failure, acute hepatitis, chronic hepatitis,

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Table 1. Course of laboratory parameters in the clinical follow-up of the patient

	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	Albumin (g/dL)	INR (s)
At the time of hospitalization	2914	1514	156	73	22.6	12.7	4.07	1.19
1st day	2698	1357	138	60	22.2	12.2	3.68	1.14
3rd day	2517	1264	143	52	23.6	13.1	3.58	1.15
5th day	2264	1313	126	43	24.5	13	3.44	1.31
7th day	2190	1331	150	42	28.9	14.4	3.83	1.21
10th day	1702	1169	186	45	35.4	18.1	3.93	0.97
13th day	1153	919	158	41	34.9	15	3.6	0.94
16th day	1013	954	188	45	33.2	15.4	4.15	0.98
20th day	456	447	186	43	38.3	18.5	3.43	1.04
25th day	525	495	227	39	36.8	17.9	3.56	1.06
28th day	456	447	114	49	44.7	18.9	3.47	1.17
After the first session plasmapheresis (29th day)	175	129	156	26	22.6	17.9	3.74	0.92
After the second session plasmapheresis (32nd day)	94	60	113	26	20.2	16.3	3.2	0.87
60th day	78	49	119	21	3.9	3	3.3	0.85
90th day	19	23	113	39	1.35	0.52	4.3	0.87

ALT: Alanine aminotransferase (normal value 10–40 U/L); AST: Aspartate aminotransferase (normal value 10–35 U/L); ALP: Alkaline phosphatase (normal value 40–150 U/L); GGT: Gamma-glutamyl transferase (normal value 9–64 U/L); INR: International normalized ratio (normal value 0.8–1.2 s).

cholestatic hepatitis, and granuloma-like hepatitis, and rarely, prolonged use of hepatotoxic drugs may cause cirrhosis.[7] In our case, hepatocellular-type liver damage with prolonged jaundice developed due to FPV use. FPV is structurally very similar to pyrazinamide, an antituberculosis drug. A typical side effect of pyrazinamide is hepatotoxicity.[8] FPV can be considered a potential hepatotoxic drug due to this structural similarity. In our literature reviews, a case report of suspected cholestatic liver damage due to FPV by Yamazaki et al.[9] and Cai et al.[10] We did not find a study on liver damage of FPV, except for the nonrandomized control study reported by Cai et al.[10] There is no information in the literature about hepatocellular liver damage with prolonged jaundice due to FPV use. In this respect, our case will be the first to be reported. In our case, we concluded that FPV-related hepatotoxicity developed on the basis of normal laboratory parameters before FPV treatment, the absence of other drugs and alcohol use, liver and biliary tract disease, the absence of other hepatotoxic agents in the investigations performed for etiology, and due to the complete normalization of liver enzymes and bilirubin values during follow-up. The diagnosis of DILI needs to be confirmed histologically, but a histological examination could not be performed because our patient did not accept a liver biopsy.

As a result, FPV is a potential hepatotoxic agent. Used in high doses in the treatment of COVID-19, this drug can cause liver damage with prolonged jaundice. For this reason, liver enzymes and bilirubin values should be closely monitored during and after FPV use. Physicians should be alert in terms of hepatotoxic side effects of FPV, and it should not be ignored that there is a long-term side effect potential even though the drug is discontinued.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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