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Fingolimod induced fulminant liver failure requiring liver transplantation: A case report

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Abstract

Fingolimod has been used for about ten years to treat multiple recurrent sclerosis. It has been reported that Fingolimod causes an elevation in liver enzymes. In this case report, the clinical and laboratory parameters improved after discontinuation of the drug. However, there is no publication in the literature regarding acute liver failure and liver transplantation following Fingolimod treatment. In this article, we presented a 33 – year – old female patient who developed acute liver failure and underwent liver transplantation after Fingolimod treatment for recurrent multiple sclerosis.

Keywords: Acute liver failure; drug-induced liver injury; fingolimod; liver transplantation; multiple sclerosis.

Introduction

Acute hepatic failure is the development of severe acute liver injury with encephalopathy and impaired synthetic function international normalized ratio (INR) ≥1.5). In a patient without cirrhosis or pre-existing liver disease,[1] the prognosis of the disease is poor if not treated properly. Also, timely diagnosis and management of patients with acute liver failure are essential.[2]

Viral and drug-induced hepatitis are adults' most common causes of acute liver failure. In Australia, Denmark, the United Kingdom, and the United States, acetaminophen is the most common cause of acute liver failure. In some parts of Asia and Europe, viral hepatitis is the most common cause.[3]

Fingolimod (FTY720) is a sphingosine 1 – phosphate receptor modulator that selectively and reversibly inhibits T-lymphocytes with pure and central memory in the lymph nodes and prevents them from circulating to other tissues, including the central nervous system (CNS).[4]

In this study, we aimed to present the first case of a patient with Fingolimod-induced fulminant liver failure who needed a liver transplant.

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Case Report

The case study involves a 33-year-old female patient who checked into and was undergoing follow up in different healthcare centers. The patient, with a diagnosis of acute hepatitis and a 5-year history of Multiple Sclerosis (MS), was admitted into our institution due to a progressive increase in her liver function tests, INR. After an immediate follow-up, the patient's requirement was a case of liver transplantation using Fingolimod.

At the time of the first application, there were no pathological physical examination findings except for jaundice in the sclera and skin. Hepatitis A-B-C-E, Ebstein-Barr Virus (EBV), Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Parvovirus and Rubella Ig-M were negative. Antinuclear antibodies (ANA), Anti – mitochondrial antibodies (AMA), and Anti-smooth muscle antibodies (ASMA) were negative. Serum Ig G-A-M levels were within the normal range. The patient's history did not include any alcohol or herbal product use. The patient's abdominal ultrasound (USG) and computerized abdominal tomography (CT) showed increased edema in the liver parenchyma, peri–hepatic fluid, and gall bladder wall thickness. These findings were consistent with acute hepatitis.

The patient's history stated acute hepatitis developed after interferon–β use in May 2014. She did not take any drug before and with interferon–β, the laboratory findings were compatible with hepatitis (R=44.3, ALT 1371 U/L, AST 1444 U/L, ALP 96 U/L). The clinical symptoms and laboratory findings improved after discontinuing the drug. Intravenous hydration and supportive treatment were initiated during hospitalization. After this period, the patient did not receive any treatment for MS for two years.

The patient was given 0.5 mg/day of Fingolimod treatment orally due to recurrent MS (08/26/2016). Before Fingolimod treatment, the ALT and AST values were 27 U/L and 15 U/L, respectively. She did not take any drug or medication before, and none too with Fingolimod. Additionally, the patient received no prescription or herbal and dietary supplements before initiating Fingolimod treatment. On the 12th day of Fingolimod treatment (09/07/2016), the patient complained of fatigue and weakness. On the 14th day of treatment, the elevation of liver function tests was detected, and Fingolimod treatment was discontinued on the 15th day. The patient was hospitalized at the gastroenterology clinic for follow-up. Submassive hepatic necrosis and plasma cells were observed in the liver biopsy. A liver biopsy was primarily evaluated as toxic hepatitis. She was admitted to our institution due to a progressive increase in liver function tests, INR, and close follow-up requirements in the case of liver transplantation.

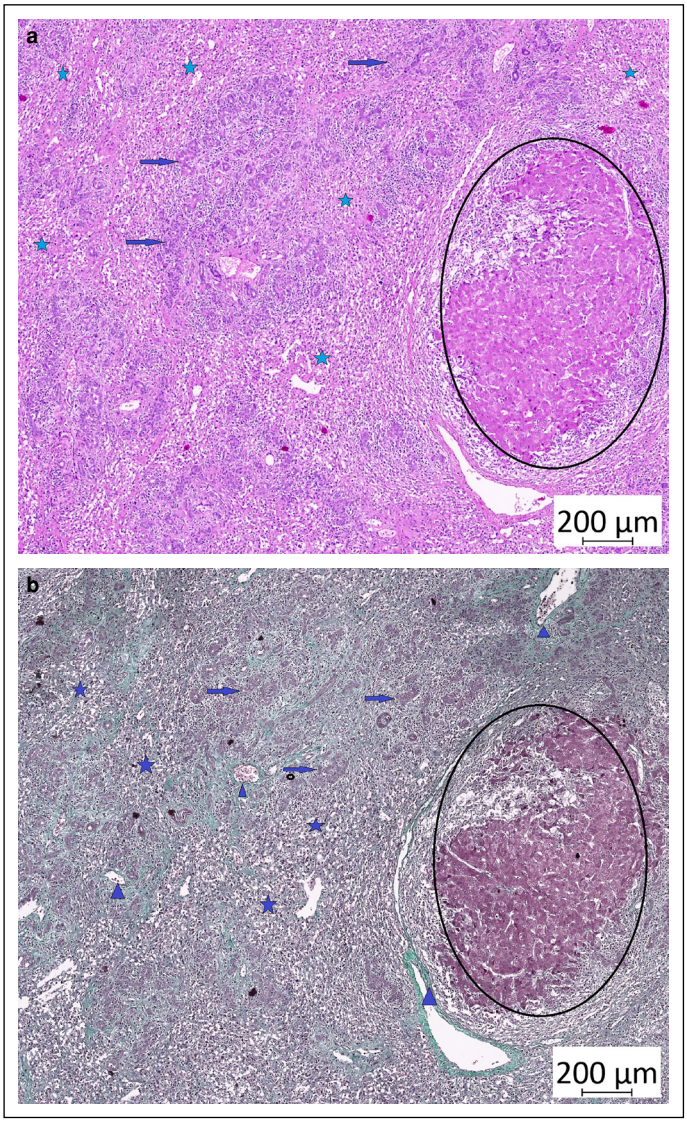

Figure 1. (a) Massive necrosis (stars) accompanied by inflammation including bile duct proliferation (arrows) and a cluster of intact hepatocytes (circled). (H&E 25X). **(b)** The circled area shows intact hepatocytes, the stars show areas of massive necrosis, the arrows show proliferating bile ducts, and the arrowheads show perivascular normal connective tissue. The thin and slightly green appearance on the ground is the liver's own usual connective tissue matrix. (Masson Trichrome; 25X).

The first laboratory test values of the patient in our clinic were; WBC 7.3x10^9/L, Hb 12.2 g/dL, PLT 176x10^9/L, eosinophils 1.2x10^9/L, INR 3.7, creatinine 0.66 mg/dL, total protein 5.1 g/dL, albumin 2.8 g/dL, total bilirubin was 36.7 mg/dL, direct bilirubin 22.1 mg/dL, AST 646 U/L, ALT 517 U/L, ALP 128 U/L, LDH 354 U/L, ammonia 104 ug/dl, arterial blood Ph 7.3, lactate level was 2 mmol/L. The R factor is calculated as the patient's ALT÷your lab's upper limit of regular ALT/patient's ALP÷your lab's upper limit of normal ALP. The current features were evaluated as hepatocellular involvement (R=11.4).

Intravenous hydration and supportive treatment were initiated during hospitalization at our clinic. The patient had not been given steroids before the transplant. The patient underwent three therapeutic plasmapheresis sessions due to an increase in total bilirubin level. Hepatic encephalopathy developed on the 7th day of follow-up. A cadaveric liver request was made from the Ministry of Health for liver transplant. On the 9th day of our follow-up, a cadaveric liver transplant was performed 44 days after Fingolimod treatment initiation (10/0/2016). Massive necrosis was detected in the pathological examination of the explanted liver (Fig. 1).

Table 1. The information about fingolimod treatment and liver injury

Duration of treatment	15 days
Onset of symptoms	12th day
Determination of laboratory values	14th day
R ratio- at the first application to our hospital	11.4 – Hepatocellular pattern
Severity	5+: Fatal
Modified RUCAM	+ 8 (Probable)

Fingolimod Treatment and Liver Injury: Duration of Treatment, Onset of Symptoms, Laboratory Values, R-ratio, Severity, and Modified RUCAM.

The information about Fingolimod treatment and liver injury is presented in Table 1, and the results of the laboratory tests in our clinic are denoted in Table 2. The patient is healthy and complies with the liver transplantation outpatient clinic for routine follow-ups. Informed consent was obtained from the patient for the publication of this information.

Discussion

MS is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system.[5] It affects more than 2.3 million people over the globe and is the most common cause of non-traumatic disability in young adults.[6]

Fingolimod was the first oral agent approved by the US Food and Drug Administration (FDA) for recurrent MS treatment in September 2010. As of Aug 31, 2020, more than 307.200 people (836.200 patient-years) with Multiple Sclerosis have been treated with Gilenya.[7]

Common side effects include: lymphopenia, headache, diarrhea, cough, runny nose, and back and abdominal pain. Rare but potentially severe adverse events include: viral infections, atrial arrhythmia, macular edema, progressive multifocal leukoencephalopathy (PML), posterior reversible encephalopathy syndrome (PRES), and acute hypersensitivity reactions.[8]

In the FREEDOMS study, 1.272 patients with recurrent MS, who had been treated with Fingolimod (0.5 or 1.25 mg/day) or a placebo for 24 months, were evaluated. The ALT levels increased more than three times the normal range in 8.5-12.5% of the cases in the Fingolimod group and 1.7% in the placebo group.[9]

In the TRANSFORMS study that evaluated 1.280 patients with recurrent MS who were followed up for 12 months with Fingolimod (0.5 or 1.25 mg/day) or interferon – β (30 mg/week) treatment, the ALT level increased more than three times with the normal range in the Fingolimod group (7% and 8%). The ALT level increased more than three times the normal range in the beta interferon group (2%). Despite this, clinical hepatitis disease did not develop in the patients.[10]

In the second FREEDOMS study, the ALT level increased more than three times the normal range of 10% in the Fingolimod 1.25 mg group, 8% in the fingolimod 0.5 mg group, and 2% in the placebo group.[11]

Table 2. The results of the laboratory tests in our clinic

	ALT (0-55 U/L)	AST (5-34 U/L)	ALP (40-150U/L)	Albumin (3.5-5.0 g/dL)	T. Bilirubin (02-1.2 mg/dL)	LDH (125-243 U/L)	Creatinine (0.57-1.11 mg/dL)	INR	PLT (15-400. 10^9/L)	Ammonia (31-123 ug/dl)
1st day	517	646	128	2.8	36.7	354	0.66	3.7	176	104
2nd day	434	586	117	2.4	34	417	0.62	4.7	154	
4th day	266	391	115	2.8	29.1	396	0.56	2.9	82	
7th day	151	178	101	3.3	21	325	0.6	1.5	104	185
8th day	155	143	107	3.1	24.3	322	0.59	3.3	96	117
9th day	131	115	88	3.2	19.9	352	0.55	2.4	71	130

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; T. Bilirubin: Total bilirubin; LDH: Lactate dehydrogenase; PLT: Platelets.

An increase in liver function tests usually occurred in the first month of treatment, and liver function tests returned to an average two months after discontinuing Fingolimod treatment. An increase in liver enzyme levels was the most common cause of treatment discontinuation in Phase III and extension studies.[12]

In a study including 920 patients who were treated with Fingolimod (0.5 mg or 1.25 mg) had increased serum liver enzyme levels in 13% and 19% of the cases at the end of the first year, 7% and 8% of the cases at the end of the second year.[13]

In the 4-year follow-up of 122 patients receiving Fingolimod treatment, 25% had AST and ALT increase, and 4% had AST and ALT levels three times higher than the normal range. None of the patients developed clinical hepatitis, and there was no need to discontinue the drug.[14]

In a review of 38.563 patients who had received Fingolimod treatment, liver injury was observed in 1.823 (2.32%) patients, and severe liver injury developed in 496 (1.13%) patients.[15]

The European Medicines Agency (EMA) communication reported 3 patients who were on Fingolimod and developed acute liver failure and ultimately had emergency liver transplantation.[16] Additionally, a 41-year-old inactive HBsAg carrier Taiwanese woman with relapsing multiple sclerosis developed re-activation of Hepatitis B after 35 months of treatment with Fingolimod. She responded to tenofovir despite the continuation of Fingolimod.[17]

Liver function tests should be conducted before the initiation of treatment, during 1, 3, 6, 9, and 12 months. Liver function tests should be monitored more frequently if serum AST or ALT levels exceed 3 times the upper limit of normal (ULN). Fingolimod should be discontinued if ALT or AST levels exceed fivefold the normal range.[7]

Conclusion

Fingolimod causes elevations in liver function tests, and there is clinical and laboratory improvement in patients after discontinuation of the drug. In this article, we presented this patient because of the absence of clinical improvement despite treatment discontinuation. This was the first case of Fingolimod-induced hepatitis that progressed to acute liver failure requiring liver transplantation. Before initiating Fingolimod treatment, it is recommended to investigate the patients' previous drug reaction history and follow up on cases that develop acute hepatitis with extreme caution.

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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