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Case Report

Drug-Induced Liver Injury Caused by Telotristat Etiprate

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ABSTRACT

It is important to diagnose Drug Induced Liver Injury (DILI), because especially the acute hepatocellular-type carries a high risk of mortality and chronic injury. Liver failure has been described in patients receiving telotristat etiprate, a drug used to treat carcinoid syndrome in patients with neuroendocrine tumors, but was generally attributed to progression of liver metastases. We present a case of a patient with a diagnosis of drug-induced liver disease as assessed by the RUCAM score, the most commonly used tool for diagnosis of DILI and causality assessment. The patient suffered from an acute injury, grade of severity 1 and both biochemically and histologically hepatocellular injury was the suggested pattern. Patients on telotristat etiprate should be carefully monitored for liver function abnormalities and a high suspicion for a possible diagnosis of DILI is warranted.

Keywords: Hepatic enzyme; Telotristat; Liver failure; Injury; Drug

INTRODUCTION

Hepatic enzyme elevations have been reported in patients receiving telotristat etiprate [1-3]. Telotristat ethyl is a prodrug of telotristat, an inhibitor of tryptophan hydroxylase, which mediates the rate-limiting step in serotonin biosynthesis. It is formulated as telotristat etiprate -a hippurate salt of telotristat ethyl. Telotristat ethyl is used in combination with somatostatin analogue (SSA) therapy for the treatment of adults with diarrhea associated with carcinoid syndrome that SSA therapy alone has inadequately controlled [1-3]. A few patients in the TELESTAR and TELECAST trials experienced acute or chronic hepatic failure. Most patients in the studies had underlying metastatic NET and liver failure was attributed to progression of liver metastases. It is important to know whether a drug can induce liver injury. We describe a case with a histological image suggestive for hepatocellular injury. Imaging and laboratory tests exclude other etiologies (Figure 1).

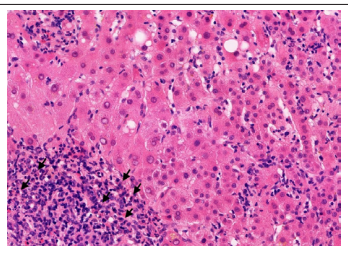

Figure 1: The liver biopsy shows marked portal inflammation with diffuse interface activity and moderate to severe lobular inflammation. The portal tracts display lymphocytic inflammation with prominent plasma cells, often arranged in small clusters (arrows). Few eosinophils and neutrophils are also observed. The lobules show predominant lymphocytic inflammation with rare plasma cells, neutrophils and eosinophils with scattered apoptotic and necrotic hepatocytes. In addition, mild macrovesicular steatosis is observed (HE, x 30).

CASE STUDY

A 74 year old woman was diagnosed with a Neuroendocrine Tumor (NET) with liver metastases and carcinoid syndrome in 2004. She started treatment with lanreotide 120 mg/28 days and the dose was doubled in 2013 because of worsening of the carcinoid syndrome. In April 2015 treatment with telotristat etiprate 3 x 500 mg/d had to be started.

In February 2016, an elevation of liver enzymes was noted (Table 1). The dose of telotristat was reduced to 3 x 250 mg/d. Other reasons for liver toxicity were excluded: clinical examination and biochemical, serologic and virologic tests were negative for acute viral hepatitis A, B and C, CMV, EBV, chronic hepatitis B and C, autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis (Table 2). Abdominal ultrasound showed no evidence of biliary obstruction or vascular disease. There was no history of hypotension, shock or ischemia and no alcohol abuse. Regular check-ups with the cardiologist showed no problems. The patient had been taking a coffee containing Ganoderma lucidum, a mushroom powder that has been associated with acute liver failure [4]. The coffee was stopped on April 7. Because of a further rise in liver tests, telotristat was stopped on April 14. Somatostatin 0,5 µg subcutaneously 3 x/d was started because of worsening of the carcinoid symptoms.

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Table 1: Evolution of liver tests: stop telotristat April 14–reintroduction October 13–stop November 17.

Evolution of liver tests: stop telotristat														
2016	feb	13/04	20/04	29/04	13/07	21/09	5/10	25/10	16/11	30/11	15/12	28/12	11/01	26/01
ALP	175	290	326	296	111	105	106	101	149	144	131	118	114	117
G-GT	228	642	731	556	61	28	28	64	136	114	81	58	53	43
AST	103	360	411	335	38	18	19	16	118	138	110	64	38	30
ALT	168	477	524	449	33	11	13	12	146	200	163	91	46	32
LDH	318	395	423	409	258	290	307	435	341	306	275	249	247	313

Table 2: Biochemical, serologic and virologic tests

Biochemical, serologic and virologic tests				
17/03/2016	Value		Nl range	ICU
Alfa 1 antitrypsine	2.47	g/dl	0.9-2.0	
Immunoglobuline G	23.3	g/L	7.0-16.0	
Immunoglobuline M	1.72	g/L	0.40-2.48	
Immunoglobuline A	3.93	g/L	0.71-3.65	
Copper	195	µg/dl	80-155	
Ceruloplasmine	0.479	g/L	0.2-0.6	
ANA	homogenous			
ANA intensity	1+ negative			
Anti-mitochondrial AB	negative			
Anti-smooth muscle AB	negative			
Anti LKM AB	negative			
SLA and LC1 AB	negative			
EBV IgM	negative			>1=pos
EBV IgG	189	U/ml		>30
CMV IgG	>250	AU/ml		≥ 6=pos
CMV IgM	0.09			≥ 1=pos
HIV	negative			
Hep A IgM	negative			>1=pos
Hep A IgG	>80	mIU/mL		≥ 20=immune
Hep B sAB	<9	mIU/mL		>11=immune
Hep B cAB				
Hep C AB	negative			

A biopsy showed marked portal inflammation with moderate to severe lobular hepatitis, matching a drug reaction, acute viral hepatitis or Auto-Immune Hepatitis (AIH), the latter being not probable according to the simplified AIH score of 4 (Table 3). The liver tests slowly improved to normal by the end of July. Hyperbilirubinemia was never noted, nor were other signs of liver failure.

Table 3: Simplified AIH score.

Simplified AIH score	
Elevated IgG	1
ANA or ASMA	0
LKM	0
SLA/LP	0
Histology	1
Absence of viral hepatitis	2
Simplified AIH score	4

Telotristat was reintroduced October 13th at a dose of 3 x 250 mg/d, and permanently discontinued after a new rise in liver function tests (Table 1).

The liver tests returned to normal, but the patient developed carcinoid heart disease and died during work-up for valve surgery.

DISCUSSION

Hepatic enzyme elevations have been described in patients receiving telotristat, most cases being reported upon treatment with the higher dose (3 x 500 mg). Mostly elevations in ALT>3× upper limit of normal (ULN) or ALP>2 ULN were noted, not associated with concomitant elevations in total serum bilirubin [1-3]. The increases were largely reversible on dose interruption or reduction, or recovered whilst maintaining treatment at the same dose. A few patients in the TELESTAR and TELECAST trials experienced acute or chronic hepatic failure. Most patients in the studies had underlying metastatic NET with liver involvement and the most common cause of death in patients with metastatic NET in general is liver failure due to progression of liver metastases. The investigators stated that there were uncertainties with regard to the risk of liver injury given the sample size and presence of hepatic metastases in the study population.

The manufacturer indicates that laboratory monitoring of hepatic enzymes prior to and during telotristat therapy should be performed. In patients with hepatic impairment, continuous monitoring for adverse events and worsening of liver function is recommended. Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes tested and telotristat should be discontinued if liver injury is suspected. Therapy with telotristat should not be resumed unless the liver injury can be explained by another cause.

In our case telotristat was reinitiated with caution because the intake of Ganoderma lucidum could be the possible cause of drug-induced liver injury and because there were no good alternatives.

The manifestations of DILI are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure. Knowledge of the commonly implicated agents and a high index of suspicion are essential in diagnosis. The temporal profile is crucial to establish the diagnosis of DILI, as the onset of liver disease follows drug ingestion. However, the manifestation of liver toxicity may occur weeks or months after drug ingestion and even after the drug has been stopped. Liver enzyme elevations can persist for up to several months after the drug has been discontinued.

The CIOMS (Council for International Organizations of Medical Sciences)/RUCAM (Roussel Uclaf Causality Assessment Method) system is the most commonly used tool for diagnosis of DILI and causality assessment by scoring parameters such as time to onset of symptoms, laboratory data, additional drug regimen, known toxicity of suspected drug, non-drug causes, and response to rechallenge [5]. The CIOMS/RUCAM scale involves a scoring system which categorizes the suspicion into "definite or highly probable" (score>8), "probable" (score 6-8), "possible" (score 3-5),

"unlikely" (score 1-2) and "excluded" (score ≤ 0).

The criteria established by the CIOMS/RUCAM scale also help to classify liver injury as hepatocellular, cholestatic or mixed. This is done by calculating the R value, which equals (actual ALT/ALT ULN)/(actual ALP/ALP ULN). DILI is categorized as (1) Hepatocellular injury, if ALT ≥ 3 ULN and R ≥ 5; (2) Cholestatic injury, if ALP ≥ 2 ULN and R ≤ 2; (3) Hepatocellular-cholestatic mixed injury, if ALT ≥ 3 ULN, ALP ≤ 2 ULN and 2<R<5. If ALT and ALP do not reach the aforementioned criteria, the patient's condition is called "liver biochemical test abnormalities".

In our patient, the calculated R value equals 6,22 (As measured on 20/4: (524/31)/(326/120)) and ALT ≥ 3 ULN, indicating hepatocellular injury.

The case for DILI can be strengthened by the histological picture [6,7]. However, since diverse histological patterns of DILI can mimic virtually any primary liver disease, appropriate imaging and laboratory tests are necessary to exclude other etiologies. The presence of bile duct injury, prominent eosinophilic infiltrate, granulomas, sharply defined perivenular necrosis, or cholestasis out of proportion to hepatocellular injury, favours adverse drug reaction, but none of these features is specific [8]. In general, intrinsic hepatotoxicity manifests with hepatocellular necrosis with little inflammation, while idiosyncratic drug reactions often show inflammation-dominant hepatic injury.

In our patient, a biopsy was performed and histological examination showed prominent periportal and intralobular hepatitis without periportal fibrosis. Plasma cells, forming small clusters, were prominent. The histopathologic differential diagnosis included auto-immune hepatitis, a drug reaction, as well as an acute viral hepatitis. Important to note is that drug-induced hepatitis can closely mimic auto-immune hepatitis, both serologically and histologically [9]. Scoring systems should be used to help to differentiate between Auto-Immune Hepatitis and Drug-Induced Hepatitis [10].

Rechallenge with the drug can help establish the (drug) etiology, but it is often not done due to the inherent risk involved. In our patient, treatment with telotristat was reintroduced with caution. A rise in liver function tests was noted after 4 weeks, strengthening the diagnosis of DILI.

The RUCAM causality assessment was calculated on the basis of parameters including time to onset, course, risk factors, concomitant drugs, exclusion of other causes of liver injury, previous information on hepatotoxicity of the drug and response to readministration and added up to 9, meaning a definite or highly probable causality [11,12]. In conclusion, we believe we can withhold a diagnosis of acute DILI caused by telotristat etiprate, with hepatocellular injury, RUCAM score 9 and a grade of severity 1 (elevations in serum ALT and/or ALP levels, total bilirubin <2.5 ULN (2.5 mg/dL), INR <1.5). To our knowledge, this is the first case in which telotristat has been described to cause DILI up until now.

It is important to distinguish liver biochemical test abnormalities from Drug-Induced Liver Injury (DILI). For the majority of patients with DILI, full recovery is expected during dechallenge. In general, the hepatocellular injury phenotype carries a worse prognosis. The level of bilirubin is one of the important elements in grading the severity of DILI. Hy's law, created by Hy Zimmerman and used by the FDA in a modified form to establish the severity of DILI in clinical trials, also includes an appreciation of the level of bilirubin [13]. Zimmerman stated that a bilirubin level of 3 or more times the ULN in the context of hepatocellular-type DILI indicated a risk of death that is approximately 10% (range, 5%-50%). Elevated bilirubin level in hepatocellular-type DILI is a reflection of the severity of injury, cell death, and hepatocellular dysfunction.

The US National Institutes of Health funded a consortium of academic institutions, the Drug Induced Liver Injury Network (DILIN), which developed the DILIN Prospective Study, an observational longitudinal study of patients with suspected DILI [14]. This study provides an opportunity to further characterize DILI in the United States in a large cohort of patients who are carefully followed and assessed in a standardized fashion. They found that acute DILI carried an 8% risk of mortality and 13% risk of unresolved or chronic injury at 6 months following onset.

CONCLUSION

We present a case of a patient with a definite or highly probable diagnosis of drug-induced liver disease caused by telotristat etiprate as assessed by a RUCAM score 9. The patient suffered from an acute injury, grade of severity 1 and both biochemically and histologically hepatocellular injury was the suggested pattern. It is important to distinguish DILI from liver biochemical test abnormalities, because acute DILI, especially the hepatocellular-type, carries a high risk of mortality and chronic injury. Patients on telotristat etiprate should be carefully monitored for liver function abnormalities and a high suspicion for a possible diagnosis of DILI is warranted.

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