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Short Communication

Idiosyncratic drug-induced liver injury caused by givosiran in a patient with acute intermittent porphyria

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ABSTRACT

A 39-year-old woman with biochemically and clinically active acute intermittent porphyria (AIP) developed moderately severe liver injury after receiving her second dose of givosiran. Serologic evaluation ruled out hepatitis caused by viral, autoimmune, or other metabolic etiologies. The updated Roussel Uclaf Causality Assessment Method (RUCAM) score was 8 and the Revised Electronic Causality Assessment Method (RECAM) score for givosiran was 9. Results of liver tests returned to normal after givosiran was discontinued, and she has not received any more givosiran.

1. Introduction

Drug-induced liver injury (DILI) is one of the leading causes of acute liver injury and failure in the western world [1]. DILI can be divided into two primary categories: intrinsic and idiosyncratic. Intrinsic DILI is defined as a dose-dependent response that typically occurs soon after drug exposure while idiosyncratic DILI is a dose-independent response likely related to an immune-mediated reaction that typically manifests 15–120 days after the start of a drug [2]. Hepatic injury can further be described clinically as hepatocellular, cholestatic, or mixed injury. Hepatocellular injury (R[1]>5) shows a predominant elevation of serum aminotransferases, cholestatic injury ($R < 2$) shows a predominant elevation of alkaline phosphatase (AP), and mixed injury ($R = 2–5$) shows features of both [1]. Here we report a case of idiosyncratic hepatocellular DILI due to givosiran.

2. Case report

A 39-year-old woman with a history of AIP with the hydroxymethylbilane synthase mutation c.500 G > A Arg167Gln and with autoimmune diathesis came to our Center with a 27-year history of recurrent episodes of epigastric abdominal pain, nausea, vomiting, general fatigue, and weakness. Her symptoms worsened during the luteal phase of her menstrual cycle. She reported a 15-pack-year history of cigarette smoking and no alcohol use. She reported previous adverse reactions to multiple drugs, including opioids, sulfa drugs, and barbiturates. Three years prior, she had experienced a severe acute attack requiring hospital admission and hematin intravenously in the arms. This led to significant thrombophlebitis. At baseline at our Center, a liver FibroScan revealed E (stiffness estimate) of 5.6 kPa and a CAP score of 178 dB/m. Her ALT was 13 U/L, AP was 68 U/L, total bilirubin was 0.4 mg/dL, homocysteine was 17.2 μmol/L, urinary delta-aminolevulinic acid (ALA) was 7.0 mg/g creatinine (Cr) and total urinary porphobilinogen (PBG) was 22.0 mg/g Cr (Table 1). Both ALA and PBG are neurotoxic and can cross the blood-brain barrier, so even though her ALA was mildly elevated, it was likely the combination of her elevated ALA and PBG that was responsible for this severe acute attack.

Givosiran was initiated and laboratory tests were drawn each month immediately prior to receiving her monthly doses. Her second monthly dose, her ALT was 559 U/L, homocysteine was 87.9 μmol/L, total urinary ALA was 3.6 mg/g Cr, total urinary PBG was 3.2 mg/g Cr, and total urinary porphyrins were 152 nmol/g Cr (Table 1). She reported no relief from her typical porphyria symptoms. In light of evidence of hepatocellular liver injury ($R = 11.36$), highly likely due to givosiran (RUCAM score of 8 and RECAM score of 9., givosiran was discontinued. She also reported severe fatigue and bilateral back pain after each dose of givosiran. Her symptoms of DILI continued for two months, and she reported right upper quadrant tenderness and multiple episodes of intermittent

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[1] R is ALT/ULN of ALT divided by AP/ULN of AP, where ALT is serum alanine aminotransferase, AP is serum alkaline phosphatase, and ULN is upper limit of normal.

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Table 1
Selected lab studies and liver FibroScan results before, during and after givosiran treatment.

Labs	Before Givosiran (12/2020)	Just prior to Dose 1 (2/2021)	Just prior to Dose 2 (4/2021)	1 month after 2nd dose (5/2021)	8 months after 2nd dose (12/2021)	Reference Range
Serum ALT (U/L)	13	19	559	226	16	5–50 U/L
Serum AST (U/L)	15	15	382	145	17	5–40 U/L
Serum alkaline phosphatase (U/L)	68	72	123	112	74	25–125 U/L
Serum total bilirubin (mg/dL)	0.4	0.4	0.5	0.6	0.4	0.1–1.2 mg/dL
Serum albumin (g/dL)	4.4	4.4	4.2	4	4.4	3.5–5 g/dL
INR	–	–	–	1	0.95	0.8–1.1
Plasma homocysteine (μmol/L)	17.2	14.5	87.9	14.2	15.1	< 15 μmol/L
BUN (mg/dL)	7	10	8	5	9	8–24 mg/dL
Serum creatinine (mg/dL)	0.58	0.69	0.83	0.68	0.69	0.5–1.5 mg/dL
eGFR (mL/min/1.73 m^2)	>90	>90	88	>90	>90	≥ 90 mL/min/1.73m^2
Urinary ALA (mg/g Cr)	7.0	–	3.6	5.3	4.6	<7 mg/g Cr
Urinary PBG (mg/g Cr)	22.0	–	3.2	6	17.2	<4 mg/g Cr
Urinary total porphyrins (nmol/g Cr)	–	–	152	250	486	<300 nmol/g Cr
FibroScan Stiffness (kPa)	5.6	–	–	21.7	5.7	2–6 kPa
FibroScan CAP score (dB/m)	178	–	–	249	245	100–238 dB/m

non-bloody, bilious vomiting in the morning and post-prandially with no relief from ondansetron. Serologic evaluation one month after discontinuation of givosiran showed negative tests for antinuclear antibodies and smooth muscle antibodies, and she had normal quantitative immunoglobulins, serum ceruloplasmin, alpha-1 antitrypsin (protease inhibitor phenotype MM), iron profile, and lipid profile. She was also negative for active or recent CMV, EBV, HAV, HBV, HCV, or HEV infections. Her liver enzymes gradually returned to baseline after discontinuing givosiran; however, her urinary porphyrin labs and FibroScan results continued to increase (Table 1). Repeat liver FibroScan after eight months from discontinuation revealed improvement in liver stiffness (E = 5.7 kPa).

3. Discussion

DILI is a diagnosis of exclusion, and after serologically ruling out hepatitis from viral, autoimmune, and inherited metabolic etiologies, we concluded that the acute liver injury was likely caused by givosiran. Her RUCAM and RECAM scores were 8 and 9, respectively, with an R of 11.36, indicating hepatocellular-type DILI [3,4]. [5] From the patient's FibroScan results from baseline to 1 month after discontinuation, her CAP score increased from 178 to 249 dB/m, suggesting a mild increase in hepatic steatosis, and her stiffness score increased from 5.6 to 21.7 kPa, concerning for the development of hepatic fibrosis. Fortunately, seven months later, the Fibroscan stiffness score had decreased back to baseline at 5.7 kPa, suggesting that this elevation was more likely due to active hepatic inflammation, not rapid development of fibrosis.

The patient reported no relief of her chronic and recurring AIP symptoms after receiving two doses of givosiran even though she had evidence of down-regulation of hepatic ALA synthase-1 (ALAS1) as shown by reductions in urinary ALA, PBG, and total porphyrins (Table 1). In a recent 24-month interim analysis report of the open-label extension of the ENVISION study, a total of 10 patients (11%) had alanine aminotransferase (ALT) levels >3 times the upper limit of normal (ULN), of whom 3 patients (3%) had ALT levels >5 times ULN. One patient with ALT >8 times the upper limit of normal, reported as an SAE of liver function test abnormal, discontinued treatment (due to a protocol-defined stopping rule) and withdrew from the study at the end of the double-blind period. The ALT elevations generally occurred approximately 3 to 6 months after givosiran was started, and then resolved subsequently. We have also observed another patient who achieved biochemical normalization of urinary ALA, PBG, and porphyrins but who continued to experience monthly porphyric attacks while on givosiran, (Ma, Faust, & Bonkovsky, JIMD Reports, in press).

In the patient herein described, as anticipated, urinary ALA, PBG, and total porphyrins increased gradually after she discontinued givosiran. Also, worthy of note was the transient moderate hyperhomocysteinemia, observed after her second givosiran dose. Hyperhomocyteinemia has been observed in AIP with increases being sometimes attributed to givosiran [7–10].

Givosiran frequently leads to mild elevations in serum aminotransferases and decreases in eGFR. In more rare instances, as in our patient, significant elevations in serum aminotransferases, accompanied by symptoms of DILI, have required cessation [6,11]. Although the mechanism of hepatotoxicity from givosiran is still unknown, the liver injury is likely due to immune-mediated mechanisms as is common in idiosyncratic DILI [12,13]. Givosiran targets and down-regulates ALAS1 expression in the heme biosynthesis pathway with selective localization in hepatocytes to ultimately decrease the levels of ALA and PBG [14]. Givosiran is degraded intracellularly *via* nucleases and is not metabolized by the cytochrome P450 enzymes, so it seems unlikely that high givosiran levels *per se* are contributing to hepatic injury [15,16].

Based upon this case and those reported by Balwani et al. [14], and Ventura et al. [6], it seems likely that givosiran may give rise to potentially severe immune-mediated acute DILI. Thus, although givosiran represents a welcome advance for the treatment of patients with AIP who are experiencing frequent acute attacks, patients initiating therapy should be monitored closely for DILI or other adverse drug reactions during the first 3–4 months and, if tolerated well, periodically thereafter [17–19].

Author statement

C.D.M. and H.L.B. conceptualized the project, completed chart review and wrote the manuscript. D.F. assisted with chart review and reviewed the manuscript. All authors have read and approved submission of the final manuscript.

Data availability

The data that has been used is confidential.

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