Dapagliflozin-Induced Acute-on-Chronic Liver Injury

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ABSTRACT

Sodium-glucose cotransporter 2 inhibitors are a new class of oral hypoglycemic agents, and thus safety data are limited. We present a 48-year-old woman with type 2 diabetes mellitus and Child’s Class A cirrhosis secondary to nonalcoholic steatohepatitis presenting with jaundice and acute cholestatic liver injury. Other than starting dapagliflozin, she reported no medication changes or supplement use. Before treatment, her total bilirubin was 1.2 mg/dL. On admission, her liver values were elevated and liver biopsy was consistent with drug-induced liver injury. This report raises awareness about the potential hepatotoxic effects of dapagliflozin, particularly in patients with chronic liver disease.

INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is closely associated with insulin resistance and is the most prevalent cause of chronic liver disease in the Western world. Pharmacologic treatments for NASH are lacking, and reduction in metabolic risk factors, such as tight glycemic control, is recommended. While metformin is suggested as a first-line therapy for type 2 diabetes mellitus (T2DM), there are no current recommendations on which second agent should be used as adjuvant therapy or for those who cannot tolerate metformin. Recently, dapagliflozin (AstraZeneca, London, UK), a sodium-glucose cotransporter 2 (SGLT2) inhibitor, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of T2DM.

Identifying drug-induced liver injury (DILI) is challenging, as cases are rare and can have variable presentations. In 2012 the FDA delayed the approval of dapagliflozin partly because of concerns for liver toxicity as one patient developed acute liver injury during the Phase III trial. Further analysis, however, showed that the patient suffered from autoimmune hepatitis and not from DILI, so the FDA subsequently approved dapagliflozin for use in early 2014. As with most drugs in development, dapagliflozin was not tested in patients with significant hepatic disease. Therefore, post-marketing surveillance of medications among special populations, such as those with chronic liver disease, is critical to understanding potential severe effects of new medications.
CASE REPORT

A 48-year-old white woman with T2DM, hypertension, Child’s Class A cirrhosis secondary to NASH, and no history of alcohol use, presented to her primary physician for routine follow-up. Her physical exam was negative for scleral icterus or abdominal distension. Her body mass index was 39 kg/m². Laboratory serologies were notable for aspartate aminotransferase (AST) 77 U/L, alanine aminotransferase (ALT) 43 U/L, total bilirubin 1.2 mg/dL, and alkaline phosphatase 220 U/L. Her physician changed her diabetic regimen from pioglitazone 10 mg daily due to weight gain on pioglitazone. No other medications were started at that time. She noted dark urine 3 days after starting dapagliptin but did not contact her primary physician until her scheduled follow-up appointment 10 weeks later. At that visit she was jaundiced with abdominal distention, and dapagliptin was stopped. She was admitted to our institution for further management.

Upon admission, the patient was jaundiced and in no acute distress. She had icteric sclera, a distended, non-tense abdomen without hepatosplenomegaly, mild ascites with positive shifting dullness, 1+ pitting edema bilaterally to the knees, absence of asterixis, and absence of spider angiomata. She was alert and oriented to time, person, and place, but mentation was delayed. She denied any behavior changes or disorientation. The patient denied alcohol use, drug use, and other medication changes or supplement use (including acetaminophen). Laboratory serologies demonstrated AST 22 U/L, ALT 78 U/L, total bilirubin 20 mg/dL, alkaline phosphatase 188 U/L, international normalized ratio (INR) 1.5, creatinine 0.82 mg/dL, platelets 102 K/µL, and factor V 28 mg/dL. Her calculated model for end-stage liver disease (MELD) score was 22. Her hepatitis A antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis C serologies were negative. Quantitative immunoglobulin G (IgG) was 2,230 mg/dL, IgA was 794 mg/dL, and IgM was 391 mg/dL. Her antinuclear, antimitochondrial, and anti-smooth muscle antibody titers were negative. Alpha 1 antitrypsin level was 245 mg/dL, and her phenotype was MM. A liver ultrasound showed an enlarged liver with patent vasculature and no focal lesions. Computed tomography (CT) demonstrated cirrhotic liver morphology without biliary ductal dilation, portal hypertension, or gastroesophageal junction varicosity.

Her liver biopsy demonstrated mild macronesicular fatty change, mild non-specific portal inflammation with ductular reaction, mild cholestasis, and focal balloon degeneration (Figure 1). Occasional Mallory bodies were also identified (Figure 1). Portal inflammation was predominantly composed of lymphocytes, and interface activity was not identified. Trichrome stain highlighted portal fibrosis with focal bridging, consistent with stage 2 to 3 fibrosis, as well as pericellular fibrosis (Figure 1). Periodic acid-Schiff-diastase and iron stains were unremarkable. The overall morphological findings indicated a non-specific healing process that was most consistent with drug toxicity. During her hospitalization, her liver synthetic function failed to improve, and she was listed for liver transplantation. She was discharged 2 weeks later with AST 87 U/L, ALT 30 U/L, total bilirubin 18.3 mg/dL, INR 2.0, creatinine 1.8 mg/dL, Factor V 58 mg/dL, platelets 99 K/µL, and a MELD of 25. The patient underwent a successful orthotopic liver transplantation from a deceased donor 4 months later and continues to do well with excellent graft function. Post-transplant, her laboratories showed AST 24 U/L, ALT 27 U/L, total bilirubin 1.3 mg/dL, creatinine 0.66 mg/dL, INR 1.0, and platelets 208 K/µL.

DISCUSSION

The constellation of patient history, physical exam, and pathologic findings in this case implicates idiosyncratic DILI from dapagliptin as the most likely cause of her liver injury necessitating transplantation. Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity encompassing an acute deterioration of liver function in patients with cirrhosis. The patient’s decompensation included lower extremity edema, ascites, hepatic encephalopathy, and worsening discriminate function, and thus she met the definition of ACLF.4 ACLF is usually associated with a precipitating event, such as alcoholic hepatitis, DILI, superimposed viral hepatitis, portal vein thrombosis, or ischemic hepatitis, and results in the failure of one or more organs with high short-term mortality.5 Extrahepatic insults including trauma, surgery, variceal bleeding, or infection can lead to ACLF. DILI is a diagnosis of exclusion that requires a thorough investigation for other
causes of liver injury, all of which were negative in this case. Risk factors for DILI include obesity and female gender, which were present in this case.6 The patient’s symptoms began 3 days after initiation of dapaglifoxin and discontinuation of pioglitazone. The liver biopsy was consistent with DILI and lacked the hallmarks of autoimmune hepatitis, such as plasma cells or interface hepatitis.7 The biopsy did not reveal worsening steatohepatitis or cirrhosis, suggesting that her liver injury was not a result of discontinuation of pioglitazone, which has been associated with improvement in steatosis among patients with NASH.8 Furthermore, worsening cirrhosis from withdrawal of pioglitazone would not lead to cholestasis or acute liver injury, both of which were present in this case. Therefore, her acute-on-chronic liver injury was likely DILI from dapaglifoxin.

NASH is highly prevalent among patients with T2DM and is associated with increased morbidity and mortality that can lead to cirrhosis and hepatocellular carcinoma, and it is rapidly becoming a leading indication for liver transplantation.6,9 Steatosis has been shown to significantly decrease with weight loss, exercise, and improvement in glycemic control.10 Initiation and maintenance of lifestyle intervention are extremely difficult, however, so finding pharmacologic therapies for the treatment of NASH is of great interest. Metformin has failed to show improvement in the histologic features in NASH.9 Pioglitazone, a thiazolidinedione, decreases hepatic steatosis among diabetics, although it does not improve the more advanced features of NASH, such as portal inflammation or fibrosis.8 Pioglitazone is also associated with weight gain that persists even after drug discontinuation, as well as an increased risk of bladder cancer and bone fractures.12 Thus, newer glycemic agents, such as dapaglifoxin, which have been shown to have secondary weight loss benefits, may be prescribed in NASH patients to achieve improved glycemic control.

A theoretical pathologic link of dapaglifoxin as possibly causing direct liver damage may be supported by the presence of SGLT1 in biliary duct cells and intestines,13 SGLT2, which is inhibited by dapaglifoxin, is a glucose transporter located in the proximal tubule of the kidney and is responsible for 90% of renal glucose reabsorption.14 SGLT1 is also part of the SGLT family of glucose transporters and is similar in sequence to SGLT2. Given that dapaglifoxin has a 1,200x greater affinity for SGLT2 than for SGLT1, and that several trials (with this drug and others in its class with varying selectivity, such as empaglifoxin, canagliflozin) have demonstrated minimal liver-related adverse events, it appears this would likely be a rare and idiosyncratic event.15-18 Larger postmarketing studies are needed to better define the hepatotoxic potential of dapaglifoxin and others in this class. These data will be particularly useful among patients with NASH or cirrhosis who have potential for high utilization of these medications.

DISCLOSURES

Author contributions: J. Levine, M. Rogers, and L. VanWagner wrote the manuscript. A. Lo prepared the pathology figures and description. A. Wallia assisted in the writing of this manuscript. L. VanWagner is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received September 9, 2015; Accepted February 29, 2016

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