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CASE REPORT
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Drug-induced Liver Injury Caused by Ipragliflozin Administration with Causality Established by a Positive Lymphocyte Transformation Test (LTT) and the Roussel Uclaf Causality Assessment Method (RUCAM): A Case Report

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ABSTRACT

A 75-year old male patient had been regularly visiting our hospital for the management of his type 2 diabetes mellitus since he was diagnosed at age 64 years. When he developed hypoglycemic episodes with sulfonylurea, ipragliflozin (50 mg/day) was started to replace the sulfonylurea therapy. However, 49 days after starting ipragliflozin, his AST increased from 13 to 622 U/L, ALT increased from 9 to 266 U/L, ALP increased from 239 to 752 U/L, and γ-GTP increased from 19 to 176 U/L. ZTT was 3.5 U, TTT was 0.4 U, and total bilirubin was 0.7 mg/dL. IgM hepatitis A antibody, hepatitis B antigen, hepatitis C virus antibody, IgM CMV antibody, and IgM EB VCA antibody were negative, whereas a lymphocyte transformation test for ipragliflozin was positive. Abdominal CT scan showed mild fatty liver but no sign of nodular lesions. Following admission to our hospital, he received liver supportive therapy with the discontinuation of ipragliflozin therapy. He was discharged from the hospital 18 days later with AST and ALT levels reduced to 20 U/L and 13 U/L, respectively. Based on the clinical presentation of this patient, it is highly important to monitor liver function along with other possible clinical complications (e.g., dehydration, ketosis, and urinary tract infection) associated with SGLT2 inhibitor therapy.

Key words. Ipragliflozin. Drug-induced liver injury. Diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a significant risk factor for nonalcoholic fatty liver disease (NAFLD), nonalcoholic fatty liver (NAFL), and nonalcoholic steatohepatitis (NASH).[1] For example, 33-50% of patients with diabetes mellitus have NAFLD.[2] Recently, the usefulness of sodium glucose cotransporter 2 (SGLT2) inhibitors for animal NASH models has been reported.[3] However, because of its relatively short history as an antidiabetic drug, the long-term safety of SGLT2 2 inhibitors has not been established.[4] Recently, we encountered a case of ipragliflozin-induced liver injury. As there is a possibility of the future use of SGLT2 inhibitors to treat patients with diabetes mellitus presenting alone or with concomitant NAFLD, NAFL, and NASH, this case report will provide important clinical information about their safety.

CASE REPORT

A 75-year-old Japanese male patient had been regularly visiting our hospital for control of his type 2 diabetes mellitus and hypertension since his diagnosis at 64 years of age. He had diabetic peripheral neuropathy but not diabetic retinopathy. This caused slight bilateral peripheral numbness on his legs. A spot urine test showed a urine protein/creatinine ratio of 6.284, and he had an estimated glomerular filtration rate (eGFR) of 63.1 (mL/min/1.73 m^2). As he developed hypoglycemic episodes with sulfonylurea, it was replaced with ipragliflozin (50 mg/day) in

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February 2016. However, 49 days after starting ipragliflozin, he developed easy fatigability. The following laboratory test results led to a diagnosis of clinical liver injury (Table 1A): aspartate aminotransferase (AST) increased from 13 to 622 U/L (normal range, 10-40 U/L), alanine aminotransferase (ALT) increased from 9 to 266 U/L (normal range, 5-45 U/L), alkaline phosphatase (ALP) increased from 239 to 752 U/L (normal range, 100-325 U/L), and γ-glutamyl transpeptidase (γ-GTP) increased from 19 to 176 U/L (normal value, ≤ 80 U/L). Zinc sulfate turbidity test (ZTT) was 3.5 U (normal range, 2-12 U), thymol turbidity test (TTT) was 0.4 U (normal value, ≤ 4 U), total protein was 6.4 g/dL (normal range, 6.7-8.3 g/dL), albumin was 3.2 g/dL (normal range, 3.8-5.3 g/dL), and total bilirubin was 0.7 g/dL (normal range, 0.2-1.2 mg/dL). Hepatitis A virus antibody (Anti-HAV-IgM), hepatitis B virus antigen, antibody, and DNA (HBsAg, anti-HBc-IgM, HBV-DNA), hepatitis C antibody (anti-HCV), IgM cytomegalovirus (CMV) antibody and Epstein-Barr virus (EB) viral capsid antigen (VCA)-IgM antibody were negative. Abdominal computed tomography (CT) showed mild fatty liver but there were no nodular lesions. The lymphocyte transformation test (LTT), which is used to determine whether a patient has developed a T-cell response against a certain drug,[5] was positive for ipragliflozin (Table 1B). Glycosylated hemoglobin (HbA1c) decreased from 6.8% to 6.4% after starting ipragliflozin treatment without any reported hypoglycemic episodes.

He was admitted to our hospital and iplagliflozin was discontinued. He was discharged from the hospital 18 days later with his AST and ALT levels reduced to 20 U/L and 13 U/L, respectively. Thereafter, his liver function remained within the normal range until the time of this writing.

DISCUSSION

Ipragliflozin reportedly has therapeutic effects on nonalcoholic steatohepatitis in mice.[6] However, we have identified an individual who developed liver injury 49 days after starting ipragliflozin therapy, and recovered 11 days after its termination (Table 1A). We confirmed that hepatitis A virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, and Epstein-Barr virus did not cause the elevated levels of AST, ALT, ALP, or γ-GTP. We also ruled out the potential of a tumor mass by abdominal CT examination. Since the patient had mild fatty liver, we used the updated Roussel Uclaf Causality Assessment Method (RUCAM) scale to determine if patient had cholestatic or mixed liver injury of DILI (drug induced liver injury) or HILI (herb induced liver injury). This patient had cholestatic liver injury as his R (= ALT/ALP) value was ≤ 2. His updated RUCAM score was 7, according to recent literature,[7,8] (Table 1B) and indicated that our case was probably of a DILI. We also confirmed that drug-induced lymphocyte transformation test was positive for ipragliflozin (Table 1C). Therefore, we concluded that liver injury was caused by ipragliflozin. At the time of writing this report, we are unable to identify any similar case studies in our PubMed searches. Since 33-50% of patients with diabetes mellitus have NAFLD,[2] and NAFLD can be considered as a risk factor for DILI,[8,9] it is prudent to occasionally monitor liver function and assess patients for indications, such as dehydration, ketosis, and urinary tract infections, before prescribing SGLT2 inhibitors.

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DISCLOSURE

None of the authors have any potential conflicts of interest associated with this case study.

Table 1A. Changes in liver function and HbA1c.

	Before Ipragliflozin administration	49 days after Ipragliflozin administration	4 days after Ipragliflozin termination	11 days after Ipragliflozin termination
BW (kg)	68.7	60		63
AST (U/L)	13	140	622	20
ALT (U/L)	9	112	266	13
ALP (U/L)	239	752		180
γ-GTP (U/L)	19	176		64
HbA1c (%)	6.8	6.4		6.5
Blood glucose (mg/dL)	196	167		
Urine glucose (mg/dL)	-	++++		+

Changes in liver function and HbA1c, blood glucose, urinary glucose with/without ipragliflozin are shown. The blood glucose value corresponded to the patient's blood glucose two hours after breakfast.

Table 1B. Evaluation of the updated Roussel Uclaf Causality Assessment Method (RUCAM) for the cholestatic or mixed liver injury of DILI and HILI for ipragliflozin.

Updated RUCAM for the cholestatic or mixed liver injury of DILI and HILI.
Items for Cholesta3c or Mixed Liver Injury Score Result
1. Time to onset from the beginning of the drug/herb: +2 **5-90 days (rechallenge: 1-90 days) +2** < 5 or > 90 days (rechallenge: > 90 days) +1 Alternave: Time to onset from cessation of the drug/herb (except for slowly metabolized chemicals: 30 days) +1
2. Course of ALP afer cessation of the drug/herb: +2 Percentage difference between ALP peak and N **Decrease I 50% within 180 days +2** Decrease < 50% within 180 days +1 No information, persistence, increase, or continued drug/herb use 0
3. Risk factors: +1 Alcohol use current drinks/d: > 2 for women, > 3 for men) +1 Alcohol use (current drinks/d: 2 for women, 3 for men) 0 Pregnancy +1 **Age I 55 years +1** Age < 55 years 0
4. Concomitant use of drug(s)/herb(s): 0 **None or no information 0** Concomitant drug/herb with incompatible time to onset 0 Concomitant drug/herb with compatible or suggestive time to onset 1 Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset 2 Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test) 3
5. Search for alternative causes: 0 Group I (7 causes) **HAV: Anti-HAV-IgM** **HBV: HBsAg, anti-HBc-IgM, HBV-DNA** HCV: Anti-HCV, HCV-RNA HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA **Hepatobiliary sonography/colour Doppler sonography of liver vessels/endosonography/CT/MRC** **Alcoholism (AST/ALT I 2)** **Acute recent hypotension history (particularly if underlying heart disease)** Group II (5 causes) Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases. Infection suggested by PCR and titer change for CMV (anti-CMV-IgM, anti-CMV-IgG) EBV (anti-EBV-IgM, anti-EBV-IgG) HSV (anti-HSV-IgM, anti-HSV-IgG) VZV (anti-VZV-IgM, anti-VZV-IgG) Evaluation of group I and II All causes-groups I and II-reasonably ruled out +2 The 7 causes of group I ruled out +1 **6 or 5 causes of group I ruled out 0** Less than 5 causes of group I ruled out -2 Alternative cause highly probable -3
6. Previous hepatotoxicity of the drug/herb: +2 **Reaction labeled in the product characteristics +2** Reaction published but unlabeled +1 Reaction unknown 0
7. Response to unintentional reexposure: 0 Doubling of ALP with the drug/herb alone, provided ALP below 2N before reexposure +3 Doubling of ALP with the drugs(s)/herbs(s) already given at the time of first reaction +1 Increase of ALP but less than N in the same conditions as for the first administration -2 Other situations 0
Total score for the case 7

Words in bold represent corresponding items for this patient, and his score is shown on the right side of each heading. A total score of 7 is shown at the bottom of this table.

Table 1C. Result of lymphocyte transformation test.

	Measurement (cpm)	Transformation rate (%)	Normal range (%)	Result
Ipragliflozin	913	275	≤ 179	Positive

The lymphocyte transformation rate by ipragliflozin is shown. The result was positive, suggesting that ipragliflozin caused liver injury in our patient.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from the patient prior to inclusion in the study.

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