Idiosyncratic Liver Injury Induced by Vildagliptin With Successful Switch to Linagliptin in a Hemodialyzed Diabetic Patient

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Recently, cases of liver injury associated with dipeptidyl peptidase-4 (DPP-4) inhibitors have been reported (1,2). Some postulate the liver injury is mediated by class effect of DPP-4 inhibitors (1), as DPP-4 is identical to CD26 expressed in lymphocytes and macrophages and DPP-4 inhibitors suppress CD26-induced T-cell activation, thereby contributing to immunomodulation (3). However, no report presents whether liver injury associated with DPP-4 inhibitors is class effect or drug-specific. Here, we report a potential case of idiosyncratic liver injury associated with vildagliptin.

A 65-year-old woman receiving hemodialysis due to diabetic nephropathy presented with slowly progressive liver dysfunction. She was treated with insulin (4 units/day), acarbose (150 mg/day), and gliclazide (10 mg/day). With this regimen, her A1C was 7.6% (60 mmol/mol). After confirmation that her liver function test was unremarkable (March 2013), vildagliptin (50 mg/day) was started to replace insulin. Three weeks after the first vildagliptin administration, her liver function was slightly elevated (April 2013). However, acarbose, gliclazide, and vildagliptin were continued. Eight months after the first vildagliptin administration, her serum aminotransferase levels increased up to aspartate aminotransferase of 178 units/L and alanine aminotransferase of 299 units/L (November 2013) (Table 1). Serum alkaline phosphatase and γ-glutamyl transpeptidase levels were also elevated. Hepatitis B surface antigen, hepatitis C virus antibody, antinuclear antibody, and antimitochondrial antibody were undetectable. Unenhanced abdominal computed tomography scan showed her liver and biliary tract were unremarkable. Both acarbose and gliclazide were discontinued.

One week after the discontinuation of acarbose and gliclazide, the lymphocyte transformation test (LTT, also known as drug-induced lymphocyte stimulation test) for vildagliptin was found to be positive (stimulation index 3.1 [reference ≤1.8]). Idiosyncratic liver injury associated with vildagliptin was diagnosed, and vildagliptin was switched to 5 mg of linagliptin. In addition, gliclazide was resumed. Liver function monitoring performed every week confirmed that her serum aminotransferase levels gradually decreased after the vildagliptin discontinuation. Additional investigation revealed that LTT for linagliptin was negative (stimulation index 1.4). Four months after the vildagliptin discontinuation, her liver function tests returned to almost normal levels (April 2014) (Table 1).

The present case suggests that liver injury associated with vildagliptin is drug-specific in view of several findings that are not reported in the literature. First, a switch to linagliptin resulted in amelioration of elevated aminotransferase levels. Second, the LTT, which is often used for the diagnosis of drug-induced liver injury (4), was found to be positive for vildagliptin but negative for linagliptin.

Several limitations must be noted. First, the possibility of liver injury induced by other antidiabetes agents may not be completely excluded. However, elevated aminotransferase levels with plausible time relationship to vildagliptin intake and improvement in these aminotransferase levels with vildagliptin withdrawal support that vildagliptin caused the liver injury. Second, DPP-4 inhibitors except for linagliptin need dose adjustment for

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dialysis patients (5). However, overdose of vildagliptin is less likely in this case as 50 mg of vildagliptin was administered to dialysis patients in a recent trial (5).

Further research is warranted to understand the mechanism of DPP-4 inhibitors associated with liver injury.

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Table 1—Time series for patient's biochemical data

	2012		2013										2014		
	September*	November†	January	March‡	April	June	September	November§	December 17‖	December 24	December 31	January	March	April
Total bilirubin, mg/dL								0.5	0.4	0.4	0.4	0.4	0.2	0.2
AST, units/L (ref. 10–40 units/L)	11	17	12	10	38	78	38	178	71	54	39	24	25	15
ALT, units/L (ref. 6–40 units/L)	3	5	3	3	58	131	58	299	85	62	43	27	15	13
ALP, units/L (ref. 100–350 units/L)	301	327	357	322	349	358	349	641	558	529	456	395	408	382
γ-GTP, units/L (ref. ≤48 units/L)	11	12	11	11	12	28	23	84	147	156	139	107	74	35
A1C, %	8.4	8.1	7.5	7.6	7.5	6.9	7.0					25.9	24.0	26.1
Glycoalbumin, %								25.8	27.0					

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, γ-glutamyl transpeptidase; ref., reference. *Acarbose was started at 150 mg/day. †Gliclazide was started at 10 mg/day. ‡Vildagliptin was started at 50 mg/day. §Acarbose and gliclazide were discontinued after obtaining biochemical data. ‖Vildagliptin was discontinued 1 week before obtaining biochemical data.