



A Case of Macrovascular Complications after Treatment with DPP-4 Inhibitor, Sitagliptin, in a Patient with Type 2 Diabetes Mellitus

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Abbreviations

BP: Blood pressure, BMI: Body mass index, CBP: Clinic blood pressure, HbA1c: Glycated hemoglobin A1c, HBP: Home blood pressure, NGSP: National glycohemoglobin standardization program, T2DM: Type 2 diabetes mellitus

Green et al. recently investigated 14,671 patients with type 2 diabetes mellitus (T2DM) treated for 3 years with sitagliptin, a dipeptidyl peptidase (DPP)-4 inhibitor [1]. They found no increase in the risks of major adverse in cardiovascular events or hospitalization for heart failure. That is, no increases in macrovascular complications or other adverse events were seen compared with other hypoglycemic drugs. Other studies have supported these results [2,3]. However, we report herein a case of worsened cardiovascular complications after treatment with sitagliptin in patients with T2DM. Accordingly, caution is required regarding sitagliptin therapy in patients with T2DM and a history of macrovascular complications.

Our case involved a 72-year-old woman [height, 1.47 m; body mass index (BMI), 19.9 kg/m²] with T2DM and cardiovascular disturbance. She had been diagnosed with non-obese T2DM (BMI, 20 kg/m²; anti-GAD antibody, negative) during examination for coldness of the lower extremities attributed to cerebral ischemic attack or transient ischemic attack (TIA) in June 2008 (at 65 years old). In August 2015 (at 72 years old), hemoglobin (Hb) A1c (NGSP) had decreased from 6.5% at the initial diagnosis of T2DM to 6.3%. She had received treatment with an oral DPP-4 inhibitor,alogliptin (Nesina[®]; Takeda Pharmaceuticals, Tokyo, Japan) at 25 mg/day once daily after the morning meal in August 2008 (at 65 years old), and oral sitagliptin (Januvia[®]; MSD, Tokyo, Japan) at 50 mg once daily at bedtime and oral biguanide (Metogluco[®]; Sumitomo-Dainippon, Tokyo, Japan) at 500 mg 3 times a day after meals for T2DM since July 2014 (at 71 years old). Miglitol (Seibule[®]; Sanwa, Tokyo, Japan) had been administered at 50 mg 3 times a day just before meals for T2DM from June 2008 (at 65 years old) to April 2014 (at 71 years old). Other drugs prescribed included an oral angiotensin II receptor

blocker (4 mg/day, Blopess[®]; Takeda Pharma, Tokyo, Japan) twice daily after morning and evening meals, and Ca⁺⁺ blocker (5 mg/day, Amlodin[®]; Sumitomo Dainippon) once daily after the morning meal for hypertension from June 2008 (at 65 years old) to May 2014 (at 71 years old), which showed morning hypertension of 150 mmHg for systolic home blood pressure (HBP) and 89 mmHg for diastolic HBP on waking and a normal clinic BP (CBP) of 109 mmHg for systolic CBP and 61 mmHg for diastolic CBP in April 2014 (at 71 years old). This was changed in May 2014 (at 71 years old) to an oral α -blocker (4 mg/day, Cardenalin[®]; Pfizer, Tokyo, Japan) and Ca⁺⁺ blocker (5 mg/day, Amlodin[®]; Sumitomo-Dainippon) once daily at bedtime for hypertension, and at presentation, HBP was 114/64 mmHg, and CBP was 97/75 mmHg [4]. A HMG-CoA reductase inhibitor, oral rosuvastatin (5 mg/day, Crestor[®]; AstraZeneca, Tokyo, Japan) was administered once daily after morning meal for dyslipidemia from June 2008 (at 65 years old) to April 2014 (at 71 years old). In April 2014 (at 71 years old), this was changed to oral pitavastatin (1 mg/day, Livalo[®]; Kowa, Tokyo, Japan) once daily at bedtime. Blood lipid profiles were within normal ranges (total cholesterol, 169 mg/dl; high-density lipoprotein cholesterol, 47 mg/dl; low-density lipoprotein cholesterol, 95 mg/dl; triglyceride, 129 mg/dl). She had also received anti-coagulant (100 mg/day, Byaspirin[®]; Bayer, Tokyo, Japan) for TIA since December 2008 (at 66 years old). Acute myocardial infarction was diagnosed in November 2011 (at 69 years old) during a health examination, and arteriosclerosis causing coldness of the lower extremities was identified in December 2014 (at 71 years old). She was then treated with percutaneous intervention therapy in December 2014 (at 71 years old) and oral administration of the anticoagulant clopidogrel (75 mg/day, Plavix[®]; Sanofi, Tokyo, Japan) from April 2015 (at 72 years old) to the present. No new macrovascular events have been seen since initiating treatment with oral anticoagulants. The patient did not smoke or drink alcohol, and no congenital defects of the coagulation system were identified.

Since receiving treatment, the patient has shown no risk factors for macrovascular complications [3,4]. Seven years earlier, she had experienced a TIA event and then received DPP-4 inhibitors for

T2DM. However, a cardiovascular event developed despite the lack of hypertension, dyslipidemia, smoking or alcohol habits, and the absence of congenital defects of the coagulation system.

Green et al. and Paneni recently reported that patients with T2DM treated with sitagliptin appeared to show no increase in the risks of major adverse cardiovascular events or hospitalization for heart failure [1], and DPP-4 inhibitors have thus been considered safe [1,3]. Nevertheless, macrovascular events occurred during treatment with DPP-4 inhibitors and inadequate anticoagulation in this case. We should recognize that the use of DPP-4 inhibitors and inadequate treatment for blood pressure and anti-coagulant therapy may not prevent macrovascular events in patients with T2DM and a history of macrovascular events.

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References

1. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, et al. (2015) Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Eng J Med* 373: 232-242.
2. Fonseca AV (2010) Potential effects of DPP-4 inhibitors on cardiovascular disease. *Hot Topics in Cardiometabolic Disorders* 2:17-21.
3. Paneni F (2015) DPP-4 inhibitors, heart failure and type 2 diabetes: all eyes on safety. *Cardiovasc Diagn Ther* 5: 471-478.
4. Kamoi K (2015) Usefulness of morning home blood pressure measurements in patients with type 2 diabetes mellitus: results of a 10-year, prospective, longitudinal study. *Clin Exp Hypertens* 37: 122-127.