Letter to the Editor

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Effect of switching from dulaglutide to tirzepatide on blood glucose and renal function

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SUMMARY The case reports a woman in her 70s, with type 2 diabetes and chronic kidney disease in G4 stage. The patient had elevated HbA1c, and she was switched from linagliptin, a dipeptidyl peptidase 4 inhibitor, to dulaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA). Thereafter, the HbA1c level decreased; however, since the dulaglutide supply became a problem, the patient was switched to tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RA. To date, no clinical studies have evaluated the efficacy and safety of switching from GLP-1RA to GIP/GLP-1RA, but we report this case because efficacy was observed in this patient. The therapeutic effects after switching to tirzepatide included decrease in HbA1c, increase in eGFR, and decrease in BUN, when compared to when dulaglutide was used. A change from dulaglutide to tirzepatide, could inhibit renal impairment progression and improve renal function.

Keywords tirzepatide, dulaglutide, chronic kidney disease

Letter to the Editor,

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia caused by insufficient insulin action. Type 2 diabetes (T2DM), accounts for about 90% of all diabetic patients. T2DM treatment requires a stepwise approach that combines diet and exercise therapy with pharmacotherapy.

Incretin-related drugs were developed because incretin, a hormone secreted by gastrointestinal endocrine cells upon ingestion of food and other factors, plays a major role in hypoglycemic effects by stimulating insulin secretion. Incretins include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 in particular, has various effects, including blood glucose lowering and weight loss effects, *via* inhibition of glucagon secretion and delayed gastric emptying (*1*). GLP-1 receptor agonists (GLP-1RA) are recommended in major international diabetes treatment guidelines (*2*). Conversely, GIP has been neglected as a target for diabetes drugs due to its lack of insulin secretagogue action and concerns over weight gain due to its fat storage effect (*3*). However, a chimeric peptide that has elements of both GLP-1 and GIP and can activate both receptors has been demonstrated to have remarkable weight loss and blood glucose lowering effects in obese T2DM patients (*4*). Tirzepatide was launched as a drug that acts on both GIP and GLP-1 receptors *via* a single molecule. There are no reports of clinical trials evaluating the efficacy and safety of switching from GLP-1RA to GIP/GLP-1RA.

We describe our experience with a patient who switched from dulaglutide (*5*) to tirzepatide, the most commonly used GLP-1RA in Japan, and who exhibited improvement not only in glycemic control but also in renal function values.

The case is a woman in her 70s, with type 2 diabetes and chronic kidney disease at G4 stage. She refuses to receive nutritional guidance and does not stop eating between meals. Because of increased HbA1c and decreased renal function, she was switched from linagliptin of dipeptidyl peptidase 4 inhibitor to dulaglutide. The HbA1c level decreased; however, due to dulaglutide supply challenges, the patient was switched to tirzepatide. Figure 1 shows the changes in HbA1c, eGFR, and BUN from the start of dulaglutide to after change to tirzepatide. Following change to tirzepatide, HbA1c and eGFR and BUN values improved, when compared to when dulaglutide was used. After the change to tirzepatide, treatment has continued without any significant side effects. The patient's informed consent obtained and was given in writing.

Diabetes is considered a risk factor for chronic kidney disease, and diabetic nephropathy is a major cause of dialysis induction in many countries. The development of diabetic nephropathy is not only a risk factor for end-stage renal disease (ESRD) and the introduction of dialysis, but

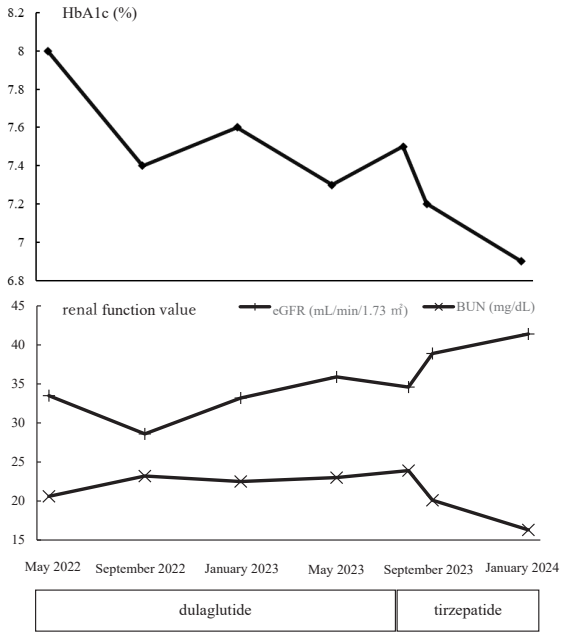

Figure 1. Course of treatment after dulaglutide initiation and change to tirzepatide.

also increases the rate of cardiovascular events and all-cause mortality due to decreased eGFR (*6,7*). Therefore, delaying progression to ESRD and introduction of dialysis is considered a key strategy for the maintenance of patient quality of life but also life support. Dulaglutide, a GLP-1RA, reportedly increases eGFR in addition to decreasing HbA1c and weight loss (*8*). However, when patients were switched to tirzepatide, a GIP/GLP-1RA, there was a further decrease in HbA1c, an increase in eGFR and a decrease in BUN compared to when dulaglutide was used. In a recent clinical trial in obese or associated overweight patients, tirzepatide was shown to reduce body weight and other cardio-renal risk factors (blood pressure, low-density lipoprotein cholesterol, glycated hemoglobin, and albuminuria) and to potentially prevent chronic kidney disease (*9*). However, the results were not reported when switching from GLP-1RA to GIP/GLP-1RA. The cases suggest that tirzepatide is more effective than dulaglutide in controlling blood glucose and preventing renal impairment progression or improving renal function. Dulaglutide, as a once-weekly formulation, has been reported to have a higher retention rate than the daily dosing formulation (*10*). Tirzepatide, similar to dulaglutide, is a once-weekly formulation; therefore, a high continuation rate can be expected. Furthermore, while changes in self-injection formulations, such as insulin and GLP-1RA, may involve issues such as operability due to changes in injectors, the injector for both dulaglutide and tirzepatide is the same, Ateos®. Therefore, there are no concerns regarding the operability of the injector for the patient following drug change.

Finally, GLP-1RA have different indications for patients with impaired renal function and should be used according to renal function as well. Although dulaglutide has no restrictions in the package insert, its clinical results in patients with severe renal dysfunction are limited, and careful administration is advised. A change from dulaglutide to tirzepatide, could inhibit the progression of renal impairment and improve renal function.

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