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UPDATE

Updates of incretin-related drugs for the treatment of type 2 diabetes

Because the number of patients with type 2 diabetes is increasing, antidiabetic drugs that are effective and have little risk of causing hypoglycemia have been required over recent decades, especially in aged societies.

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been widely used, especially in East Asia, and are the most used antidiabetic drugs in Japan because of their safety and no negative impact on bodyweight[1, 2]. In addition to their safety, several reports have shown the efficiency of the drugs in individuals of East Asian origin[3–5]. A recent report from Korea also showed that the addition of teneligliptin to patients with type 2 diabetes who were inadequately controlled by oral triple combination therapy (metformin, sulphonylureas [SUs] and sodium–glucose cotransporter 2 inhibitors) significantly decreased glycated hemoglobin (HbA1c) levels compared with a placebo (intergroup difference was −0.75%) without increasing adverse events (AEs)[6].

Although the risk is not so high, bullous pemphigoid is one of the AEs with DPP-4 inhibitors that we have to be aware of. Recent reports showed that the risk was increased 3 months from the first use of DPP-4 inhibitors[7], and Lee *et al.*[8] showed that age, race and the class of the drug are related to a higher risk of bullous pemphigoid. A current study also reported that the administration of DPP-4 inhibitors might be associated with Graves' disease exacerbation; therefore, we have to pay attention when we use the drug in patients with Graves' disease[9].

Besides the safety and efficacy of DPP-4 inhibitors, meta-analysis of randomized trials showed that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduced the risk of major adverse cardiac events, all-cause mortality, hospital admission for heart failure and the composite kidney outcome, without an increase of adverse effects[10]. In addition to the protective effects on cardiovascular diseases and kidney function[11], GLP-1 RAs can reduce bodyweight[12].

GLP-1 RAs lower glucose levels by direct and indirect actions on several organs, including the central nervous system, heart, arteries, kidneys, liver and pancreas[13]. A recent systematic review and meta-analysis[14] also showed that GLP-1RAs significantly reduce both visceral adipose tissue and subcutaneous adipose tissue, and the decrease of visceral adipose tissue was greater than that of subcutaneous adipose tissue when compared with the control group.

GLP-1RAs are an attractive alternative treatment for bolus insulin injections because of their lower risk of hypoglycemia and weight loss benefit, especially for obese patients with type 2 diabetes. A recent report showed that simplification from an intensive insulin injection regimen (basal + bolus insulin injection) to liraglutide maintained the HbA1c level with stable glucose variability in patients with well-controlled type 2 diabetes receiving multiple daily insulin injection therapy[15]. Furthermore, the replacement of the therapy decreased the total insulin dose and quality of life score, which are significantly associated with injection frequency.

For some older patients with diabetes, even once daily injection is still difficult. Under such a situation, the use of weekly GLP-1 RAs has been approved in Japan. Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) trials elucidated that injection of once-weekly semaglutide achieved better glycemic control, greater reduction of bodyweight and waist circumference, and a lower rate of major adverse cardiac events without increasing serious adverse effects than a placebo or comparators[16]. Type 2 diabetes patients in East Asian countries are characterized by lower body mass index (BMI) arising from β-cell dysfunction and relatively low insulin secretion capacity compared with those of white people. Age is also an important issue when deciding the treatment of diabetes in a 'super-aged' society, such as Japan. From these points of view, SUSTAIN Japan monotherapy and SUSTAIN Japan oral antidiabetes drug assessed the efficacy and safety of semaglutide versus comparators (sitagliptin in the monotherapy study, SUs, glinides, α-glucosidase inhibitors or thiazolidinedione) in Japanese type 2 diabetes patients across subgroups defined by baseline age and BMI[17]. The study showed both 0.5 mg or 1.0 mg semaglutide administration induced greater reduction of HbA1c and bodyweight in all age subgroups (<65 years or ≥65 years), all BMI subgroups (BMI <25 kg/m^2 or ≥25 kg/m^2), and all age and BMI subgroups (combination of the former two groups). Although gastrointestinal AEs were more common with semaglutide than comparators, AE rates were broadly similar in all age and BMI subgroups, and no severe or blood glucose-confirmed symptomatic hypoglycemic episodes were reported with semaglutide 0.5 mg or a comparator (only one with semaglutide 1.0 mg).

In addition to weekly subcutaneous semaglutide, the safety and efficacy of oral semaglutide were investigated in global trials and also in two Japanese trials (Peptide Innovation for Early Diabetes Treatment [PIONEER] 9 and 10)[18, 19], and oral semaglutide was recently approved in Japan for the treatment of type 2 diabetes. PIONEER 9 showed that 26 (and also 52) weeks of oral

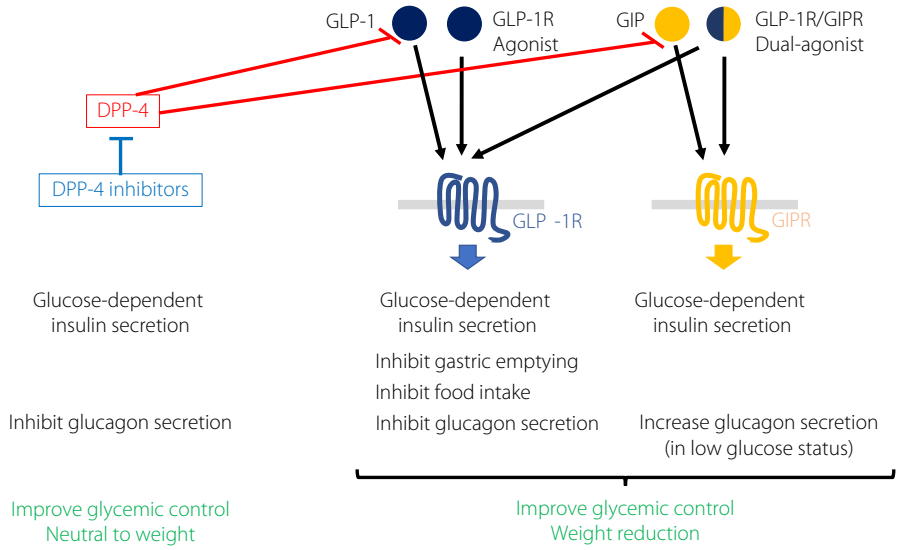

FIGURE 1 | Mechanisms of dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor (GLP-1R) agonists and GLP-1R/glucose-dependent insulinotropic polypeptide receptor (GIPR) dual-agonist in glycemic control and weight loss. Glucagon-like peptide-1 (GLP-1), GLP-1R agonists and glucose dependent insulinotropic polypeptide (GIP) bind to each receptor and induce specific effects through each receptor signaling pathway. GLP-1R/GIPR dual-agonists can bind to both GLP-1R and GIPR. DPP-4 is the enzyme that inactivates both GLP-1 and GIP through their digestion. DPP-4 inhibitors are designed to inhibit DPP-4 activity, and thereby postpone the endogenous GLP-1 and GIP activity. DPP-4 inhibitors, as well as GLP-1R agonists and GLP-1R/ GIPR dual-agonists, can improve glycemic control. GLP-1R agonists and GLP-1R/GIPR dual-agonists further result in weight loss through their pharmaceutically high concentrations. Potential effects of each receptor signaling that contribute to weight loss and/or better glycemic control are listed below each receptor. Clinical features of DPP-4 inhibitors, GLP-1R agonists and GLP-1R/ GIPR dual-agonists are written in green letters.

semaglutide (3, 7 or 14 mg) significantly reduced HbA1c compared with a placebo in a dose-dependent manner, and at the 14-mg dose, it also showed a significant reduction of HbA1c compared with once-daily liraglutide 0.9 mg. PIONEER 10, evaluating the safety and efficacy of oral semaglutide versus dulaglutide once-weekly injection in patients with type 2 diabetes who were receiving oral antidiabetic monotherapy (SUs, glinides, thiazolidinedione, α-glucosidase inhibitors or sodium–glucose cotransporter 2 inhibitors), showed similar rates of AEs in the oral semaglutide and dulaglutide groups. The study also showed that semaglutide at the 14-mg dose reduced HbA1c, and the 7- and 14-mg doses significantly reduced bodyweight, compared with 0.75 mg dulaglutide. The reduction of HbA1c in these two trials was greater than those in other PIONEER trials in which most of the participants were white. A subgroup analysis of these two trails also elucidated that higher baseline HbA1c (≤8.0, >8.0–≤9.0 or >9.0%) related to higher HbA1c reduction, whereas BMI (<25, ≥25–<30 or ≥30 kg/m^2) and background medication showed no interaction[20]. For AEs, there was no apparent difference between subgroups.

Recently, several clinical trials of tirzepatide, a dual agonist of GLP-1R and glucose-dependent insulinotropic polypeptide receptor have been reported. The SURPASS-2 trial, an open-label, 40-week, phase III trial, demonstrated that all three doses (5,10 or 15 mg) of tirzepatide lowered HbA1c and reduced bodyweight significantly greater than 1 mg of semaglutide, without increasing AEs[21]. The SURPASS J-mono study enrolled 636 Japanese patients with type 2 diabetes, and compared the safety and efficacy of three doses (5,10 or 15 mg) of tirzepatide with 0.75 mg of dulaglutide for 52 weeks. The reduction of HbA1c was superior in all doses of tirzepatide (−2.37 ~ −2.82%) when compared with dulaglutide (−1.29%), and the reduction of bodyweight was also superior in all groups of tirzepatide (−5.8 ~ −10.7 kg *vs* −0.5 kg). The most common AEs observed with tirzepatide were gastrointestinal, which were comparable with dulaglutide[22]. The safety and efficacy of tirzepatide have also been reported in SURPASSJ-combo, in which tirzepatide was added on to single oral antihyperglycemic medication (SUs, biguanides, α-glucosidase inhibitors, thiazolidinedione, glinides or sodium–glucose cotransporter 2 inhibitors) in Japanese patients with type 2 diabetes[23].

Among incretin-related drugs, because the DPP-4 inhibitors are effective to reduce HbA1c with little risk of hypoglycemia and are neutral to the bodyweight, they might be preferred for older patients with type 2 diabetes. In contrast, GLP-1RAs show greater efficacy in HbA1c reduction and significant reduction in bodyweight. They also provide the patients with multiple choices of administration, such as once or twice-day injection, once-weekly injection and oral administration. Furthermore, they might have protective benefits for atherosclerotic diseases.

Therefore, they can be used for obese patients with diabetes and high risk of cardiovascular diseases. Tirzepatide might have greater effects in HbA1c and bodyweight reductions than GLP-1RAs (Figure 1). Therefore, it can also be used for obese patients with type 2 diabetes, but it lacks the evidence for the benefits for cardiovascular diseases at this point.

DISCLOSURE

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REFERENCES

1. Yagi N, Komiya I, Arai K, *et al*. Current status of oral antidiabetic drug prescribing patterns based on the body mass index for Japanese type 2 diabetes mellitus patients and yearly changes in diabetologists' prescribing patterns from 2002 to 2019 (JDDM61). *J Diabetes Investig* 2022; 13: 65–73.
2. Bouchi R, Sugiyama T, Goto A, *et al*. Retrospective nationwide study on the trends in first-line antidiabetic medication for patients with type 2 diabetes in Japan. *J Diabetes Investig* 2022; 13: 280–291.
3. Ahrén B. Glucose-lowering action through targeting islet dysfunction in type 2 diabetes: Focus on dipeptidyl peptidase-4 inhibition. *J Diabetes Investig* 2021; 12: 1128–1135.
4. Cho YM. Incretin physiology and pathophysiology from an Asian perspective. *J Diabetes Investig* 2015; 6: 495–507.
5. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: Focus on East Asian perspectives. *J Diabetes Investig* 2016; 7: 102–109.
6. Lee M, Lee Wj, Kim JH, *et al*. Effectiveness and safety of teneligliptin added to patients with type 2 diabetes inadequately controlled by oral triple combination therapy: A multicentre, randomized, double-blind, and placebo-controlled study. *Diabetes Obes Metab* 2022; 24: 1105–1113.
7. Kuwata H, Nishioka Y, Noda T, *et al*. Association between dipeptidyl peptidase-4 inhibitors and increased risk for bullous pemphigoid within 3 months from first use: A 5-year population-based cohort study using the Japanese National Database. *J Diabetes Investig* 2022; 13: 460–467.
8. Lee H, Chung HJ, Pawar A, *et al*. Evaluation of Risk of Bullous Pemphigoid with Initiation of Dipeptidyl Peptidase-4 Inhibitor vs Second-generation Sulfonylurea. *JAMA Dermatol* 2020; 156: 1107–1114.
9. Sekizaki T, Kameda H, Nomoto H, *et al*. Dipeptidyl peptidase-4 inhibitor might exacerbate Graves' disease: A multicenter observational case–control study. *J Diabetes Investig* 2021; 12: 1978–1982.
10. Sattar N, Lee MMY, Kristensen SL, *et al*. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 2021; 9: 653–662.
11. Kim MK, Kim DM. Effects of glucagon-like peptide-1 receptor agonists on kidney function and safety in type 2 diabetes patients. *J Diabetes Investig* 2021; 12: 914–916.
12. Li HY. Revisiting the strategies for the pharmacological management of type 2 diabetes – From glycemic control, organ protection, safety to weight reduction. *J Diabetes Investig* 2022; 13: 3–5.
13. Kimura T, Kaku K. New prospects for incretin-related drugs in the treatment of type 2 diabetes. *J Diabetes Investig* 2021; 12: 1141–1143.
14. Duan K, Yan X, Gao Z, *et al*. Effect of glucagon-like peptide-1 receptor agonists on fat distribution in patients with type 2 diabetes: A systematic review and meta-analysis. *J Diabetes Investig* 2022; 13: 1–12.
15. Ando Y, Shigiyama F, Hirose T, *et al*. Simplification of complex insulin regimens using canagliflozin or liraglutide in patients with well-controlled type 2 diabetes: A 24-week randomized controlled trial. *J Diabetes Investig* 2021; 12: 1816–1826.
16. Aroda VR, Ahmann A, Cariou B, *et al*. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1–7 trials. *Diabetes Metab* 2019; 45: 409–418.
17. Yabe D, Yamada Y, Kaku K, *et al*. Efficacy and safety of once-weekly semaglutide in Japanese individuals with type 2 diabetes by baseline age and body mass index. *J Diabetes Investig* 2022; 13: 1161–1174.

18. Yamada Y, Katagiri H, Hamamoto Y, *et al*. Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2020; 8: 377–391.
19. Yabe D, Nakamura J, Kaneto H, *et al*. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. *Lancet Diabetes Endocrinol* 2020; 8: 392–406.
20. Yabe D, Deenadayalan S, Horio H, *et al*. Efficacy and safety of oral semaglutide in Japanese patients with type 2 diabetes: A subgroup analysis by baseline variables in the PIONEER 9 and PIONEER 10 trials. *J Diabetes Investig* 2022; 13: 975–985.
21. Frías JP, Davies MJ, Rosenstock J, *et al*. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med* 2021; 385: 503–515.
22. Inagaki N, Takeuchi M, Imaoka T, *et al*. Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomised, phase 3 trial. *Lancet Diabetes Endocrinol* 2022; 10: 623–633.
23. Kadowaki T, Chin R, Imaoka T, *et al*. Safety and efficacy of tirzepatide as an add-on to single oral antihyperglycaemic medication in patients with type 2 diabetes in Japan (SURPASS J-combo): a multicentre, randomised, open-label, parallel-group, phase 3 trial. *Lancet Diabetes Endocrinol* 2022; 10: 634–644.

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