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Editorial

New era for useful add-on therapy (AOT) to diabetes by combined agents of insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA)

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Among many patients with type 2 diabetes mellitus (T2DM), the proportion of achieving treatment goals has been not enough [1]. T2DM patients using basal insulin can achieve less than HbA1c 7% in about 30% [2]. These cases with good control tend to be under 7.0% of HbA1c within one year. There is a variety of factors possibly exacerbating diabetic control in daily life, and then earlier stable control would be crucial for clinical practice [3].

The doses of basal insulin are known to show a ceiling effect. It means that fasting glucose may decrease smaller than expected as increasing doses [4]. The response of the ceiling effect usually occurs at a level of insulin 0.5 units/kg/day. However, some patients may show a ceiling effect at 0.3 units/kg/day [5]. There was a study about obese T2DM patients, where administration of insulin glargine 0.5 units/kg/day did not show a lowering effect on blood glucose so much [6].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have belonged to a crucial therapeutic class for T2DM. There are several kinds of GLP-1 RAs, approved by the Food and Drug Administration (FDA). Furthermore, novel GLP-1 RAs are still under development, where rapid elimination has been an important challenge for clinical application [7].

For the treatment for T2DM patients, there is a fixed-ratio combination (FRC) of long-acting insulin analog and glucagon-like peptide-1 receptor agonist (GLP-1RA), which is Insulin Degludec/Liraglutide (IDegu/Lira, Xultophy™) [8]. It has been approved in many countries such as the Europe and North America as the diabetic agent of add-on therapy (AOT). For T2DM patients with experienced or insulin-naïve adults, once-daily injection as AOT to an oral hypoglycemic agent (OHA) has been effective and convenient for durable glycemic control. The results included delayed time to conduct intensified treatment. It also showed some efficacy of reduced risk of hypoglycemia and weight gain in comparison with previous basal-bolus or basal insulin therapy. As a whole, Xultophy has been well tolerated with convenient once-daily injection.

There has been the rationale for administrating combined agents of Xultophy in order to treat patients with T2DM. T2DM is characterized by its hyperglycemia, which is from reduced insulin secretion and increased peripheral insulin resistance [9]. It is important to set personal treatment goals and strategies for maintaining better glucose variability. Then, it can delay the onset and exacerbation of macrovascular and microvascular complications associated with T2DM [10,11].

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The administration of Xultophy has been reported in 413 patients [12]. As a result, the mean HbA1c reduction for six months was -0.65%. In detail, the changes were -0.16% (n=279) with previous HbA1c as less than 9%, and -1.67% (n=134) as 9% or more. As for age studies, HbA1c change was -0.79% under 65 years, and -0.50% at 65 or more than 65 years. Similarly, BMI showed -0.46% for those with less than 30, and -0.75% for those 30 or more than 30.

This high persistence is in line with the finding of a physicians' survey study [13] that reported high patient satisfaction with the switch to Xultophy and with the Dual Action of Liraglutide and insulin degludec (DUAL) results that indicated a significant improvement of several patient-reported outcomes (PROs) measures [14,15]. Xultophy has also been observed to demonstrate a higher durability effect of treatment when compared to insulin glargine U100, with a significantly longer time until the need for intensification (median of two years, compared to only one year with glargine U100) [16]. This high durability may contribute to the persistence found in real-world evidence (RWE). Indeed, a recent RWE study demonstrated that 94% of patients initiating Xultophy persisted with treatment for six months and 84% persisted for one year. This higher persistence was accompanied by improved glycemic control [17].

The change to the FRC was associated with a significant reduction in HbA1c. The reduction was also clinically significant with more than a quarter of patients improving their HbA1c level by 1% [12]. The proportion of days covered (PDC) was significantly improved in all patients of the group who switched to the FRC, with those who improved most having a lower PDC in the baseline period. Adherence to antihyperglycemic medications is often suboptimal in patients with T2DM, a behavior that contributes to poor glycemic control, increased hospitalization, and the development of diabetic complications. It is important to measure and assess medication adherence when using medications in a real-world setting. Adherence is evaluated using PDC, a tool developed, validated, and approved by the Pharmacy Quality Alliance as a high-quality measure of medication adherence [18].

There have been various reports on the clinical effects of IDegLira on T2DM. Among them, the reports showing relatively clear effects are shown below. Xultophy is the FRC of IDegLira, which is available in the European Union (EU) countries for inadequately controlled T2DM [19]. From several results, the once-daily subcutaneous injection would be a useful AOT option for adult patients with inadequately controlled T2DM. From several studies of Xultophy, it showed an effective, simple, less burdensome regimen, with a lower risk of weight gain or hypoglycemia than that of insulin-only treatment [20]. In order to study the continuation of Xultophy treatment, 2432 patients with T2DM were followed up for 18 months [21]. As a result, 84% of them had continued IDegLira with a mean decrease of HbA1c 1%, and of body weight 1.1 kg by daily 33 doses in the mean.

In addition, there is the latest report of DUAL studies on Xultophy. There was a study of DUAL II Japan with phase 3a randomized, treat-to-target trial for half a year. It compared the effect of IDegLira with degludec for 210 T2DM cases [22]. The results revealed that the mean HbA1c / weight reduction was 1.6% / 1.5 kg, respectively for six months. The mean daily insulin dose was 34.2 dose steps. IDegLira can result in HbA1c values reduced, which is comparable with that of basal-bolus (BB) therapy [23]. The effect of once-daily IDegLira was assessed compared with BB. BB includes insulin aspart \leq 4 times/day and once-daily insulin glargine. All subgroups showed that IDegLira therapy had similar reductions of HbA1c, lower end-of-trial (EOT) total daily insulin dose, less severe hypoglycemia, and weight loss. As a whole, the mean EOT daily insulin dose showed 0.43-0.52 U/kg with IDegLira and 0.74-1.07 U/kg with BB.

In summary, recent topics concerning Xultophy were introduced in this article. Xultophy has been rather highly evaluated for its clinical efficacy. It can contribute to better glucose variability for T2DM. This report will be hopefully a useful reference for future diabetic research and practice.

Conflict of interest

The authors declare no conflict of interest.

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References

1. Kazemian P, Shebl FM, McCann N, Walensky RP, Wexler DJ. Evaluation of the cascade of diabetes care in the United States, 2005–2016. *JAMA Intern Med* 2019;179:1376–85.
2. Blonde L, Meneghini L, Peng XV, Boss A, Rhee K, Shaunik A, et al. Probability of achieving glycemic control with basal insulin in patients with type 2 diabetes in real-world practice in the USA. *Diabetes Ther* 2018;9:1347–58.
3. Brunton S. Therapeutic inertia is a problem for all of us. *Clin Diabetes* 2019;37:105–6.
4. Meece J. Basal insulin intensification in patients with type 2 diabetes: a review. *Diabetes Ther* 2018;9:877–90.
5. Umpierrez GE, Skolnik N, Dex T, Traylor L, Chao J, Shaefer C. When basal insulin is not enough: a dose-response relationship between insulin glargine 100 units/mL and glycaemic control. *Diabetes Obes Metab* 2019;21:1305–10.

6. Wang Z, Hedrington MS, Joy NG, Briscoe VJ, Richardson MA, Younk L, et al. Dose-response effects of insulin glargine in type 2 diabetes. *Diabetes Care* 2010;33:1555–60.
7. Yu M, Benjamin MM, Srinivasan S, Morin EE, Shishatskaya EI, Schwendeman SP, et al. Battle of GLP-1 delivery technologies. *Adv Drug Deliv Rev* 2018;130:113–30.
8. Heo YA. Insulin degludec/liraglutide in type 2 diabetes: a profile of its use. *Drugs & Therapy Perspectives* 2020;36:219–29.
9. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. *Diabetes Care* 2020;43(Suppl 1):S14–31.
10. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2020;63:221–8.
11. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. *Diabetes Care* 2020;43(Suppl 1):S98–110.
12. Melzer-Cohen C, Chodick G, Nafftelberg S, Shehadeh N, Karasik A. Metabolic control and adherence to therapy in type 2 diabetes mellitus patients using IDegLira in a real-world setting. *Diabetes Ther* 2020;11:185–96.
13. Drummond R, Baru A, Dutkiewicz M, Basse A, Tengmark B. Physicians' real-world experience with IDegLira: results of a European survey. *BMJ Open Diabetes Res Care* 2018;6:e000531.
14. Billings LK, Doshi A, Gouet D, Oviedo A, Rodba HW, Tentolouris N, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. *Diabetes Care* 2018;41:1009–16.
15. Philis-Tsimikas A, Billings LK, Busch R, Portillo CM, Sahay R, Halladin N, et al. Superior efficacy of insulin degludec/liraglutide versus insulin glargine U100 as add-on to sodium-glucose co-transporter-2 inhibitor therapy: a randomized clinical trial in people with uncontrolled type 2 diabetes. *Diabetes Obes Metab* 2019;21:1399–408.
16. Aroda VR, Gonzalez-Galvez G, Gron R, Halladin N, Haluzik M, Jermendy G, et al. Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, openlabel, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;7:596–605.
17. Eliasson B, Ekelund T, Miftaraj M, Ranthe MF, Mardby A, Fernandes JDR, et al. Use of IDegLira is associated with high persistency rates up to 12 months and improved HbA1c after 6 months in Swedish clinical practice. *Diabetes* 2019;68[Suppl 1]:1110-P.
18. Centers for Disease Control and Prevention. Available from: <https://www.cdc.gov/dhdsp/docs/medadherence-evaluation-tool.pdf>.
19. Greig SL, Scott LJ. Insulin Degludec/Liraglutide: a review in type 2 diabetes. *Drugs* 2015;75:1523–34.
20. Harris S, Abrahamson MJ, Ceriello A, Charpentier G, Evans M, Lehmann R, et al. Clinical considerations when initiating and titrating insulin Degludec/Liraglutide (IDegLira) in people with type 2 diabetes. *Drugs* 2020;80:147–65.
21. Eliasson B, Ekelund J, Miftaraj M, Ranthe MF, Mardby A, Fernandes JDR, et al. Persistence with IDegLira in patients in clinical practice: a nationwide observational study in Sweden. *Diabetes Ther* 2020;11:1807–20.
22. Watada H, Ross Agner BF, Doshi A, Bardtrum L, Ranthe MF, Billings LK. IDegLira improves glycemic control in Japanese patients with uncontrolled type 2 diabetes on premixed insulin therapy. *Diabetes Ther* 2020;11:331–339.
23. Billings LK, Agner BFR, Altuntas Y, Grøn R, Halladin N, Klonoff DC, et al. The benefit of insulin Degludec/Liraglutide (IDegLira) compared with basal-bolus insulin therapy is consistent across participant subgroups with type 2 diabetes in the DUAL VII Randomized Trial. *J Diabetes Sci Technol* 2020;1932296820906888.