GSL Journal of Nutrition and Metabolism

Global Scientific Library

Commentary

Various Evidence-Based Effects of Insulin Degludec/Liraglutide (Ideglira) for Type 2 Diabetes Mellitus

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Keywords: Insulin Degludec/Liraglutide; Glucagon-like peptide-1 receptor agonists; Dual Action of Liraglutide and insulin degludec; Type 2 diabetes mellitus; Xultophy

Abbreviations: GLP-1 RAs: Glucagon-Like Peptide-1 Receptor Agonists; IDegu/Lira: Insulin Degludec/Liraglutide; T2DM: Type 2 Diabetes Mellitus; DUAL: Dual Action of Liraglutide and Insulin Degludec; FRC: Fixed-Ratio Combination

Commentary

There are two common standard guidelines for diabetes, which are the American Diabetes Association (ADA) Standards of Medical Care in Diabetes-2020 and the 2019 "Consensus Statement by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) on the Comprehensive Type 2 Diabetes Management Algorithm" [1,2]. Both guidelines have recommended physicians to consider the combination of injection treatment for post-prandial hyperglycemia in the cases who show basal insulin doses 0.5 units/kg/day with higher HbA1c level [1].

Various agents for diabetes include Oral Hypoglycemic Agents (OHAs) and injections. Their effective molecule in the blood are primarily cleared by renal filtration. Then, it may restrict the treatment options for diabetic patients with Chronic Kidney Disease (CKD) or Diabetic Kidney Disease (DKD). There are several kinds of GLP-1RA so far. Among them, dulaglutide is not cleared by the kidneys, and shows lower risk of hypoglycemia than insulin treatment [3].

Several Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) have been already used in the diabetic practice. The clinical application of GLP-1 RA would be considered before starting basal insulin administration for many T2DM patients [1]. Furthermore, GLP-1 RA can be added to T2DM patients with unsatisfactory control [2]. This recommendation is from the beneficial effect of GLP-1 RA, which has greater weight reduction and lower risk of hypoglycemia in comparison with those of insulin [4,5]. Further, GLP-1 RA has been known to reduce mortality and Major Adverse Cardiovascular Events (MACE) of patients with Atherosclerotic Cardiovascular Disease (ASCVD) and ASCVD risk [6].

For convenient treatment for T2DM, the combination of insulin and GLP-1 RA was expected to show clinical efficacy for improved glucose variability [7]. There was a comparative study of degludec/liraglutide vs glargine for 557 patients with T2DM. At 26 weeks, each group showed HbA1c reduction as -1.81% vs -1.13% (-0.59% difference), respectively. As for changes in weight, each group showed -1.4 kg vs +1.8 kg (-3.20 kg difference). Further, confirmed hypoglycemic episodes (episodes/patient-year exposure) showed 2.23 vs 5.50 (0.43 difference ratio) [7]. In clinical practice, there have been already agents for them, which are insulin glargine and lixisenatide (Soliqua 100/33, Sanofi-Aventis US) and insulin degludec and liraglutide (Xultophy 100/3.6, Novo Nordisk) [8]. From clinical studies, their significant reductions of HbA1c was 1.1-1.6% for Soliqua, and 1.6-1.9% for Xultophy, respectively [7,9,10].

The combination of insulin degludec plus liraglutide (IDeg/Lira) equals to recently-introduced Xultophy [11]. When Xultophy® (100/3.6) is injected, 1 unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide. It can be injected from 10-50 units. The Xultophy® pen is prefilled by 300 units of Xultophy® 100/3.6 (300 units insulin degludec/10.8 mg liraglutide) [11]. It has no push-button extension, and the dose button does not extend while dialing the amount, no matter how the dose is. It has once-daily regimen, and shows less hypoglycemia weight gain compared with intensive insulin regimens. Furthermore, it shows reduced GI adverse effects compared with GLP-1 RA alone. Usually, dose adjustments would be conducted according to target fasting blood glucose every 3 to 4 days [11].

As a new pharmacologic option, Xultophy has a Fixed-Ratio Combination (FRC) of basal insulin and GLP-1 RA [12]. The FRC has been adequate for glucose variability, then it has been shown to decrease the bedtime-morning difference more than monotherapy by insulin glargine [12]. There are some comments concerning the indication of insulin degludec/liraglutide. It was approved in several countries such as EU and USA for T2DM [9,11]. As to the EU, this combined agent is indicated for T2DM as an adjunct treatment to diet and exercise therapy in addition to OHAs [9,11]. Regarding the USA, it is indicated as an adjunct treatment in order to improve glycemic control when this was not given by first-line therapy [9,11]. From these situations, we can get general method how to initiate and titrate Xultophy for T2DM based on prior antidiabetic therapy [13]. There was a comparative study between insulin IDegLira versus insulin glargine 100 units/mL (IGlar U100) [14]. It was multi-centered open-label, international 2-year, phase 3b RCT study, which was known as Dual Action of Liraglutide and insulin degludec (DUAL) VIII. As a result, 1012 T2DM patients were assigned to two groups. Fewer cases in IDegLira group are necessary for intensified treatment than those in IGlar U100 group as 37% vs 66%.

Clinical efficacy of Xultophy as an Add-On Therapy (AOT) to OHAs was investigated in several DUAL studies. They included 9 global randomized, active/placebo-controlled, phase three DUAL from I to iX trials [7,10,13-15]. Furthermore, they included two phase 3 DUAL -I and -II Japan trials, in which inadequately controlled T2DM patients were followed up for 26-104 weeks [17,18]. In the former (DUAL-I to -IX), enrolled patients were ≥18 years,

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Received: Sep 17, 2020; **Accepted:** Sep 30, 2020; **Published:** Oct 02, 2020

HbA1c 7-11% and BMI 20-40 kg/m2 [7,10,13-16]. In the latter (DUAL-I and II Japan), enrolled patients were ≥ 20 years, T2DM for ≥ 6 month, HbA1c 7-11% and a BMI of ≥ 20 [17] or ≥ 23 kg/m2 [17,18]. Generally, baseline characteristics in both groups were similar, and analyses were conducted from various fully analyzed data [13-18].

Recently, some impressive reports were found associated with clinical evidence. There was a comparative study of IDegLira vs IGlar U100 for parallel-group, treat-to-target trial [16]. The results (n=210) showed that the former has -1.9% and the latter has -1.7%, with former superiority. Furthermore, the former showed lower weight gain and hypoglycemia risk. A post hoc meta-analysis conducted by Vilsbol et al. also indicated consistently lower levels of LDL with IDegLira compared with comparators across subgroups in all trials, with statistical significance achieved in men, participants aged > 65 years and both diabetes duration subgroups in DUAL II and in all subgroups, with the exception of participants with diabetes duration > 10 years, in DUAL V [19].

A series of the DUAL investigation have been conducted. They have reported several aspects for the efficacy of dual injection by DUAL trial investigators. For DUAL VIII, uncontrolled T2DM cases with Oral Antidiabetic Drugs (OADs) were randomly divided to IDegLira or IGlar U100 [14,20]. As a result, HbA1c reductions at 26 weeks showed -2.0% vs -1.5% in those groups, and the incidence of hypoglycaemia was observed 44% lower in the former group than the latter group.

From a variety of studies mentioned above, IDeg/Lira (Xultophy) seems to be clinically useful and beneficial compared with other treatments in T2DM patients with inhomogeneous complications. Authors have reported the efficacy of IDeg/Lira in T2DM [21]. This article hopefully becomes a reference for future diabetic research and practice.

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