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COMMENTARY

Glucagon-like peptide-1 therapy for youth with type 2 diabetes

Youth-onset diabetes (YOD) is a variant of type 2 diabetes with heterogeneous pathophysiology that occurs in adolescents. It is different from young-onset diabetes, which denotes diabetes diagnosed before the age of 40 years. Genetic and ethnic background might play an important role in the pathogenesis of YOD, in that it is associated with a strong family history of diabetes and a particular ethnic group, such as Hispanic people[1]. The incidence of YOD is currently rising in accordance with the increasing prevalence of obesity in adolescents.

Compared with adult-onset type 2 diabetes, YOD shows a more severe impairment in pancreatic β-cell function, which is further complicated by increasing insulin resistance associated with obesity and puberty. Furthermore, YOD is frequently associated with higher rates of microvascular and macrovascular complications, despite a shorter disease duration than other types of diabetes. The development of these complications at an earlier age leads to increased mortality of patients with YOD. The mortality rate of YOD is even higher than that of type 1 diabetes[1]. To make matters worse, there are very limited antidiabetic drugs approved for the treatment of YOD. To date, no medication has proven to be effective in preventing the rapid and relentless deterioration of β-cell function in YOD. Even the therapeutic failure rate of metformin, which is used as the first-line drug for type 2 diabetes, is higher[2].

Glucagon-like peptide-1 receptor agonists, liraglutide and exenatide, have been approved for the treatment of YOD. Recently, the results of a new clinical trial titled the Assessment of Weekly Administration of LY2189265 in Diabetes–Pediatric Study (AWARD-PEDS) to examine whether once-weekly dulaglutide is effective and safe for youth (age 10 to <18 years) with type 2 diabetes has been published[3]. This study was a double-blind, placebo-controlled, 26-week phase III trial that included patients treated with lifestyle modifications, metformin, basal insulin or metformin plus basal insulin. The primary end-point was the change in glycated hemoglobin (HbA1c) after 26 weeks from baseline. After the double-blind treatment period, an open-label extension period of another 26 weeks was followed, where all participants received dulaglutide treatment.

The mean age of the study participants was 14.5 ± 2.0 years (the proportion of Tanner stage 5 was 70% in females and 59% in males), and the mean body mass index was 34.1 ± 8.8 kg/m^2. Their mean HbA1c at baseline was 8.1 ± 1.3%, and the duration of diabetes was 2.0 ± 1.7 years. At the time of enrollment, the study participants were treated with diet and exercise only (9%), metformin only (63%), basal insulin only (3%) and metformin plus basal insulin (25%). The completion rate of this study was as high as 95% for the first 26 weeks, and 90% for the additional 26-week extension period.

At the end of the 26-week double-blind treatment, HbA1c increased by 0.6% in the placebo group, but decreased by 0.6% in the 0.75 mg dulaglutide group and 0.9% in the 1.5 mg dulaglutide group, compared with the respective baseline value. The rate of attaining HbA1c <7% at 26 weeks was 51% in the dulaglutide (0.75 and 1.5 mg) group and 14% in the placebo group. During the open-label extension period, the HbA1c-lowering effect persisted in the group assigned to receive dulaglutide at a dose of 1.5 mg a week. However, there was an obvious tendency of increase in HbA1c in the dulaglutide group during the extension period, which again indicates that the β-cell function decline in YOD is unavoidable, even with dulaglutide therapy. Unlike the results with dulaglutide in adults with type 2 diabetes, the body mass index did not differ between the dulaglutide and the placebo groups. As for the adverse effects of dulaglutide, as is generally known, gastrointestinal symptoms, such as nausea and vomiting were, most common. All of the above-mentioned results were similar to those of the Ellipse trial with liraglutide in children and adolescents with type 2 diabetes[4], with similar baseline clinical characteristics to the AWARD-PEDS trial (Table 1).

Poor adherence to the treatment regimen is often a big problem when treating YOD patients. In this regard, a once-weekly administration schedule might be helpful in improving treatment adherence. However, as shown in the extension period, the durability of the HbA1c-lowering efficacy of dulaglutide wanes with time, despite the high rates of treatment adherence. In this regard, it needs to be determined whether higher doses of dulaglutide (3.0 and 4.5 mg weekly) are more efficacious in terms of glycemic control and obesity management than the doses adopted in this study (0.75 and 1.5 mg weekly). Recently, a more potent glucagon-like peptide-1 receptor agonist showed an outstanding weight loss effect in adolescents. A once-weekly 2.4-mg dose of subcutaneous semaglutide decreased body mass index by 16.7% at week 68 from baseline in adolescents with overweight or obesity compared

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Table 1 | Comparison of the trials with liraglutide and dulaglutide in youth with type 2 diabetes

Study name	Ellipse	AWARD-PEDS
Drug	Liraglutide	Dulaglutide
Dosage	Up to 1.8 mg daily	0.75 mg or 1.5 mg weekly
Trial design	26-week double-blind period followed by 26-week open-label extension period	26-week double-blind period followed by 26-week open-label extension period
Randomized patients (*n*)	135	154
Age (years)	14.6 ± 1.7	14.5 ± 2.0
Duration of diabetes (years)	1.9 ± 1.5	2.0 ± 1.7
Baseline HbA1c (%)	7.8 ± 1.3	8.1 ± 1.3
Placebo corrected HbA1c change at week 26 (%)	−1.1 (−1.7 to −0.5)	−1.4 (−1.9 to −0.8)
Baseline BMI (kg/m^2)	33.9 ± 9.3	34.1 ± 8.8
Placebo corrected BMI change at week 26 (*z* score)	−0.05 (−0.15 to 0.06)	−0.01 (−0.10 to 0.08)

Numbers in parenthesis denote 95% confidence interval. AWARD-PEDS, Assessment of Weekly Administration of LY2189265 in Diabetes–Pediatric Study; BMI, body mass index; HbA1c, glycated hemoglobin.

with placebo[5]. Although the weight loss effect of semaglutide treatment was remarkable, the placebo-subtracted change in HbA1c was rather small (−0.3%, 95% confidence interval −0.3 to −0.2) in a small proportion of the study participants (4%) who had YOD[5]. Therefore, we desperately need newer therapy targeting β-cell deterioration and other potential mechanisms of YOD (e.g., inflammation, premature cellular senescence, etc.). Combination therapy, dual or triple incretin receptor agonists, or metabolic/bariatric surgery might be promising options, which necessitates future studies.

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