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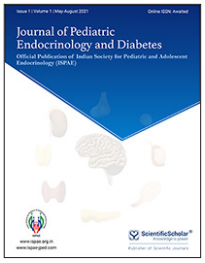
Journal of Pediatric Endocrinology and Diabetes



Ped Endo Journal Scan

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Received : 30 September 2022
Accepted : 30 September 2022
Published : 15 November 2022

DOI
10.25259/JPED_28_2022

Quick Response Code:

Once-weekly dulaglutide for the treatment of youths with type 2 diabetes

Arslanian SA, Hannon T, Zeitler P, Chao LC, Boucher-Berry C, Barrientos-Pérez M, *et al.* for AWARD-PEDS Investigators.

N Engl J Med. 2022 Aug 4;387(5):433-443.

Objective: The objective of this study was to study the safety and efficacy of dulaglutide, a glucagon-like peptide-1 receptor agonist in improving glycemic control in youth with type 2 diabetes (T2D).

Study Methodology and Results: This was a double-blind, multicenter, placebo-controlled randomized trial that enrolled children with T2D between the ages of 10 and 18 years who were being treated with lifestyle modifications alone or in addition to metformin/basal insulin. Participants were randomized in a 1:1:1 manner to receive either placebo or weekly subcutaneous dulaglutide at a dose of 0.75 mg or 1.5 mg for 26 weeks, followed by a 26-week extension period during which placebo-treated subjects received 0.75 mg dulaglutide weekly. The primary efficacy endpoint was a change in glycosylated hemoglobin (HbA1C) at week 26 and secondary endpoints were HbA1C <7% and a change in fasting blood glucose (FBG) and body mass index (BMI). Additional secondary endpoints were HbA1C <6.5%, changes in BMI standard deviation score (BMI SDS), body weight, and weight circumference.

An intention-to-treat analysis was performed. The study included 154 youth who were randomized and 146 (95%) completed the initial 26 weeks. At week 26, HbA1C was reduced by 0.8% in the dulaglutide group with an increase of 0.6% in the placebo group. A higher percentage of participants in the dulaglutide arm had an HbA1C <7% (51% vs. 14%, $P < 0.01$) and a lower FBG (−18.9 vs. 17.1, $P < 0.01$) as compared to the placebo arm. No significant change in BMI was noted in the dulaglutide group. HbA1C at 52 weeks was lower in the dulaglutide group as compared to baseline; however, the degree of reduction was lower than that at week 26. A higher rate of gastrointestinal side effects was reported in the dulaglutide group and led to treatment discontinuation in one participant.

Critical Review: This is an important study as it adds to the very limited therapeutic armamentarium in pediatric T2D. It demonstrates that dulaglutide is effective in improving HbA1C and FBG as compared to placebo at 26 weeks with persisting effects at week 52. The lack of effect on weight in contrast to adult studies is difficult to explain and may be related to the more severe hyperglycemia and insulin resistance seen in youth T2D. The availability of a weekly medication with the potential for dose up-titration is a welcome addition to the pharmacopeia.

Closed-loop therapy and preservation of C-peptide secretion in type 1 diabetes

Boughton CK, Allen JM, Ware J, Wilinska ME, Hartnell S, Thankamony A, *et al*. for-CLOuD Consortium

N Engl J Med. 2022 Sep 8;387(10):882-893.

Objective: The objective of this study was to assess whether intensive glucose control in new-onset type 1 diabetes (T1D) using hybrid closed-loop therapy can ameliorate the decline in C-peptide in comparison to standard insulin treatment.

Study Methodology and Results: This open-label, parallel-group, randomized trial enrolled 10.0–16.9-year-old participants with T1D, within 21 days of diagnosis. Subjects were randomized to receive either hybrid closed-loop therapy or standard insulin therapy for 24 months. The closed-loop system used the Cambridge model predictive control algorithm, and the control group was started on multiple daily insulin injection regimens, however, could switch to pump therapy if clinically indicated. The primary endpoint was the C-peptide area under the curve (AUC) at 12 months following a mixed-meal tolerance test. Key secondary endpoints were the percentage of time in the target range (70 to 180 mg/dL), HbA1C, and percentage of time <70 mg/dL. An intention-to-treat analysis was performed.

A total of 97 participants were randomized, 51 to closed loop, and 46 to the control arm. About 29% of the participants had DKA at diagnosis. There was no difference in the AUC of C-peptide at 12 months between the two groups, geometric mean, of 0.35 pmol/mL (IQR, 0.16–0.49) with closed-loop therapy, and 0.46 pmol/mL (IQR, 0.22–0.69] with control therapy; mean adjusted difference, −0.06 pmol/mL [95% CI, −0.14–0.03]). Time spent in the target range was not significantly different between the groups. C-peptide levels declined in both groups and the C-peptide AUC was not different between the groups at 12 months (mean adjusted difference, −0.04 pmol/mL 95% CI, −0.14–0.06). HbA1C was lower in the closed-loop group both at 12 months [−0.4% (95% CI, 0.0–0.7 percentage points)] and at 24 months (−1.0%; [95% CI, 0.5–1.5 percentage points]). Five episodes of severe hypoglycemia were documented in the closed-loop arm and one in the control arm, with one case of DKA recorded in the closed-loop group and none in the control.

Critical Review: This interesting study demonstrates that closed-loop therapy was unable to halt the inevitable reduction in C-peptide in children with T1D despite better glycemic control as compared to the control group. It is, therefore, probable that the C-peptide decline is related to the ongoing autoimmune process and is not affected by improved glycemic control. The strengths of this study are its long duration and use of real-world settings without limiting technology use in the control group which allows the findings to be generalized to the wider T1D population.

Impaired brain satiety responses after weight loss in children with obesity

Roth CL, Melhorn SJ, De Leon MRB, Rowland MG, Elfers CT, Huang A, *et al.*

J Clin Endocrinol Metab. 2022 Jul 14;107(8):2254-2266.

Objective: The objective of this study was to analyze the changes in neural responses to visual food cues and hormonal alterations following 24 weeks of family-based behavioral treatment (FBT) for obesity.

Study Methodology and Results: The study participants included 9 to 11-year-old children with obesity (OB) (n = 28) and at least one overweight parent and healthy weight (HW) children as controls (n = 17). Participants underwent hormonal testing, body composition analysis, and functional magnetic resonance imaging (fMRI) at baseline and 6 months, following completion of FBT therapy. Neural responses to food were tested by displaying alternating images of high- versus low-calorie foods and non-food objects.

At 6 months, OB children had significant reductions from baseline and as compared to HW children in their BMI Z-score, body fat mass, leptin levels, and an increase in % lean body mass. Greater reduction in leptin levels was associated with greater BMI reduction (r = −0.59, $P < 0.001$). The OB children with a higher reduction of BMI Z-score following FBT had less meal-induced suppression of neural activation by high-calorie versus low-calorie food cues ($Pint$ = 0.02 adjusted). Lower suppression of meal-induced brain activation was also found to be associated with a higher change in a meal-induced reduction in ghrelin and greater meal-induced stimulation in peptide YY and glucagon-like peptide-1 (all $P < 0.05$).

Critical Review: This is a thought-provoking study that analyzes peripheral and central hormonal and satiety responses to anthropometric changes in children with obesity following FBT. Following weight loss, while peripheral satiety mechanisms support weight loss, there is a weakening of central satiety mechanisms regulating reward and motivation for food. These central mechanisms seek to preserve body weight and could lead to overeating and weight regain after FBT. This comprehensive study brings to light important pathophysiological aspects of weight loss interventions and subsequent risk of weight regain in obese children and the need for long-term management.

Weekly somapacitan is effective and well tolerated in children with GH deficiency: The randomized phase 3 REAL4 trial

Miller BS, Blair JC, Rasmussen MH, Maniatis A, Kildemoes RJ, Mori J, *et al.*

J Clin Endocrinol Metab. 2022 Sep 5:dgac513. doi: 10.1210/clinem/dgac513.

Objective: The objective of this study was to evaluate the efficacy, safety, and tolerability of once-weekly somapacitan, a reversible albumin-binding GH derivative, compared to daily GH in prepubertal, treatment-naïve children with GHD.

Study Methodology and Results: This was a multinational, open-label, and phase 3 randomized control trial that studied the safety and efficacy of treatment with once-weekly somapacitan (0.16 mg/kg/week) for 52 weeks in children with GHD compared to daily GH (Norditropin, Novo Nordisk; 0.034 mg/kg/day). The study enrolled 200 GH naïve children with GHD who were randomized 2:1 to weekly somapacitan or daily GH. The primary endpoint was annualized height velocity (HV, cm/year) at week 52. Secondary efficacy endpoints included change from baseline to week 52 in HV standard deviation score (HV SDS), height SDS (HSDS), bone age (BA) versus chronologic age (CA) ratio, IGF-1 SDS, patient-reported outcomes, and safety measures.

Height velocity (HV) was similar in both the groups at the end of 52 weeks (11.2 in somapacitan vs. 11.7 cm/year in daily GH) thereby confirming non-inferiority. Similar increases in HV SDS and HSDS were noted in both the groups and bone age also advanced at a matching rate in both. IGF-1 SDS values were similar between treatment groups at week 52 (+0.28 vs. +0.10 for somapacitan and Norditropin, respectively) and within the normal range (–2 to +2). Following somapacitan injection, the IGF-1 profile showed a peak of +1.66 (0.90) (mean [SD]) at 57.6 (7.9) h (average time [SD]). The safety profile was similar in both groups with injection site reactions reported in 5.3% and 5.9% in the somapacitan and daily GH treatment groups, respectively.

IGF-1 levels > +2.0 SDS were measured at some time during the study by 27.3% versus 4.4% of participants in the somapacitan and daily GH treatment groups. A greater treatment burden reduction was observed for somapacitan.

Critical Review: This study is an important addition to the data on long-acting GH preparations and demonstrates the non-inferiority of somapacitan compared to daily GH. While the weekly preparation is a welcome reduction to the treatment burden, the intermittent increase in IGF-1 levels noted in the study is concerning and would need longer follow-up studies to clarify its significance and confirm the safety profile of somapacitan.

Adjuvant rituximab-exploratory trial in young people with Graves' disease

Cheetham TD, Cole M, Abinun M, Allahabadia A, Barratt T, Davies JH, *et al*.

J Clin Endocrinol Metab. 2022 Feb 17;107(3):743-754.

Objective: The objective of this study was to study whether administration of rituximab (RTX), along with a short course of thionamide anti-thyroid drugs (ATD), would result in improved remission rates in young people with Graves' hyperthyroidism.

Study Methodology and Results: This was an open-label, multicenter, single-arm, phase 2 trial which enrolled young people (12–20 years) with Graves' hyperthyroidism. The primary objective was to establish whether a single 500 mg dose of RTX, with a 12-month course of ATDs, would result in enhanced remission rates in young onset Graves' disease. Intravenous (IV) RTX was administered within 6 weeks of diagnosis along with initiation of ATD treatment using a dose titration strategy. ATDs were stopped at 12 months and participants were followed for another year to assess for remission, however, treatment was continued if participants were thyrotoxic.

A total of 27 participants completed the study, of which 13 were in remission at 24 months [48% (90% one-sided CI, 34.5–100%)]. Of these 13, two had raised TSH receptor antibodies (TRAb) suggesting the probability of relapse in the future. The median carbimazole (CBZ) dose at the end of the first 12 months was 5 mg (range, 0–60 mg) and 21 of the participants were on a dose of 5 mg or less. The treatment was well tolerated with no serious adverse events including infections, related to the trial interventions.

Critical Review: This study addresses the important question of immunotherapy for pediatric Graves' hyperthyroidism, which is notorious for the poor remission rates seen with conventional ATD therapy. It demonstrates that a single RTX dose in addition to a short course of ATD can increase remission rates to almost twice of that seen with usual ATD regimens with a relatively safe adverse event profile. However, the long-term adverse effects of this therapy and its potential to cause lasting remission are unknown. Therefore, while encouraging, these results need to be confirmed in a larger cohort of patients in a randomized control trial (RCT) setting with a longer follow-up.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

How to cite this article: Joshi K. Ped endo journal scan. J Pediatr Endocrinol Diabetes 2022;2:92-4.