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Research article

Efficacy of the Novel Degludec/Aspart Insulin Co-formulation in Children and Adolescents with Type 1 Diabetes: A Real-life Experience with 1-year IDeg/Asp Therapy in Poorly Controlled and Non-compliant Patients

Kirkgoz T et al. IDegAsp in Real-life Management of T1DM

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What is already known on this topic?
Achieving optimal metabolic control can be extremely challenging in some children and adolescents with type 1 diabetes (T1DM). Adherence to multiple insulin injections is poor in a subgroup of those children leading to frequent hospitalizations with ketoacidosis (DKA). Degludec/Aspart co-formulation (70%IDeg+30%IAsp-IDegAsp) can be beneficial in challenging cases with poor glycemic control and acute complications of diabetes by providing the longer-duration of basal insulin with simplified basal-bolus treatment in 3 injections instead of 4-5 injections.

What this study adds?
The real-life experience demonstrates that IDegAsp is non-inferior to classic basal-bolus regimen regarding to glycemic control in children with T1DM. Simplified basal-bolus regimen with IDegAsp could be an alternative in patients with frequent hypoglycemia and DKA attacks, who have poor compliance with 4-5 injections per day.

Abstract
Objective: To evaluate efficacy of Degludec/Aspart (IDegAsp) insulin co-formulation in children and adolescents with poorly controlled type 1 diabetes (T1DM)
Methods: A total of 50 patients with poorly-controlled T1DM on basal-bolus insulin regime and having compliance problems related to insulin injections and switched to IDegAsp were included. Data on HbA1c levels, hypoglycemic episodes, diabetic ketoacidosis (DKA) frequency and insulin doses were recorded at baseline and 1-year after the IDegAsp treatment.
Results: Fifty patients (22 girls) were started on IDegAsp. The mean age and duration of diabetes were 12.9±3.4 (4-18) and 5.2±3.1 years (1.0-13.7), respectively. At the end of one year, 38 patients were still on IDegAsp, whereas 12 patients returned to their original treatments on their will. In those, who continued on IDegAsp, HbA1c levels did not change, but the number of self-reported mild-moderate hypoglycemia decreased significantly ($p<0.05$). In the year before switching to IDegAsp 11 DKA attacks in 9 patients were observed, whereas this decreased to 4 DKA attacks in 4 patients after 1-year of IDegAsp therapy ($p=0.06$).
Conclusion: IDegAsp regimen could be useful in T1DM patients poorly controlled on basal-bolus insulin regimen with frequent hypoglycemia and DKA attacks as well as a poor compliance with multiple injections. Although, simplified basal-bolus regimen with IDegAsp is an attractive option for the patients with T1DM, some of the patients may not adapt to the treatment due to fixed IAsp dose of IDegAsp.
Keywords: Type 1 diabetes mellitus, hypoglycemia, diabetic ketoacidosis, co-formulation, insulin degludec, insulin aspart, IDegAsp

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Introduction
Currently, basal-bolus insulin regimes are the most commonly used treatment modality in children and adolescents with type 1 diabetes mellitus (T1DM) worldwide. Insulin pump therapy, although permitting a more physiological insulin delivery, is not available to all patients due to high cost that hinders patient access to treatment (1-3).
Optimal glycemic control is considered the key factor in reducing the risk of long term microvascular and macrovascular complications in diabetes patients (1), while only 14-30% of the patients are considered to achieve target HbA1c levels (2). Furthermore, achievement of glycemic control is more challenging in adolescent population due to poor patient compliance with anti-diabetic treatment, insulin injections in particular (2,3). Accordingly, these patients are more prone to encounter acute complications of T1DM such as recurrent diabetic ketoacidosis (DKA) and hypoglycemia (2,3). Given that standard

basal-bolus insulin regime requires 4-5 injections per day, increasing the likelihood of omitting insulin injections, longer acting basal insulins seem to offer an alternative treatment approach with a potential to enable better glycaemic control and reduced risk of recurrent DKA in children and adolescents with T1DM and poor treatment compliance. New long acting insulin analogue Degludec (IDeg), developed by removal of threonine at B30 of human insulin and adding a glutamic acid spacer to a 16-carbon diacid at B29, has a mean half-life of 25 hours, while half-life of the longest acting insulin (Glargin) in the market is 12 hours (4). IDeg is considered to offer a stable coverage of basal insulin needs due to its flatter and more consistent pharmacodynamic profile with a duration of action exceeding 42 h and four times less within-subject variability compared to insulin glargine (5,6). Furthermore, IDeg can be mixed with rapid acting insulin analogue-insulin Aspart (IAsp) without affecting pharmacokinetics of both molecules, while other long acting insulin analogues could not be mixed or co-formulated (5,6).

Insulin degludec/insulin aspart (IDegAsp; 70 % IDeg and 30 % IAsp) is a soluble combination of two individual insulin analogues in one product, designed to provide mealtime glycemic control by the IAsp component and basal glucose-lowering effect by the IDeg component. IDegAsp could provide flat and stable basal insulin coverage (provided by IDeg at steady-state conditions) and bolus mealtime insulin control with reduced injection burden compared to standard basal and bolus therapy (7). In addition, IDegAsp has been approved for use in T1DM patients over 2 years of age.

In this study, we aimed to investigate the effectiveness of IDegAsp in T1DM children and adolescents with poor glycemic control and acute complications due to noncompliance with insulin injections in a one year period.

Subjects, Materials and Methods

Study population

A total of 50 T1DM patients (39 pubertal 11 prepubertal) with poor glycemic control (HbA1c >8.5% [69.4 mmol/mol]) on basal-bolus regimen (4-5 injections per day) and frequent omission of insulin injections who were switched to IDegAsp (3 injections per day) were included in this study. Diabetes duration of >1 year, poor glycemic control on basal bolus regimen and poor treatment compliance were the inclusion criteria of the study.

Written informed consent was obtained from parent/legal guardian of each patient following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Marmara University Medical Faculty Research Ethic Committee (Protocol No: 70737436-050.06.04).

Assessments

Patient demographics, body weight and height measurements and pubertal status were retrieved from the hospital records. Data on HbA1c levels, daily insulin doses, the number of basal and bolus insulin injections per day, the number of total severe hypoglycemia episodes per year, self-reported mild to moderate hypoglycemia per week and the number of DKA episodes requiring hospital care were recorded before and 1-year after the change of the insulin regimen to IDegAsp. Severe hypoglycemia was defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions and neurological recovery following the normalization of plasma glucose levels, or both.

Switching to IDegAsp

Since, bolus IAsp dose is fixed in IDegAsp (30%), firstly, we determined from the dietary history, the main meal which the patient consumes relatively fixed and high amount of carbohydrate and IDegAsp injection was placed to that meal. The dose of IDegAsp was calculated based on the IAsp requirement at that meal which is 30% of the IDegAsp total dose. In the remaining two main meals, the patients received their usual IAsp dose according to insulin carbohydrate ratios. The further dose adjustments of IDegAsp were made based on postprandial glucose after IDegAsp meal and fasting glucose levels.

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). The paired t-test and Mann-Whitney U test were used for analysis of parametric and nonparametric variables, respectively. Data were expressed as mean±standard deviation (SD), median(min-max) and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

Results

Baseline characteristics

The study population was composed of 39 pubertal and 11 prepubertal patients. The mean±SD patient age was 12.9±3.4 years (range, 4 to 18 years) and 28(56.0%) of 50 patients were boys. The mean±SD duration of diabetes was 5.2±3.1 years (range, 1 to 13.7 years). Overall, 34 patients were switched to IDegAsp from glargine and 16 patients from detemir as basal insulins. Twenty-three patients were on two doses of basal (total of five injections/per day) injections with glargine (n: 12) or Levemir (n: 11) and 27 patients were on single basal (total of four injections/per day) injections with glargin (n: 22) or levemir (n: 5).

In addition to poor glycemic control and omission of insulin injections, there were frequent episodes of hypoglycemia (in 11 patients), excessive daily glucose variability (in 10 patients) and frequent DKA (in 9 patients) among patients.

Twelve patients who were switched to IDegAsp did not want to continue on IDegAsp and switched back to their old regimens. The reasons of discontinuation were the persistent hyperglycemia (in 7 patients), difficulty in making dose adjustment due to fixed dose of IAsp within the IDegAsp (in 4 patients) and transition to insulin pump therapy (in 1 patient).

Overall 1-year treatment outcome with IDegAsp in continuers (n=38)

Overall, 38 patients (25 boys and 13 girls) completed the 1-year IDegAsp therapy.

Mean±SD and median(min-max) age of continuers were 12.8±3.3 years and 13.2 (4.1- 17.7) years, respectively.

When values before and 1-year after IDegAsp therapy were compared, no significant difference was noted in body mass index standard deviation score (BMI SDS; 0.34±1.01 vs. 0.21±1.07, p= 0.26), in HbA1c levels (9.3 ±1.7 % vs. 9.6±1.9%, p >0.05) (Table 1). 1-year IDegAsp therapy was associated with significant reduction in the number of insulin injections (4.78±0.41 vs. 3.08±0.30, $p<0.05$), total daily insulin dose (basal+bolus insulin: 1.19±0.34 vs. 1.01±0.22 U/kg/day, $p<0.05$), long acting/total insulin ratio (0.46±0.09 vs. 0.43±0.05, $p<0.05$), long acting/ rapid acting insulin ratio (0.91±0.31 vs.

0.76±0.17, p<0.05) and long acting insulin dose (28.75±13.73 vs. 23.2±9.09 U/day and 0.55±0.17 vs. 0.44±0.11 U/kg/day, p<0.05) when compared to baseline pre-switch values (Table 1).
After 1-year IDegAsp therapy, a significant decrease was noted in the number of blood glucose-confirmed mild-to-moderate hypoglycemia episodes (2.1±1.9 vs. 0.98±1.16 episodes/week, p<0.05) but not in the total number of severe hypoglycemia episodes (2 episodes in 2 patients before and after therapy, 0.05±0.22 episodes per year in each, p>0.05) when compared to baseline values (Table 1).
Albeit not significant, there was a tendency for a decrease in total DKA episodes/year after 1-year IDegAsp therapy when compared to baseline values (0.28±0.56 vs. 0.10±0.31 episodes per year, p>0.05). Overall 11 DKA episodes occurred in 9 patients in the year before switching to IDegAsp therapy and 4 DKA episodes were noted in 4 patients after 1-year of IDegAsp therapy (Table 1).
Insulin doses at 3rd month of IDegAsp therapy in pre-switch daily basal injection subgroups
Before switching to IDegAsp, 20 patients were on once daily (OD) and 18 patients were on twice daily (TD) basal injection and there was a non-significant tendency for higher total daily basal and bolus insulin doses in twice daily vs. once daily group at the time of switch.
At the 3rd month of IDegAsp therapy, total (1.13±0.27 vs. 1.03±0.19 U/kg/day in pre-switch OD group and 1.26±0.41 vs. 1.07±0.27 U/kg/day in pre-switch TD group, p<0.05 for each) and basal (0.49±0.15 vs. 0.44±0.09 U/kg/day in OD group and 0.57±0.21 vs. 0.47±0.14 U/kg/day in TD group, p<0.05 for each) daily insulin doses decreased significantly from baseline, similarly in both pre-switch OD and pre-switch TD subgroups (Table 2).
No significant difference was noted between pre-switch OD and pre-switch TD subgroups in terms of bolus insulin dose (U/kg/day) at baseline vs. 3rd month of IDegAsp therapy as well as in IDegAsp doses (U/kg/day) at onset and 3rd month of therapy (Table 2).

Discussion

IDegAsp is the fixed-ratio co-formulation of two different insulin analogues, which provides an option for long-lasting basal insulin coverage and rapid acting post-prandial control in a single injection. It may provide an opportunity to decrease the number of insulin injections and could therefore be preferable in noncompliant patients frequently missing injections. IDegAsp has been confirmed to be non-inferior to IDet+IAsp regarding HbA1c reduction along with similar hypoglycemia rates in children (8). Representing the first real-life study evaluating the efficacy of IDegAsp in noncompliant patients, our findings revealed that IDegAsp is non-inferior to basal bolus regimens regarding glycemic control despite fewer injections. Additionally, IDegAsp therapy was associated with lesser likelihood of non-severe hypoglycemia and DKA episodes in the current study. Albeit not statistically significant, a tendency for lower frequency of DKA episodes was noted after switching to IDegAsp, from 11 DKA episodes in 9 patients at baseline to 4 DKA episodes in 4 patients at the first year of IDegAsp therapy. These data demonstrate the potential of IDegAsp to reduce the rate of metabolic decompensation and DKA in children with T1DM who are not compliant with insulin injections on a regular basal-bolus regime. This effect seems to be related to the longer duration of action of IDeg which provides better and durable basal insulin coverage and prevent ketone production unless the patient omits IDegAsp injection. Similarly, Thalange et al. also reported that in children with T1DM, IDegAsp as compared with basal bolus regimen with detemir was associated with a decrease in the rate of ketosis (9). IDegAsp, permits reduced number of injections which could be motivating for the patients and might increase the compliance.
The studies on the effectiveness of IDegAsp in children and adolescents with T1DM are scarce (8-10). In adult patients with T1DM, once-daily treatment with IDegAsp and IAsp as bolus insulin for remaining meals was reported to be associated with significantly lower risk of nocturnal hypoglycemia, improved glycemic control and showed non-inferiority compared with IDet+IAsp (11). Although we could not evaluate nocturnal hypoglycemia, real-life experience with IDegAsp in our noncompliant T1DM patients resulted in decreased number of total non-severe hypoglycemia. The achievement of intensive insulin therapy goals with three injections under IDegAsp+IAsp instead of a minimum of four injections under conventional basal–bolus insulin regimen was considered to be actual value of this therapy, enabling reduced injection burden and thereby potentially improving patient adherence and quality of life. Additionally, no significant change in BMI SDS has been observed after switching to IDegAsp, neither in our study nor in the previous studies (10,12-14).
Only a few studies in children with IDegAsp have been published and there are no standard protocols for switching doses in children. The switching protocol used in the current study was based on the decreased basal insulin doses with optimal IAsp dose for injection at meal time when IDegAsp is injected to avoid postprandial hypoglycemia. At the end of 3rd month after initial dose adjustment our patients' insulin doses decreased 11% in total and 16% in basal doses. In a pediatric study, dose reduction of 15% in total daily insulin and 26% in basal insulin was also reported (8). Thus, when deciding the initial dose of IDegAsp, a 20-30% reduction in basal insulin dose seems to be logical and a safe starting dose.
In addition, at the end of 3rd month after initial dose adjustment, insulin doses decreased by 9% for patients who were on once daily basal insulin and by 15% for those on twice daily basal insulin before switching. IDegAsp doses have become 0.63±0.13 and 0.65±0.16 U/kg/day, respectively. Thus, when deciding the initial dose of IDegAsp, previous basal daily injection and doses should be taking into account together with IAsp dose. Nonetheless, starting with 0.5-0.6 U/kg/day or half of the daily total insulin doses seems to be a good strategy.
Although simplified basal-bolus regimen with IDegAsp in T1DM is an attractive option for some patients, significant number of the patients could not adapt to the treatment and returned back to their old regimens. The main reason of the discontinuing IDegAsp therapy were difficulty of dose adjustment and inflexibility of fixed IAsp dose within IDegAsp, which requires fixed amount of carbohydrate consumption in the meal when IDegAsp is injected. For that reason, IDegAsp may not be suitable for every patient with T1DM and regimen change should be applied after careful evaluation along with explaining advantages and disadvantages in each patient.

Study limitations

Although, our study did not have any non-IDegAsp treated control group, treatment with a different regimen in previous year was the used to compare the effectiveness of IDegAsp treatment in the same background of the patients. Another limitation

of the study was glucose monitorization and hypoglycemia frequency was obtained from self-determined blood sugar measurements and patients'/families' statements. Utilising a continuous glucose monitoring system could have resulted with more accurate picture of glycemic control.

Conclusion

In conclusion, this real-life experience study indicated that IDegAsp was non-inferior to basal-bolus regimen in terms of glycemic control, while revealed significant reduction in the number of daily injections and frequency of mild-to-moderate hypoglycemia along with likelihood of lower risk of DKA in children with T1DM. Accordingly, use of a simplified basal-bolus regimen with IDegAsp could be an alternative in T1DM patients with frequent hypoglycemia and recurrent DKA, who have poor compliance with 4-5 injections per day in whom insulin pump treatment is not available.

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Figure 1. HbA1c levels before (previous year) and after the first year of IDegAsp (a) and insulin dose changes under IDegAsp treatment (b)

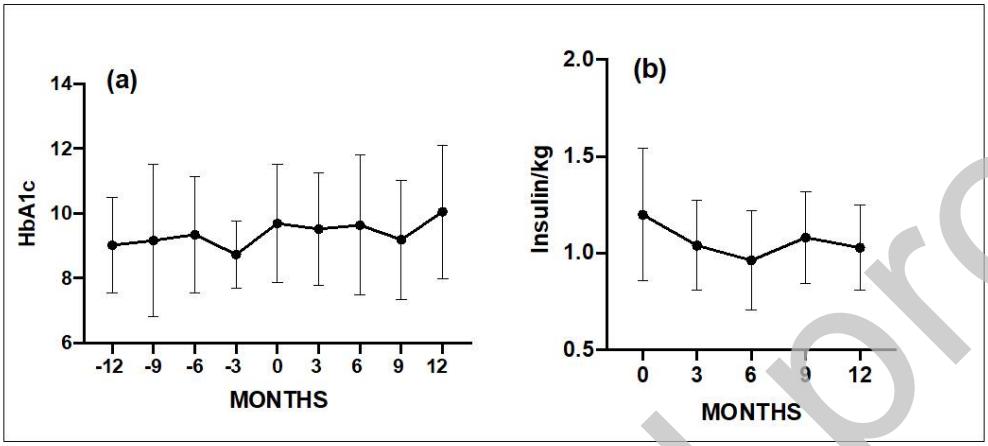

Table 1. Study parameters at baseline and 1-year after IDegAsp therapy in continuers (n=38)				
		IDegAsp continuers (n=38)		
Mean±SD		**Baseline (pre-switch)**	**1-year after IDegAsp**	**p value**
HbA1c*	%	9.3±1.7	9.6±1.9	>0.05
BMI SDS		0.34±1.01	0.21±1.07	>0.05
Number of insulin injections		4.78±0.41	3.08±0.30	**<0.05**
Insulin dose (U/kg/day)		1.19±0.34	1.01±0.22	**<0.05**
Long acting/total insulin ratio		0.46±0.09	0.43±0.05	**<0.05**
Long acting/ rapid acting insulin ratio		0.91±0.31	0.76±0.17	**<0.05**
Rapid acting insulin dose	U/day	32.83±14.63	31.79±13.3	>0.05
	U/kg/day	0.65±0.25	0.60±0.17	>0.05
Long acting insulin dose	U/day	28.75±13.73	23.2±9.09	**<0.05**
	U/kg/day	0.55±0.17	0.44±0.11	**<0.05**
Mild-to-moderate hypoglycemia (total episodes/week)		2.1±1.9	0.98±1.16	**<0.05**
Severe hypoglycemia (total episodes/year)		0.05±0.22	0.05±0.22	>0.05
DKA (total episodes/year)		0.28±0.56	0.10±0.31	>0.05
BMI SDS: Body mass index standard deviation score; DKA: Diabetic ketoacidosis *Mean HbA1c levels of the previous year before changing to IDegAsp and first year of IDegAsp treatment.				

Table 2. Insulin doses at baseline vs. 3rd month of IDegAsp therapy in pre-switch once daily and twice daily basal injection subgroups			
	Baseline (pre-switch)	**3rd month after IDegAsp**	**p value**
Total daily doses (Unit/kg/day)			
Once daily basal injection[a] (n=20)	1.13±0.27	1.03±0.19	<0.05
Twice daily basal injection [b] (n=18)	1.26±0.41	1.07±0.27	<0.05
Basal insulin Dose (Unit/kg/day)			
Once daily basal injection[a] (n=20)	0.49±0.15	0.44±0.09	<0.05
Twice daily basal injection[b] (n=18)	0.57±0.21	0.47±0.14	<0.05
Bolus insulin dose (Unit/kg/day)			
Once daily basal injection[a] (n=20)	0.62±0.19	0.60±0.14	>0.05
Twice daily basal injection[b] (n=18)	0.70±0.3	0.68±0.18	>0.05
IDegAsp dose (Unit/kg/day)			
Once daily basal injection[a] (n=20)	0.58±0.13[c]	0.63±0.13	0.34
Twice daily basal injection[b] (n=18)	0.61±0.19[c]	0.65±0.16	0.18

[a]total 4 injections/day, [b] total 5 injections/day, [c]calculated IDegAsp dose at the initiation of treatment.