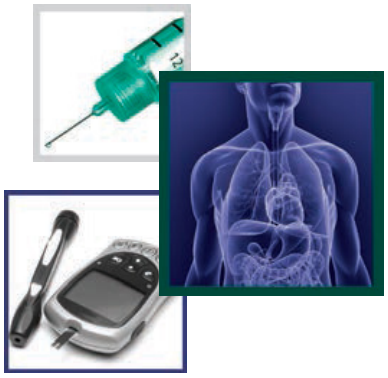
RESEARCH ARTICLE

Diabetes Management



Switching from insulin glargine to insulin degludec: Safety and efficacy in Colombian adolescents with type 1 diabetes

Myrey Siuffi D*

ABSTRACT

Introduction: Degludec (Ideg) is an ultra-long acting insulin, with a more stable pharmacodynamic profile than other commonly used insulin analogues. The effect of Ideg has not been adequately evaluated in real-world conditions for the management of adolescent patients with type 1 diabetes (DM1). Methods: A prospective, before-and-after study was conducted including adolescent DM1 patients managed on an outpatient basis at the endocrinology unit of the Clínica Farallones in Cali, Colombia. The impact of switching from a Glargine insulin to a basal insulin regimen with Ideg for a year on glycated hemoglobin (HbA1c) levels, the frequency of hospitalizations for diabetic ketoacidosis and frequency of episodes of hypoglycaemia were evaluated on a quarterly basis. Results: 15 patients 13.6 +/- 1.5 years old were recruited. There was a reduction in HbA1c levels of -1.46% (95% CI -0.77, -2.15, p=0.0004) 12 months after switching to Ideg. The percentage of patients presenting at least one episode of hypoglycaemia <54 mg/dL decreased from 80% to 0% (p<0.001). The rate of hospitalizations decreased from 2.4 +/- 1.8 to 1.4 +/- 0.83 events (p<0.01); such findings are retained in the subgroup of patients with occasional forgetfulness in insulin administration and poor adherence to strict glucose self-monitoring recommendations. Conclusions: Our results suggest that Ideg treatment significantly reduces episodes of hypoglycaemia and diabetic ketoacidosis hospitalizations, besides improving metabolic control in adolescents with DM1.

Introduction

The direct relationship between sustained chronic hyperglycemia and the incidence of chronic microvascular complications of type 1 diabetes (DM1) has been clearly demonstrated in studies such as Diabetes Control and Complications trial (DCCT) [1,2]. Therefore, different international associations recommend to set stricter goals of glycaemic control in children and adolescents [3,4]. Achieving optimal glycaemic control is associated with particular challenges in adolescent patients, such as hormonal and growth changes, psychological changes, special family dynamics, and difficulties in providing management outside home in the school environment [5]. Under real-world management conditions, there are additional factors that may make it more difficult to reach such management goals, like limited accessibility to interventions within different health systems, or restrictions associated with socio-economic characteristics. The presence of episodes of hypoglycaemia is a limiting factor for achieving good glycaemic control in insulin treated patients with type 1 diabetes [6,7]. Multiple studies have shown the association between hypoglycaemia and a decrease in the cognitive function of children with type 1 diabetes [8,9], which entails school and social implications [10]. The insulin degudec (Ideg) is a basal insulin of ultra-long action that is available for the management of patients with DM1. Its effect is based on the formation of multi hexamers soluble in the subcutaneous

Endocrinology Unit, Clinica Farallones, Cali Valle del Cauca, Colombia

**Author for correspondence: mireysiuffi2@hotmail.com*

KEYWORDS

- type 1 diabetes
- insulin degludec
- adolescents
- children

ABBREVIATIONS

- (DM1) Type 1 diabetes
- (HbA1c) Glycated hemoglobin
- (Ideg) insulin degludec

tissue, creating a deposit that releases monomers slowly and continuously to finally be absorbed into circulation, thus leading to a more stable pharmacokinetic profile, and lower fluctuations in glucose levels [11,12]. These pharmacokinetic properties have been shown to be maintained in adolescents with DM1 [13], which may help overcome multiple limiting factors to achieve good glycaemic control. The impact of treatment with insulin degludec has been poorly assessed in adolescent patients with type 1 diabetes. The aim of the present real-world study is to evaluate the impact on glycaemic control and the incidence of episodes of hypoglycaemia, when changing from an insulin Glargine scheme to a basal insulin regimen with Ideg in a group of adolescent patients with type 1 diabetes after one year of management.

Methods

A prospective, before-and-after study was conducted with patients managed on an outpatient basis at the endocrinology unit of the Clínica Farallones in Cali, Colombia. Patients were recruited to the study between November 2015 and July 2016. The inclusion criteria were age between 12 and 18 years, DM1 of at least 1 year, receiving treatment with basal insulin scheme (Glargina) associated with bolus insulin (Aspart, Lispro or Glulisine), episodes of severe hypoglycaemia (<45 mg/dL) or HbA1c levels >7% and systematic glucose self-monitoring (SMBG) with at least four capillary blood glucose measurements per day. Any type of cardiac pathology was considered as exclusion criteria. During an initial visit, assent and informed consent were requested to both the patient and his/her family, data on baseline demographic and clinical characteristics were obtained from a structured interview, and HbA1c sampling was conducted. In addition, the systematic records of the quarterly clinical assessments performed prior to the start of the study were assessed, including record of episodes of hypoglycaemia and hospitalizations for complications of diabetes over the 12 months prior to the study. All baseline HbA1c measurements were processed using techniques approved by the National Glycohemoglobin Standardization Program (NGSP). In this initial visit, both the patients and their parents were trained on how to administrate the insulin degludec treatment, including information regarding its mechanism of action, the form of administration and the scheme for dose titration. Indication was to administrate Ideg with breakfast to avoid nocturnal hypoglycaemia. The Ideg initial dose was calculated by reducing the dose received of insulin Glargine by 10% and was adjusted based on preprandial glucose measurements, reaching doses between 0.6 and 1.2 u/kg/day. Patients were instructed to maintain fast-acting insulin doses before each meal. Quarterly follow-up office visits were conducted for 1 year. At each follow-up visit, detailed aspects of self-control were reviewed, including the knowledge, attitudes and abilities of the family and/or the adolescent to make changes in insulin doses, taking into account self-monitoring, feeding and exercise level. Measures to prevent episodes of hypoglycaemia were also stressed, and verification was made on the existence of favorable circumstances. Finally, the presence of complications leading to hospitalization (specifically diabetic ketoacidosis events), presence of hypoglycaemia suggestive symptoms (dizziness, tachycardia, tremor, sweating, and blurred vision) and the self-monitoring results with seven capillary glucose measurements per day were sistematically registered. An episode of hypoglycaemia was defined as interstitial glucose levels below 54 mg/dL [14]. In the last visit, 12 months after study entry, HbA1c levels were again recorded. For continuous variables, mean and standard deviations are reported for those variables with normal or median distribution, and interquartile range if this assumption was not met. For categorical variables, frequency and percentages tables are reported. To evaluate the change over time in HbA1c levels and the number of episodes of hospitalizations for diabetic ketoacidosis, a paired t-test was run, comparing the baseline value to the level after twelve months of treatment. The proportion of patients in goals and patients with at least one episode of hypoglycaemia before and 12 months after Ideg was compared using a McNemar chi-square test. Statistical STATA 15.0 software package was used for the analysis.

Results

15 patients were recruited to the study, 8 men and 7 women. The patients demographic and clinical data are shown in **TABLE 1**. The mean age was 13.6 ± 1.5 years. All participants were in high school, ranging from sixth to tenth grade, most of them lived with their parents (86.7%). The mean BMI was 22.17 +/- 1.3 kg/m^2. No patient met obesity criteria nor had evidence of

microvascular complications. During the follow-up year, 93% of the patients had no limitations on access to the medication from the health system, however, 47% reported occasional forgetfulness in the administration of insulin degludec doses. 67% met at least 4 daily blood glucose measurements and only 54% met the goal of 6 or 7 daily measurements of capillary glucose measurements. The average HbA1c prior to initiation of insulin degludec therapy was 9.46% +/- 1.59% and decreased within the 12 months after switching treatment to 8.0% +/- 1.0%. The mean difference was -1.46% (95 % CI, -0.77, -2.15), p=0.0004. The analysis of change in HbA1c levels showed that the change was clinically and statistically significant even in patients who performed fewer capillary glucose measurements per day, as well as among those who reported unintentional omission of insulin doses **(TABLE 2)**. The percentage of patients with HbA1c <7% at the start of the study was 13.3%, and increased to 40% after 12 months of treatment with insulin degludec (McNemar's test, p=0.04). 80% percent of patients had at least 1 episode of severe hypoglycaemia in the year prior to switching treatment to insulin degludec, with a median of 2 events per patient (interquartile range 1,4). After switching treatment and over the follow-up year no new episodes of severe hypoglycaemia occurred in any of the patients recruited (McNemar's test, p<0.001). The mean number of hospitalizations due to complications of the disease in the year prior to switching treatment was 2.4 +/- 1.8 and decreased to 1.4 +/- 0.83 events (paired T, p<0.01). This reduction was clinically and statistically significant in the subgroup of patients who performed fewer capillary blood glucose measurements per day and among those reporting unintentional insulin dose omissions **(TABLE 3).**

Table 1. Basal Characteristics of Included Patients

Variable	n=15
Sex Male, n (%)	8 (53.3)
Age in years, mean (sd)	13.6 (1.50)
BMI (Kg/m²), mean (sd)	22.18 (1.30)
HbA1c (%), mean (sd)	9.46 (1.59)
Economic status, n (%)	
High	3 (20)
Medium	9 (60)
Low	3(20)

SD: Standard deviation, BMI: Body mass index, HbA1c: Glycated hemoglobin.

Discussion

In this real-word study it was found that switching from glargine therapy to Ideg for 12 months significantly reduced episodes of hypoglycaemia and hospitalizations for diabetic ketoacidosis, besides to improving metabolic control in adolescents with DM1. Few previous studies have assessed Ideg in adolescents with DM1. In a randomized clinical trial, Thalange [15] analized 350 patients, who were randomized to treatment with degludec or detemir, showing discrete decreases in HbA1c levels with respect to baseline values for both groups. Specifically in the subgroup of 127 patients between 12 and 17 years reductions of -0.10% and -0.14% in HbA1c levels were found in patients treated for 52 weeks with Ideg and detemir respectively; the conclusion was that Ideg is not inferior with respect to detemir. Similar findings were reported by Urakami [16], who performed a randomized cross-over study evaluating changes in HbA1c levels in a group of 18 patients aged 7 to 14 years, comparing treatment with basal glargine or insulin degludec, and no significant changes in metabolic control were found. In the present study a very significant reduction was found in HbA1c levels of -1.46% which may be associated with the poorer metabolic control that our patients presented on average at the time of

Table 2. Change in HbA1c levels according to adherence to insulin scheme and glucometric control recommendations

Group		n	Baseline % ± SD	12 months % ± SD	Mean difference (95% CI)	P*
Adherence	Occasional forgetfulness	7	9.71 ± 1.25	8.43 ± 0.98	-1.28 (-2.31,-0.26)	0.02
	Daily dosage	8	9.25 ± 1.91	7.62 ± 0.92	-1.63(-2.8,-0.45)	0.01
Capillary glucose measurements	≤ 5	7	10.28 ± 1.25	8.57 ± 0.98	-1.71 (-2.74,-0.68)	<0,01
	6 or 7	8	8.75 ± 1.58	7.50 ± 0.76	-1.25 (-2.41,-0.09)	0.04
	Total	15	9.46 ± 1.60	8.00 ± 1.00	-1.46 (-2.15,-0.78)	<0,01

CI: confidence interval. *Paired t-test

Table 3. Change in the number of hospitalizations for diabetic ketoacidosis according to adherence to insulin scheme and glucometric control recommendations.

Group		n	Baseline % ± SD	12 months % ± SD	Mean difference (95% CI)	P*
Adherence	Occasional forgetfulness	7	2.71 ± 2.05	1.57 ± 1.13	-1.14 (-2.13,-0.15)	0.03
	Daily dosage	8	2.13 ± 1.64	1.25 ± 0.46	-0.88 (-2.01, 0.26)	0.12
Capillary glucose measurements	≤ 5	7	3.00 ± 2.23	1.57 ± 1.13	-1.42 (-2.61,-0.25)	0.02
	6 or 7	8	1.88 ± 1.25	1.25 ± 0.46	-0.63 (-1.51,0.26)	0.14
	Total	15	2.40 ± 1.80	1.40 ± 0.83	-1.00 (-1.66,-0.34)	<0.01

CI: confidence interval. *Paired t-test

switching to insulin degludec (9.46% +/- 1.59%) compared to baseline HbA1c levels in patients recruited to the two mentioned studies (8.3% and 7.7%). Regarding the incidence of episodes of hypoglycaemia <54 mg/dL, Thalange found no significant differences in the incidence of events when comparing degludec to detemir [15], unlike Urakami who did not find differences in the incidence of general hypoglycaemia, but does report a significant decrease in nocturnal hypoglycaemia events when patients received degludec compared to glargine [16]. The present study found a very significant reduction in the incidence hypoglycaemia episodes <54 m/dL, considering that no patient showed new episodes after starting insulin degludec despite that 80% of them had had episodes in the year prior to change therapy. Similar findings have been reported in different patient populations. For example, the recently published DEVOTE study [17], a clinical trial recruiting more than 7000 patients with DM2, found statistically significant reduction of severe hypoglycaemia events in patients treated with IDeg compared to those who received glargine (4.9% *vs.* 6.6%, RR 0.60, P <0.001), or cross-over studies performed in adult patients diagnosed with DM1 [17] with hypoglycaemia risk factors, where a reduction in the rate of clinically significant and severe hypoglycaemia events were reported. Further randomized clinical trials in adolescent patients with DM1 should be performed to determine the actual impact of degludec treatment on these patient's hypoglycaemia incidence. Similar to what was found in this study, Thalange [15] found a lower incidence of episodes of hyperglycemia and ketoacidosis episodes in patients treated with Ideg compared to those treated with glargine. This reduction can be attributed to the better pharmacokinetic profile of Ideg, which produces lower variations in insulin levels for prolonged periods. The present study shows the experience of a series of patients for whom management was changed from glargine to degludec, representing more directly the usual characteristics of patients attending the outpatient clinic of pediatric endocrinology in real-world conditions, unlike patients recruited in randomized clinical trials where treatment and assessment are performed under ideal conditions, and therefore the external validity of the findings is lower. Our patients reported forgetfulness in the administration of some insulin doses in a high percentage (47%), and the frequency of capillary glucose measurements was lower than the one recommended and initially planned, in a significant percentage of the cases (47%). A striking finding in the present study is that the reduction in the hypoglycaemia incidence, hospitalizations for diabetes complications, as well as the positive impact on the glycaemic control are retained in these subgroups of patients. These findings are very significant taking into account that the daily routine of children and adolescents can vary substantially, and that an insulin that allows greater flexibility in administration may promote better clinical outcomes. In fact, it has already been shown that greater flexibility in Ideg administration is possible without compromising the glycaemic control in adult patients with DM1 [18] and DM2 [19], and that the favorable characteristics of the reported Ideg pharmacokinetic profile in adults are retained in children and adolescents [13]. This study has limitations to consider. In first place, the low number of patients recruited to the study limits the evaluation of safety outcomes, especially when analyzing subgroups of the population. In fact, the low number of patients did not allow to specifically assess the impact on the incidence of nocturnal hypoglycaemia, where treatment with Ideg could have a significant impact. Further studies with more adolescent patients are needed to confirm our findings. A second limitation is the lack of a control group, which makes it difficult to assess whether the improvement in the clinical

outcomes is associated with not measuring other factors, such as a better adherence to the insulin scheme, the life style recommendations, or greater motivation for self-care after switching to degludec, or if the findings are the result of a more active education and training scheme by health professionals. However, these changes may better reflect what actually happens in real-world conditions. Despite these limitations, the present study suggests that treatment with insulin degludec may have significant clinical benefits in the management of adolescents with DM1. These results should be confirmed with randomized clinical trials and validated by new, real-world studies involving a larger number of patients.

Conflict-of-Interest Disclosure

NO

Acknowledgements

Medical writing and editorial assistance was provided by Dr. Oscar Muñoz and funded by a grant from Novo Nordisk. The author takes full responsibility for the content and conclusions stated in this manuscript. Novo Nordisk neither influenced the content of this publication nor was it involved in the study design, data collection, analysis or interpretation.

References

1. Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *New. Engl. J. Med*. 329(14), 977–986 (1993).
2. Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA*. 287(19), 2563–2569 (2002).
3. Rewers MJ, Pillay K, de Beaufort C *et al.* Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatr. Diabetes*. 15(S20), 102–114 (2014).
4. Chiang JL, Kirkman MS, Laffel LMB *et al.* Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. *Diabetes. Care.* 37(7), 2034–2054 (2014).
5. Halvorson M, Yasuda P, Carpenter S *et al*. Unique Challenges for Pediatric Patients With Diabetes. *Diabetes. Spectr*. 18(3), 167–173 (2005).
6. Cryer P. Hypoglycaemia: The limiting factor in the glycaemic management of Type I and Type II Diabetes. *Diabetologia*. 45(7), 937–948 (2002).
7. Chase HP, Lockspeiser T, Peery B *et al.* The Impact of the Diabetes Control and Complications Trial and Humalog Insulin on Glycohemoglobin Levels and Severe Hypoglycemia in Type 1 Diabetes. *Diabetes. Care*. 24(3), 430–444 (2001).
8. Golden MP, Ingersoll GM, Brack CJ *et al.* The Longitudinal relationship of asymptomatic hypoglycemia to cognitive function in IDDM. *Diabetes. Care*. 12(2), 89–93 (1989).
9. Rovet JF, Ehrlich RM, Czuchta D. Intellectual characteristics of diabetic children at diagnosis and one year later. *J. Pediatr. Psychol*. 15(6), 775–788 (1990).
10. Draelos MT, Jacobson AM, Weinger K *et al.* Cognitive function in patients with insulin-dependent diabetes mellitus during hyperglycemia and hypoglycemia. *Am. J. Med*. 98(2), 135-144 (1995).
11. Jonassen I, Havelund S, Hoeg-Jensen T *et al.* Design of the Novel Protraction Mechanism of Insulin Degludec, an Ultra-long-Acting Basal Insulin. *Pharm. Res.* 29(8), 2104–2114 (2012).
12. Heise T, Hermanski L, Nosek L *et al.* Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes. Obes. Metab*. 14, 859–864 (2012).
13. Biester T, Blaesig S, Remus K *et al.* Insulin degludec's ultra-long pharmacokinetic properties observed in adults are retained in children and adolescents with type 1 diabetes. *Pediatr. Diabetes*. 15(1), 27–33 (2014).
14. International hypoglycaemia study group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes. Care*. 40(1), 155–7 (2017).
15. Thalange N, Deeb L, Iotova V *et al.* Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes. *Pediatr. Diabetes*. 16(3), 164–76 (2015).
16. Urakami T, Mine Y, Kuwabara R *et al.* A randomized crossover study of the efficacy and safety of switching from insulin glargine to insulin degludec in children with type 1 diabetes. *Endocr. J.* 64(2), 133–140 (2017).
17. Lane W, Bailey TS, Gerety G *et al.* Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes. *JAMA*. 318(1), 33–44 (2017).
18. Mathieu C, Hollander P, Miranda-Palma B *et al.* Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. *J clin endocrinol metab*. 98(3), 1154–1162 (2013).
19. Meneghini L, Atkin SL, Gough SC *et al.* The Efficacy and Safety of Insulin Degludec Given in Variable Once-Daily Dosing Intervals Compared With Insulin Glargine and Insulin Degludec Dosed at the Same Time Daily: A 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes. Care*. 36(4), 858–864 (2013).