

Ultralong Analogue Insulin Degludec in Type 1 Diabetes: Reduction of Hypoglycemic Events

Lilian Sanhueza^{1*}, Pilar Durruty² and Manuel García de los Ríos†³

¹Associated Professor, Faculty of Medical Sciences, University of Santiago of Chile, Santiago, Chile

²Associated Professor, Faculty of Medicine, University of Chile, Santiago, Chile

³Titular Professor, Faculty of Medicine, University of Chile, Santiago, Chile

***Corresponding Author:** Lilian Sanhueza, Associated Professor, Faculty of Medical Sciences University of Santiago of Chile, Santiago, Chile.

Received: December 16, 2020; **Published:** January 20, 2021

Abstract

Long-acting insulins analogues are related with the reduction of hypoglycemic events.

Objective: Ultralong-acting insulin analog Degludec (IDeg) in type 1 diabetic patients (T1D) previously treated with Glargine (U-100) with severe hypoglycemic events and poor metabolic control.

Patients and Method: 230 T1D patients were followed for 18 months, average 34 years old and 14 years of the diabetes diagnosed. Hypoglycemia, biochemical parameters and insulin requirements were analyzed in a period of 18 months. All the patients were on a basal bolus regimen with IDeg as basal adjusted fortnightly, and ultra-fast bolus insulin pre-meals three times a daily.

Results: At 3 months fasting glycemia decreased from 253 mg/dl to 180 mg/dl; at 6 months 156 mg/dl; at 12 months 151 mg/dl and at 18 months 150 mg/dl. Glycated hemoglobin (HbA1c) initially 10.6%, decreased at 3 months to 8.7% at 6 months 8.3% at 12 months 9.0%, at 18 months 9.0%. All these results were statistically significant $p < 0.05$. Hypoglycemic events, milds, moderate, severe, and nocturnal, decreased significantly throughout the study, improving the quality of life of patients

Conclusion: IDeg in T1D showed to reduce fasting glycemia, HbA1c, and hypoglycemic events.

Keywords: Clinical Parameters; Fasting Glycemia; Metabolic Control

Introduction

In the last ten years, insulin analogues have appeared due to modifications in the chemical structure of the hormone, obtaining insulins with ultrafast and ultralong action, in order to maintain more stable glycemic control, replicating the physiological secretion of the hormone and reduction of hypoglycemia [1-3]. The first basal insulin Glargine-U100 and Detemir do not cover 24 hours activity and in many cases, they must be used in divided doses every 12 hours. IDeg an ultralong acting analog, is the result of changes made to the human insulin molecule: removal of the amino acid threonine at position B30, and addition to amino acid lysine at position 29 of a 16-carbon fatty acid through glutamic acid [4]. This modification gives IDeg properties which allows it to form a soluble deposit of multi-hexamers after its subcutaneous injection. There is a gradual release of zinc ions and gradual dissociation of insulin monomers, which pass into the circulation slowly and steadily. Degludec begins its action 2 hours after having been injected. Its pharmacokinetic profile is flat and stable. The half-life is approximately 25 hours, but its plasma levels can be found up to 42 hours and its glycemic variability is less compared to Glargine U-100 [4-6]. Birkeland, *et al.* [7] presents a multicenter study comparing the efficacy and safety of IDeg versus Glargine-U100 in T1D, with a daily injection and the addition of ultrafast aspartic insulin in bolus pre-meals. The authors conclude that IDeg had a similar efficacy to Glargine, but with less frequency of hypoglycemia. Our group also found it, but in a short time of observation [8]. It is known

that the strict glycemc control is associated with a high frequency of hypoglycemia, especially in T1D, given to the glycemc instability that characterizes this pathology. Dzygalo., *et al.* [9] reached the same conclusion, adding that the use of IDeg was also associated with lower insulin requirements.

From 2016 the Pharmacy Committee of the Hospital San Juan de Dios, Chilean Public Hospital approved the incorporation of IDeg to the therapeutic arsenal. We decided to use IDeg in T1D patients in order to study the efficacy, metabolic control and the number of hypoglycemic events.

Patients and Method

230 T1D, 120 men and 110 women participated in this study. Average 34 years old (rank 15-58), duration of diabetes of 14 years (rank 3-46). The patients were under control and followed-up during 18 months in the Diabetes Unit of the Hospital San Juan de Dios, Santiago, Chile.

The patients had treatment with Glargine U-100 in two doses daily as basal insulin, and ultra-fast insulin pre-meals. All the patients had HbA1c higher than 10% and some presented comorbidities (Table 1). All of them signed the informed consent for insulin change.

	Comorbidity
Hypertryglyceridemia	53%
Arterial Hypertension	45%
Diabetic Nephropaty	35%
Corony heart disease	30%

Table 1

Two patients were on three-week hemodialysis and another two had kidney transplants. Glargine insulin U-100 was changed to IDeg, starting with 0.3 U/kg weight and fortnightly adjustments according to the individual records of three daily capillary glycemias per day: fasting, before lunch and before dinner. The IDeg was injected in a daily morning dose. Ultra-fast acting insulin pre-meals at a fixed dose, and adjustments according to the pre-established requirements of each patient and the carbohydrate count. Medical controls were performed every15 days.

Patients were evaluated with clinical and biochemical parameters, at the initial, 3, 6, 12 and 18 months after starting the IDeg treatment. The following parameters were checked: body mass index (BMI kg/m²), systolic and diastolic blood pressure (mmHg), total cholesterol (mg/dl), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), triglycerides (mg/dL), and creatinine (mg/dL). Glycemia, HDL, and TG were measured using enzymatic colorimetric methods in an Architect c8000 clinical chemistry analyzer, with coefficients of variation (CV)< 5%. Hexokinase-6 was used for glycemia. An accelerator selective detergent for HDL and TG. HbA1c was determined in high-resolution liquid chromatography (HPLC) columns with a CV of < 5%, using HPLC Variant 2000 equipment. Blood pressure was measured with a Hg sphygmomanometer; in two repetitions while patients were sitting, and not having smoked or eaten recently. Weight and size were measured on scales with eye-level beam Seca brand. BMI was calculated and expressed as kg/m².

Hypoglycemia was defined as a capillary glycemia < 70 mg/dl (American Diabetes Association Standars 2021) daytime and nighttime episodes. The degree of severity was classified mild, moderate, and severe. Mild hypoglycemia was considered when the patients did not have neurologic compromise, so it was treated by themselves. Moderate, when patients had altered consciousness, but they had enough awareness to be treated by themselves. And severe when they needed the attention of others.

Clinical, anthropometric, and laboratory variables were expressed as average and rank. Patients were checked every 15 days for capillary glycemia and monitoring hypoglycemia, with constant re-education in its management.

Average and rank were used in the statistical analysis. The normality of the variables was evaluated with the Swilk test, for categorical variables were Chi² or Fisher, and for continuous were ANOVA or Kwallis, as applicable. The analysis was performed in Stata 12.0, with a value of p < 0.05 considered statistically significant.

Results

Patients had a significant decrease in fasting glycemia of 253 to (rank 243-270) mg/dl at 180 mg/dl (172-240) at 3 months (p < 0.05), 156 (137-180) at 6 months (p < 0.05), 151 (50-328) (p < 0.01), at 12 months and 150 (50-321) (p < 0.01) at 18 months (Figure 1). Fasting glycemia drops until 6 months and then remains.

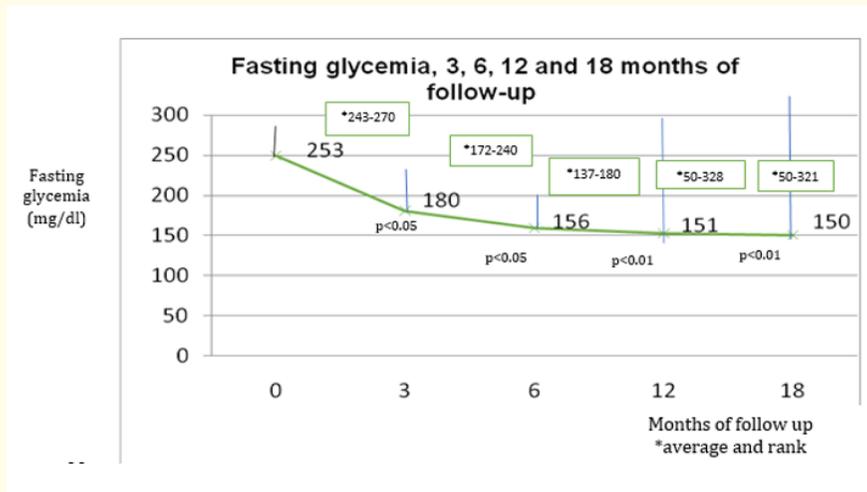


Figure 1

Similar behavior was observed concerning HbA1c levels, basal value with glargine U-100 was 10.6% (rank 10.3-12.2), at 3 months decreased to 8.7% (8.2-11.1) (p < 0.05), at 6 months 8.3% (8.0-9.6) (p < 0.05) at 12 months 9.0% (5.9-14.5)(p < 0.001), at 18 months 9.0% (5.9-14.6) (p < 0.001) (Figure 2).

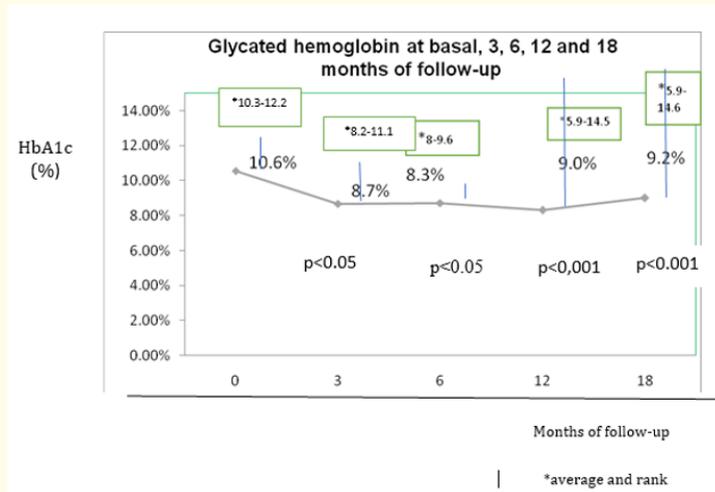


Figure 2

The anthropometric, clinical, and metabolic characteristics of the 230 DM1 patients are presented in table 2.

	Initial	3 months	6 months	12 months	18 months	p
BMI (kg/m ²)	24 (23-26)	25 (24-27)	24 (22-26)	25 (23-26)	25 (23-34)	NS
Sistolic Blood Pressure (mm Hg)	123 (112-144)	130 (113-145)	127 (110-150)	118 (108-150)	120 (120-143)	NS
Diastolic Blood Pressure (mm Hg)	63 (60-75)	68 (63-80)	60 (57-70)	61 (55-76)	61 (58-78)	NS
Total Cholesterol (mg/dl)	192 (179-206)	186 (177-196)	193 (182-205)	184 (172-196)	174 (130-370)	NS
HDL Cholesterol (mg/dl)	53 (46-61)	51 (45-57)	53 (47-59)	53 (47-58)	52 (20-104)	NS
LDL Cholesterol (mg/dl)	113 (99-126)	111 (98-123)	116 (102-129)	119 (99-125)	103 (55-190)	p < 0.05
Triglycerides (mg/dl)	182 (104-259)	184 (132-237)	151 (115-186)	149 (120-178)	117 (142-561)	p < 0.05
Creatinine (mg/dl)	0.8 (0.6-1.8)	0.8 (0.7-1.8)	0.8 (0.6-1.8)	0.8 (0.6-1.7)	0.8 (0.5-1.6)	NS

Table 2: Antropometric, clinical and metabolic characteristics of 230 dm1 patients at initial, 3, 6, 12 and 18 months of follow-up*
*average and rank.

It is observed that there were no major changes in BMI throughout the follow-up although the statistically significant reduction of LDL cholesterol and triglycerides (p < 0.05). There was no significant changes in the other parameters.

The dose of glargine insulin administered to patients before changing to IDeg was 0.7 U/kg weight (rank 0.6-0.8). IDeg was started at 0.3 U/kg weight, maintained at three months, and rose to 0.5 U/kg weight (0.3-0.5) during the follow up.

The ultra-fast acting insulin dose stayed the same; in only 3 cases there was no need to continue injecting it. Liver tests were maintained in normal ranks. There were no manifestations of lipodystrophy or allergy at the puncture site.

Concerning hypoglycemia, a monthly average of 19 hypoglycemias were recorded in each patient during the first 3 months of treatment: 14 mild, 4 moderate, and one severe; at 6 months 8 mild and 2 moderates and non-severe, at 12 months one mild, at 18 months 1 mild and 1 moderate. Nighttime hypoglycemia was reported in only 4 patients in this group.

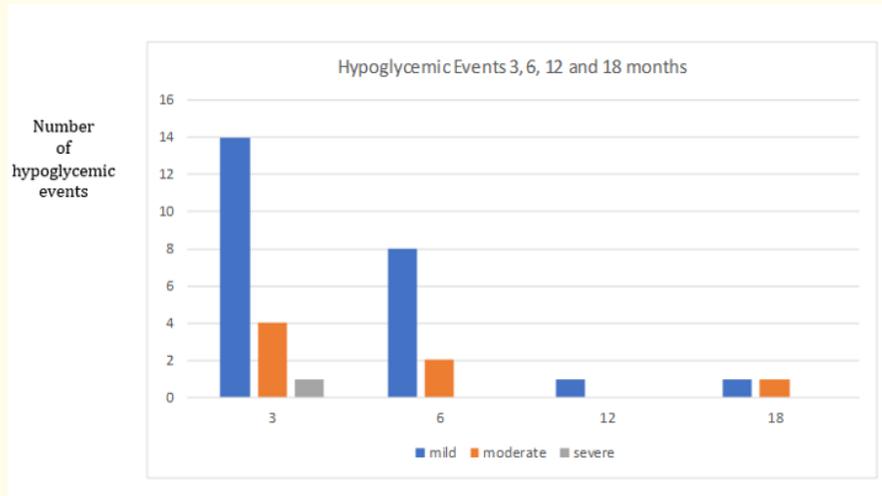


Figure 3

Patients stated that their symptoms of hypoglycemia such as headache, palpitations and sweating were drastically reduced the same as their frequency.

Discussion

The strength of our study is the number of patients, 230 cases and the longer time of observation 18 months. The Clinical Trial Switch 1 had a larger sample and longer follow-up [10]; in other publications the two conditions were minor [7,11-13].

In this investigation, we considered the possibility of bias due to very close surveillance of the patients. The age of T1D fluctuated in a very wide range, 18 to 58 years, with different motivations and metabolic situations, that could have influenced the results.

This work has the disadvantage of lacking a control group.

The 52-weeks study BEGIN [12] proved that IDeg was no superior to glargine in the reduction of fasting glycemia and HbA1c; different from our study, we observed a reduction in fasting glycemia and HbA1c in the first 6 months and remained constant until the end of the observation. We did not have the possibility of having a continuous glucose monitoring sensor; which would have provided greater objectivity to the results. Levels of anti-insulin antibodies were not measured, and there was not weight reduction, despite the decrease in insulin doses.

In our analysis, in relation to insulin doses, they remained at 0.5 U/ kg weight at 18 months, slightly lower than that reported by Nakae, *et al.* [13], who found that they decreased from 0.71 to 0.67 U/kg weight at 6 months after using IDeg. Dzygalo, *et al.* in a meta-analysis, also confirm the reduction of insulin doses compared to other slow-acting analogs [9]. Yamamoto, *et al.* reports that the dose of IDeg was reduced by 25%, however, glycemic variability in 24h was no different than glargine U-100 [5]. The author concludes that the two doses of this insulin can be replaced by a daily injection of IDeg. These findings are fully consistent with the analysis published by almost all authors [8,9,13-15]. Double dose of insulin replaced by a daily injection, increased enormously adherence to the treatment.

Disappearance of severe of hypoglycemia from 6 months and a smaller number of moderate and mild episodes, was a very important achievement.

Regarding hypoglycemia and contrary to Nakae, *et al.* [13] reported, who did not observe differences in frequency and severity of hypoglycemia when comparing with insulin glargine U-100; our study showed a reduction in hypoglycemia during the 18 months of observation, disappearance of severe hypoglycemia from 6 months and a smaller number of moderate and mild episodes. Other research on the clinical use of IDeg concludes that this insulin minimizes the risk of nocturnal hypoglycemia [2,17-19].

It should be mentioned that glycemia does not decrease during the first 10 days, rather it increases, probably secondary to the rise of anti-insulin antibodies. It is recommendable to advise the patient about this situation.

Gold, *et al.* [15] said that severe episodes of hypoglycemia are less common in patients in alertness, and those at risk of these events would be due to a lack of glucagon and a reduced response of counterregulatory hormones. The study published by Koehler, *et al.* [16] observed the acute physiological response to insulin-induced hypoglycemia in 38 T1D randomized to IDeg or glargine U-100, did not record differences in symptoms or cognitive function. However, IDeg patients had moderately higher levels of growth hormone, cortisol, adrenaline, and norepinephrine.

The reduction of hypoglycemia may be related to the stability of hexamers in the subcutaneous tissue and their passage through the vascular endothelium.

Other publications with IDeg report a reduction in hospital bed-days, which is very favorable for the patient and reduce hospital costs [20-22].

Conclusions

We can conclude that IDeg in T1D compared to glargine U-100, reduced fasting glycemia and HbA1c, a metabolic effect that covers 24 hours, as well as a lower risk of hypoglycemia.

Bibliography

1. Simó R. "Nueva insulina basal de acción ultralenta: insulina degludec". *Avances en Diabetología* 29 (2013): 4-11.
2. Muñoz M. "Degludec, una nueva insulina basal de acción ultra-lenta para el tratamiento de la diabetes tipo 1 y 2: avances en investigación clínica". *Endocrinología y Nutrición* 61 (2014): 153-159.
3. Vora J, *et al.* "Clinical use of insulin degludec". *Diabetes Research and Clinical Practice* 109 (2015): 19-31.
4. Berard L and MacNeill G. "Insulin degludec, a long-acting-daily basal analogue for type 1 and type 2 diabetes mellitus". *Canadian Journal of Diabetes* 39 (2015): 4-9.
5. Yamamoto C, *et al.* "Degludec is superior to glargine in terms of daily glycemic variability in people with type 1 diabetes mellitus". *Endocrine Journal* 63(2016): 53-60.
6. Heise T, *et al.* "Steady state is reached within 2-3 days of once-daily administration of degludec, a basal insulin with an ultralong duration of action". *Diabetes* 8 (2016): 132-138.
7. Birkeland KI, *et al.* "Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine". *Diabetes Care* 34 (2011): 661-665.
8. Sanhueza L, *et al.* "Experiencia con insulina degludec en pacientes diabéticos tipo 1 del Hospital San Juan de Dios, Santiago, Chile". *Revista Chilena de Endocrinología y Diabetes* 10 (2017): 131-136.

9. Dzygalo K., *et al.* "The beneficial effect of insulin degludec on nocturnal hypoglycaemia and insulin dose in type 1 diabetic patients: a systematic review and meta-analysis of randomised trials". *Acta Diabetology* 52 (2015): 231-238.
10. Lane W., *et al.* "Effect of degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes. The SWITCH 1 randomized clinical trial". *JAMA* 318 (2017): 33-44.
11. Vora J., *et al.* "Insulin degludec versus Insulin Glargine in type 1 and type 2 Diabetes Mellitus: A Meta-Analysis of Endpoints in Phase 3a Trials". *Diabetes Therapy* 5 (2014): 435-446.
12. Heller S., *et al.* "Insulin Degludec, an ultra-long-acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal Bolus Type1): A phase 3, randomised, open-label, treat-to-target, non-inferiority trial". *Lancet* 379 (2012): 1489-1497.
13. Nakae R., *et al.* "Medium-Term "Effects of Insulin Degludec on Patients with Type 1 Diabetes Mellitus". *Drugs* 14 (2014): 133-138.
14. Ratner RE., *et al.* "Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials". *Diabetes, Obesity and Metabolism* 15 (2013): 175-184.
15. Gold AE., *et al.* "Frequency of severe hypoglycemia in patients with type 1 diabetes with impaired awareness of hypoglycemia". *Diabetes Care* 17 (1994): 697-703.
16. Koehler G., *et al.* "Insulin degludec is not associated with a delayed or diminished response hypoglycemia compared with insulin glargine in type 1 diabetes: a double-blind randomized crossover study". *Diabetologia* 47 (2014): 40-49.
17. Home PD., *et al.* "Improved health status with insulin degludec compared with insulin glargine in people with type 1 diabetes". *Diabetes Medicine* 29 (2012): 716-720.
18. Woodward A., *et al.* "Nocturnal hypoglycemia in type 1 diabetes-frekuensi and predictive factors". *QJM* 102 (2009): 603-607.
19. Lane W., *et al.* "Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients with Type 1 Diabetes. The SWITCH 1 Randomized Clinical Trial". *JAMA* 318 (2017): 33-44.
20. Karamat MA., *et al.* "Clinical and Cost Implications of Insulin Degludec in Patients with Type 1 Diabetes and Problematic Hypoglycemia: A Quality Improvement Project". *Diabetes Therapy* 9 (2018): 839-849.
21. Pollock RF and Tikkanen CK. "A short-term cost-utility analysis of insulin degludec versus insulin glargine U100 in patients with type 1 or type 2 diabetes in Denmark". *Journal of Medical Economics* 20 (2017): 213-220.

Volume 5 Issue 2 February 2021

© All rights reserved by Lilian Sanhueza., *et al.*