



Original research

Reduction of glycemic variability with Degludec insulin in patients with unstable diabetes



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SUMMARY

Introduction: Degludec (IDeg) is an ultralong-acting insulin, with stable pharmacodynamic profile which leads to lower fluctuations in glucose levels. The effect of IDeg has not been specifically assessed in patients with unstable diabetes, defined as increased glycemic variability (GV).

Methods: A prospective before-after pilot study was conducted, including patients managed at Hospital Universitario San Ignacio in Bogotá, Colombia. The impact of the switch from a Gargine or Detemir insulin to a basal insulin regimen with IDeg for 12 weeks on GV measured by continuous glucose monitoring, on A1c levels, and on the incidence of episodes of global and nocturnal hypoglycemia was assessed in a group of patients with (coefficient of variation > 34%) or without increased basal GV using a Generalised Estimating Equation (GEE) analysis.

Results: 60 patients with basal bolus therapy and history of hypoglycemia were included. 18 patients had High GV (HGV). In this group a significant reduction of 11.1% of CV (95% CI: 6.3, 15.9, $p = 0.01$) was found. GEE analysis confirmed a higher impact over time on patients with HGV ($p < 0.001$). The percentage of patients with at least 1 episode of hypoglycemia decreased from 66.6% to 22.2% ($p = 0.02$) and from 37.14% to 5.71% ($p < 0.01$) for global and nocturnal hypoglycemia, respectively. Changes were not significant in patients with low GV. A reduction of A1c was observed in both groups ($p < 0.001$).

Conclusions: The results suggest that treatment with IDeg reduces GV, A1c levels and the incidence of global and nocturnal hypoglycemia events in patients with HGV, but not in patients with low GV.

Introduction

Hypoglycemia events are a risk factor for cardiovascular events [1]

and mortality in patients with diabetes mellitus (DM). Occurrence of hypoglycemia episodes is a limiting factor for achieving an adequate metabolic control in diabetes mellitus (DM) patients treated with

Abbreviations: DM1, Type 1 diabetes; DM2, Type 2 diabetes; CGM, Continuous glucose monitoring; TDD, total daily insulin dose; BMI, Body mass index; IQR, interquartile range; SD, Standard deviation; A1c, Glycated hemoglobin; CV, coefficient of variation; MAG, mean absolute glucose change; MAGE, mean amplitude of glucose excursion; CONGA, continuous overall net glycemic action; LBGI, low blood glucose index; MOOD, mean of daily difference; UD, Unstable diabetes; HGV, High glycemic variability; LGV, low glycemic variability; IDeg, Insulin degludec

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insulin [2], which leads to an increased number of visits and hospitalizations [3].

The risk of asymptomatic hypoglycemia is directly related to increased glycemic variability (GV) [4,5], therefore, it has been proposed that reducing fluctuations in glucose levels should be considered as an important issue in the development and evaluation of new therapies; additionally, glycemic variability should be an assessed outcome [6].

Insulin degludec (IDeg) is an ultralong-acting basal insulin that is available for the management of patients with DM1 and DM2. Its effect is based on the formation of soluble multi-hexamers in subcutaneous tissues, creating a depot from which monomers are released slowly and continuously, to be finally absorbed into the blood flow; this leads to a more stable pharmacokinetic profile, and lower fluctuations in glucose levels [7]. These characteristics, particular to IDeg, should bring greater clinical benefits to those patients with increased glycemic variability, however, its effect has not been formally assessed in such population.

The aim of this pilot study is to assess the impact of the switch from a Glargine or Detemir insulin regimen to a basal insulin regimen with IDeg on GV, measured by continuous glucose monitoring (CGM), on metabolic control and on the incidence of hypoglycemia episodes in a group of patients with and without unstable diabetes, defined as increased GV.

Methods

A prospective before-after study was conducted, including patients treated at the diabetes center of Hospital Universitario San Ignacio in Bogotá, Colombia. Recruitment was conducted along the period between May 2015 and September 2016. Patients with DM1 or DM2 older than 18 years were recruited, who were under continuous treatment with a basal insulin, basal bolus or basal plus regimen (including Insulin Glargine or Insulin Detemir) for at least 3 months, and had A1c levels > 7% (53 mmol/mol) or recurrent episodes of non-severe symptomatic hypoglycemia. Exclusion criteria were: medical history of severe recurrent hypoglycemia, liver failure or Child type B or C liver cirrhosis, renal failure at stage 5 (glomerular filtration rate < 15 mg/dL) or active oncological disease. The protocol was approved by the ethics committee of Hospital Universitario San Ignacio and Pontificia Universidad Javeriana.

In a first visit, data on baseline demographic and clinical characteristics were obtained from an interview with the patient and from the systematic records kept in his/her medical history. All baseline A1c measurements were processed using techniques approved by the National Glycohemoglobin Standardization Program (NGSP). Those who met the inclusion criteria were requested to sign an informed consent.

At that same visit, an CGM equipment was set using the iPRO2® device (Medtronic, Northridge, CA). The Enlite sensor (Medtronic, Minneapolis, MN) was inserted subcutaneously into the anterior abdomen area and held in place for 6 days. Calibration of the CGM device was performed following the recommendations of the iPRO2® manufacturer by capillary glucose measurements at the first and third hour after the insertion of the subcutaneous sensor, and then measurements were made before each meal, until the end of the study. At the end of 6 days, the device was removed and data downloaded using the iPRO CareLink version 3.0 software. Subsequently, treatment with Degludec insulin (IDeg) was started. Because all the patients had history of hypoglycemia, the IDeg initial dose was calculated by reducing the previous requirements of Glargine or Detemir insulin by 20% for each patient. The dose was titrated on the basis of fasting blood glucose levels with a target of 91–126 mg/dL (5.1–7.0 mmol/L). Patients were asked to avoid intense physical activity, to maintain a diet similar to that previously received and to inform the investigators about any changes in the device insertion site.

After 12 weeks of IDeg treatment, a second CGM was performed, following the same guidelines as for the initial CGM. At the end of the

study, new samples were taken for A1c measurement. Data obtained from CGM were exported for analysis by a calculation software in MATLAB®, where records were pre-processed to discard those days with consecutive losses greater than 50 samples. Lower losses were linearly interpolated. Based on these data, different metrics of glycemic variability and glycemic risk were calculated, including standard deviation (SD), coefficient of variation (CV), mean absolute glucose change (MAG), interquartile range (IQR), mean of daily difference (MODD), continuous overall net glycemic action (CONGA 1, 2 and 4 h), low blood glucose index (LBGI) and mean amplitude of glucose excursion (MAGE).

An episode of clinically significant hypoglycemia was defined as interstitial glucose levels lower than 54 mg/dL for at least 20 min [8,9], and nocturnal hypoglycemia was defined as those episodes which occurred between 00:01 and 05:59 [10,11].

For continuous variables, mean and standard deviations are reported for normal distribution variables, or median, and interquartile range were reported if this assumption was not met. For categorical variables, frequency and percentages tables are reported. Based on the results of the first CGM, patients were classified according with basal CV values on low glycemic variability (LGV) or high glycemic variability (HGV), with a coefficient of variation threshold of 34% [12]. A sensitivity analysis was conducted using a cut point of 36%, as suggested by Monnier to define unstable diabetes (UD), with similar results [13]. To assess the change over time for each subgroup in A1c levels, glycemic variability measurements and in mean insulin doses, a paired *t*-test or a Wilcoxon signed rank test were used, comparing baseline values with values after 12 weeks of the switch of the treatment. The incidence of global and nocturnal hypoglycemia before and after treatment with IDeg was compared using a McNemar chi-square test.

In order to estimate the trend over time on glycemic variability measured with the CV, and A1c levels we additionally performed a longitudinal analysis using generalized estimating equations (GEE). The advantage of GEE is that it take into account the fact that the serial observations of the same patient are autocorrelated, and let us to evaluate how the average of a response variable of a subject changes with covariates. In the present study, an exchangeable correlation structure was used. As a sensitivity analysis, we fitted GEE models also assuming either an unstructured or an “independent” correlation structure, without significant changes in the results. Multivariable GEE was used to identify the coefficients of each covariate for the presented response variables after stratifying the patients as LGV or HGV according with the basal CV measure. The time model with a significant contribution (*p*-value < 0.05) and the lowest quasi-likelihood information criterion (QIC) represents the best model for the data [14]. A statistical STATA 15.0 package was used for the analyses.

Results

60 patients were invited to participate and underwent the first CGM. Most patients had type 2 diabetes (72.4%); they were mainly women (55%), receiving Insulin Glargine (66.6%), and a basal bolus regimen (71.6%) before switching to IDeg. The mean A1c value pre-treatment was 8.28% (67 mmol/mol) ± 1.74% and after 12 weeks of treatment with IDeg was 7.16% (55 mmol/mol) ± 1.54%. The mean difference was −1.04% (95% CI, −0.42, −1.67), *p* = 0.0013. The mean TDD was reduced from 0.45 units per kg of weight during the pre-intervention period to 0.37 units per kg of weight after 12 weeks of IDeg treatment (*p* = 0.022) in all patients recruited.

The demographic and clinical data of patients according with basal glycemic variability sub groups are shown in Table 1. 42 patients were classified as LGV and 18 had basal CV values higher than 34% and were classified as HGV. Patients with HGV had significantly higher values of A1c (8.84% ± 2.08 vs 7.63 ± 1.31, *p* = 0.01), and used higher dose of basal insulin (0.40 ± 0.21 U/kg vs 0.58 ± 0.51 U/kg, *p* = 0.01) The indication of degludec was different between groups

Table 1
Baseline characteristics of patients with high or low glycemic variability (Coefficient of variation threshold 34%).

Variable	Low glycemic variability n = 42	High glycemic variability n = 18	p- value
Sex Male, n (%)	20 (47.6)	7 (38.9)	0.53
Age in years, mean (SD)	60.6 (17.4)	54.6 (16.2)	0.21
BMI (kg/m ²), mean (SD)	28.32 (5.10)	25.43 (3.4)	0.04
Type 1 diabetes, n (%)	5 (12.5)	6 (33.3)	0.06
Duration of diabetes in years, mean (SD)	15.77 (12.0)	19.11 (9.5)	0.31
A1c (%), mean (SD)	7.63 (1.3)	8.84 (2.1)	0.01
Microvascular complications, n (%)	17 (40.5)	5 (27.8)	0.35
Retinopathy, n (%)	8 (19.0)	4 (22.2)	0.77
Nephropathy, n (%)	14 (33.3)	3 (16.3)	0.18
Neuropathy, n (%)	8 (19.0)	1 (5.6)	0.18
Macrovascular complications, n (%)	5 (11.9)	1 (5.6)	0.53
Degludec indication, n (%)			0.04
Deficient metabolic control exclusively	3 (7.2)	0 (0)	
Non severe Hypoglycemic episodes	31 (73.8)	9 (50)	
Both	8 (19.0)	9 (50)	
TDI U/kg, mean (SD)	0.40 (0.2)	0.58 (0.5)	0.01
Type of basal insulin, n (%)			0.44
Glargine	26 (61.9)	14 (77.7)	
Detemir	16 (38.1)	4 (22.2)	
Basal insulin regime, n (%)			0.09
Baseline	13 (31.0)	1 (5.6)	
Basal-bolus	26 (61.9)	17 (94.4)	
Basal plus	3 (7.2)	0 (0)	

SD: Standard deviation, BMI: Body mass index, A1c: Glycated hemoglobin, TDD: Total Daily Insulin dose.

with more patients having simultaneously deficient metabolic control and non severe hypoglycemic episodes in HGV group. Other characteristics were not significantly different between groups (Table 1).

The results showed a significant reduction in glycemic variability regardless of the measuring method in patients with HGV (Table 2). A specific analysis of the change in the coefficient of variation showed a 11.1% absolute reduction (95% CI 6.3, 15.9, $p < 0.001$) in this subgroup of patients 12 weeks after the switch to degludec. In patients with low basal GV we did not find significant change in GV metrics. Using the GEE to analyse the serial glycemic variability using CV%, the longitudinal analysis showed an average decline of 2% of CV over the 12 weeks ($p = 0.05$) (Table 3). Patients with basal HGV had a higher impact over time on CV% compared to LGV patients ($p < 0.001$). Fig. 1 shows the changes in mean levels and the standard deviation of glucose when comparing CGMs before and after IDeg intervention,

Table 2
Glycemic variability for IDeg pre-treatment and 12 weeks post-treatment.

GV Metrics.	Low glycemic variability n = 42			High glycemic variability n = 18		
	Baseline	12 weeks	p-value	Baseline	12 weeks	p-value
Mean of glucose	142.6 ± 32	143.1 ± 37	0.930	161.1 ± 45	149.0 ± 49	0.234
%CV	24.4 ± 5.01	26.2 ± 9.1	0.214	44.7 ± 7.3	33.6 ± 10.1	< 0.001
SD:	35.4 ± 12.5	37.6 ± 15.6	0.377	71.3 ± 19.5	49.8 ± 20.0	< 0.001
MODD	33.5 ± 11.2	39.1 ± 18.0	0.029	73.9 ± 30.0	57.1 ± 29.1	0.011
CONGA1	24.2 ± 7.45	25.2 ± 10.4	0.514	43.6 ± 12.4	34.1 ± 10.8	0.004
CONGA2	35.1 ± 11.1	36.2 ± 15.4	0.622	66.1 ± 17.8	50.3 ± 17.9	0.001
CONGA4	44.7 ± 15.3	46.6 ± 20.9	0.575	89.0 ± 25.6	64.6 ± 23.4	< 0.001
IQR	49.5 ± 21.0	53.4 ± 24.1	0.359	104.6 ± 42.4	69.8 ± 34.2	< 0.001
LBGI	1.41 ± 1.17	2.21 ± 2.51	0.067	8.05 ± 5.58	4.64 ± 4.39	0.066

(CV) coefficient of variation, (SD) standard deviation, (MOOD) mean of daily difference, (CONGA) continuous overall net glycemic action, (IQR) interquartile range, (IQR) interquartile range, (LBGI) low blood glucose index, (MAG) mean absolute glucose change, (MAGE) mean amplitude of glycemic excursion.

Table 3
Analysis using Generalised Estimating Equation (GEE) showing the factors affecting the evolution of Glycemic variability and glycaemic control (based on A1c) on patients after switch to insulin degludec.

Glycemic variability (based on CV%)			
Factors	Coefficient	95% CI	p
Time (12 weeks)	−0.023	−0.047, −0.007	0.050
HGV ^a	0.136	0.103, 0.170	< 0.001
Glycemic control (based on A1c)			
Time (12 weeks)	−0.69	−1.09, −0.28	0.001
HGV ^a	0.93	0.32, 1.54	0.003
Mean Glucose	0.017	0.005, 0.028	0.005
DMT2 ^b	0.67	0.21, 1.13	0.004

(CV) coefficient of variation, (HGV) High glycemic variability, (LGV) Low glycemic variability, DMT1 (type 1 diabetes mellitus), DMT2 (type 2 diabetes mellitus).

^a Compared to LGV.

^b Compared to DMT1.

showing an important reduction in glycemic variability.

A non significant reduction was observed in the total number of hypoglycemia episodes < 54 mg/dL for the total population, from 65 in the first CGM to 53 for CGM post-treatment ($p = 0.37$). However this change reach statistical significance in the group of patients with HGV reducing from 53 to 26 ($p = 0.01$). The proportion of patients with at least one hypoglycemia episode < 54 mg/dL within 24 h decreased from 66.6% to 22.2% ($p = 0.02$) in HGV group, but not in low basal GV group ($p = 0.59$).

For episodes of nocturnal hypoglycemia, a reduction in the number of episodes < 54 mg/dL was observed, from 26 for the first CGM, to 19 for post-treatment CGM ($p < 0.05$). The percentage of patients who had at least one episode of nocturnal hypoglycemia < 54 mg/dL decreased from 37.14% to 5.71% (RR 0.154, 95% CI, 0.017–0.678, $p < 0.01$). Nocturnal glucose alert value, defined as episodes < 70 mg/dL, showed similar outcomes with a reduction from 53 to 27 events ($p = 0.07$). No complications were reported in the catheter insertion site nor hospitalizations for diabetes decompensation during the recruited patients follow-up period.

A significant reduction of A1c was observed in both groups, from 7.6% (60 mmol/mol) ± 1.3 to 7.0% (53 mmol/mol) ± 0.8 in LGV patients ($p < 0.001$), and from 8.8% (73 mmol/mol) ± 2.1 to 7.6% (60 mmol/mol) ± 2.0 in HGV patients ($p < 0.001$). GEE analysis for serial A1c data points, showed an average decline of 0.69% of A1c over the 12 weeks ($p = 0.001$) controlling by other factors (Table 3). On average, patients with HGV at enrolment compared to LGV had a higher impact on A1c (0.93%, $p 0.003$). Compared with DM1 patients, those with DM2 had higher A1c by 0.67%.

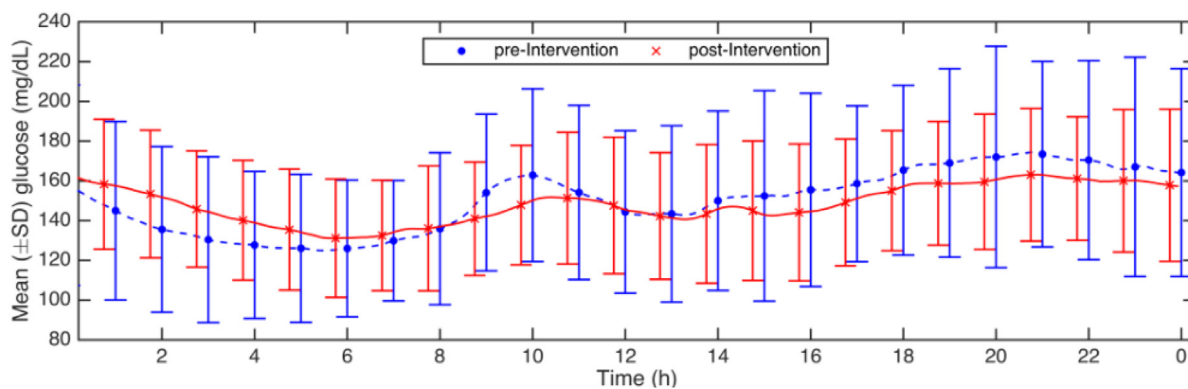


Fig. 1. Pre-intervention and End-of-The-Study 24-h Mean Glucose Profile as Measured by Continuous Glucose Monitoring. Dots represent pre-intervention mean glucose value and “Xs” represent mean level at the end of study, after 12 weeks of treatment with insulin degludec. Mean and SD are calculated based on glucose measures at specific hours.

Discussion

In the present pilot study we found that switching a therapy with glargine or detemir to IDeg for 12 weeks significantly reduced fluctuations in glucose levels, the incidence of global and nocturnal hypoglycemia events, and improved glycaemic control for a group of patients with increased basal glycaemic variability.

Several previous studies have evaluated the changes in glycaemic variability, measured by CGM, in DM1 patients who switched to IDeg. Three studies did not find significant changes in GV, or in 24-h analyses, or in nocturnal measurements [15–17], compared with the study of Iga [18] where improvements in day-to-day variability measurements were observed, but not changes in MAGE or in J-index. In a cross-over study, where a 24 h analysis of CMG was performed, a statistically significant decrease in the standard deviation was observed for patients receiving IDeg, compared to those receiving Insulin Detemir twice a day [19]. Recently the DEVOTE 2 [20] was published, in which day-to-day fasting glycaemic variability was evaluated using three pre-breakfast SMBG measurements from each month and expressed as the geometric coefficient of variation. The group with high GV presented greater risk of severe hypoglycemia (SH). However, no significant reduction of GV was documented when comparing IGLar vs IDeg [21].

In the present study, we found that intraday GV decreased significantly in the population with HGV but not in those with basal LGV, this significant decrease in GV was evident with all measuring methods, including within-day variability metrics, day-to-day variability metrics and glycaemic risk metrics. These findings may be evident because we measured GV using CGM and analysed separately patients with LGV and HGV, taking into account that these last group of patients are more likely to benefit from the more stable pharmacokinetic and pharmacodynamic profile of IDeg. Subgroups were generated based in a previous study showing that coefficient of variation, used to determine glycaemic variability, is the method that best predicts hypoglycemia episodes, and that a threshold of CV of 34% allows to adequately differentiate patients with a high risk of developing hypoglycemia [26]. A similar cut-off point was suggested by Monnier [12], who showed that values of coefficient of variation > 36% allow to identify patients with unstable glycaemic levels and, consequently, with a high risk of hypoglycemia, among those treated with oral hypoglycaemic agents, as well as those who are receiving insulin. We conducted a sensitivity analysis using both cut points with similar results.

Reducing GV is a clinically relevant factor, because such reduction is associated with a decrease in the number of events of clinically significant hypoglycemia and severe hypoglycemia [12]. Recently, the DEVOTE study was published, which was designed to establish the cardiovascular safety of IDeg vs Insulin Glargine. This study included more than 7000 patients diagnosed with DM2, out of whom 85% had a

determined cardiovascular disease, and found a statistically significant reduction of severe hypoglycemia events in patients receiving IDeg, compared to those receiving Insulin Glargine (4.9% vs 6.6%, RR 0.60: $P < 0.001$) [20]. These findings are consistent with cross-over treat-to-target studies in diagnosed DM1 [10] and DM2 [11] patients with risk factors for hypoglycemia, where a reduction in the rate of clinically significant hypoglycemia and severe hypoglycemia events was described. Likewise, a lower percentage of nocturnal hypoglycemia was reported, which may be related to a decrease in GV.

Our study found a lower incidence of nocturnal hypoglycemia, consistent with findings of previous studies [15,22], and also showed a significant decrease in the incidence of total episodes of hypoglycemia determined as < 54 mg/dL throughout the day, as reported in a meta-analysis of phase 3 studies where IDeg had been assessed in both DM1 and DM2 [23]. A comparison of the extent of the effect is very limited, considering the various methods used to determine the presence of hypoglycemia episodes. Additionally, it is possible to detect many more events using CGM than using capillary glucometry (SMBG) for self-monitoring. However, our data suggest that a reduction in the incidence of hypoglycemia may be very significant in the group of patients with increased basal GV. These data should be evaluated with future RCTs.

Regarding glycaemic control, previous studies in patients with DM1 have shown a minimum impact, which ranges from small reductions in A1c levels [15,24], to an absence of changes [16,18]. Similar results were found when comparing IDeg to glargine in patients with DM2 who were insulin naïve [25,22]. Crossover studies SWITCH 1 and 2 [10,11] showed no impact on metabolic control when switching between these drugs, this was similar to the results reported in the DEVOTE study [20], where no significant differences were found in metabolic control when comparing IDeg to insulin Glargine. However, a significant reduction in A1c levels was observed for both drugs when comparing baseline values to final values of the study. A noteworthy finding in this study was a significant reduction in A1c levels in both groups but higher in subgroup of patients with HGV after treatment for 12 weeks. Similar findings have been reported in real-life studies similar to ours in patients with DM2, in which A1c was significantly reduced from 7.9% to 7.1% ($p < 0.0001$) after 3–15 months of switching to IDeg [20]. In a review of 81 clinical studies conducted in Japanese populations, 84% reported reduced levels of A1c [20]. These results suggest that a decrease in the frequency of hypoglycemia episodes and the reduced fear of such episodes allow for titration of IDeg doses until achieving an improved metabolic control in this group of patients. New specific RCTs in populations with a high risk of hypoglycemia should be conducted to confirm these findings.

Consistent to existing evidence [14,19,24], we found in this study a significant reduction in the required insulin doses after a switch to IDeg insulin. This reduction might range between 3 and 10% [19] compared

to baseline requirements. Similarly, there has been a reduction in the number of injections per day from 1.3 to 1.1 ($p = 0.0097$) [25]. These results should be taken into account when switching to this therapy.

This study has limitations to consider. The treatment period was short, consequently, the results of A1c levels could be influenced by the titration period of insulin. However, this should affect the estimation of effects to an absence of differences. The lack of a control group (without degludec) makes it difficult to evaluate other factors that could potentially influence our results. Patients may have made specific additional changes at the onset of IDeg, including changes in treatment and dietary recommendations adherence, or in physical activity level. However, these changes may better reflect what actually happens in real life conditions.

Despite these limitations, this study suggests that the treatment with insulin IDeg may offer very significant clinical benefits, especially in the group of patients with increased glycemic variability. These results should be confirmed with randomized clinical trials with a longer follow up and validated by new, real-life studies.

Conflict-of-interest disclosure

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