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Insulin doses requirements in patients with type 1 diabetes using glargine U300 or degludec in routine clinical practice

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ABSTRACT

There are not many real-world studies evaluating daily insulin doses requirements (DIDR) in patients with type 1 diabetes (T1D) using second-generation basal insulin analogs, and such comparison is necessary. The aim of this study was to compare DIDR in individuals with T1D using glargine 300 UI/mL (IGlar-300) or degludec (IDeg) in real clinical practice. An observational, retrospective study was designed in 412 patients with T1D (males: 52%; median age 37.0±13.4 years, diabetes duration: 18.7±12.3 years) using IDeg and IGla-300 ≥6 months to compare DIDR between groups. Patients using IGla-300 (n=187) were more frequently males (59% vs 45.8%; p=0.004) and had lower glycosylated hemoglobin (HbA1c) (7.6±1.2 vs 8.1%±1.5%; p<0.001) than patients using IDeg (n=225). Total (0.77±0.36 unit/kg/day), basal (0.43±0.20 unit/kg/day) and prandial (0.33±0.23 unit/kg/day) DIDR were similar in IGla-300 and IDeg groups. Patients with HbA1c ≤7% (n=113) used significantly lower basal (p=0.045) and total (p=0.024) DIDR, but not prandial insulin (p=0.241), than patients with HbA1c between 7.1% and 8% and >8%. Patients using IGla-300 and IDeg used similar basal, prandial and total DIDR regardless of metabolic control subgroup. No difference in basal, prandial and total DIDR was observed between patients with T1D using IGla-300 or IDeg during at least 6 months in routine clinical practice.

Significance of this study

What is already known about this subject?

- Despite the fact that glargine U300 (IGla-300) and degludec (IDeg) basal analogs were introduced in 2015, to date, few comparative studies have been published and information about comparative daily insulin dose requirements (DIDR) comes only from studies in patients with type 2 diabetes, which reported that patients treated with IGla-300 had higher daily insulin doses requirements compared with IDeg.
- To date, only limited studies comparing IGla-300 with IDeg insulins in people with type 1 diabetes (T1D) are available.
- There are not many real-world studies evaluating daily insulin doses requirements in patients with T1D using second-generation basal insulin analogs, and such comparison is necessary.

INTRODUCTION

Type 1 diabetes (T1D) is a chronic disease with personal, socioeconomic and health burdens. In long term, poor metabolic control in patients with T1D promotes development and progression of late microvascular and macrovascular complications, mean cause of morbidity, mortality and decreased quality of life.[1] Results of the Diabetes Control and Complications Trial (DCCT)[2] and the Epidemiology of Diabetes Interventions and Complications Study (EDIC)[3] demonstrated that intensive insulin therapy in patients with T1D, to achieve glycosylated hemoglobin (HbA1c) levels as close to normal as possible, delayed the development and progression of microvascular and macrovascular complications compared with conventional insulin therapy. Recently, the DCCT/EDIC study group reported that 30 years of excellent versus poor glycemic control substantially reduced all-cause mortality and resulted in a gain of ~1.62 quality-adjusted life-years and averted ~US$90 900 in costs of complications per participant.[4]

Since the publication of DCCT, there have been numerous and important innovations in the treatment of diabetes, such as the release of new basal and prandial insulin analogs that have a more 'physiological' effect and are safer,[5 6] implementations of structured advances education programs[7] and development and increase in use both of continuous subcutaneous insulin infusion devices and continuous and flash glucose monitoring systems.[8 9] However, despite these advances, some studies in EE.UU and Europe in patients with T1D have reported

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Significance of this study

What are the new findings?

- A total of 412 patients with T1D who were receiving IGla-300 or IDeg during at least 6 months immediately preceding the inclusion date were included in the study.
- Total (0.77±0.36 unit/kg/day), basal (0.43±0.20 unit/kg/day) and prandial (0.33±0.23 unit/kg/day) daily insulin doses requirements were similar between IGla300 and IDeg groups.
- Patients with glycosylated hemoglobin (HbA1c) levels ≤7% (n=113) used significantly lower basal and total daily insulin doses, but not prandial insulin than both patients with HbA1c levels between 7.1% and 8% (n=151) and >8% (n=148).
- Those patients with worst metabolic control (HbA1c ≥8%) used higher basal, prandial and total daily insulin doses than patients in the other two subgroups of metabolic control.
- Patients using IGla-300 and IDeg had similar basal, prandial and total daily insulin doses requirements in all metabolic control subgroups.

How might these results change the focus of research or clinical practice?

- Our study provides relevant information about our patients with T1D with stable basal-bolus insulin injections, using IGla-300 or IDeg as the basal insulin, in whom we did not observe any difference in basal, prandial or total daily insulin doses requirements.

a worsening in time in metabolic control, mainly in adolescent patients.[10 11]

The second-generation long-acting insulin analogs, glargine U300 UI/mL (IGla-300) and degludec (IDeg), were introduced in 2015 and have shown, in randomized controlled trials (RCTs), an increased stability, which translates to an increased flexibility in timing of administration[12 13] and reduced risk of hypoglycemia compared with glargine U100 UI/mL insulin (IGla-100),[14 15] results that have been reproduced in several real-world studies (RWS),[16–21] although others have reported no differences in hypoglycemia between first-generation and second-generation basal analogs.[22–25] Otherwise, a number of RCTs and RWS have reported higher daily insulin doses requirements (DIDR) with IGla-300[12 15 20] and lower with IDeg,[13 14 18 21] compared with IGla-100, although some studies failed to detect these difference.[17 23–31]

To date, only limited studies comparing IGla-300 and IDeg in people with T1D are available.[32–34] In this sense, there are not many RWS evaluating DIDR in patients with T1D using second-generation basal insulin analogs, and such comparison is necessary. This study aimed to compare the DIDR in individuals with T1D using IDeg and IGla-300 in real clinical practice.

MATERIALS AND METHODS

Data source and subjects

The study was designed as a retrospective, single-center, observational study including patients with T1D who attended their routine checkups in Endocrinology Unit during the period from 1 June 2019 to 31 December 2019. Anonymized participant data were collected from cumulative database of patients with T1D, used for clinical research and quality control, which incorporate predefined variables coming both from electronic clinic history and other health variables daily included by endocrinologists and diabetes specialized nurses.

Selected patients must satisfy all inclusion criteria and not meet any exclusion criteria. Inclusion criteria include (1) individuals with T1D aged 17–69 years and at least 1 year of diabetes duration; (2) treatment for at least 6 months with stable basal-bolus insulin injections, with IGla-300 or IDeg as the basal insulin and rapid-acting insulin analogs before at least one meal. Exclusion criteria were: (1) pregnancy women; (2) those patients using an insulin pump or another long-acting (NPH, Determir, IGla-100) or premixed insulin during 2019. All patients wih T1D attended to in our specialized unit were incorporated in an individualized education program, including management of diet and physical activity, and many patients were instructed on carbohydrate counting education. Generally, all patients were instructed to optimize both basal insulin doses, to maintain morning fasting glucose between 80 and 130 mg/dL, and rapid-acting insulin to keep 2-hour postprandial glucose <180 mg/dL.

Variables

The following data included in the database were evaluated: (1) health variables: gender, age, diabetes duration, active smoking, body weight, height and body mass index (BMI, kg/m^2); (2) analytical variables: HbA1c levels obtained within the previous 3 months and measured in our hospital laboratory. HbA1c was standardized to the DCCT reference range (20–42 mmol/mol; 4.05%–6.05%). Patients were subclassified in three metabolic control subgroups: HbA1c ≤7%, HbA1c 7.1%–8% and HbA1c ≥8%. Albuminuria obtained within the previous 3 months. The clinical definition of microalbuminuria used was two positive tests from three samples taken within 1 year, with an albumin/creatinine ratio of 30–300 mg/g (approximately 3–30 mg/mmol). Macroalbuminuria was defined as an albumin/creatinine ratio >300 mg/g (approximately 30 mg/mmol); (3) treatment variables: type of basal insulin (IGla-300 or IDeg), units of basal, prandial and total daily, use of non-insulin hypoglycemic agents, patients using prandial insulin adjustment by carbohydrate counting, patients using FreeStyle Flash glucose monitoring system, antihypertensive treatment, lipid-lowering treatment; (4) diabetic complications: macrovascular disease (known ischemic heart disease, stroke, peripheral vascular disease or amputation), diabetic retinopathy (presence of any type of diabetic retinopathy or treatment with laser and/or surgery), diabetic nephropathy (defined as albuminuria, dialysis or kidney transplant).

Statistical analysis

All statistical analyses were performed with SPSS V.12.0 for Windows (IBM, Armonk, New York, USA). Variables were preliminarily tested for normal distribution with the Kolmogorov-Smirnov test. Descriptive statistics are presented in terms of means with SD or counts

Table 1 Clinical characteristics and chronic complications in T1D (n=412)

	All patients (n=412)	Glargine U300 (n=187)	Degludec (n=225)	P value
Age (years)	37.0±13.4	37.7±14.1	36.6±12.8	0.376
Gender male	214 (52%)	111 (59.4%)	103 (45.8%)	0.004
Diabetes duration (years)	18.7±12.3	17.6±12.6	19.8±11.9	0.112
Weight (kg)	72.0±14.9	71.7±13.7	72.3±15.9	0.759
BMI (kg/m^2)	25.3±4.6	25.1±4.5	25.4±4.8	0.551
HbA1c (%)	7.8±1.4	7.6±1.2	8.1±1.5	<0.001
Patients with HbA1c ≤7%	113 (27.4%)	65 (35.3%)	48 (21.5%)	0.001
Patients with HbA1c ≥8%	148 (35.9%)	53 (28.3%)	95 (42.2%)	0.003
Carbohydrate counting (%)	106 (25.7%)	47 (25.1%)	59 (26.2%)	0.458
Patients with FSL (%)	80 (19.0%)	27 (14.4%)	44 (19.6%)	0.107
Time in range 70–180 mg/dL (%)	47.3±18.0	51.1±14.6	45.0±19.5	0.183
Time in hypoglycemia <70 mg/dL (%)	6.8±6.6	9.2±8.3	5.8±4.4	0.053
Time in hyperglycemia >180 mg/dL (%)	46.5±19.9	39.6±16.4	50.5±20.7	0.023
Active smoking (%)	101 (24.5%)	44 (23.5%)	57 (25.3%)	0.379
Antihypertensive treatment (%)	78 (18.9%)	33 (17.6%)	45 (20.0%)	0.307
Lipid-lowering treatment (%)	147 (35.7%)	65 (34.7%)	82 (36.4%)	0.349
Diabetic retinopathy (%)	194 (47.0%)	79 (42.2%)	115 (51.1%)	0.056
DR mild-to-moderate	114 (27.6%)	43 (23.0%)	71 (31.5%)	
Laser therapy	53 (12.9%)	29 (15.5%)	24 (10.6%)	
Surgery	27 (6.6%)	7 (3.6%)	20 (8.9%)	
Diabetic nephropathy	52 (12.6%)	20 (10.7%)	32 (14.2%)	0.327
Albuminuria	42 (10.2%)	16 (8.6%)	26 (11.6%)	
Dialysis of kidney transplant	10 (2.4%)	4 (2.1%)	6 (2.7%)	
Macrovascular complications (%)	23 (5.6%)	9 (4.8%)	14 (6.2%)	0.089

BMI, body mass index; DR, diabetic retinopathy; FSL, freestyle libre; HbA1c, glycosylated hemoglobin; T1D, type 1 diabetes.

and percentages depending on the nature of the variable described. Intergroup differences of normally or non-normally distributed data were tested for significance with the unpaired Student's t-test or Mann-Whitney U test, respectively. Differences in categorical variables were analyzed by χ^2 test or Fisher's exact test, as appropriate. Setting daily basal insulin dose and daily total insulin dose as the dependent variables, two separate linear regression analysis were performed. Independent variables included in linear regression analysis were age, gender, diabetes duration, HbA1c, type of basal insulin, prandial insulin dose and microvascular complication. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

A total of 412 patients with T1D (males: 52%; median age: 37.0±13.4 years, median diabetes duration: 18.7±12.3 years; median HbA1c: 7.8%±1.4%) who were receiving IGla-300 or IDeg during at least 6 months immediately preceding the inclusion date were included in the study. The patients in IGla-300 group were more frequently males (59% vs 45.8%; p=0.004), had lower HbA1c levels (7.6±1.2% vs 8.1%±1.5%; p<0.001), higher proportion of patients with HbA1c ≤7% (35.3% vs 21.5%; p=0.001) and lower proportion of patients with HbA1c ≥8% (28.3% vs 42.2%; p=0.003) than patients using IDeg (table 1). There were no statistical difference (42% vs 53% vs 53%, p=0.122, in HbA1c ≤7%, 7.1%–8% and >8% subgroups, respectively) between metabolic control subgroups.

Non-insulin hypoglycemic agents and DIDR in IGla-300 and IDeg groups are presented in table 2. Non-insulin hypoglycemic agents were prescribed in 30 patients (7.2%) and more frequently were metformin (26 patients; 6.3% of total) and sodium-glucose co-transporter-2 inhibitors (12 patients; 2.9% of total). Total (0.77±0.36 unit/kg/day), basal (0.43±0.20 unit/kg/day; 58% of total insulin) and prandial

Table 2 Non-insulin hypoglycemic agents and daily insulin doses requirements in T1D using glargine U300 or degludec (n=412)

	All patients (n=412)	Glargine U300 (n=187)	Degludec (n=225)	P value
Non-insulin antidiabetics (%)	30 (7.3)	11 (5.9)	19 (8.4)	0.233
Basal insulin				
Unit/day	31.5±16.9	30.1±14.9	32.2±18.4	0.759
Unit/kg/day	0.43±0.20	0.43±0.19	0.44±0.21	0.563
Prandial insulin				
Unit/day	23.5±16.9	22.5±16.1	23.2±16.0	0.603
Unit/kg/day	0.33±0.23	0.32±0.23	0.33±0.20	0.851
Total insulin				
Unit/day	54.0±29.1	52.8±27.4	55.4±29.5	0.383
Unit/kg/day	0.77±0.36	0.76±0.35	0.76±0.33	0.683
Basal/Total insulin ratio	0.58±0.14	0.59±0.14	0.58±0.14	0.441

T1D, type 1 diabetes.

Table 3 Daily insulin doses requirements by metabolic control subgroups in T1D using glargine U300 or degludec

	HbA1c ≤7% (IGla: 65 P; IDeg: 48 P)		HbA1c 7.1%–8% (IGla: 69 P; IDeg: 82 P)		HbA1c ≥8% (IGla: 53 P; IDeg: 95 P)	
		P value		P value		P value
Basal insulin						
Unit/day						
IGla-300	25.8±13.4	0.781	30.8±15.7	0.780	35.1±13.8	0.779
IDeg	26.6±16.8		31.6±19.0		35.8±18.1	
Unit/kg/day						
IGla-300	0.36±0.16	0.558	0.43±0.17	0.870	0.51±0.18	0.643
IDeg	0.38±0.20		0.42±0.21		0.49±0.21	
Prandial insulin						
Unit/day						
IGla-300	18.7±12.4	0.552	25.1±19.9	0.055	24.5±14.6	0.185
IDeg	20.0±9.8		19.7±11.1		28.4±20.2	
Unit/kg/day						
IGla-300	0.26±0.17	0.404	0.35±0.27	0.070	0.37±0.21	0.451
IDeg	0.29±0.11		0.27±0.16		0.40±0.26	
Total insulin						
Unit/day						
IGla-300	44.7±22.2	0.893	56.2±32.3	0.285	59.6±24.7	0.342
IDeg	45.3±24.1		51.0±25.1		64.3±33.2	
Unit/kg/day						
IGla-300	0.64±0.29	0.857	0.79±0.37	0.135	0.88±0.34	0.782
IDeg	0.64±0.24		0.69±0.28		0.89±0.38	
B/T ratio						
IGla-300	0.60±0.15	0.032	0.58±0.15	0.217	0.60±0.13	0.269
IDeg	0.55±0.11		0.61±0.14		0.57±0.15	

B/T, basal/total insulin; HbA1c, glycosylated hemoglobin; IDeg, insulina degludec; IGla-300, insulina glargina 300 UI/mL; P, patients; T1D, type 1 diabetes.

(0.33±0.23 unit/kg/day; 42% of total insulin) DIDR were similar between IGla-300 and IDeg groups. A sensitivity analysis for DIDR by metabolic control groups was made and results are shown in table 3. Patients with HbA1c levels ≤7% (n=113) used significantly lower basal (p=0.045) and total daily insulin doses (p=0.024), but not prandial insulin (p=0.241) than both patients with HbA1c levels between 7.1% and 8% (n=151) and >8% (n=148). Those patients with worst metabolic control (HbA1c ≥8%) used higher basal, prandial and total daily insulin doses than patients in the other two subgroups of metabolic control. No difference was observed in the basal/total insulin ratio between metabolic control subgroups. Finally, patients using IGla-300 and IDeg had similar basal, prandial and total DIDR in all metabolic control subgroups. In the linear regression analysis, age (β=−0.144, p=0.041 and β=−0.091, p=0.009), HbA1c (β=0.240, p<0.001 and β=0.134, p<0.001), prandial doses (β=0.301, p<0.001 and β=0.805, p<0.001) and microvascular complication (β=0.184, p=0.007 and β=0.096, p=0.003) were significantly associated with daily basal insulin doses and total daily insulin doses, respectively, without association with type of basal insulin (β=−0.042, p=0.421 and β=−0.024, p=0.403).

DISCUSSION

The present descriptive, retrospective study has evaluated DIDR in different subgroups of patients with T1D treated with second-generation basal insulin analogs for at least 6 months in real-life conditions and revealed no difference in DIDR between IGla-300 and IDeg neither globally nor in any of metabolic control subgroups analyzed. Despite the fact that both basal analogs were introduced in 2015, to date, few comparative studies have been published[32–36] and information about comparative DIDR come only from studies in patients with type 2 diabetes, which reported that patients treated with IGla-300 had higher DIDR compared with IDeg.[35 36]

Many studies have analyzed the DIDR in patients with T1D switching from basal insulins to IGla-300 or IDeg with non-concluding results. Thus, some recent RWS reported that patients with T1D using IGla-300, transferred from another basal insulin, have significant reductions in HbA1c levels,[17 22 23] with no change in weight[17 22 23] or DIDR.[17 23 30] However, other studies in routine practice settings have reported higher DIDR ranged from 6.5% to 10.1% after switching to U300 from U100, mainly in the first 6 months.[19 20 29] On the other hand, in RCTs comparing IDeg with either glargine or detemir in patients with T1D, IDeg daily doses at end point are usually lower than comparators.[13 26 37] In RWS with patients with T1D, switching to IDeg from IGla-100 or detemir is associated with a 12%–13% reduction of both basal and prandial daily insulin doses,[18 21 28] mainly in patients who were previously on two injections of basal insulin. However, other studies in real-life conditions informed that IDeg doses in patients with T1D transferred from IGla-100 once-daily were equivalent.[25–27 31]

Discrepancies in basal and total DIDR observed in studies with patients with T1D may potentially be, at least partly, explained by differences in the treated populations (HbA1c levels, age, race, weight and so on) and use of different insulin adjustment algorithms, mainly in RCTs where titration schedules for basal insulin are rather different from those used in routine clinical practice. Therefore, approximately half (40%–60%) of total daily insulin doses in patients with T1D using multiple daily injections is given as basal insulin, dependent on body weight and insulin sensitivity, and the rest is divided into meal-related doses, mainly based on carbohydrate content.[38 39] In our population, daily basal insulin doses were 58% of the daily total doses, similarly to other national studies in T1D reporting that daily basal doses ranged 55%–63% of daily total insulin doses and could be explained, in part, for Mediterranean diet and lifestyle followed by the Spanish populations,[20 40] in contrast with studies in other countries in patients with T1D where daily basal insulin requirements usually are ≤50%.[21 27 31 39]

RCTs have a high degree of internal validity but lower generalizability and its results cannot always be extrapolated to an unselected population. However, RWS provides a valuable additional source of evidence that complements clinical trial data by assessing the external validity of new therapies, thus bridging the knowledge gap between RCTs and clinical practice.[41] The strengths of our study have been to reflect the current therapeutic approach in patients with T1D in real-life practice and have shown no difference in total, basal and prandial DIDR between patients with T1D using IGla-300 or IDeg.

There are some limitations to our study. First, observational retrospective studies can be limited by real-world-related biases with numerous confounders. However, retrospective observational studies may be closer to actual clinical practice that prospective observations that tend to alter the spontaneous behaviors of both clinicians and patients. Moreover, in our center the clinical and therapeutic data from patients with T1D are prospectively incorporated into a cumulative database, which is annually evaluated for quality control. This strategy allows us to detect and correct incomplete and erroneous clinical data and this makes the available information in the database to be robust. Second, the limited size of the sample enrolled in the present study warrants caution in the interpretation of results. Also, this retrospective survey was performed in a single specialist clinic for diabetes care, limiting the generalization of results. Finally, another potential limitation to the study is that hypoglycemic episodes and residual β-cell functions were not evaluated because those data were not incorporated into our database. Only time in hypoglycemia <70 mg/dL in patients using freestyle libre has been analyzed and no difference was found between groups. However, the retrospective nature of the study would not have allowed reliable information on total and nocturnal hypoglycemia, whereas the expected incidence of severe hypoglycemia was probably too low to produce meaningful results on this sample size.

In conclusion, despite the fact that second-generation basal insulin analogs (IGla-300 and IDeg) were introduced in 2015, to date, clinicians have insufficient information about differences or similarities in DIDR in patients with T1D using both long-acting basal insulin analogs. Our study provides relevant information in our patients with T1D with stable basal-bolus insulin injections, using IGla-300 or IDeg as the basal insulin, in whom we did not observe any difference in basal, prandial or total DIDR. However, prospective, randomized, multicenter study comparing both second-generation basal insulin analogs in patients with T1D is needed.

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