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Efficacy of Insulin Degludec/Insulin Aspart (IDegAsp) vs. Insulin Glargine (IGlarU300) in Insulin-Naïve Patients with Type 2 Diabetes: A Retrospective Study

ABSTRACT

Objective: To investigate the efficacy of insulin degludec/insulin aspart (IDegAsp) co-formulation versus insulin glargine U300 (IGlarU300) in insulin-naïve individuals with type 2 diabetes (T2D) who had inadequate glycemic control with three oral antidiabetic drugs.

Materials and methods: In this multicenter, retrospective, observational study, insulin-naïve individuals with T2D were subjected to standard care. Healthcare practitioners across this multicentric study initiated treatment with either IDegAsp (group 1) or IGlarU300 (group 2) as the insulin of choice. The participants' glycometabolic parameters, such as weight, body mass index (BMI), creatinine, hemoglobin A1c (HbA1c), fasting blood glucose (FBG), and postprandial blood glucose (PPBG) levels were analysed over 6 months. Changes in these parameters over 6 months were evaluated. Statistical significance was determined using the t-test.

Results: Both treatment groups showed equivalent improvements in glycometabolic parameters, such as HbA1c, creatinine, FBG, PPBG levels, and hypoglycemic episodes over 6 months when compared to the baseline levels. Additionally, at every follow-up, the weight and BMI of both groups were similar. No severe hypoglycemic events were observed in either treatment group.

Conclusions: Our findings support that IDegAsp is non-inferior to IGlarU300 and may be considered for treatment in insulin-naïve people with inadequately controlled T2D as an initiation insulin option.

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Keywords: insulin naïve, type 2 diabetes, insulin degludec/aspart, insulin glargine

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Introduction

Therapeutic inertia is a significant factor in optimal management of type 2 diabetes (T2D) [1, 2]. India has an estimated 77 million adults with T2D and an additional population of 25 million adults with prediabetes [3, 4]. Failure to initiate insulin early in people with uncontrolled hyperglycemia who are on up to four oral therapies may lead to multisystemic complications, such as cardiovascular, renal, and neurovascular complications [5–7]. According to the American Diabetes Association

(ADA), European Association for the Study of Diabetes (EASD), Research Society for the Study of Diabetes in India (RSSDI), and all global consensus guidelines, early insulinization is an appropriate way to control diabetes and delay the onset of complications [8–10].

The RSSDI guidelines recommend insulin therapy if optimal doses of three or more oral antidiabetic drugs (OADs) for 3–6 months fail to achieve HbA1c targets or if organ dysfunction contraindicates the use of OADs [10]. The advent of new insulin analogs has revolutionized T2D management. The second-generation basal insulin analogs, such as IDeg and IGlarU300 provide a range of compelling therapeutic benefits over first-generation analogs, such as insulin glargine 100 U/mL and insulin detemir, with improved pharmacokinetics, reduced risk of hypoglycemia, longer duration of action, and improved glycemic control [11–15]. The glycemic pentad including fasting blood glucose (FBG), postprandial blood glucose [PPBG], and hemoglobin A1c (HbA1c) levels, glycemic variability, and quality of life must be effectively managed considering the carbohydrate-rich Indian diet [16]. Both FBG and PPBG levels need to be controlled for better outcomes. The RSSDI consensus suggests the initiation of the IDegAsp co-formulation as an alternative to basal insulin for better management of the glycemic control in T2D [17, 18]. The IDegAsp co-formulation insulin analog is a promising insulin therapy, non-inferior to premixed insulin formulations, and a potential alternative to basal-only and basal-bolus insulin therapies for T2D management [19]. The IDeg provides long-acting basal insulin that controls FBG levels, and the insulin aspart bolus component (IAsp) controls PPBG. On the other hand, IGlarU300 is the widely accepted basal ultra-long-acting second-generation insulin that provides a steady and sustained basal insulin level. Although the use of the co-formulation IDegAsp and IGlarU300 has been shown to lower FBG levels and frequency of hypoglycemia compared to other premix insulin preparations, no study or meta-analysis has compared the efficacy of IDegAsp and IGlarU300 in managing T2D in the Indian cohort [18–20]. A comparative efficacy study of both widely prescribed second-generation insulin analogs, IDegAsp versus IGlarU300, will elucidate the potential equivalent usage of either choice molecule as an insulin initiator in insulin-naïve patients with T2D. Additionally, there are limited data supporting the RSSDI guideline recommendations for IDegAsp as an initiator insulin in individuals who are insulin-naïve and have uncontrolled T2D [10].

We aim to investigate whether IDegAsp demonstrates non-inferiority compared to IGlarU300 when used as the initial insulin regimen. To address this objective, we performed a multicenter, clinical observational study to retrospectively evaluate the efficacy of IDegAsp versus IGlarU300 in two groups of insulin-naïve individuals with uncontrolled T2D levels subjected to either of the therapies from the day of treatment initiation to 6 months in a real-world setting. We assessed the 1) changes in weight, body mass index (BMI), HbA1c, creatinine, FBG, and PPBG levels over 6 months; 2) withdrawal of insulin in both treatment groups at subsequent visits and at the end of treatment; and 3) the rate of improvement in glycemic profiles and frequency of hypoglycemia in both treatment groups.

Materials and methods

Study design

This multicenter, retrospective, observational study was conducted at five centers, of which three were from Ahmedabad, Gujarat, India, and two were in Mumbai, Maharashtra, India. The study was conducted for six months (24 weeks), spanning from December 2022 to May 2023, in compliance with the EU Clinical Trial Directive 2001/20/EC, the International Conference on Harmonization guidelines for Good Clinical Practice, and the ethical principles of the Declaration of Helsinki. The study was approved by an independent ethics committee that complied with the local regulatory requirements.

Study participants

We included insulin-naïve adults (age 8–65 years) with T2D and HbA1c levels > 9% who were unresponsive to triple OAD therapy. The data of individuals with type 1 diabetes, pregnant females, and critically ill patients were excluded. IDegAsp and IGlarU300 were prescribed according to the routine standard of care. The study cohort was divided into two study groups: individuals treated with IDegASP were assigned to one group (IDegAsp group) and those treated with IGlarU300 to the other group (IGlarU300). Propensity score matching was performed between groups, and an identical cohort was used for the study. Each group included 80 insulin-naïve patients with T2D (Suppl. Fig. 1). The baseline characteristics were recorded at the initial visit and upon completion of treatment for a comprehensive overview of the patients' profiles over the study duration.

Data collection

The data were recorded from clinical observations and laboratory test reports of glycometabolic parameters, such as weight, BMI, creatinine, HbA1c, FBG, and PPBG, of participants at baseline and during follow-up. The height and weight were measured using a calibrated clinic stadiometer and digital weighing scale, respective-

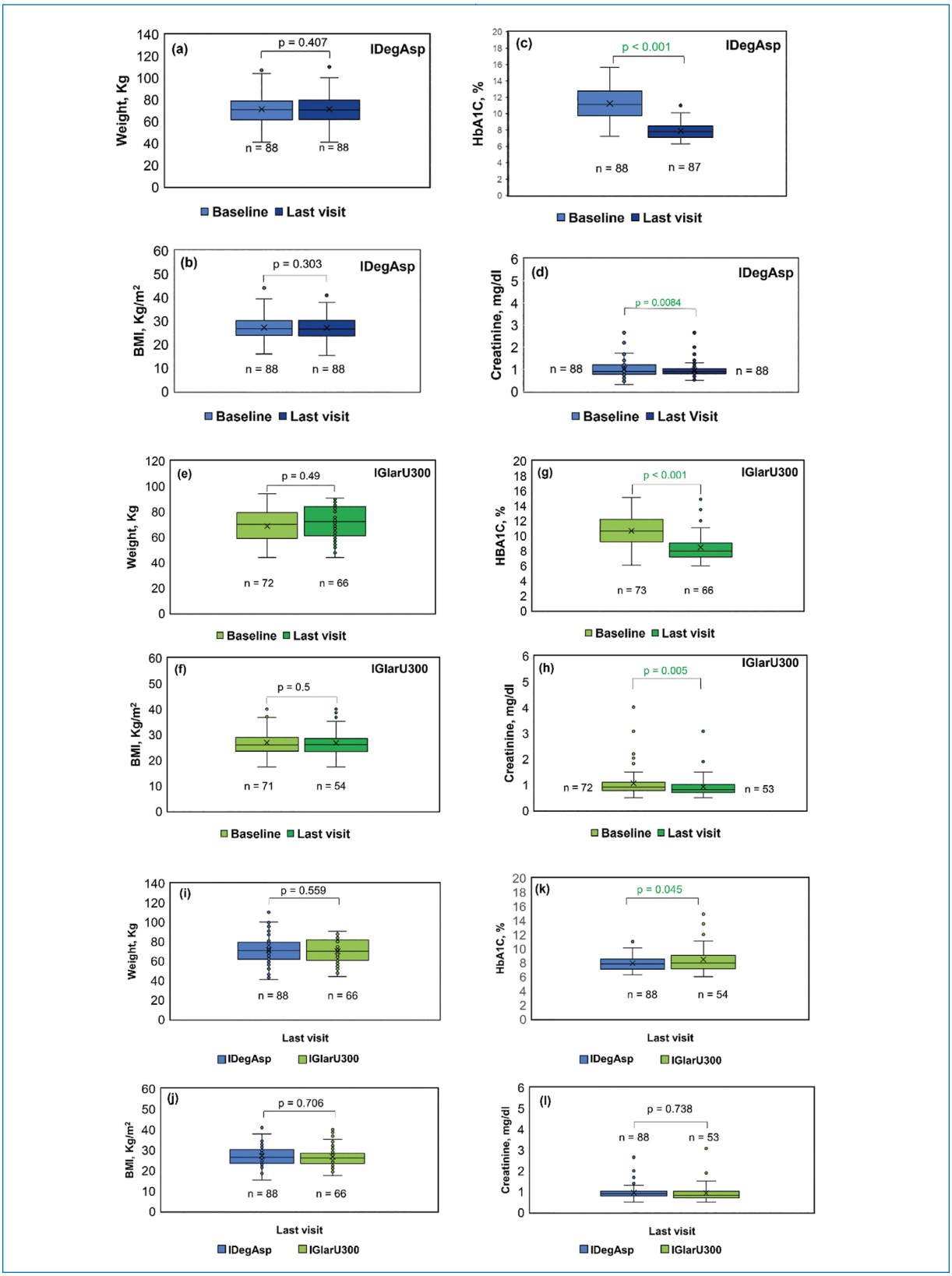

Figure 1. Comparison of the Effects of IDegAsp and IGlarU300 on the Participants' Glycometabolic Parameters. Changes in **A.** weight; **B.** BMI; **C.** HbA1c; and **D.** creatinine in response to 6 months of IDegAsp treatment; changes in **E.** weight; **F.** BMI; **G.** HbA1c; and **H.** creatinine in response to 6 months of IGlarU300 treatment; comparison of **I.** weight; **J.** BMI; **K.** HbA1c; and **L.** creatinine levels after 6 months of treatment with IDegAsp and IGlarU300

$p < 0.05$ is considered statistically significant

BMI — body mass index; HbA1c — glycated hemoglobin; IDegAsp — co-formulation insulin degludec/insulin aspart; IGlarU300 — insulin glargine 300 U/mL; n — number of individuals

ly. Owing to the retrospective nature of the study, the instruments could not be standardized across the centers. Data were recorded on a standardized Microsoft Excel sheet and distributed to the centers. The prescribing information was retrieved from the electronic health records of the participants. Additionally, the estimated glomerular filtration rate (eGFR) of the participants at baseline and each follow-up visit was recorded. FBG and PPBG levels were calculated using the glucose oxidase-peroxidase (GOD-POD) coupled method.

The GOD-POD method is linear up to 500 mg/dL, with good precision (coefficient of variation = 0.7% to 1.4%) and accuracy (average deviation = 0.97). Data were collected on documented or undocumented hypoglycemic events. Intake of supporting drugs, OADs, lipid-lowering agents, blood pressure-lowering agents, and multivitamins was recorded.

Evaluating outcome measures

At baseline (visit 1), the medical history of all participants, including any prior medical conditions and concurrent medication, was recorded in a case record form. Data were collected at baseline and follow-up visits for 6 months. The following parameters were studied to determine the insulin efficacy in both groups: (I) changes in glycometabolic parameters in response to medication in the IDegAsp group; (II) changes in glycometabolic parameters in the response to medication in the IGlarU300 group (III) differences in the glycometabolic parameters of both groups at the end of the study; (IV) changes in the FBG levels of both groups in response to medication at follow-up visits; (V) changes in the PPBG levels of both groups in response to medication at follow-up visits.

Assessment of changes in BMI, weight, HbA1c, and creatinine levels

The metabolic parameters recorded over 6 months were evaluated. The mean changes in BMI, weight, HbA1c, and creatinine values from baseline (visit 1/day 0) to the last visit (visit 5/day 180) were analyzed group-wise. Additionally, changes in the participants' BMI, weight, HbA1c, and creatinine levels on taking IDegAsp and IGlarU300 were compared at 6 months (last visit/day 180).

Assessment of changes in FBG and PPBG levels

The changes in the FBG and PPBG levels of the participants in response to either IDegAsp or IGlarU300 were evaluated over 6 months. The FBG and PPBG levels of individuals treated with IDegAsp and IGlarU300 at baseline (0 days), 2nd (30 days), 3rd (60 days), 4th (150 days), and 5th (180 days) visits were compared.

Table1. Baseline Characteristics

Baseline characteristics		
	IDegAsp	**IGlarU300**
	N = 80	**N = 80**
Age [years]	56	56
Weight [kg]	71.25	69.53
BMI [kg/m^2]	27.14	26.89
HbA1c [%]	11.24	10.63
Creatinine	1.01	1.022
After 6 months of treatment (24 weeks)		
	IDegAsp	**IGlarU300**
Weight [kg]	71.16	69.92
BMI [kg/m^2]	27.05	26.76
HbA1c [%]	7.88	8.49
Creatinine	0.95	0.93

BMI — body mass index; HbA1c — glycated hemoglobin; IDegAsp — co-formulation insulin degludec/insulin aspart; IGlarU300 — insulin glargine 300 U/mL

Statistical analyses

The total sample size was 160, evenly distributed with 80 individuals in each group. We utilized Cohen's d formula to determine the effect size, revealing a small effect size.

The weight, BMI, Hb1Ac, creatinine, FBG, and PPBG levels of both groups were compared at baseline and follow-up. The data are represented as boxplots. Statistical analyses were performed using Microsoft Excel (Microsoft 365, Version 2305). The t-test was used to compare categorical variables. The two groups were compared using either a two-tailed equal variance or two-tailed unequal variance t-test, depending on whether the comparison was carried out within the same or different groups of participants, respectively. A confidence interval of 5% was used, and a p-value of less than 0.05 ($p < 0.05$) was considered to indicate statistically significant differences. At a significance level of alpha = 0.95, we attained a power > 95%, calculated using G*Power 3.1.9.7.

Results

Matched cohorts with similar baseline characteristics were included in the study and divided into two groups based on treatment with a once-daily dose of either IDegAsp or IGlarU300 for 6 months.

Baseline characteristics

The participants' baseline characteristics and outcomes are summarized in Table 1. The IDegAsp group had a slightly higher mean baseline weight (71.25 kg)

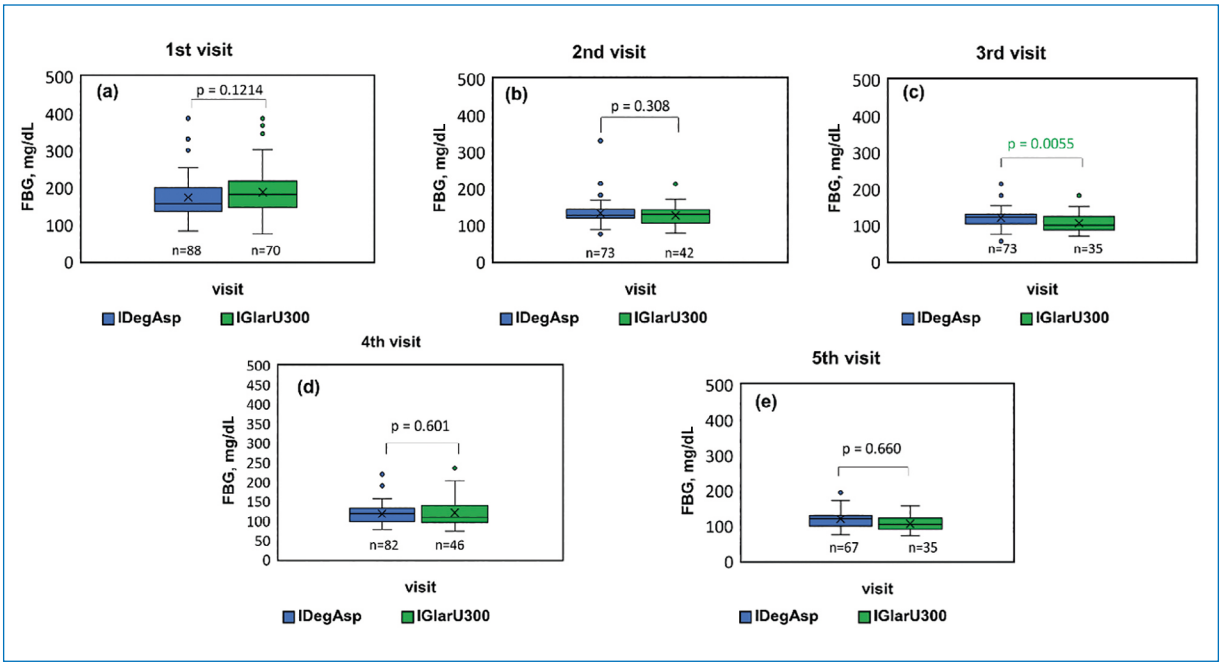

Figure 2. Comparison of FBG Levels at Each Visit during 6 Months of Treatment with IDegAsp and IGlarU300
$p < 0.05$ is considered statistically significant
FBG — fasting blood glucose; IDegAsp — co-formulation insulin degludec/insulin aspart; IGlarU300 — insulin glargine 300 U/mL; n — number of individuals

and BMI (27.14 kg/m^2) compared to the IGlarU300 group (69.53 kg and 26.89 kg/m^2, respectively). Additionally, the IDegAsp group started with a higher baseline HbA1c level (11.24%) compared to the IGlarU300 group (10.63%). Creatinine levels were similar at baseline, with IDegAsp at 1.01 and IGlarU300 at 1.022. Notably, both groups exhibited reductions in weight, BMI, and HbA1c after initiation, with minor variations in creatinine levels.

Changes in weight, BMI, HbA1c, and creatinine levels

Figure 1 summarizes the effect of IDegAsp and IGlarU300 alone on the participants' weight, BMI, HbA1c, and creatinine levels. At 6 months of IDegAsp treatment, the participants' HbA1c and creatinine levels had decreased significantly compared to those at baseline ($p < 0.05$); however, the changes in their weight and BMI were insignificant (Fig. 1A–D). At 6 months of IGlarU300 treatment, the participants' HbA1c and creatinine levels decreased significantly from baseline ($p < 0.05$) but no significant changes in weight and BMI were observed (Fig. 1E–H)

The weight, BMI, HbA1c, and creatinine levels of both groups were compared at 6 months (visit 5) (Fig. 1I–L), and the HbA1c values of patients taking IDegAsp were found to be significantly lower than those taking IGlarU300 ($p < 0.05$).

Quantitative evaluation of IDegAsp and IGlarU300 efficacy

The cumulative percentages of participants with complete insulin withdrawal at the 2nd, 3rd, 4th, and 5th visits were as follows: IDegAsp group, 2.27%, 9.09%, 22.73%, and 31.82%, respectively; IglarU300 group, 4.23%, 11.27%, 21.13%, and 29.58%, respectively. A steady increase was observed in the number of participants with complete insulin withdrawal after the 2nd visit. At 6 months, approximately 30% of the participants in both groups withdrew insulin completely.

Changes in FBG levels across treatment groups

The mean FBG value of both groups before treatment initiation was ~200 mg/dL (visit 1/day 0) (Fig. 2A). There was no significant difference in the mean FBG value across both groups at any visit, except at the 3rd visit (Fig. 2C). At the 4th visit, it decreased to ~100 mg/dL (90 days) and was maintained until the 5th visit (180 days) (Fig. 2D and 2E). No severe hypoglycemic events were observed in either treatment group.

Changes in PPBG levels across treatment groups

The mean PPBG value of both groups was ~350 mg/dL at baseline (visit 1/day 0) (Fig. 3A). It decreased to ~200 mg/dL at the 2nd visit (30 days) and remained stable after the 3rd visit (60 days) (Fig. 3B

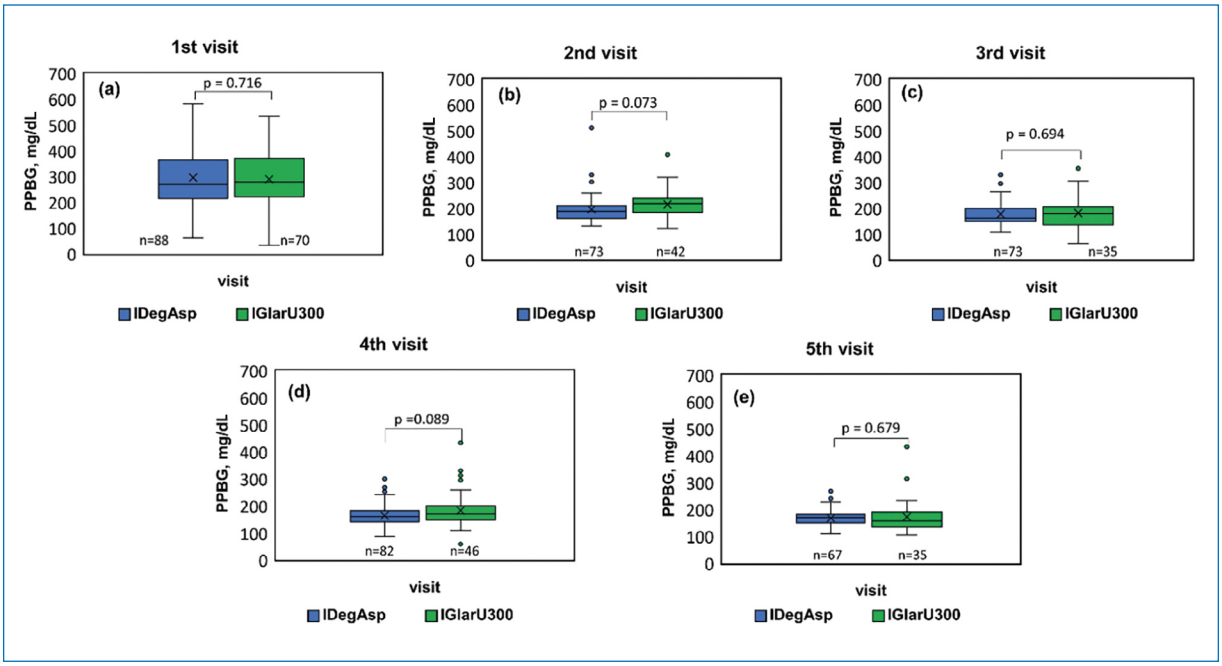

Figure 3. Comparison of PPBG Levels at Each Visit during 6 Months of Treatment with IDegAsp and IGlarU300
$p < 0.05$ is considered statistically significant
IDegAsp — co-formulation insulin degludec/insulin aspart; IGlarU300 — insulin glargine 300 U/mL; n — number of individuals; PPBG — postprandial blood glucose

and 3C). At 4th and the 5th visits, the mean PPBG values of both groups decreased to ~180 mg/dL (Fig. 3D and 3E). However, there was no statistically significant difference in the mean PPBG levels of both groups at any of the visits. No severe hypoglycemic events were observed in either treatment group. The data pertaining to Self-Monitoring of Blood Glucose, (SMBG) and Continuous Glucose Monitoring (CGM), has been reserved for a future manuscript.

Discussion

This retrospective multicenter study compared the efficacy of IDegAsp and IGlarU300 in insulin-naïve individuals with uncontrolled T2D levels over 6 months. Both therapies led to similar improvements in glycometabolic parameters, such as HbA1c, creatinine, FBG, PPBG levels, and hypoglycemic episodes at 6 months compared to the baseline levels. The weight and BMI of both groups were similar across the study duration. Initiation of IDegAsp or IGlarU300 in insulin-naïve individuals with T2D resulted in a significant reduction in HbA1c, FBG, and PPBG levels. However, the participants' weight and BMI remained similar at baseline and at the end of treatment. Glycemic control is critical in T2D management. Therefore, early initiation and intensification of insulin are necessary to ensure adequate insulin levels. However, there is clinical inertia regarding early insulinization in T2D [21, 22]. Second-generation insulin analogs are associated with a reduced risk of hypoglycemia, counseling time, fear, and anxiety. Moreover, early insulinization with novel insulin analogs can help preserve β-cell function and achieve faster improvement in target HbA1c levels [23]. However, no comparative study has reported the efficacy of the IDegAsp co-formulation and second-generation insulin analog, IGlarU300, in the Indian population with T2D. Therefore, the primary objective of this multicenter, retrospective study was to evaluate the effectiveness of IDegAsp versus IGlarU300 in insulin-naïve Indian patients with T2D inadequately controlled with OADs.

To accomplish this objective, the glycometabolic profile of individuals with T2D was treated with insulin analogs (IDegAsp or IGlarU300) over 6 months. The possibility of insulin-related weight gain in individuals with T2D poses a therapeutic challenge and frequently delays the initiation of insulin therapy. Therefore, managing insulin-related weight gain is critical to prevent metabolic and cardiovascular complications in T2D [24–26]. In the present study, there was no significant increase in the weight and BMI levels from baseline in both groups. According to the RSSDI clinical practice recommendations for the management of T2D 2022, IDegAsp causes the least weight gain compared to basal insulin and other premixed insulin preparations [24].

However, Kisioglu et al. [20] retrospectively observed significant weight gain in patients treated with IDegAsp and IGlarU300. Additionally, we observed a significant decrease in the mean creatinine values of both treatment groups from baseline, suggestive of improvement in kidney function or stabilization of kidney disease progression due to improved glycemic control. However, improvement in kidney parameters could not be confirmed from the results of this study.

In the present study, there was an equivalent significant decrease in the mean HbA1c levels of both groups when compared to those at baseline. In the past, few studies have reported similar results. Kisioglu et al. [20] observed a significant decrease in the HbA1c and creatinine levels of patients treated with IDegAsp and IGlarU300. Similarly, Heise et al. [27] reported that insulin-naïve people with T2D subjected to once-daily IDegAsp versus once-daily IGlarU300 showed comparable significant improvement in glycemic control and low rates of hypoglycemia. In contrast, Tibadi et al. [28] performed a real-world comparative effectiveness study of IDeg vs. IGlarU300 in insulin-naïve adults with T2D, revealing that treatment with IDeg results in substantially greater reductions in HbA1c and a 30% lower risk of hypoglycemia than treatment with IGlarU30027.

In the study, several patients in both IDegAsp and IGlarU300 groups progressively stopped insulin treatment, indicating successful complete withdrawal at 6 months. Notable reductions in FBG and PPBG levels were observed in both treatment groups. However, no statistically significant difference in the mean FBG values of either group, in response to IDegAsp and IGlarU300, was observed at any visit, except visit 3. No statistically significant difference in the mean PPBG value was observed between the groups at any visit. These findings align with those of the BRIGHT trial, a randomized study comparing the efficacy of IGlarU300 and IDeg in insulin-naïve individuals with T2D. The BRIGHT trial showed that IGlarU300 was non-inferior to IDeg in reducing HbA1c and FBG levels [29]. Cindro et al.'s cross-over, open-label, randomized trial [30] revealed no significant difference in the mean FBG levels of insulin-naïve patients with T2D subjected to either IDegAsp or IGlarU300; however, they observed significant differences in low-density lipoprotein cholesterol levels]. The present findings aligns with expert guidelines recommending IDegAsp initiation in insulin-naïve patients with inadequate glycemic control on OADs alone [19, 24, 31].

One strength of the present study was the inclusion of an insulin-naïve population. Comparing IDegAsp and IGlarU300 directly in an insulin-naïve population allowed for more accurate evaluation of the relative benefits and effectiveness of the two treatments and eliminated potential confounding factors associated with prior insulin use, such as variations in treatment regimens, previous insulin sensitivity, or resistance. This study demonstrates that the IDegAsp co-formulation is a viable and non-inferior option to IGlarU300 for initiating insulin therapy, which could alleviate concerns regarding the complexity and perceived risks of starting insulin injections in T2D management. However, the current study had some limitations. First, the sample size was small, and a larger sample might be more beneficial to compare the efficacy of both drugs. Second, in this trial, the daily glucose profile of everyone subjected to either drug was not evaluated, and neither participant was requested to self-monitor their FBG levels. Third, this was a retrospective study, and a pan-India prospective survey of the opinions of healthcare professionals could provide better insights into the impact of diet and habitat on IDegAsp and IGlarU300 efficacy in T2D management.

Conclusions

Our results indicate that IDegAsp was non-inferior to IGlarU300 and therefore has potential utility as an initiator molecule. Both drugs adequately improved glycemic parameters with a low risk of hypoglycemia in insulin-naïve patients with T2D. These findings support expert panel recommendations, suggesting IDegAsp as a preferred choice for initiating insulin therapy in individuals with uncontrolled T2D.

Article information

Supplementary material

The Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/98892

Data availability

Original contributions presented in the study are included in the article.

Ethics statement

The study was conducted between December 2022 and June 2023 in compliance with EU Clinical Trial Directive 2001/20/EC, the International Conference on Harmonization (ICH) guideline for Good Clinical Practice, and the ethical principles of the Declaration of Helsinki, and was approved by the Rudraksha Hospital Ethical Committee.

Author contribution

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Analysis or interpretation of data: Dr. Dhruvi Hasnani, Dr. Banshi Saboo, Pusala Lakshmi Prasanna, Dr. Ami Sanghvi, Dr. Alpana Sowani, and Dr. Vipul Chavda

Drafting and Revising the Manuscript: Dr. Dhruvi Hasnani, Dr. Santosh Jha, Dr. Vipul Chavda and Pusala Lakshmi Prasanna

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Conflicts of interest

The authors declare no conflict of interest.

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