

Retrospective evaluation of insulin degludec/insulin aspart co-formulation therapy in patients with type 2 Diabetes Mellitus: A single-center experience

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Abstract

Aim: Insulin degludec/aspart (IDegAsp) co-formulation therapy is a novel drug in Turkey and the aim of this study was to retrospectively evaluate the effects of IDegAsp therapy on glycemic control and hypoglycemia in a single tertiary center in Turkey.

Material and Methods: The medical records of patients with type 2 diabetes mellitus, who were evaluated at diabetes clinic of Cerrahpasa Medical Faculty between January and April 2018 and had started to use IDegAsp, were investigated. The demographic characteristics of the patients, anti-diabetic medications they were currently using, causes of treatment change, the IDegAsp doses, fasting blood glucose (FBG), HbA1c and hypoglycemic episodes at treatment onset, the third and sixth months of therapy were evaluated.

Results: Sixty-six patients (F/M:34/32; mean age:57.8±11,6years) were evaluated. Uncontrolled hyperglycemia (80.3%) and frequent hypoglycemic attacks (19,7%) were the causes of treatment change. IDegAsp was started as a single dose in 53% and double dose in 47% of patients. Sixty-two patients (93.9%) were using insulin and the number of injections were significantly reduced with IDegAsp ($p<0.001$). There was no statistically significant difference in terms of insulin doses in sixth months of treatment ($p=0.054$), whereas FBG ($p<0.001$), HbA1c ($p<0.001$) levels and hypoglycemic attacks ($p<0.001$) were reduced and the improvement in glycemic control occurred particularly in the first 3 months of therapy.

Conclusion: Glycemic control and hypoglycemic episodes were improved and the number of daily injections decreased with 6-months of IDegAsp treatment. IDegAsp, which is a novel drug for our country, may increase the treatment compliance of the patients and thus facilitate reaching the glycemic targets.

Keywords: Glycemic control; hypoglycemia; insulin degludec/insulin aspart; type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease with increasing prevalence and becoming a worldwide serious public health problem. The aim of the effective therapy is to prevent the disease-related comorbidities and hence to maintain a long and high-quality life to the patients.

Insulin therapy is the most effective treatment modality in T2DM. Patients with T2DM need insulin over the years due to the progressive beta cell loss and initiation of basal insulin added to oral anti-diabetic agents is recommended by different guidelines as the most convenient method of treatment intensification. If patients on basal insulin require addition of prandial insulin for glycemic regulation,

premeal short acting insulin is added alone (basal plus) or multiple preprandial injections (basal bolus insulin regimens) (1,2) or two injections of pre-mixed insulin treatment is initiated.

Basal plus or basal bolus insulin treatment regimens improve both fasting and post prandial glucose regulation in type 2 diabetes mellitus, but it has been reported that treatment adherence is significantly low in patients on multiple daily injections compared to those on premixed insulins (3,4). On the other hand, premixed aspart/protamine aspart or lyspro/protamine lyspro insulins may increase the risk of both nocturnal and daytime hypoglycemia because of the peak effect of their intermediate acting components and therefore are not

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the ideal alternatives for multiple daily insulin injection treatment in type 2 diabetic subjects (5).

Another barrier to optimal glycemic control with insulin intensification is the low adherence to home blood glucose measurement and dose titration protocols. The increased number of injections parallels the risk of hypoglycemia. Frequent glucose measurement reveals the importance of patient compliance, which is the basic condition for preventing the risk of hypoglycaemia caused by an increased number of insulin injections. The recent studies demonstrated that the patients' compliance with the treatment became more difficult as the number of injections increased (6,7).

Insulin degludec/insulin aspart (IDegAsp) is the first soluble insulin co-formulation of 70% ultra-long acting insulin analog "insulin degludec" and 30% fast-acting insulin analog "insulin aspart". Insulin degludec provides the basal, pre-meal glycemic control and the insulin aspart regulates the post-meal glycemia.

IDegAsp can be used as single or twice daily injections according to the needs of the patients. It has been shown that IDegAsp therapy provides effective glycemic control with a low risk of hypoglycemia in patients with T2DM (8).

IDegAsp co-formulation therapy was launched in Turkey in September 2017 and there is no national real-life study in literature about this new formulation, yet. The aim of this study was to retrospectively evaluate the effects of IDegAsp co-formulation therapy, as a single dose or 2 doses per day, on glycemic control and the risk of hypoglycemia in a single-center in Turkey.

MATERIAL and METHODS

The medical records of patients with T2DM, who admitted to diabetes outpatient clinic of Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty between January-April 2018 were retrospectively evaluated. 66 patients whose treatment was changed to IDegAsp and who took at least 6 months of IDegAsp treatment were enrolled in the study. The demographic and disease characteristics of the patients, the anti-diabetic treatments they were recently using and the causes of treatment modifications were recorded from the medical files. The changes of fasting plasma glucose and HbA1c levels, the number of hypoglycemic attacks and daily dose of IDegAsp at the initiation, after three and six months of treatment were evaluated. Glycemic control was classified as uncontrolled if the HbA1c levels were above 8%. Hypoglycemia was defined according to ADA suggestions, as blood glucose ≤ 70 mg/dl and/or hypoglycemia symptoms warranting treatment with fast-acting carbohydrate and adjustment of glucose-lowering therapy (9). We classified hypoglycemia as "mild" if the patient was able to treat the symptoms of hypoglycemic episodes unaided and "severe" if patients needed help or medical intervention from others. The frequency of hypoglycemia was evaluated as the number of hypoglycemic attacks in the last 3 months.

IDegAsp treatment was started twice daily for patients with a daily total insulin requirement of 0.5 U/kg and above, and as a single dose for others.

The study was approved by the local ethics committee of Istanbul University Cerrahpaşa Medical Faculty (Istanbul-University-Cerrahpaşa, Cerrahpaşa Medical Faculty Ethics Committee; Date and Number: 04/04/2019-53251) in accordance with the ethical standards of the 1964 Helsinki Declaration.

Statistical analysis

The data was statistically analyzed using the Statistical Package for the Social Sciences for Windows version 21.0 software package (SPSS, Chicago, IL). Quantitative variables have been expressed as mean \pm Standard Deviation (SD) and median [Interquartile Range] in the text and tables. Normality of distribution was assessed using the Shapiro-Wilk test.

Independent samples Student's t-test or Mann-Whitney U test were used to compare 2 independent variables and repeated measures ANOVA or Friedman tests were used to compare >2 dependent variables according to their normality of distribution. $p < 0.05$ was considered as statistically significant

RESULTS

Table 1. The anti-diabetic treatments that the patients were using before the IDegAsp treatment

Anti-diabetic treatments	Number of Patients (%)
Metformin	49 (74.2)
DPP-IV inhibitors	43 (65.2)
Sitagliptin	20
Vildagliptin	12
Linagliptin	9
Saxagliptin	2
SGLT-2 inhibitors	6 (9.1)
Dapagliflozin	4
Empagliflozin	2
Pioglitazone	3 (4.5)
Sulfonylurea	10 (15.2)
Acarbose	4 (6.1)
Insulin treatment	61 (92.4)
Basal insulin	28 (42.4)
Intensive insulin	24 (36.4)
Pre-mixed insulin	9 (13.6)

**DPP-IV inhibitors: Dipeptidylpeptidase-4 inhibitors;
SGLT-2 inhibitors: Sodium-glucose co-transporter-2 inhibitors**

Sixty-six patients (Female/Male: 34/32; mean age: 57.8 \pm 11.6years) with type 2 diabetes mellitus were enrolled in the study. The mean duration of diabetes was 12.7 \pm 7.9 years. Antidiabetic medications patients

were using before IDegAsp was initiated were shown in Table 1. All oral antidiabetic drugs were continued, but previous insulins were changed to IDegAsp. Uncontrolled hyperglycemia due to low treatment adherence was the reason for the initiation of IDegAsp therapy in 53 patients (80.3%), whereas in 13 patients (19.7%) IDegAsp treatment was started because of frequent hypoglycemic attacks with the previous insulin regimens.

HbA1c, fasting plasma glucose and total daily IDegAsp doses of the participants and the number of patients with hypoglycemic attacks at the beginning, at the third and

sixth months of IDegAsp treatment were shown in Table 2. The changes in fasting plasma glucose levels between the initiation and the 3rd month ($p=0.001$) and the initiation and the 6th month ($p<0.001$) of IDegAsp treatment were statistically significant. But, FPG didn't change significantly from the 3rd to the 6th month of IDegAsp treatment ($p=0.14$). However the change in HbA1c levels was statistically significant between all the time points (Initiation vs 3rd month $p<0.001$; Initiation vs. 6th month $p<0.001$; 3rd month vs 6th month $p=0.006$, respectively).

Table 2. The comparison of HbA1c, fasting plasma glucose, total IDegAsp doses and the number of patients with hypoglycemic attacks at the initiation, third and sixth months of IDegAsp treatment

	Initiation of treatment	3 rd month of treatment	6 th month of treatment	p
HbA1c(%)	8.6±1.4	8.0±1.0	7.7±1.0	<0.001
Fasting plasma glucose (mg/dl)	176.4±68.5	150.4±51.8	144.1±57.5	<0.001
Total IDegAsp dose (IU)	38.2±21.0	39.5±20.8	39.4±20.1	0.054
Hypoglycemia (n)	13	7	5	<0.001

Table 3. The changes in IDegAsp dose, fasting plasma glucose, HbA1c levels and hypoglycemia status of the participants according to their daily usage pattern of IDegAsp

	IDegAsp q.d (n=35)	IDegAsp b.i.d (n=31)	p
IDegAsp dose (IU)			
Initiation	25.6 ± 13.0	50.2 ± 20.3	<0.001
3 rd month	28.1 ± 15.2	52.1 ± 19.2	<0.001
6 th month	28.5 ± 15.5	51.9 ± 17.4	<0.001
Fasting plasma glucose (mg/dl)			
Initiation	162.2 ±68.3	190.8±65.2	0.08
3 rd month	154.5 ± 51.5	145.0 ± 51.8	0.46
6 th month	148.1 ± 67.5	139.5 ± 44.3	0.56
Delta*	18 [2.5-48.5]	51 [12.5-90.0]	0.02
HbA1c (%)			
Initiation	8.6 ± 1.4	8.7 ± 1.4	0.85
3 rd month	8.0 ± 1.1	7.9 ± 0.8	0.67
6 th month	7.7 ± 1.1	7.7 ± 1.0	0.96
Delta*	0.6 [(-0.05)-1.3]	0.9 [0.1-1.4]	0.61
Hypoglycemia			
Initiation	7	6	0.94
3 rd month	4	3	0.93
6 th month	3	2	0.93

q,d: Once a day; b,i,d: twice a day; IDegAsp: Insulin degludec/insulin aspart co-formulation therapy
Delta shows the change between the initial and the 6th month parameters

Thirteen patients were experiencing hypoglycemia before IDegAsp treatment. Five of 13 patients had severe and 8 had mild hypoglycemic attacks. The number of patients experiencing hypoglycemia was significantly decreased from the beginning of the treatment to the 6th months ($p < 0.001$). At the end of the 6th month of treatment, all mild hypoglycemic attacks improved and we didn't observe any severe hypoglycemia episode.

Sixty patients (92.4%) were using insulin before the initiation of IDegAsp. The median total daily insulin dose patients were previously using was significantly higher than the initial IDegAsp dose (41 [24-62] vs 32 IU/day [24-50]; $p = 0.01$) and the mean number of daily injections of these 61 patients was significantly decreased after IDegAsp therapy (2.54 ± 1.57 vs. 1.92 ± 0.75 ; $p < 0.001$). The HbA1c changes of the patients on insulin before IDegAsp treatment were shown in Figure 1. Although there were significant reductions in HbA1c levels in patients previously using intensive insulin and basal insulin, there was no difference found in pre-mixed insulin group.

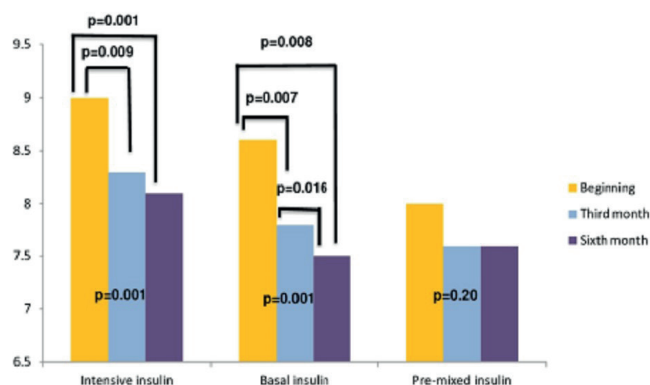


Figure 1. HbA1c changes of the patients with insulin use (n=61) according to the type of insulin they were using before IDegAsp treatment

IDegAsp treatment was started as a single dose in 53% and twice daily in 47% of patients. While in 20 of 28 patients on basal insulin IDegAsp started with one injection at dinner, in 14 of 24 subjects on intensive insulin and in 8 of 9 patients on premixed insulins IDegAsp initiated as twice daily injection before breakfast and dinner. The duration of diabetes (Single dose/double dose: 11.9 ± 7.2 years / 13.7 ± 8.7 years; $p = 0.35$) and HbA1c levels (Single dose/double dose: $8.1 [7.6-9.2]$ vs $8.3 [7.6-9.7]$; $p = 0.69$) were similar between the groups.

The changes in IDegAsp dose, fasting plasma glucose, HbA1c levels and hypoglycemia status of the participants according to their daily I-DegAsp injection protocol were shown in Table 3.

DISCUSSION

In this study, we found that 6-monthly treatment with insulin IDegAsp improved glycemic control, with a reduction in the number of daily injections and the

frequency of hypoglycemic attacks. This is the first real-life study in Turkey comparing the effects of once or twice daily IDegAsp treatment and we demonstrated that these two treatment modalities had similar effects in terms of glycemic control and hypoglycemia frequency.

In our real-life study, we found that the majority of patients were already using insulin before the initiation of IDegAsp. This may be related to the long disease duration of these subjects. In addition, uncontrolled hyperglycemia was the most common cause of transition to IDegAsp treatment in patients with type 2 diabetes that may be related to the low adherence to previous insulin treatment protocol and the lack of home blood glucose monitoring accompanied with proper insulin dose adjustments.

We demonstrated that the fasting plasma glucose levels were decreased after a six monthly treatment with IDegAsp, whereas the most significant change occurred at the end of the first 3 monthly period and there was no statistical change determined between the third and sixth months of treatment. In contrary, we found that HbA1c levels changed significantly at all time points. The better post-meal glycemic control might be the cause of the HbA1c improvement.

In our study, HbA1c levels were significantly decreased in patients who previously used intensive or basal insulin treatments, whereas there was no significant change in the group previously using pre-mixed insulin. The most probable cause of this discrepancy may be the very small number of the patients in the pre-mixed insulin group.

One of the most impressive aspects of our study was that it was a real-life study that included patients with both once and twice daily usage of IDegAsp treatments. Moreover, the number of patients in these two groups was similar to allow a relevant comparison. As described above, IDegAsp treatment was started as twice daily injections in patients with a daily total insulin requirement of at least 0.5 U/kg. We determined that the transition to IDegAsp treatment from basal insulins was mostly in the form of a single dose regimen, whereas transition from pre-mixed or intensive insulins was mainly in a twice daily manner. Importantly, the change in fasting blood glucose levels in 6 months-treatment was significantly higher in twice daily group; that might correspond to better pre-meal glycemic control in the twice daily usage.

Studies in literature have been conducted either in insulin-naive patients or in patients who had all switched from insulin therapy to IDegAsp in T2DM. (1, 10-13). There is only one published real-life IDegAsp study (14) which was a multi-center 52 week study conducted in India on 48 patients, most of whom were switched to double dose of IDegAsp treatment. Similar to our results, they also showed better glycemic control in terms of HbA1c and fasting plasma glucose without significant hypoglycemic episodes.

There are some limitations in our study. The most important ones are the retrospective design and the the

small number of the study group. Another limitation is the probability of a positive study effect on improved glycemic control in subjects using IDegAsp because of the initiation of a new treatment. Our study demonstrated a real-life experience of IDegAsp treatment and it was done in the first months of IDegAsp regimen begun to be used in our country, therefore we had to design it retrospectively and with a small number of patients. In contrary, the most significant power of our study is that it is the first real-life study comparing a single and double doses of IDegAsp treatment in Turkey, without taking any pharmaceutical company support.

CONCLUSION

Our study demonstrated that the IDegAsp treatment, which is a relatively novel insulin regimen for Turkey, may increase the compliance of the patients to treatment and thus facilitates achievement of glycemic targets if it is used in the appropriate patient groups with appropriate posology.

****This study was presented as an oral presentation at the 55th National Diabetes Congress in Turkish Republic of Northern Cyprus.*

Competing interests: The authors declare that they have no competing interest.

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