

Clinical use of Insulin Degludec: Practical Experience and Pragmatic Suggestions

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Abstract

Insulin degludec (IDeg) is an ultralong acting basal insulin. IDeg has unique pharmacokinetic and pharmacodynamic properties which allow once a daily dosage, at any time of the day. Its use is associated with a significantly lower risk of hypoglycemia. This review discusses the pragmatic use of IDeg, based on available evidence. A complete search of all nine original research papers (BEGIN® clinical trial program) pertaining to IDeg, listed in PubMed, was made to prepare this article.

Keywords: Basal insulin, Insulin degludec, Diabetes, Insulin, Insulin analog, Person-centered care, Pragmatic use

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Introduction

Insulin degludec (IDeg) is an ultra long acting basal insulin which is available for use in many countries, including the European Union, India, Japan, Bangladesh, and Mexico. IDeg has unique pharmacokinetic and pharmacodynamic properties which allow once a daily dosage, at any time of the day. Its use is associated with a significantly lower risk of hypoglycemia, particularly nocturnal hypoglycemia and well-maintained quality of life. These advantages suggest that IDeg should be the basal insulin of choice, both as a basal regime and as part of a basal-bolus regime.

In out of pocket markets, where medications are not covered by insurance, the relative cost of IDeg does not allow it to be used for all patients requiring insulin. There is paucity of observational studies on IDeg so far, keeping its recent introduction into the market. The clinical use of IDeg is based upon the

results from randomized controlled trials, as well as from clinical experience. This brief communication aims to clarify clinical situations in which IDeg can be of benefit, and collate collective personal experience of endocrinologists who manage diabetes on a day-to-day basis [Table 1]. A complete search of all the original research papers (BEGIN® clinical trial program) pertaining to IDeg, listed in PubMed ($n = 9$) was made to prepare this article.

Pharmacology of IDeg

IDeg is an ultra long acting insulin with a half-life of more than 24 h and a duration of action of more than 42 h.^[3] IDeg forms soluble and stable dihexamer in the pharmaceutical formulation with the help of phenol and zinc. After the injection, phenol diffuses away from the formulation leading to formation of a soluble depot in the form of long multihexamer chains experience slow diffusion of zinc from the end of their multihexamers causing a gradual, continuous, and extended release of monomers from the depot of injection site.^[8] This helps in achieving a steady state concentration, with a half-life of over 25 h, and duration of action of up to 42 h. Achievement of steady state concentration helps IDeg to have one-fourth glycemic variability as compared to insulin glargine (IGlar) at steady state concentration.^[7] This translates into a lower risk of hypoglycemia,

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especially nocturnal hypoglycemia as seen in various clinical trials.^[4,6]

The protein sequence of IDeg is based on human insulin, modified by acylating DesB30 at the e-amino group of LysB29 with hexadecandioic acid via a c-L-glutamic acid linker. IDeg (pH 7.4) is a clear, colorless solution with a pH-dependent solubility and an isoelectric point similar to that of human insulin, and it is administered subcutaneously.^[8]

Initiation Therapy with IDeg

IDeg has been extensively studied in the BEGIN[®] programme in a range of patients with type 1 or type 2 diabetes. The BEGIN[®] programme covered the spectrum of patients with diabetes who require insulin treatment (insulin-naive type 2 diabetes, insulin-treated type 2 and type 1 diabetes including basal-bolus therapy, basal plus oral therapy, and basal vs oral therapy, and also the flexible dosing options) [Table 1]. In a year-long trial that randomized 1,030 previously insulin-naive adult patients to once-daily degludec or glargine as addition to metformin ± dipeptidyl peptidase 4 (DPP-4) inhibitor, glycated hemoglobin (HbA1c) reduction was noninferior for degludec, while the fasting plasma glucose (FPG) reduction was significantly greater using similar insulin doses.^[2] Though overall hypoglycemia rates were low and similar for degludec and glargine, nocturnal hypoglycemia occurred at a significantly lower rate (36%) with degludec. Severe hypoglycemias occurred rarely and at significantly (86%) lower frequency with degludec. Similar results were seen in other trials of 26 weeks duration and, in which number of insulin naïve subjects were less in number.^[1,5,9,10] The dose titration algorithm followed in the BEGIN studies are presented in Table 2.

Switch Therapy to IDeg

Randomized controlled trials have been conducted, in which IDeg has been used to replace other basal insulins such as IGlAr or neutral protamine Hagedorn (NPH). Participants receiving once-daily basal insulin prior to the study were switched to IGlAr or IDeg on a unit for unit dose basis; whereas, those on a twice-daily basal insulin regimen were switched to lower (20-30%) starting doses of IGlAr. At the end, doses were similar in all arms.^[10,11] In terms of HbA1c reduction, IDeg was noninferior to IGlAr. In addition, there was no significant between-group difference in the proportion of patients achieving an HbA1c of <7%. The rate of nocturnal hypoglycemia was significantly 25% lower with degludec than glargine,^[1,2] while rates of overall hypoglycemia were similar.^[10-12] In another study, rates of overall and nocturnal hypoglycemia were significantly lower with degludec than glargine, being reduced by 18 and 25%, respectively.^[13] The difference in nocturnal hypoglycemia rates became more evident after about 16-20 weeks, perhaps indicating that this difference is more likely to manifest after initial titration when patients have reached stable doses of basal insulin.^[11]

Practical Experience, Pragmatic Suggestions

Insulin initiation

IDeg can be used as basal insulin, or as part of a basal-bolus or basal-plus regime in persons with type-2 diabetes. It can also be used to initiate basal-bolus therapy in newly diagnosed type1 diabetes patients. It must be noted that IDeg is currently not approved for use in children below the age of 18, and in pregnancy.

Table 1: Clinical trial program of IDeg (BEGIN)

Clinical trial	Study population	Efficacy: Reduction in HbA1c with IDeg vs IGlAr, ETD (%)	Dose of IDeg (first week of trial) U/Kg	Dose of IDeg (end of trial) U/Kg	Dose of insulin glargine (1 st week of trial) U/Kg	Dose of insulin glargine (end of trial) U/Kg
BEGIN_: T1 ^[1]	T1DM	-0.01; noninferior	0.35	0.35	0.33	0.39
BEGIN_: Flex T1 ^[2]	T1DM	0.17; noninferior	0.35	0.40	0.35	0.42
BEGIN_: Once Long ^[3]	T2DM, insulin naive	0.09; noninferior	0.12	0.11	0.59	0.60
BEGIN_: Low Volume ^[4]	T2DM, insulin naive	0.04; noninferior	10 U (not based on U/Kg)	0.53	10 U (not based on U/Kg)	0.60
BEGIN_: BB ^[5]	T2DM	0.08; noninferior	0.45	0.75	0.44	0.69
BEGIN_: Flex ^[6]	T2DM, insulin naive and insulin treated	0.04; noninferior	Not mentioned	Not mentioned	Not mentioned	Not mentioned
BEGIN_: Once Asia ^[7]	T2DM, insulin naive	0.11; noninferior	0.14	0.28	0.14	0.35

IDeg = Insulin degludec, HbA1c = Glycated hemoglobin, IGlAr = Insulin glargine, T1DM = Type 1 diabetes mellitus, T2DM = Type 2 diabetes mellitus, ETD = Estimated treatment difference

The indications for use of IDeg as initial basal therapy do not differ from those for other basal insulins [Table 3]. There is fair acceptance of this molecule by patients, though some verbalize their concern about cost. The ability to inject IDeg at any time of the day is a major driver for acceptance of this drug, in spite of its cost. The characteristic of ultra long acting IDeg appeals to busy persons with erratic lifestyle routines, and to persons who are dependent upon others for injections,

for example, elderly persons with limited manual dexterity or cognitive function, nursing home residents, and indoor patients. However, the ability to inject IDeg more flexibly should not detract from the message that it should be injected at the same time each day.^[10,11]

IDeg finds excellent acceptance as part of initial basal-bolus therapy, in patients with severe, acute comorbid conditions requiring immediate control. These include life-threatening conditions such as diabetic ketoacidosis (DKA), organ threatening complications like vitreous hemorrhage or chronic renal failure,^[14] and limb-threatening illness such as complicated diabetic foot ulcer. Major infections, for example, tuberculosis, lung abscess, skin and soft tissue infections, and preoperative patients requiring glycemic control, are also indications where the pharmacodynamic properties of IDeg can be utilized as part of a basal-bolus regime [Table 3].

Table 2: BEGIN Once Simple titration algorithms^[8]

Pre-breakfast SMBG		Dose adjustment IDeg simple ^a	Dose adjustment IDeg step-wise ^b
mmol/L	mg/dL	U	U
<3.1	<56	-4	-4
3.1-3.9	56-70		-2
4.0-5.0	71-90	0	0
5.1-7.0	91-126	+4	+2
7.1-8.0	127-144		+4
8.1-9.0	145-162		+6
>9.0	>162		+8

IDeg = Insulin degludec, SMBG = self-measured blood glucose. ^aBased on a single measurement on the day of titration, ^bBased on the lowest of 3 consecutive days' measurements

Switch therapy

IDeg can be used in persons not responding to other basal insulins.^[14] The concept of basal insulin failure as a single homogenous entity has been challenged by recent developments in pharmacotherapeutics. The

Table 3: Insulin degludec: Pragmatic usage patterns

Regime	Prior therapy	Justification	Remarks	
Initiation therapy As basal insulin	Dual/triple/quadruple OHA therapy	Poor control, especially high fasting glucose	Fair acceptance Concern about cost Ability to inject at any time of day is a major driver Reduction in hypoglycemia	
	Dual/triple/quadruple OHA therapy	Severe, acute comorbid condition requiring intensive glycemic control	Good acceptance in life-threatening (DKA), limb-threatening (diabetes foot), sight-threatening (vitreous hemorrhage), organ-threatening (lung) conditions	
Switch therapy From other basal insulin	NPH/glargine/detemir once or twice daily	Poor control in spite of adequate dosage. Excessive variability of control, e. g., Somogyi phenomenon and Dawn phenomenon	Fair acceptance Concern about cost Good acceptance if patient is dependent a family member or health care professional to inject insulin at specific time of day/on two basal injection Patients accept finite trial of degludec to assess impact on variability and control Reduction in hypoglycemic episodes	
	From premixed insulin once daily	Biphasic insulin od	Poor fasting control	Same as above
	From other basal bolus regimes	3 prandial + 1 or 2 basal insulin	Overall poor control in spite of high doses. Variability; frequently hypoglycemia	Good acceptance if existing doses are higher/two basal injection used Patients welcome the freedom to adjust timing of injections Cost containment: Regular insulin tds + degludec od

OHA = Oral hypoglycemic agent, NPH = Neutral protamine hagedorn, DKA = Diabetic ketoacidosis

improved pharmacokinetic and pharmacodynamic properties of basal insulin analogs facilitate better glycemic control. This means that a person who is labeled as having basal insulin failure, because of lack of response to a particular molecule, may respond to different basal insulin. For example, a person on NPH insulin or glargine who is unable to achieve glycemic targets without experiencing significant hypoglycemia may respond to IDeg.^[10-14]

This advantage of IDeg holds true in both basal and basal-bolus regimes. While there is a concern about cost, most patients accept a finite trial of IDeg to experience its efficacy, tolerability, and safety. Patients who are unable to achieve glycemic control in spite of high doses of once daily or twice daily conventional basal insulin accept IDeg easily. Patients who experience variability with conventional insulin, for example, Somogyi phenomenon, or report poor control, for example, Dawn phenomenon, are also candidates for IDeg. The peakless, long duration of action of IDeg helps improve glycemic control in such persons. This benefit is experienced in both type 1 and type 2 patients.

Some patients on basal-bolus regime using NPH insulin or glargine, in fact, may be able to shift to basal-plus regimes with IDeg. This is perceived as a major advantage by persons who find it difficult to adhere to a lunch time injection of insulin.

At times, persons on once daily premixed insulin, who request flexibility in injection times, or who experience hypoglycemia, may benefit from a switch to once daily IDeg. Such a switch, however, should be made carefully, under close medical supervision.

Dosage

Most randomized controlled trials on degludec report a similar dose requirement of degludec, as compared to other basal analogs. Some trials, however, find a slightly lesser dose requirement of degludec (14-20%) [Table 1].^[5,12]

In practice, however, we find that a 20-30% lesser dose is required for this drug, as compared to other basal insulins. This is reflected in recommendations to consider a dose reduction of 20-30% if a twice daily basal regime is converted to once daily analog.^[14,15] This feature encourages switch from other basal insulins to IDeg.

Adherence to therapy

Lack of adherence to insulin therapy is a significant contributor to the lack of improvement in average HbA1c levels across the world. The flexibility of taking IDeg at any time of the day, with an acceptable interinjection

period of 8-42 h provides welcome convenience to the person with diabetes which comes with efficacy along with a much lower risk of hypoglycemia. This in turn instills a sense of confidence in the user as well as her or his family, and reduces the fears related to hypoglycemia.^[11]

Conclusion

This brief communication describes collated experiences of endocrinologists in the use of IDeg. It supplements the knowledge gained from preclinical trials and clinical randomized controlled trials, with understanding gleaned from extensive clinical experience. This information will be of benefit to other diabetes care professionals who wish to use IDeg in their clinical practice.

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