

Degludec insulin: A novel basal insulin

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ABSTRACT

This paper reviews a novel insulin analogue, degludec, which has the potential to emerge as an ideal basal insulin. It reviews the limitations of existing basal insulin and analogues, and highlights the need for a newer molecule. The paper discusses the potential advantages of degludec, while reviewing its pharmacologic and clinical studies done so far. The paper assesses the potential role of insulin degludec and degludec plus in clinical diabetes practice.

Key words: Basal insulin analogue, degludec, insulin analogue, second-generation insulin analogue, type 1 diabetes, type 2 diabetes

THE HISTORY OF BASAL INSULIN

The discovery of insulin was a landmark in the history of modern medicine.^[1] Initial insulin products, extracted from pancreata of freshly slaughtered pigs and cows, were able to drastically reduce mortality in patients with type 1 diabetes mellitus, while improving their quality of life. However, limitations in processing, purification and manufacture of the early insulins soon became painfully obvious to patients and physicians alike.

Patients treated with the early insulins were often unable to normalize blood glucose. It was difficult to titrate the frequent doses of insulin needed to achieve normoglycemia, without causing hypoglycemia. This was partly due to the fact that the traditional insulins were unable to provide a continuous, low level of basal insulin output to mimic the normal secretory pattern of the beta cells. It was realized by researchers that the healthy beta cells secreted insulin continuously at a low level, along with spurts of insulin in response to food intake to maintain euglycemia.^[2] The

insulin used for treatment was able to provide the spurts or “bolus” peaks, but could not replicate the 24-hour basal output of the pancreas.

A search then began for a long-acting insulin which could be used as basal insulin along with bolus injections of fast-acting or regular insulins.

Many “basal” intermediate-acting or long-acting insulins were developed for use in the mid-20th century. Lente insulin and ultralente insulin were used extensively, but were unable to withstand the test of time.

A high coefficient of variability in absorption and action, as well as the development of better alternatives, led to their discontinuation.^[3]

PRESENTLY AVAILABLE “BASAL” INSULINS

Neutral Protamine Hagedorn (NPH) insulin is a traditional, intermediate-acting insulin to which protamine is added to ensure a slow dissociation and a “long” (12–16 hours) duration of action. NPH has been used successfully as monotherapy, in combination with oral hypoglycemic drugs, and in combination with bolus insulins, to achieve glycemic control. It exhibits a highly variable absorption profile and has a peak in action after 6 hours. Hypoglycemia may occur with this drug.^[3]

The limitations of NPH insulin led to the development of

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long-acting basal insulin analogues such as insulin glargine and insulin detemir.

Glargine is formulated in an acidic solvent and it has an altered isoelectric point. The drug precipitates after injection into the subcutaneous tissue and is slowly redissolved and absorbed from here. It has a “peakless” action, but its use is linked with weight gain. Recently, the drug was linked with an increased incidence of malignancy. It is used as a once-daily injection, with oral drugs, as well as in combination with prandial insulin or insulin analogues, in type 1 and type 2 diabetes.^[4]

Detemir insulin has a fatty acid side chain that binds it to albumin in a reversible manner and facilitates hexamer formation at the injection site. This leads to slower dissociation and longer duration of action.^[5] While the drug has a lower variability coefficient, there is concern about its duration of action in type 1 diabetes. Detemir is used in once-daily or twice-daily dosage, with oral drugs or in combination with rapid acting insulins; it can be used in both type 1 and type 2 diabetes.^[6]

REQUIREMENTS OF IDEAL BASAL INSULIN

An ideal basal insulin should be a formulation which is able to deliver a steady, stable, peakless, continuous insulin concentration for at least 24 hours, in a predictable manner, with low intra-individual and inter-individual variability, without causing side effects such as weight gain or hypoglycemia, while ensuring that mitogenicity is not induced because of excessive binding to non-insulin receptors. It should have the ability to be used as monotherapy and as part of a basal-bolus regime, as well as in combination with oral hypoglycemic. It should be equally efficacious, safe and well tolerated in type 1 and type 2 diabetes.^[3]

The existing basal insulins (i.e, NPH insulins) and basal insulin analogues (i.e, glargine insulin and detemir insulin), while being an improvement on earlier traditional insulins, are unable to fulfill this definition.

NPH insulin does not provide 24-hour control, and is associated with a distinct peak at 6 hours, which may cause hypoglycemia. The high coefficient of variability, both inter-individual and intra-individual, makes it difficult to predict the action of the drug.

Glargine insulin is said to be “peakless”, but studies show that the drug is associated with inter-individual variability, and many patients exhibit peaks in action, especially at higher doses. *In vitro* studies have demonstrated that

glargine binds preferentially to insulin-like growth factor-1 (IGF-1) receptors more than to insulin receptors. This may create a mitogenic potential, especially with long-term use. Recently, controversy related to the effect of glargine on malignancy was sparked by epidemiological studies.

Detemir insulin is a peakless, stable insulin, which is effective as once-daily injection in larger doses.

However, it may need to be injected twice daily in type 1 diabetes and when given in smaller doses.

THE NEED FOR A NOVEL BASAL INSULIN

Because of these limitations and shortcomings, there is a need for a novel basal insulin which fulfils the requirements mentioned earlier. This paper reviews such an insulin, degludec insulin, and its other formulations.

FORMULATION OF EGLUDEC

Insulin degludec (IDeg) is a new basal insulin that forms soluble multihexamer assemblies after subcutaneous injection, resulting in an ultra-long action profile.

Degludec has an action duration of more than 24 hours. To demonstrate that this multihexamer formation leads to an ultra-long acting profile of IDeg, a multiple dose clinical pharmacology study was conducted in subjects with type 1 diabetes (n = 12). IDeg was found to have a t_{1/2} longer than 24 hours and was detectable in circulation for at least 96 hours after injection.^[7]

Another study was designed to investigate the metabolic responses and molecular safety of IDeg.^[8] Insulin receptor binding kinetics of IDeg were similar to that of human insulin (HI). In albumin-free conditions, the affinity of IDeg for both human insulin receptor isoforms (HIR-A and -B) was similar (13% and 15% relative to HI), while the affinity for the human IGF-1 receptor was lower (2% relative to HI).

The mitogenic effect of IDeg was determined by measuring 3H-thymidine incorporation into L6 myoblasts expressing HIRs, primary human mammary epithelial cells as well as COLO-205 and MCF-7 cell lines (from human colon and mammary adenocarcinomas, respectively). The *in vitro* mitogenic potencies determined with no added albumin ranged from 4 to 14% relative to HI.

The metabolic effects of IDeg were determined by lipogenesis in rat adipocytes, glycogen accumulation in rat hepatocytes and glycogen synthesis in rat skeletal muscle

cells, L6-HIR and MCF-7 cells. In all these cells, IDeg elicited the same metabolic responses and same maximal effect as HI. Furthermore, in cellular assays where no albumin was added (hepatocytes and MCF-7 cells), the *in vitro* metabolic potency was determined to be in the range of 8–20% resulting in a mitogenic/metabolic potency ratio of ≤ 1 .^[8]

The low IGF-1 receptor binding affinity and the low mitogenic/metabolic potency ratio indicate IDeg to have molecular safety similar to that of HI.

Insulin degludec/insulin aspart (IDegAsp) is a soluble formulation of the novel basal analogue IDeg (70%) and insulin aspart (IAsp: 30%). An alternative formulation (AF) of 55% IDeg and 45% IAsp is also being studied. These formulations provide both basal and prandial insulin and can be used as premixed insulins in regimes similar to those of conventional or other analogue insulins. This combination (IDegAsp) is also known as degludec plus.

PHARMACOKINETICS AND PHARMACODYNAMICS

A randomized, double-blind, parallel-group study was carried out to compare the pharmacodynamic variability of IDeg with that of insulin glargine under steady-state conditions. Fifty-four patients with type 1 diabetes, aged 38 ± 10 years, with a mean glycosylated hemoglobin (HbA1c) of $7.7 \pm 0.9\%$, were treated with 0.4 U/kg of IDeg or glargine once daily for 12 days. Euglycemic glucose clamp was performed for 24 hours, and within-subject variability was estimated on log-transformed pharmacodynamic end-points derived from glucose infusion rate profiles noted during clamp studies. IDeg with associated with significantly lesser pharmacodynamic variability than glargine on all protocol pharmacodynamic variability parameters, including total metabolic effect ($P < 0.0001$). The individual within-subject variability was much lower for IDeg compared with glargine. IDeg metabolic effect was exactly evenly distributed between the first and the second 12 hours, and this distribution was less variable than with glargine ($P < 0.001$). Both insulins were well tolerated. No serious adverse events or severe hypoglycemic episodes were reported. The rate of hypoglycemic episodes was 166 (20 nocturnal) in the IDeg group compared with 182 (37 nocturnal) in the glargine group. IDeg administered once daily was found to be significantly less variable and more stable in maintaining euglycemia as compared to glargine. The total metabolic effect (AUC-GIR0-24h) tended to be higher with IDeg than with IGLar^[9]

CLINICAL STUDIES: DEGLUDEC IN TYPE 2 DIABETES

In a large 16-week, randomized, open-label, parallel-group, phase 2 trial conducted at 28 sites in four countries, participants aged 18–75 years, with type 2 diabetes and HbA1c of 7.0–11.0%, were randomly allocated in a 1:1:1:1 ratio randomization to receive IDeg either once a day or three times a week or insulin glargine once a day, all in combination with metformin. Of 367 patients screened, 245 were eligible for inclusion. Sixty-two participants were randomly allocated to receive IDeg three times a week [starting dose 20 U per injection (1 U = 9 nmol)], 60 to receive IDeg once a day [starting dose 10 U (1 U = 6 nmol); group A], 61 to receive IDeg once a day [starting dose 10 U (1 U = 9 nmol); group B], and 62 to receive insulin glargine [starting dose 10 U (1 U = 6 nmol)] once a day. At conclusion, mean HbA1c levels were similar in all treatment groups, at 7.3% (SD 1.1), 7.4% (1.0), 7.5% (1.1), and 7.2% (SD 0.9), respectively. Estimated mean HbA1c treatment differences from IDeg by comparison with insulin glargine were 0.08% (95% CI: -0.23 to 0.40) for the three-dose per week schedule, 0.17% (-0.15 to 0.48) for group A, and 0.28% (-0.04 to 0.59) for group B. The incidence of hypoglycemia and adverse events was similar across all groups, with no apparent treatment-specific pattern. This study demonstrated that IDeg provides comparable glycemic control to insulin glargine without additional adverse events and might reduce the dosing frequency due to its ultra-long action profile.^[10] This holds better potential for better patient compliance and tolerability, while maintaining safety and efficacy.

CLINICAL STUDIES: DEGLUDEC PLUS IN TYPE 2 DIABETES

In a 16-week, open-label trial, subjects [mean age 59.1 years, A1c 8.5%, body mass index (BMI) 30.3 kg/m^2] were randomized to once-daily degludec aspart ($n = 59$), alternative formulation (AF) (55%IDeg and 45% IAsp) ($n = 59$), or glargine ($n = 60$), all in combination with metformin. Insulin was administered before the evening meal and dose-titrated to an FPG target of 4.0–6.0 mmol/L. After 16 weeks, mean A1c decreased in all groups to comparable levels (degludec aspart: 7.0%; AF: 7.2%; glargine: 7.1%). A similar proportion of subjects achieved A1c $< 7.0\%$ without confirmed hypoglycemia in the last 4 weeks of treatment (degludec aspart: 51%; AF: 47%; glargine: 50%). Mean 2-hour post-dinner plasma glucose increase was lower for degludec aspart (0.13 mmol/L) and AF (0.24 mmol/L) than glargine (1.63 mmol/L), whereas

mean FPG was similar (degludec aspart: 6.8 mmol/L; AF: 7.4 mmol/L; glargine: 7.0 mmol/L). Hypoglycemia rates were lower for degludec aspart and glargine than AF (1.2, 0.7, and 2.4 events/patient year). Nocturnal hypoglycemic events occurred rarely for degludec aspart (1 event) and glargine (3 events) compared with AF (27 events). In this proof-of-concept trial, once-daily degludec aspart was found to be safe, well tolerated, and efficacious. Similar low rates of hypoglycemia, but better post-dinner plasma glucose control were noted.^[11]

Thus, efficacy and safety data are available for both degludec (basal) and degludec aspart (premixed) insulin in type 2 diabetes.

CLINICAL STUDIES: INSULIN DEGLUDEC IN TYPE 1 DIABETES

Degludec has been studied in type 1 diabetes as well. A recently published study assessed the efficacy and safety of once-daily dose in combination with mealtime insulin aspart in people with type 1 diabetes in a 16-week, randomized, open-label trial. Subjects (mean age: 45.8 years, A1c 8.4%, FPG 9.9 mmol/L, BMI 26.9 kg/m²) received subcutaneous injections of IDeg(A) (600 µmol/L; n = 59), IDeg(B) (900 µmol/L; n = 60), or insulin (glargine n = 59), all given once daily in the evening. Insulin aspart was administered at mealtimes. At the end of study, mean A1c was comparable for IDeg(A) (7.8 ± 0.8%), IDeg(B) (8.0 ± 1.0%), and glargine (7.6 ± 0.8%), as was FPG (8.3 ± 4.0, 8.3 ± 2.8, and 8.9 ± 3.5 mmol/L, respectively). Estimated mean rates of confirmed hypoglycemia were 28% lower for IDeg(A) compared with insulin glargine (IGlar) [rate ratio (RR): 0.72 (95% CI: 0.52–1.00)] and 10% lower for IDeg(B) compared with IGLar [RR: 0.90 (0.65–1.24)]. Rates of nocturnal hypoglycemia were 58% lower for IDeg(A) [RR: 0.42 (0.25–0.69)] and 29% lower for IDeg(B) [RR: 0.71 (0.44–1.16)]. Mean total daily insulin dose was similar to baseline. The frequency and pattern of adverse events was similar in all groups. This clinical exploratory phase 2 trial in people with type 1 diabetes found degludec to be safe and well tolerated, while providing comparable glycemic control to glargine at similar doses, with reduced rates of hypoglycemia.^[12]

OTHER BASAL INSULINS IN DEVELOPMENT

A novel insulin under development is FT-105, a basal insulin consisting of a vitamin E and glutamic acid polyaminoacid polymer linked to the insulin protein. FT-105 aggregates into dense microparticles that dissolve slowly, leading to a protected action after subcutaneous injection.

PassPort is a transdermal insulin delivery system in which the patient applies a proprietary patch on the skin, presses an attached button to create micropores, and then slaps an insulin-containing patch over the site. The system provides protracted availability of basal insulin with resultant plasma insulin levels that are proportionate to the various insulin concentrations available in the patch reservoir. While not exactly a novel basal insulin, this is a new method of administering basal insulin.

V-Go is another such method, which consists of a small, patch-like insulin pump that contains no electronic components. The disposable skin patch lasts 24 hours, during which time it provides basal insulin at a steady rate. The patient can push a small button to release a few extra units of insulin at a time, as a premeal bolus.

Second-generation long-acting insulin analogues are also being developed by Sanofi Aventis, Eli Lilly and Biondi.^[13,14] However, no results have been published yet. BIOD-Adjustable Basal, a modified formulation of insulin glargine, is available in long-, medium-, and short-acting forms and could be mixed, and BIOD-Smart Basal releases insulin proportional to the subcutaneous glucose concentration.

CONCLUSION

While the existing insulin analogues have certain advantages and are able to achieve glycemic control in a safe and well-tolerated manner, currently available basal insulin analogues have some limitations.

Newerbasal insulins such as degludec have the potential to be used singly or in formulation with aspart insulin to provide glycemic control, with low variability and low incidence of hypoglycemia. The formulation can be used once daily or thrice weekly, thus representing an advance over the existing insulin. Further research needs to be carried out to characterize optimal methods of use of this insulin, as well as other basal insulins under development.

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