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EDITORIAL

Insulin Degludec: A Significant Advancement in Ultralong-Acting Basal Insulin

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ABSTRACT

This editorial discusses a novel basal insulin analog, insulin degludec. It describes the limitations of existing basal insulins, and builds the case for a better analog. The editorial discusses the evidence to support the efficacy, safety, tolerability, and flexibility of degludec, and assesses its utility as part of a person-centered approach to diabetes management.

Keywords: Basal insulin; Diabetes; Insulin; Insulin analogs; Insulin degludec

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INTRODUCTION

Major advances and developments have taken place in the field of insulin, since its discovery nearly a century ago. The engineering of insulin analogs is but one step in this journey of innovation. Insulin analogs are molecules which have been created by modifying the structure of insulin to achieve desired pharmacokinetic properties. Drugs such as insulin aspart, glulisine and lispro act as rapid-acting insulins, while insulin detemir and glargine work as long-acting basal analogs. Premixed analogs—biphasic aspart, biphasic lispro—are also used in clinical practice [1].

CURRENTLY AVAILABLE BASAL INSULINS

In spite of the various improvements in insulin pharmaco-therapeutics over the past decades, there still exist limitations in the existing basal insulin analogs. These limitations translate to shortcomings in our current therapeutic regimes, and impact our ability to achieve optimal glycemic goals without causing hypoglycemia.

Both insulin glargine and insulin detemir exhibit considerable inter-individual and intra-individual variabilities. Though this variability is less for detemir, it is nonetheless clinically significant [2]. While glargine has duration of action of up to 24 h, the action of detemir lasts 18–23 h. The duration of action of detemir is dose-dependent, and both insulins may be required in a twice-daily regime [3]. Glargine has an acidic pH, which may be associated with injection site reactions [1]. If inadvertently injected intramuscularly, glargine exhibits the kinetics of rapid-acting insulin [4]. Neither glargine nor detemir can be combined with rapid-acting analogs in a single formulation.

EXPECTATIONS FROM NEW INSULIN

Keeping these issues in mind, the need for a new basal insulin analog is clear. To be truly useful, a novel basal insulin must have a long duration of action, of over 24 h, exhibit minimal variability, maintain sustained serum concentrations without any peaks or troughs, and ensure safety and tolerability [5]. The drug must be linked with a low risk of hypoglycemia, especially nocturnal and severe hypoglycemic episodes. It is noteworthy to mention here that in the recently reported DAWN2 study, over half of all people with diabetes, and two-thirds of family members reported worrying about hypo [6, 7]. Ideally, the molecule should provide flexibility of use, without any need for administration at a constant time of day or with a specified injection–meal or injection–bed time gap. Its' use should require minimal self monitoring, and be linked with a low index of intrusion. Availability in patient-friendly delivery devices and a positive impact on quality of life will be added advantages. These qualities will ensure 'patient-centered care', in concordance with current diabetes management guidelines [1].

DEGLUDEC: PHARMACOLOGY

Insulin degludec is novel ultralong-acting insulin, recently approved for use in various countries, including the European Union, Japan, Mexico and India.

A 50-amino acid structure, it does not have the threonine present at B30 position in human insulin. Instead, a glutamic acid spacer links a 16-carbon fatty di-acid chain to the B29 amino acid residue. This change in structure allows degludec to exist in a stable di-hexameric structure in the presence of phenol, in injection solution. This is in contrast to the hexameric state of human insulin. Upon subcutaneous injection, phenol diffuses away, to allow the degludec di-hexamers to have free ends and with the help of zinc and fatty acid side chain to link up and form a soluble multi-hexameric chain. Zinc, a part of the insulin molecule, diffuses slowly from the terminal ends of this chain, allowing slow and stable absorption of insulin. This provides a long-acting, consistent delivery of drug, which is not dependent on blood perfusion of the injection site [8]. Though degludec binds reversibly to albumin, this does not contribute much to its prolonged action.

Degludec links to human insulin receptors (hIR) and to extremely low for insulin-like growth factor-1 (IGF-1) (lesser than human insulin). While it has similar affinity for both isoforms of hIR (hIR-A and hIR-B), its affinity for IGF-1 receptor is much lower. Degludec has metabolic effects which are similar to that of human insulin, but mitogenic effects of a

lower potency (4–14%). Hence, it is very safe for use, without increased risk of mitogenicity [9].

Degludec enjoys a pharmacokinetic profile which is unique among all insulin and insulin analogs: a long half-life of 25.4 h ensures that the duration of insulin degludec was beyond 42 h as detected by euglycaemic clamp studies [10]. As it has a stable pharmacokinetic profile, its concentration does not vary, once it reaches a steady-state concentration. This happens within 3 days of injection. This is unique and gives flat peakless profile of insulin degludec compared to available basal insulin which has a peak and a trough. There is minimal variability in insulin concentration and its insulin lowering action for insulin degludec after each injection. This is in contrast to glargine which has higher concentration in the first 12 h after dosing, as compared to the second 12 h post-dosing period [11]. This difference is explained by the relatively lesser amount of glargine present in the subcutaneous space after its half-life of 12.5 h is completed. The variability of glargine is found to be 4 times higher as compared to insulin degludec, when analyzed by euglycaemic clamp studies. Analysis of the 24 h pharmacodynamic profile reveals that insulin degludec is equally distributed along the day with approximately 25% in each quarter of the day, i.e., every 6 h. Pharmacokinetics of insulin degludec has also been assessed to be similar in patients with renal and hepatic impairment, irrespective of degree of impairment.

DEGLUDEC: CLINICAL TRIALS

The advantages of degludec have been borne out in clinical studies. The BEGIN studies have reported on the utility of insulin degludec as a basal insulin therapy, and as part of a basal-bolus regime, in both type 1 and type 2 diabetes. The BOOST studies evaluate a combination of degludec and aspart insulin in the same manner.

The efficacy of degludec has been proven in these treat-to-target trials. Treat-to-target trials are designed as required by the regulatory bodies like the US Food and Drug Administration (FDA), where insulins are analyzed for non-inferiority of efficacy, while safety analysis is done to establish risk benefit of the newer insulin in comparison to the existing molecule. Degludec stands out is in its ability to achieve glycemic goal with a significantly lower risk of hypoglycemia. Degludec has been analyzed in phase 3a clinical trials wherein both safety and efficacy have been analyzed in comparison with various comparators. Seven out of nine phase 3a trials are in comparison with glargine and one with detemir and one with dipeptidyl peptidase-4 (DPP4) inhibitor. As the design was treat to target, all these trials had similar fasting glucose target of 71–89 mg/dL, and all trials achieved successful glycated hemoglobin (HbA1c) reduction with both degludec and comparator. With the same targets now achieved, safety analysis showed benefit of insulin degludec consistently throughout clinical trial program.

Degludec was associated with lower incidence of confirmed hypoglycaemia as well as significant reduction in nocturnal hypoglycaemia. As part of a basal-bolus regime with insulin aspart, the rate of nocturnal hypoglycemia was 25% lower with degludec than glargine, in a phase 2 proof of concept study in type 1 diabetes, as well as in a type 2 diabetes study [12, 13]. When used as basal

therapy with oral anti-diabetic drugs in type 2 diabetes, a 36% lower rate of nocturnal hypoglycemia and 86% lower rate of severe hypoglycemia were observed [14].

Degludec, however, was associated with a numerically higher incidence of hypoglycemia in clinical trials on patients with type 1 diabetes, especially those from USA, as compared to those from Europe [15]. Among subjects with type 1 diabetes, 63.8% were randomized in the USA. Among subjects with type 2 diabetes, 32.7% were randomized in the USA. Subjects randomized outside of the USA experienced a non-statistically significant increase in the rate of confirmed hypoglycemia associated with degludec in type 1 diabetes, RR 1.28, 95% CI (0.96, 1.71), and a statistically significant decrease in confirmed hypoglycemia in type 2 diabetes, RR 0.79, 95% CI (0.69, 0.90). However, among subjects randomized in the USA, there was no observed difference in the rate of confirmed hypoglycemia between degludec and glargine in either type of diabetes: T1DM RR 0.99, 95% CI (0.81, 1.20), and T2DM RR 0.97, 95% CI (0.81, 1.15).

The prolonged duration of action of degludec allows for flexibility in its time of administration. Studies performed in both type 1 and type 2 diabetes [16, 17] have assessed that fixed time and flexible degludec regimes offer similar efficacy and safety. A forced flexible dosage schedule, involving degludec injections at intervals of 8 h, followed by 40 h, and again by 8 h, was successful in achieving glycemic target without increasing the risk of hypoglycemia. This could be an advantage for patients wherein they can take insulin degludec at any time depending on their daily schedule without affecting efficacy or possess safety concern.

PRACTICAL USAGE

Apart from consistency, efficacy, and safety (low risk of hypoglycemia), degludec offers the advantage of flexibility. This is not to suggest that all people with diabetes must necessarily be put on flexible or staggered regimes of degludec. Rather, it implies that both health care professionals and people with diabetes need not be rigid about the timing of injections. This should make insulin therapy, much easier, less intrusive, less demanding, and more acceptable. Endocrinologists may draw a parallel with the pharmacokinetic profile of other hormones. Thyroxine, though administered once daily, can be given as a weekly dose, in view of its long half-life [18]. Similarly, if one dose of oral contraceptive is missed, the recommendation is to take the pill the following day, without fear of loss of efficacy or difficulty in tolerability [19]. Human chorionic gonadotropin is also injected at 48 or 72 h intervals without much emphasis being laid on exact 48 h spacing [20].

Degludec can be used as both basal and basal-bolus therapy, in type 1 and type 2 diabetes impairment. Currently, its use has not been reported in pregnancy or in children below age of 18. Long-term studies are available in degludec for up to 2 years, and further trials are underway to collect data on cardiovascular safety of this molecule. US FDA has requested additional clinical data from a dedicated cardiovascular outcomes trial before the review of the New Drug Applications can be completed as a number of additional analyses, some of which showed an unfavorable numerical imbalance between insulin degludec and degludec/aspart premixed combination, and comparators, though pre-specified major adverse cardiac events (MACE) analysis

showed no increased cardiovascular risk versus comparator with a point estimate of 1.097 [0.681;1.768] [21].

POSOLOGY

The dosage of degludec is decided as for other basal insulins (Table 1). In a treatment-naïve person, a starting dose of 0.1–0.2 units/kg/day, at anytime of the day, is a useful starting dose [22]. Physicians may begin therapy with a standard dose of 10 U/day, and uptitrate gradually, based on fasting glucose levels, at weekly or biweekly intervals. Any dose of degludec will take 2–3 days to reach a steady-state concentration, and hence daily dose titration is not recommended. In a basal-bolus regime based on analogs, including degludec, the ratio of degludec to bolus analog will be roughly 50:50. In persons already on another basal insulin, a 1:1 ratio is followed while shifting patients from one basal insulin to another, i.e., the dose is not changed. However, if a twice-daily basal regime is converted to once-daily analog, either a 1:1 switch or a slight dose reduction may be considered [22]. Some studies have shown about 10% reduction in dose requirement with degludec. Degludec monotherapy will not be a good option for patients uncontrolled on premixed insulin or on basal-bolus regime: it must be prescribed in conjunction with rapid-acting insulin in such situations.

CONCLUSION

As degludec becomes more and more widely used, it should set off a virtuous cycle leading to good glycemic control: prescription of degludec helps in achievement of glycemic targets without hypoglycemia, without enforcing a tight prescription schedule, leading to improved patient satisfaction, further enhancing acceptance of insulin therapy. Hopefully, this novel ultralong-acting basal insulin should be the torchbearer of concerted efforts to achieve optimal glycemic control in a patient-friendly, patient-centered manner.

Table 1 Initiating degludec therapy: practical guidance

Clinical scenario	Initial dose	Titration
Insulin naive	0.1–0.2 U/kg/day, or 10 U/day; once daily	Biweekly or weekly, based on fasting glucose
Already on other basal insulin, once daily	1:1 switch; once daily	Biweekly
Already on other basal insulin, twice daily	1:1 switch; once daily	As above
On premixed insulin	Degludec + aspart premixed combination; 1:1 switch for basal component OR	Biweekly or weekly, based on fasting and postprandial glucose
	Degludec + bolus therapy	
On basal-bolus regime, with other basal insulin	1:1 switch for basal dose; once daily	As above

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