Long-acting analog insulins have been increasingly used in preference to neutral protamine hagedorn insulins since their launch some 10 years ago. Although the achieved hemoglobin A1c reduction is similar, a lower incidence of nocturnal and symptomatic hypoglycemia with the analog insulin has contributed to their increased use. In this article we examine the benefits of the new ultra-long-acting analog insulin called ‘insulin degludec’. It has favorable pharmacokinetic and pharmacodynamic properties allowing for stable background insulin levels with once a day or even less frequent administration. Its ultra-long-acting profile may reduce variation in plasma glucose levels with a reduced frequency of nocturnal and daytime hypoglycemia.

Keywords: analog insulins • insulin degludec • ultra-long-acting

The incidence of Type 1 diabetes is increasing with an annual increase in the incidence of childhood diabetes of approximately 3% [1–3]. There are estimated to be a total of 440,000 children with Type 1 diabetes [101]. Two landmark trials, the diabetes control and complications trial and the epidemiology of diabetes interventions and complications trial have demonstrated that achieving good glycemic control significantly reduces the risk of microvascular and macrovascular complications in patients with Type 1 diabetes mellitus [4–7]. The current National Institute for Health and Clinical Excellence, UK guidance sets the target hemoglobin A1c (HbA1c) to be approximately 48 mmol/l (6.5%) [8], and American Diabetes Association recommendations suggest a target HbA1c of <53 mmol/l (<7%) [9].

However, this target should not be at the expense of recurrent or life threatening hypoglycemia. Hypoglycemia remains a major downfall with intensive insulin therapy. Nocturnal hypoglycemia is a major hurdle, and many patients tend to run higher blood glucose before going to bed in order to avoid this. Hypoglycemia unawareness in long-standing diabetics is one of the major reasons for failure to recognize major hypoglycemic episodes and as a protective behavior many patients with diabetes compromise on their adherence to prescribed insulin regimes [10]. Approximately 30% of people with Type 1 diabetes experience severe hypoglycemic episodes where they need assistance from another person to treat them [11]. There could also be an under reporting of severe hypoglycemia by affected individuals as it will have serious implications and restrictions to their daily activities, especially following recent changes in the EU driving regulations [102].

Apart from the immediate physical effects of hypoglycemia, the disturbance to quality of life, time off from work and physical harm such as falls and fractures [12,13], impose a significant burden on both patients and their healthcare system. In the UK, hypoglycemia is implicated in 30 serious road traffic accidents each month and five fatalities each year [14].

Intensive insulin regimes predispose to hypoglycemia and hence insulin dose titration and adequate management of recurrent hypoglycemic episodes is essential before considering changing insulin.
Variations in plasma insulin levels depending on insulin regimes will also contribute to fasting, preprandial and postprandial hyperglycemia. The short-acting insulin specifically targets postprandial hyperglycemia. The basal insulin targets the fasting glucose. The desire for better performing basal insulin, in terms of longer duration of action, flexible dosing profile, stable plasma levels with minimum peaks and fewer hypoglycemic events has been a major driver for analog insulin development.

Insulin degludec (IDeg) is novel long-acting insulin which has shown promising results in preliminary studies. For patients, fewer numbers of injections per day, low hypoglycemia risk, flexible dosing at any time of day and better long-term control are attractive attributes for any new insulin. IDeg has the potential to offer these desirable effects.

**Currently available long-acting analog insulins**

- **Insulin glargine**

DNA recombinant technology has been shaping the development of new insulins in the last 15 years with insulin glargine (IGlar) being the first long-acting insulin analog approved for clinical use by the US FDA and European agency for the evaluation of medicinal products in 2000.

The major changes in comparison to human insulin are elongation of the C-terminus of the B chain with the addition of two arginine residues inserted at position B30 and replacement of asparagine with glycine at position A21 (Figures 1 & 2). This allows a shift in the isoelectric point towards neutral pH. These structural modifications provide stability in an acidic pH, which is maintained in the insulin delivery vial. The changes also make glargine less soluble at physiological pH in subcutaneous tissue following injection. Once in the subcutis, IGlar forms insulin hexamer complexes which dissociate very slowly thus contributing to its delayed absorption and average action up to 12–24 h. IGlar has nearly a plateau response with minimal variability compared with neutral protamine hagedron insulins [15,16].

- **Insulin detemir**

Insulin detemir (IDet) is another long-acting insulin analog which is a product of recombinant DNA technology. It is created by the deletion of the amino acid threonine at position B30 of the human insulin molecule and the addition of a myristic fatty acid residue to the e-amino group of the lysine residue at position B29 (Figures 1 & 2). This change in the structure results in higher binding affinity to albumin in the body fluids [17]. As a result, IDet dissociates slowly from the albumin and hence has extended period of activity.

Acylated insulin analogs have reduced affinity for the insulin receptor when compared with other human insulins or IGlar. Despite this, the net glucose lowering effect is similar to IGlar. In some cases, there is also the need for an increased frequency of dosing with IDet, leading to twice daily administration to achieve full 24 h cover [18]. Similarly, a study involving 20 Type 1 diabetic individuals on IGlar demonstrated that plasma insulin levels dropped towards the tail end after once-daily dosing and favored twice-daily dosing for IGlar [19]. In a double-blind, randomized, crossover study of 29 Type 2 diabetes patients, IDet and IGlar administered as once-daily dose (similar mean insulin units in both arms) showed similar patterns of 24 h glycemic control [20,21].

- **IDeg**

IDeg is an insulin analog which has been created by making changes to human insulin amino acid sequence. Threonine B30 (on the insulin B-chain) has been deleted and a 16-carbon fatty di-acid attached to the lysine at B29 via a glutamic acid spacer (Figure 3) [22,23]. The engineered structure promotes formation of multihexamers in the subcutaneous site, which are much larger molecules than the typical insulin hexamers, and lead to delayed absorption [24].

**Pharmacokinetics**

IDeg is suspended as dihexamers in the injected formulation [25]. The stability is maintained by phenol and zinc in the solution. After subcutaneous injection, phenol rapidly disperses allowing the IDeg dihexamers to bind to each other forming multihexamers, which are soluble and stable compounds [24,25]. This mechanism creates a deposition of IDeg at the injection site. The monomers of IDeg are released slowly as the zinc slowly dissipates from the multihexamers (Figure 4). IDeg monomers in turn bind to albumin both in subcutaneous tissue and in the circulation to further prolong the insulin action. This contributes to an ultra-long-acting pharmacokinetic feature. This property allows for once-daily and potentially less frequent dosing. IDeg is deemed to provide a stable insulin supply with a plateau achieved on regular administration and reduces the intra-day variations in plasma insulin levels. Jonassen et al. performed a pharmacokinetic study in patients with Type 1 diabetes (n = 12). After 6 days of once-daily IDeg administration (dosed at 0.4 units/kg) mean serum IDeg concentrations were found to be in a steady state with a t1/2 longer than 24 h and IDeg was detectable in the circulation for at least 96 h after the last injection [23].

Danne et al. conducted a randomized, double-blind, single dose, crossover trial with IDeg and IGlar. In total, 12 children, 13 adolescents and 12 adults received 0.4 U/kg single dose of IDeg.
Pharmacokinetic analyses were carried out after the first 48 h and at 72 h post dosing. The ultra-long-acting properties of IDeg seen in adults was preserved in children and adolescents. IDeg was detected 72 h after administration in all subjects without any severe hypoglycemic episodes [26].

Pharmacodynamics
Heise et al. conducted a pharmacodynamic study comparing IDeg and IGlar under steady-state conditions [27]. This was a randomized, double-blind, parallel-group study involving 54 subjects with Type 1 diabetes. The subjects received 0.4 U/kg of either IDeg or IGlar once daily for 12 days. On treatment days 6, 9 and 12, pharmacodynamic studies over 24 h were conducted with the euglycemic glucose clamp technique. End points were derived from the glucose infusion rate profiles during clamps. Within subject variation was expressed as coefficient of variation. They concluded that IDeg’s metabolic effect was exactly evenly distributed between the first and the second 12 h. Hence, IDeg showed a stable glucose-lowering effect over each 24 h period with up to four-times lower day-to-day variability compared with IGlar. The nocturnal hypoglycemic episodes were also less with IDeg compared with IGlar.

Clinical evidence in Type 1 diabetes
This novel insulin molecule is currently being studied by various study groups and evidence about its efficacy and ongoing trials are being reported. The evidence here may not be complete as new knowledge is uncovered on a regular basis.
Birkeland et al. conducted an open-label, randomized, three-arm, parallel-group trial investigating the efficacy and safety of IDeg in subjects with Type 1 diabetes [28]. IDeg 600 µmol/l (group A, 1 unit = 6 nmol; n = 59), IDeg 900 µmol/l (group B, 1 unit = 9 nmol; n = 60), or IGlar 600 µmol/l (group C, 1 unit = 6 nmol; n = 59) was administered once daily along with meal-time insulin aspart (IAsp). The baseline parameters of study group were as follows: mean age 45.8 years; mean HbA1c: 8.4%; fasting plasma glucose (FPG): 9.9 mmol/l; and mean BMI was 26.9 kg/m². Insulin dose was titrated to achieve a FPG of 4.0–6.0 mmol/l. At the end of 16 weeks, HbA1c was comparable in IDeg (A), IDeg (B) and IGlar (C) groups (7.8, 8 and 7.6% respectively). The rate of hypoglycemia was 28% lower in the IDeg (A) group and 10% lower in the IDeg (B) group compared with IGlar (C) groups (7.8, 8 and 7.6% respectively). The rate of hypoglycemia was 28% lower in the IDeg (A) group and 10% lower in the IDeg (B) group compared with IGlar (C). Furthermore, nocturnal hypoglycemia was 58% lower with IDeg (A) and 29% lower with IDeg (B) compared with IGlar. In conclusion, IDeg showed comparable efficacy to IGlar but with reduced rates of hypoglycemia.

The BEGIN Basal-Bolus Type 1 trial is a 52-week, Phase III, randomized, open-label, parallel-group, multinational study which compared IDeg with IGlar in basal-bolus therapy with meal-time IAsp in Type 1 diabetes mellitus [29]. A total of 629 Type 1 diabetics were randomized in a ratio of 3:1 to daily IDeg or IGlar along with meal-time IAsp. If they were previously on once daily basal insulin, initial doses were transferred in 1:1 ratio for both IDeg and IGlar. If pretrial basal insulin was more than once a day then basal bolus dose was calculated and transferred 1:1 in the IDeg arm, whilst it was reduced by 20–30% for the IGlar arm. A treat-to-target approach was used with the intention to achieve a self-monitored blood glucose of 3.9 to <5 mmol/l at all times. Basal insulin dose was adjusted prior to making any titration to the bolus insulin. The mean decrease in HbA1c from baseline was similar in both groups (0.39% reduction in the IDeg group and 0.40% reduction in the IGlar group). Thus the study demonstrated noninferiority of IDeg in comparison to IGlar with regards to glycemic control (a feature of the treat-to-target methodology, favored by the FDA regulatory authority). The reduction in laboratory FPG was not statistically significant between the groups, however IDeg showed a trend of greater reduction compared with IGlar. The mean prebreakfast self-measured plasma glucose was significantly lower with IDeg in comparison to IGlar (-0.55 mmol/l [95% CI: -1.03 to -0.08], p = 0.023). The mean daily basal, daily bolus and total daily insulin were lower by 14%, 10% and 11%, respectively in the IDeg arm.

Although the hypoglycemic rates were similar between the groups, the incidence of nocturnal hypoglycemia was 25% less in the IDeg group when compared with IGlar. This significant difference was seen as early as within the first 8 weeks of the trial and continued
to persist into the maintenance phase of trial (16 weeks to end of trial).

Hirsch et al. conducted a Phase III, 26-week, open-label, treat-to-target trial using IDegAsp (IDeg 70% and IAsp 30%) and IDeg in inadequately controlled Type 1 diabetes [30]. In total, 548 Type 1 diabetes individuals with mean HbA1c of 8.3% were randomized 2:1 to receive IDegAsp or insulin detemir. A bolus dose of IAsp was used at meal times in the IDeg group, whilst in the other group, IDegAsp was administered with any one meal, and IAsp with the remaining meals. The results showed similar glycemic control between the two groups (0.73 and 0.68% point reduction in HbA1c, respectively). Nocturnal hypoglycemia was 37% lower with IDegAsp.

Russell-Jones et al. conducted a 26-week, open-labeled, treat-to-target trial in subjects with Type 1 diabetes [31]. Once-daily IDeg was administered with the evening meal in 165 individuals. Another group of 164 patients were offered forced flexible dosing of IDeg allowing for alternating insulin dosing in the morning and evening on different days. This created at least 8–40 h of wide difference in timing of IDeg in an individual. At the end of 26 weeks, 84% of participants completed the trial. The glycemic control and overall rate of hypoglycemia was similar between the groups. The nocturnal hypoglycemia was significantly lower in IDeg flex group. Cooper et al. have presented an abstract recently of a 26-week extension of the above study in which all the 329 subjects were allocated to IDeg-free flexible dosing, which allowed them to dose IDeg at any time of the day [32]. They were compared with 164 Type 1 diabetics on IGLar given at same time of day, each day. The study showed similar glycemic control in both groups with less nocturnal hypoglycemia in the IDeg group. Increased dosing flexibility and ability to maintain glycemic control with flexible dosing demonstrated in this trial will help to improve patient convenience by allowing insulin injection time to vary to suit their daily activities.

Blonde et al. evaluated the effect of BMI and diabetes duration on efficacy of IDeg in a Phase IIIa trial [33]. The trial C in their study included 472 Type 1 diabetes subjects only. Individuals with lower HbA1c at baseline achieved target HbA1c of <7%. Neither BMI or duration of diabetes influenced the outcome.

Korsatko et al. conducted a randomized, double-blind, two-period crossover, multiple-dose study with 6 days of once-daily 0.4 unit/kg IDeg or IGLar [34]. A sample of 14 geriatric Type 1 diabetes subjects (mean age: 67.8 years) were compared with 13 younger (mean age: 27.1 years) Type 1 diabetes individuals. The mean IDeg concentration–time profile at steady state was similar in both the groups. The ultra-long-acting
pharmacokinetic profile was maintained in the geriatric group similar to younger adults.

Home et al. have reported on improved mental health status in IDeg-treated Type 1 diabetes compared with IGLar in a 16-week, open-labeled, randomized trial involving 59 subjects in each group [38]. They used the mental component score of the short form 36 health survey. The small-medium improvement was attributed to observed reduction in hypoglycemic events, however further large-scale trials will be needed to establish this.

Safety features
Receptor binding studies for IDeg have been conducted on recombinant human insulin receptors (hIR-A and hIR-B) and human IGF-1 receptors [36]. The affinity of IDeg for both the human insulin receptors was found to be similar (13 and 15% relative to human insulin) and IDeg had a very low affinity to human IGF-1 receptors (2% relative to human insulin). Hence the alteration made in molecular structure of human insulin to engineer IDeg has resulted in a stable molecule with ultra-long-acting profile and a good cellular metabolic effect whilst maintaining a low risk for hypoglycemic episodes and apparent cellular mitogenicity.

Future perspective
Several studies are being conducted to assess efficacy of IDeg in both Type 1 and 2 diabetes. Some of these are looking at less frequent dosing of IDeg (three-times per week vs once daily) whilst others are assessing the impact of varying the dosing time of IDeg (to assess the impact of delayed dosing as often happens in real-life diabetes management). Studies are also being conducted with an IDeg and IAsp combination, termed degludec-plus, to reduce the number of injections needed for patients with Type 2 diabetes mellitus. The initial studies published until now are encouraging as a flexible dosing long-acting insulin. For Type 2 diabetes patients, new combinations with IDeg, Phase III trials with IDeg + liraglutide combination, versus IDeg is being conducted with primary outcome looking into reduction in HbA1c and secondary end point of weight loss at end of 26 weeks.

Conclusion
The new ultra-long-acting IDeg shows encouraging pharmacokinetic and pharmacodynamic properties. Comparisons with IGLar in Type 1 diabetes mellitus show noninferiority regarding HbA1c reduction. Studies until now have shown significantly less nocturnal hypoglycemic episodes with IDeg. IDeg has also been shown to be effective during flexible dosing at any time of the day, which would be a major attribute that distinguishes it from other long-acting analogs. This means flexible dosing will make room for improved glycemic control especially in youngsters and individuals with shift working patterns who may struggle to maintain fixed daily dosing.

Financial & competing interests disclosure
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Executive summary

**Insulin analogs in the management of diabetes**

- Endogenous insulin is secreted from β cells of the pancreas in short bursts as a response to ingestion of food and in a basal pattern at a steady rate of 0.5–1 unit/h.
- In Type 1 diabetes, due to β-cell dysfunction or autoimmune destruction this physiological state is altered. Ideally this physiological state has to be simulated to achieve good glycemic control and avoid complications.
- Discovery of new analogs with better pharmacokinetic and pharmacodynamics properties is an important step towards achieving this.

**Insulin degludec**

- Insulin degludec is created by the deletion of the amino acid threonine at position B30 of the human insulin molecule and the addition of a myristic fatty acid residue to the e-amino group of the lysine residue at position B29. Its unique property of protraction and slow release has been shown to achieve an ultra-long-acting profile.
- A study has demonstrated that insulin degludec maintained stable plasma levels over a 24-h period with less variation in plasma glucose compared with other insulin analogs. Flexible dosing did not compromise on glycemic control. This unique feature makes it an ideal basal insulin allowing for greater flexibility for daily activities in subjects with difficulty managing fixed-dose timing. The incidence of nocturnal hypoglycemia was 25% less in the insulin degludec group when compared with insulin glargine. Studies available until now have shown that insulin degludec has low affinity to IGF-1 receptors and hence a low risk of mitogenecity. The clinical trials with combination of short-acting insulin analogs (insulin aspart) with insulin degludec have shown favorable response. Until now studies have demonstrated that insulin degludec is an ideal basal insulin with some unique qualities.
Insulin degludec in Type 1 diabetes

Review: Clinical Trial Outcomes

References

Papers of special note have been highlighted as:

- of interest
- - of considerable interest


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- Highlights the mechanism of protraction of degludec molecules that allows for slow absorption.


- Highlights the mechanism of protraction of degludec molecules that allows for slow absorption.


- An important study focused on Type 1 diabetes.


- A pivotal study demonstrating similar glycemlc control with insulin degludec and insulin glargine.


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**Websites**
