Efficacy and safety of ultra-long-acting insulin degludec

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Abstract: All patients with type 1 diabetes and significant numbers of those with type 2 diabetes are treated with insulin. Nonadherence to insulin regimen can impact glycaemic control. Insulin degludec is a new generation, ultra-long-acting basal insulin that forms soluble multihexamers at the injection site that slowly release insulin degludec monomers into the circulation giving a prolonged duration of action. Insulin degludec may provide a safe and convenient dosing option for patients who require some flexibility in adhering to an insulin regimen according to their lifestyle or circumstances. In this review we focus on the early phases of insulin degludec development.

Keywords: hypoglycaemia, insulin degludec, type 1 and type 2 diabetes, ultra-long-acting basal insulin.

Introduction

All patients with type 1 diabetes and significant numbers of those with type 2 diabetes are treated with insulin and it is recognised that nonadherence to an insulin regimen results in poorer glycaemic control. It is recognised that encouraging patients to adhere to their insulin regimens is challenging and requires long-lasting motivation on behalf of the patient. An online survey of patients with type 1 and type 2 diabetes treated with insulin highlighted the significance of the problem. Of the 500 patients over half (57%) reported intentionally omitting their insulin injections, while regular omission of injections was reported by 20% of the patients questioned [Peyrot *et al.* 2010]. In fact, 22% of those who were surveyed said they planned their daily activities around their insulin injections. Therefore, it seems likely that nonadherence may be due to a combination of patients' busy lifestyles and the time-fixed dosing regimens that may not suit some patients [Peyrot *et al.* 2010]. One of the greatest concerns from a patient perspective is hypoglycaemia and its avoidance which may result in poorer glycaemic control that may reflect in omission of prescribed insulin doses [Wild *et al.* 2007].

The impact of nonadherence on glycaemic control was highlighted in a study of patients with type 2 diabetes, where a significant inverse link

was found between adherence to treatment and HbA_{1c} [Donnelly *et al.* 2007]. In another study the omission of two basal insulin injections per week in patients with type 1 diabetes resulted in an increased HbA_{1c} of 0.2–0.3% [Randlov and Poulsen, 2008].

Degludec is a new insulin with a long duration of action that may help address these shortcomings. Insulin degludec (IDeg) differs from other long-acting insulin preparations in having a longer half life, flat time–action profile (less likely to cause hypoglycaemia) and less day-to-day variability (less glycaemic variability).

What is insulin degludec?

IDeg is a new-generation, ultra-long-acting basal insulin that forms soluble multihexamers at the subcutaneous injection site. The difference between human insulin and IDeg is the deletion of residue ThrB30, and the addition of a fatty diacid moiety, hexadecandioyl, attached to LysB29, via a glutamic acid spacer (Figure 1). Once the phenol in the pharmaceutical formulation has dispersed after injection, the acyl side-chain causes IDeg to self-associate, forming large soluble multihexamers; creating a subcutaneous depot. The zinc ions slowly diffuse out from this complex, allowing IDeg monomers to dissociate

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Figure 1. Insulin degludec structure; LysB29Nε-hexadecandioyl-γ-Glu desB30 human insulin.

and diffuse into the blood stream at a slow and steady rate. The slowly released IDeg monomers may provide a buffering effect against changes in absorption rate [Birkeland *et al.* 2011a]. The resultant smooth and stable pharmacokinetic profile at steady state [Jonassen *et al.* 2010] provides a longer duration of action [Zinman *et al.* 2011] and lower intrasubject variability than insulin glargine (IGlar) [Heise *et al.* 2010]. In clinical practice this potentially could mean that patients are less likely to develop hypoglycaemia or fluctuation in glycaemic control (glycaemic variability).

Initial clinical trials

In a randomised, open-label trial, 179 subjects with type 1 diabetes (mean A1C 8.4% and similar mean daily dose of insulin) received one of three types of once daily subcutaneous injections; IDeg 600 µmol/l, (IDeg₆₀₀), IDeg 900 µmol/l (IDeg₉₀₀) and IGlar while insulin aspart was administered at mealtimes [Birkeland *et al.* 2011a]. After 16 weeks, mean and standard deviation of A1C was comparable in the IDeg₆₀₀ and IDeg₉₀₀ groups; $7.8 \pm 0.8\%$ and $8.0 \pm 1.0\%$ to that of IGlar ($7.6 \pm 0.8\%$) as was fasting plasma glucose (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 IDeg₆₀₀ compared with IGlar (rate ratio [RR] 0.72 [95% confidence interval (CI) 0.52–1.00]) and 10% lower for IDeg₉₀₀ compared with IGlar (RR 0.90 [95% CI 0.65–1.24]). When compared

with nocturnal hypoglycaemia of IGlar, the rates were 58% lower in IDeg₆₀₀ (RR 0.42 [95% CI 0.25–0.69]) and 29% lower in IDeg₉₀₀ (RR of 0.71 [95% CI 0.44–1.16]). The frequency and pattern of adverse events was similar between insulin treatments; weight change from baseline was not dissimilar among the three groups, $+0.16 \pm 2.7$ kg for IDeg₆₀₀, $+1.0 \pm 2.5$ kg for IDeg₉₀₀, and $+0.7 \pm 1.6$ kg for IGlar [Birkeland *et al.* 2011a].

In a randomised open-label parallel group phase II trial involving 245 subjects with type 2 diabetes mellitus (T2DM), 62 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 IGlar (starting dose 10 U [1 U = 6 nmol]) once a day [Zinman *et al.* 2011]. At study end, mean HbA(1C) levels were much the same across treatment groups, at 7.3% (SD 1.1), 7.4% (1.0), 7.5% (1.1), and 7.2% (0.9), respectively. Estimated mean HbA(1C) treatment differences from IDeg by comparison with IGlar were 0.08% (95% CI –0.23% to 0.40%) for the three dose per week schedule, 0.17% (95% CI –0.15% to 0.48%) for group A, and 0.28% (95% CI –0.04% to 0.59%) for group B. Few participants had hypoglycaemia and the number of adverse events was much the same across groups, with no apparent treatment-specific pattern [Zinman *et al.* 2011].

Table 1. Comparison of hypoglycaemia between IGlargin and IDeg during the two 52-weeks basal-bolus insulin therapy trials.

Hypoglycaemia	Type 1 diabetes				Type 2 diabetes			
	IGlar	IDeg	ERR [95% CI]	<i>p</i>	IGlar	IDeg	ERR [95% CI]	<i>p</i>
Overall	40.2*	42.5*	1.07 [0.89–1.28]	N/S	13.6*	11.1*	0.82 [0.69–0.99]	0.03
Nocturnal	5.9*	4.4*	0.75 [0.59–0.96]	0.02	1.8*	1.4*	0.75 [0.58–0.99]	0.03

IGlar, insulin glargine; IDeg, insulin degludec; ERR, estimated rate ratio; CI, confidence interval; PG, plasma glucose; NS, not significant, *Episodes/patient-year

In a study to test the extremes of dosing intervals, in a phase IIIa trial [Atkin *et al.* 2011; Birkeland *et al.* 2011b], patients treated with IDeg were asked to alternate the timing of insulin administration to morning and evening, creating 8–40 hour intervals between doses (IDeg Flex) over a 26 week period. Other individuals in the trial were randomised to either IGlargin given once daily according to the label, or IDeg once daily administered at the same time daily with the evening meal (IDeg Fixed). Oral antidiabetic drug (OAD) therapy was added to all three arms while those who were on a basal or a twice daily insulin regimen they were changed to once daily degludec or glargine. After 26 weeks, HbA_{1c} was reduced by IDeg Flex and IGlargin by –1.28% and –1.26%, respectively, confirming noninferiority, while FPG was significantly lower in IDeg Flex compared with IGlargin 5.8 *versus* 6.2 mmol/l (*p* = 0.04) [Atkin *et al.* 2011]. HbA_{1c} dropped by –1.1% in the IDeg Fixed while FPG was reduced from 8.8 mmol/l to 5.8 mmol/l with no significant treatment differences to the IDeg Flex arm [Atkin *et al.* 2011]. Furthermore, the rates of overall and nocturnal hypoglycaemia were low and similar in all treatment groups with a trend to lower nocturnal hypoglycaemia (nonsignificant 23% relative risk reduction) for the flexible arm. The results of this study demonstrate the stable and ultra-long action profile of IDeg that has the potential of dosing flexibly without compromising blood glucose control or increasing the risk of hypoglycaemia [Atkin *et al.* 2011; Birkeland *et al.* 2011b].

Two further phase IIIa trials, one involving type 1 and the other type 2 diabetes patients, confirmed the long term (after 52 weeks) efficacy and safety of IDeg when used in basal bolus therapy compared with IGlargin [Hollander *et al.* 2011; Russell-Jones *et al.* 2011]. In patients with type 1 diabetes, treatment with either IDeg or IGlargin reduced HbA_{1c} by 0.4% in both groups. However, compared with IGlargin, IDeg resulted in

a 25% lower rate of nocturnal hypoglycaemia (PG < 3.1 mmol/l occurring between 00:01 and 05:59) events per patient per year (*p* = 0.021) [Russell-Jones *et al.* 2011]; see Table 1. In patients with type 2 diabetes, IDeg and IGlargin were associated with HbA_{1c} reductions of 1.2% and 1.3%, respectively. Risk of hypoglycaemia was significantly lower with IDeg compared with IGlargin; for overall hypoglycaemia, there was a risk reduction of 18% (*p* = 0.036) and 25% for nocturnal hypoglycaemia (*p* = 0.040) [Hollander *et al.* 2011]; see Table 1. More recently, the efficacy and safety of a coformulation of IDeg with insulin aspart (IAsp) was tested in a phase II, 16-week, open-label treat to target trial. Coformulation of 70% IDeg and 30% IAsp (IDegAsp), *n* = 61, was associated with a 58% lower rate of confirmed hypoglycaemic episodes in insulin-naïve patients with type 2 diabetes compared with biphasic IAsp 30 given twice daily, *n* = 62 (2.9 *versus* 7.3 episodes/patient-year; estimated rate ratio: 0.42 [95% CI 0.23–0.75]) [Niskanen *et al.* 2011]. In addition, mean FPG at week 16 was significantly lower for IDegAsp than biphasic IAsp 30 (6.4 *versus* 7.5 mmol/l). On the other hand there was no difference between the meal test postprandial glucose values. The rate of confirmed hypoglycaemia was 58% lower for IDegAsp than biphasic IAsp 30 [Niskanen *et al.* 2011].

The potential advantages of insulin degludec

As the number of people living with diabetes continues to increase, so will the demand for improved insulin therapies to improve and maintain diabetes control to prevent long term complications without hypoglycaemia.

Clinicians recognise that effectively treating diabetes requires a regimen that is not only capable of controlling blood glucose, but also promotes adherence. Patient surveys suggest that there may be a need for flexible insulin-dosing regimens that

is currently not adequately met by current basal insulins on the market. IDeg has a pharmacokinetic (PK)/pharmacodynamic (PD) profile and supporting clinical study data to suggest that it could be dosed on a flexible daily basis, allowing increased flexibility for patients leading demanding, unpredictable lifestyles such as shift workers or frequent travellers crossing time zones. Whilst we would envisage that IDeg would be given as a fixed dose, its inherent flexibility would provide a safety advantage whilst maintaining glycaemic control in particular situations. These situations may include patients for whom insulin is administered by a carer or a third party, who may not be able to visit the patient at the same time every day. IDeg represents a potential option in secondary care, perhaps in general ward areas where routines can be disturbed. The data from the clinical developmental programme points to the potential for the reduction in hypoglycaemic events, particularly nocturnal hypoglycaemia, whilst tight glycaemic control was maintained. The fear of hypoglycaemia, shared by both physicians and patients [Riddle, 2002], is a strong barrier to initiating insulin therapy when clinically indicated in type 2 diabetes [Polonsky *et al.* 2005]. Hence, the reduction in hypoglycaemia offered by IDeg with increased patient confidence may encourage adherence to insulin regimens and tighter glycaemic control.

Conclusion

IDeg therefore has the potential to offer tighter glycaemic control with a reduction of nocturnal hypoglycaemia compared with IGLar whilst giving patients more flexibility around the time of their basal insulin dosage.

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Conflict of interest statement

Professor Atkin has undertaken consultancy and received research money from most large pharmaceutical companies.

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