Insulin degludec – The impact of a new basal insulin on care in type 2 diabetes

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Many patients with type 2 diabetes continue to have poor glycaemic control and would benefit from insulin therapy. However, resistance to the introduction of insulin therapy can be high on both the part of the healthcare provider and the patient. A number of new, long-acting basal insulins are in development that provide good metabolic control, but with a lower risk of hypoglycaemia than currently available insulins, and greater flexibility in dosing time from day to day. These attributes may address some of the current barriers to insulin initiation and intensification that currently limit the effectiveness of diabetes care.

1. Introduction

The burden of type 2 diabetes is considerable, and people with diabetes require at least two- to three-times the healthcare resources of those who do not; therefore, diabetes care may account for up to 10–15% of national healthcare budgets, rising to 17% by 2035 [1,2]. The progressive nature of type 2 diabetes means that insulin will ultimately be required in many patients. The United Kingdom Prospective Diabetes Study (UKPDS) showed that 53% of patients with type 2 diabetes using only sulphonylurea required insulin therapy after 6 years, rising to ~75% after 9 years [3,4]. Basal insulins can be used to augment oral therapy [5]. Moreover, the emergence of modern basal insulins has led to the approach of basal-bolus therapy in which basal insulins are administered alongside faster-acting prandial insulins – an approach to exogenous insulin administration that more closely approaches physiological insulin. Nevertheless, there are many insulin regimens available, and it is difficult to identify a consensus on the best choice [6], highlighting the importance of discussion with the patient and individualization of treatment.

Even though treatment goals and guidelines are well established, many patients with type 2 diabetes continue to have poor glycaemic control [7–9]. The benefits of tight glycaemic control early in the course of disease are well established [10–12]; however, there remain clear barriers to uptake and effective use of insulin, for both physicians and patients.

From the physician’s perspective, many general practitioners perceive insulin therapy as a ‘last resort’ and 50–55% will delay insulin therapy until they consider it absolutely necessary [13]. Physicians cite a number of reasons for delaying
insulin initiation; including beliefs around its efficacy, concerns around weight gain, occurrence of hypoglycaemia and impaired quality of life or dissatisfaction for the patient [14]. This ‘clinical inertia’ – i.e. the failure to advance therapy when it is required – is reflected in low percentages of patients intensifying treatment when glycaemic control demands it. Indeed, the recent global SOLVE observational study showed that the mean glycosylated haemoglobin (HbA1c) of patients considered candidates for insulin initiation was 8.9%, although this was subject to regional variation [15]. Prescribing a once-daily long-acting insulin in combination with oral medication is less complicated than, for example, a twice-daily insulin regimen, and will likely lead to a substantial increase in insulin therapy in the primary care setting [16].

Similarly, barriers exist for patients who would benefit from insulin treatment. Complicated and inflexible insulin dosing regimens can be intimidating to patients, and many have concerns around weight gain, injection pain, fear of hypoglycaemia and the perception that they will be viewed as sick, or judged for having failed to manage their diabetes without insulin [14,16–21]. The complexity of treatment, together with the need to manage self-injection, can also adversely affect patients’ quality of life [22].

Modern, long-acting basal insulin analogues, such as insulin glargine and insulin detemir, are an improvement on older preparations, as the glucose-lowering response in a given patient is more consistent from one injection to another [23,24]. However, clinical data show that the glucose-lowering effect of current basal insulin analogues dosed once daily can vary considerably over 24 h [25]. These insulins are commonly dosed at bedtime or in the evening, reaching peak plasma levels in the early hours or at breakfast time. The rising kinetic profile coupled with variability in absorption rate can exacerbate the risk of nocturnal hypoglycaemia. This remains a significant barrier to insulin initiation and dose titration, thereby limiting the achievement of optimum glycaemic control.

These issues highlight a requirement for improvements in basal insulins, to better meet the needs of a growing population of patients with diabetes. This review considers the clinical implications of emerging data for insulin degludec, a new basal insulin, with a focus on type 2 diabetes.

2. Prolonging the action of basal insulins

Ideally, a basal insulin would need to deliver a constant and predictable level of glucose-lowering effect over 24 h from a once-daily injection. Currently available basal analogues have durations of action close to 24 h. However, there may be little or no overlap in the absorption (and hence glucose-lowering action) between consecutive doses, so once-daily dosing can result in a substantial difference between peak and minimum plasma insulin levels, which may bring periods of exacerbated risk for hypo- and hyperglycaemia [24]. An insulin with a half-life substantially longer than 24 h would allow once-daily dosing and, on reaching steady state, would provide more stable plasma insulin levels than previously possible. With such a profile, some flexibility in dose timing would also become possible, since day-to-day inconsistencies in administration time would have only a minor impact on the plasma kinetics.

3. Insulin degludec

Insulin degludec (Fig. 1) is a new long-acting basal insulin with a half-life of ≥25 h [26] and a steady-state pharmacokinetic (PK) profile that is flat and stable for >24 h [27]. Isoglycaemic clamp studies have shown that this stable PK profile gives a very stable glucose-lowering action that extends beyond 42 h. This leads to low variance in maximum and minimum plasma insulin levels that can be achieved with once-daily dosing [27].

The long and stable PK/pharmacodynamic (PD) profile of insulin degludec has a number of potential clinical implications, notably that the flat and stable PK profile, coupled with low day-to-day variability should lead to good glycaemic control with a low incidence of hypoglycaemia. In addition, the time at which once-daily injections are made each day is less critical, promising greater tolerance for flexibility in dose timing. Both of these properties were tested in the insulin degludec phase III clinical development programme.

Fig. 1 – Chemical structure of insulin degludec, in which the molecular structure of recombinant human insulin is modified to allow the formation of soluble and stable chains of hexameric insulin when injected into subcutaneous tissue. Once in the subcutaneous depot, zinc diffuses from the multi-hexamer assembly, releasing a slow, peakless and continuous delivery of insulin monomers into the circulation – a mechanism that has been described in detail elsewhere [26]. With kind permission from Springer Science + Business Media: Pharmaceutical Research, Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin, 29, 2012, page 2105, Jonassen I et al., Fig. 1, ©2012.
4. Clinical experience with insulin degludec

Once-daily insulin degludec has been investigated in the BEGIN clinical study programme, with more than 5500 patients recruited [28]. A treat-to-target protocol was used across the clinical programme, in which basal insulin doses were titrated to the same self-measured fasting plasma glucose (FPG) level. Differences in treatments are therefore evident in other end-points, such as tolerability and safety; for example, the rate of hypoglycaemia was an endpoint of primary interest.

4.1. Glycaemic control

In both type 1 and 2 diabetes, insulin degludec has been shown to be non-inferior to insulin glargine in attaining and maintaining glycaemic control [29–35]. In particular, in the BEGIN BB study, 992 patients with type 2 diabetes were randomized to receive either insulin degludec or insulin glargine for 52 weeks [29]. Both insulins were associated with similar levels of glycaemic control with change from baseline HbA1c of $-1.1\%$ in those receiving insulin degludec and $-1.18\%$ in those receiving insulin glargine. The estimated treatment difference of $0.08\%$ (95% CI 0.05 to 0.21) confirmed the non-inferiority of insulin degludec to insulin glargine. FPG was reduced by 2.3 mmol/L with insulin degludec and 2.0 mmol/L with insulin glargine. An HbA1c of $<7.0\%$ (<53 mmol/mol) was achieved by 49% and 50% of patients, respectively.

The BEGIN ONCE LONG study randomized 1030 insulin-naive patients with type 2 diabetes to receive either insulin degludec or insulin glargine, again over 52 weeks [30]. Reduction in HbA1c with degludec was similar (non-inferior) to that with glargine ($-1.06\%$ vs. $-1.19\%$), with an estimated treatment difference of degludec to glargine of $-0.09\%$ (95% CI 0.04–0.22). FPG was reduced by 3.76 mmol/L with insulin degludec and 3.31 mmol/L with insulin glargine. Again, similar proportions of patients achieved HbA1c levels of $<7\%$ at the end of the trial with degludec (52%) and glargine (54%). These data are supported by other studies from the insulin degludec clinical study programme. (Table 1) [29–31].

4.2. Hypoglycaemia

In patients with type 2 diabetes, numerical or statistically significant decreases were seen in the rates of both overall confirmed and nocturnal confirmed hypoglycaemia compared with insulin glargine. In these studies, confirmed hypoglycaemia was defined as plasma glucose $<3.1\%$ (56 mg/dL), and nocturnal confirmed hypoglycaemia as any episode occurring between midnight and 6:00 am. The BEGIN BB study showed that treatment with insulin degludec was associated with a statistically significant 18% reduction in risk of confirmed hypoglycaemia compared with insulin glargine ($p = 0.036$) over 52 weeks, with rates of 11.1 and 13.6 episodes per patient year of exposure, respectively [29]. A statistically significant reduction of 25% was also seen in the risk of nocturnal confirmed hypoglycaemia ($p = 0.04$) with rates of 1.39 versus 1.84 episodes per patient year of exposure [29]. These results are supported by data from the ONCE LONG study.
In this study, rates of overall confirmed hypoglycaemia were similar between insulin degludec and insulin glargine (1.52 vs. 1.85 events per patient year, respectively). However, the rate of nocturnal confirmed hypoglycaemia was significantly lower (by 36%; *p* = 0.038) with insulin degludec, with rates of 0.25 versus 0.39 episodes per patient year of exposure, respectively. Few episodes of severe hypoglycaemia were reported in either group, but the rate was significantly lower (by 32%) with insulin degludec, with rates of 0.003 vs. 0.023 episodes per patient year, respectively. A recent meta-analysis showed that subjects with type 2 diabetes who were treated with insulin degludec experienced significantly lower rates of overall confirmed (lower by 17%) and nocturnal confirmed hypoglycaemic episodes (lower by 32%) compared with insulin glargine (*p* < 0.05). Results were similar in insulin-experienced and insulin-naïve patients [36].

During exercise, increased glucose requirements as well as increased insulin sensitivity can lead to an increased risk of hypoglycaemia in patients with diabetes [37]. An additional meta-analysis has indicated that the proportions of patients self-reporting exercise-related hypoglycaemia, both confirmed and nocturnal, were similar between insulin degludec and insulin glargine for all patient groups. Therefore there was no increased risk of self-reported hypoglycaemia related to exercise with insulin degludec compared with insulin glargine [38].

### 4.3. Quality of life

It is widely recognized that patients with diabetes consistently report lower health-related quality of life (HRQoL) compared with those without [39,40]. Diabetes therapies can negatively affect HRQoL due to treatment complexity/rigidity, fear of hypoglycaemia and fear of injections [19,21,41,42]. Clinical studies of insulin degludec have included assessments of HRQoL, as measured using the SF-36 short-form health survey [43]. Compared with insulin glargine, insulin degludec leads to improvements in both mental and physical health status for patients with type 2 diabetes [29].

In the BEGIN BB study, a HRQoL questionnaire showed a statistically significant difference between treatment groups in favour of insulin degludec versus insulin glargine for the SF-36 domain of bodily pain (estimated treatment difference [ETD] 1.4 points [95% confidence interval (CI) 0.1–2.7; *p* = 0.032]) [29]. The ONCE LONG study showed an improvement in overall physical functioning at 52 weeks with insulin degludec versus insulin glargine, with an ETD of 1 point [95% CI: 0.1–2.0] (*p* = 0.033) and a treatment difference of 1.4 points in the physical functioning sub-domain [95% CI: 0.3–2.4] (*p* = 0.016) [30]. It should be noted, however, that statistical significance and clinical relevance may differ, and there has long been some debate over what change in SF-36 score constitutes a clinically relevant difference. This may only be meaningfully assessed in a manner that takes into consideration specific diseases, conditions, levels of severity, socioeconomic status, and nationality of patients, as well as patients’ perceptions [44].

Hypoglycaemia is known to have a substantial impact on adherence to treatment, and particularly on HRQoL, through acute symptoms, altered behaviour and fear of future events
Moreover, quality of life has been shown to decrease directly with increasing frequency of hypoglycaemic events [46]. Although the SF-36 measurement of HRQoL is not sufficiently specific to identify true causal links, the improvements in HRQoL evident with insulin degludec compared with insulin glargine may be associated with the significantly reduced incidence of both overall and nocturnal hypoglycaemia.

5. Addressing inflexibility in insulin dosing regimens

Many patients report that the restrictiveness of insulin regimens is a significant barrier to using insulin [21,41]. Indeed, 45% of patients reported restrictiveness as being a reason to avoid insulin therapy [21]. Furthermore, patients report irregular dosing of basal insulin; this may be due to busy schedules, skipped meals and self-consciousness around having to inject in a public place [42].

Up to 22% of patients plan daily activities around their insulin schedule [42]. Although a basal insulin requires dosing only once or twice daily, consistent dose timing is important. This inflexibility may lead to patients not taking their insulin as prescribed, thereby limiting the achievement of glycaemic targets. The flat and stable steady-state profile of insulin degludec means that consistency in the dosing interval should be less critical, and therefore allow for a more flexible dosing interval, while still achieving glycaemic control with low hypoglycaemia [32].

This has been tested in an extreme scenario, in which insulin degludec given once daily in a ‘forced flexible’ regimen incorporating alternating dosing intervals of 8 and 40 h between doses was compared with insulin glargine given once daily at a fixed time according to label. Meneghini and colleagues reported data for this regimen in patients with type 2 diabetes, which showed that changes in injection times could be made from day to day without compromising glycaemic control or increasing the incidence of hypoglycaemia compared with regular dosing of insulin glargine [32]. From a baseline HbA1c of 8.4%, the fixed and flexible insulin degludec regimens led to reductions of 1.1% and 1.3% points, respectively, and a reduction of 1.3% points was seen with insulin glargine. Rates of confirmed overall hypoglycaemia were 3.6 episodes per patient year in the insulin degludec groups and 3.5 episodes per patient year in the insulin glargine group; rates of confirmed nocturnal hypoglycaemia were 0.6 episodes per patient year in the insulin degludec groups and 0.8 episodes per patient year in the insulin glargine group.

While it is unwise to encourage laxity in self-management, the greater dosing flexibility afforded by insulin degludec may represent a major improvement in patient convenience by allowing injection times to be changed daily according to individual needs.

6. Next steps for insulin degludec

Insulin degludec is approved for use in Europe, Japan, Mexico and Switzerland. Additionally, in November 2012, the Endocrinologic and Metabolic Drugs Advisory Committee to the United States Food and Drug Administration (FDA) voted in favour of approval for insulin degludec in the United States. However, in February 2013, the FDA requested additional clinical data from a dedicated cardiovascular outcomes trial before review of the New Drug Application can be completed. As the focus of the insulin degludec phase 3 trials was on glycaemic efficacy and the relationship between glycaemic efficacy and the risk of hypoglycaemia, this additional study will add to the body of data available to inform the clinical use of insulin degludec.

7. Conclusions

Basal insulins form the cornerstone of many treatment regimens for patients with type 2 diabetes. The need for improvements in basal insulin has led to the development of new candidate insulins with more favourable characteristics. Insulin degludec is a new long-acting basal insulin that confers slow absorption and a flat and stable glucose-lowering action extending beyond 42 h.

This insulin provides a new approach that may help to address some of the concerns around initiating insulin therapy. The most significant clinical impact is a reduction in nocturnal hypoglycaemia. These findings are important because differences in nocturnal risk cast more light on the true differences between basal insulins than hypoglycaemia during the daytime, which is also influenced by factors such as prandial insulin, food intake and exercise. The prospect of a basal insulin with a very low nocturnal hypoglycaemia risk may be helpful in addressing both clinicians’ and patients’ fears around hypoglycaemia as well as in reducing hypoglycaemia-associated healthcare costs.

The ability to exercise greater flexibility in dosing schedules may help to lessen the effects of irregular insulin dosing and be of benefit to patients who find it difficult to adhere to a strict dosing schedule or who are reluctant to intensify to insulin treatment because of perceptions around the restrictions or intrusiveness of the regimen. Again, this may be of benefit in better optimizing glycaemic control for these patients.

Conflict of interest statement

KK has received funds for research, honoraria for speaking at meetings or served on Advisory Boards for Astra Zeneca, BMS, Eli Lilly, Jansen, MSD, Novartis, Novo Nordisk, Sanofi Aventis and Servier.

GR has received funds for research from MSD and served on Advisory Boards for Astra Zeneca, BMS, MSD and Novo Nordisk.

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Summary points

Many patients with type 2 diabetes continue to have poor glycaemic control and would benefit from insulin therapy.

Resistance to the introduction of insulin therapy can be high on both the part of the healthcare provider and the patient.

Insulin degludec is a new generation basal insulin which undergoes slow absorption from the subcutaneous depot resulting in a long duration of action, a flat and stable PK/PD profile and lower day-to-day variability providing effective glycaemic control.

Insulin degludec may be given at any time of day (preferably at the same time every day), and administration time can vary from day to day without compromising efficacy or safety (a minimum of 8 h between injections should always be ensured).

In a recent meta-analysis, patients with type 2 diabetes treated with insulin degludec showed significantly lower rates of overall confirmed hypoglycaemia (lower by up to 17%) and nocturnal confirmed hypoglycaemia (lower by 32%) compared with insulin glargine. A reduction in hypoglycaemia can improve patient quality of life.

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