Use of insulin degludec, a new basal insulin with an ultra-long duration of action, in basal–bolus therapy in type 1 and type 2 diabetes

Utilisation de l’insuline dégludec, une nouvelle insuline basale de très longue durée d’action, avec un schéma insulinique basal–bolus dans le diabète de type 1 et de type 2

Véronique Kerlan a, *, Didier Gouet b, Michel Marre c, Éric Renard d

a Centre hospitalier universitaire La Cavale-Blanche, boulevard Tanguy-Prigent, 29600 Brest, France
b Hôpital Saint-Louis, centre hospitalier de La Rochelle, rue du Docteur-Schweitzer, 17019 La Rochelle, France
c Endocrinology and Nutrition Department, hôpital Bichat, 46, rue Henri-Harvard, 75877 Paris, France
d Department of Endocrinology, Diabetes, Nutrition, Montpellier University Hospital, 191, avenue Doyen-Gaston-Giraud, 34295 Montpellier, France

Abstract

Insulin degludec is a new basal insulin analogue with an ultra-long duration of action that provides a flat and stable action profile with a duration of action greater than 42 hours. Two clinical trials comparing insulin degludec and insulin glargine in basal–bolus therapy have recently been published. Both were 52-week, multicentre, randomised (3:1), treat-to-target trials in patients already using insulin. In both type 1 (n = 629) and type 2 diabetes (n = 1006), insulin degludec was non-inferior to insulin glargine with respect to reduction in HbA1c at 52 weeks. There were also no significant differences between treatment groups with respect to fasting plasma glucose. At similar levels of glycaemic control, however, insulin degludec was associated with lower rates of hypoglycaemia than insulin glargine. In type 1 diabetes, overall confirmed hypoglycaemia (plasma glucose concentration <3.1 mmol/L or severe episodes requiring assistance) was similar in the two treatment groups, but nocturnal confirmed hypoglycaemia (occurring from 00h01 to 05h59) was 25% lower with insulin degludec (P = 0.021). In type 2 diabetes, overall confirmed hypoglycaemia was 18% lower (P = 0.0359) and nocturnal confirmed hypoglycaemia was 25% lower (P = 0.0399) with insulin degludec. Reductions in hypoglycaemia could reduce physicians’ and patients’ fears and encourage them to titrate insulin more aggressively, and to adhere more closely to treatment, with consequent better glycaemic control. The results of these trials suggest that insulin degludec has a place in the French clinical setting in basal–bolus therapy in type 1 and type 2 diabetes.

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Résumé

L’insuline dégludec est un nouvel analogue de l’insuline basale de très longue durée d’action qui offre un profil d’action plat et stable et une durée d’action supérieure à 42 heures. Deux essais cliniques comparant l’insuline dégludec et l’insuline glargine en insulinothérapie basal–bolus ont été publiés récemment. Il s’agissait dans les deux cas d’essais multicentriques, randomisés (3:1), avec des objectifs glycémiens – cibles prédéfinis sur 52 semaines, conduits chez des patients utilisant déjà l’insuline. Aussi bien dans le diabète de type 1 (n = 629) que dans le diabète de type 2 (n = 1006), l’insuline dégludec s’est avérée non inférieure à l’insuline glargine en ce qui concerne la réduction de HbA1c à 52 semaines. Il n’a pas été observé non plus de différences significatives entre les groupes de traitement en ce qui concerne la glycémie à jeun. À des niveaux similaires de contrôle glycométrique, toutefois, l’insuline dégludec a été associée à des taux inférieurs d’hypoglycémies par rapport à l’insuline glargine. Dans le diabète de type 1, le taux global d’hypoglycémies confirmées (définies rigoureusement par une concentration de glucose plasmatique <3,1 mmol/L ou un épisode sévère nécessitant une assistance) a été similaire dans les deux groupes de traitement, mais le taux d’hypoglycémies confirmées nocturnes (survenant de 00h01 à 05h59) a été inférieur de 25 % avec l’insuline dégludec (p = 0,021). Dans le diabète de type 2, le taux global d’hypoglycémies confirmées a été inférieur de 18 % (p = 0,0359) et le taux d’hypoglycémies confirmées nocturnes a été inférieur de 25 % (p = 0,0399) avec l’insuline dégludec. La réduction des hypoglycémies pourrait atténuer les craintes des médecins et des patients et les encourager à adopter un ajustement plus agressif des doses d’insuline et à adhérer plus étroitement au traitement, avec comme conséquence un meilleur contrôle de la glycémie. Les résultats de ces essais suggèrent que l’insuline dégludec a un rôle à jouer dans le contexte clinique français en insulinothérapie basal–bolus dans le diabète de type 1 et de type 2.

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* Corresponding author.
E-mail address: veronique.kerlan@chu-brest.fr (V. Kerlan).

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All insulin therapy is associated with some risk of hypoglycaemia, which adversely affects patients’ physical, mental and social functioning and is associated with increased costs for patients, healthcare authorities, and society [1–3]. Hypoglycaemia and/or fear of hypoglycaemia reduces patient adherence to treatment and may affect glycaemic control, which in turn increases the risk of diabetic complications [1]. Concern about hypoglycaemia may also cause physicians to titrate insulin less aggressively [4]. While insulin analogues have been shown to reduce the risk of hypoglycaemia relative to human insulins in type 1 diabetes and in some cases in type 2 diabetes [5], there is room for further improvement.

This brief commentary reviews the results of two recently published trials using a new basal insulin with an ultra-long duration of action, insulin degludec, in basal–bolus therapy in type 1 and type 2 diabetes [6,7]. Insulin degludec has been licensed in Japan and approved in Europe (January 2013). It consists of recombinant DesB30 human insulin acylated at the LysB29 residue with a hexadecanediol side-chain attached via a γ-t-glutamic acid spacer [8]. Upon injection, insulin degludec forms stable and soluble multi-hexamers, from which insulin monomers gradually dissociate and are subsequently absorbed into the bloodstream.

At steady state, insulin degludec exhibits flat and stable pharmacokinetic and pharmacodynamic profiles in patients with diabetes. It has a half-life of greater than 25 hours and a duration of action greater than 42 hours [9,10]. On once-daily injection of insulin degludec, steady state is reached in 2 or 3 days, giving rise to a flat and stable profile, which should result in greater consistency of effect and a reduced risk of hypoglycaemia.

The recently reported phase 3 studies of insulin degludec in basal–bolus therapy were both 52-week, multicentre, randomised, controlled, open-label, treat-to-target trials comparing insulin degludec with insulin glargine, with insulin aspart as bolus insulin in both arms. The first study enrolled 629 patients with type 1 diabetes who had been using basal–bolus insulin for greater than 1 year [6]. The second study included 1006 patients with type 2 diabetes, already treated with insulin for at least 3 months [7].

If prior basal therapy was twice daily, the total basal dose was calculated and administered once daily. For insulin degludec this involved a 1:1 transfer to the full calculated dose, while the insulin glargine dose was reduced by 20 to 30%, according to the approved labelling. In both studies the basal insulins were titrated to achieve a pre-breakfast self-measured plasma glucose target of between 3.9 and 5.0 mmol/L.

The primary endpoint was non-inferiority of insulin degludec to insulin glargine in HbA1c reduction at 52 weeks. In type 1 diabetes, HbA1c reduction was 0.40% points with insulin degludec and 0.39% points with insulin glargine, with an estimated treatment difference (ETD) (insulin degludec–insulin glargine) of −0.01% points (95% confidence interval [CI] −0.14 to 0.11). In type 2 diabetes, the reductions were 1.10% points and 1.18% points respectively (ETD 0.08% points; 95% CI −0.05 to 0.21). Both studies achieved their primary objective of demonstrating non-inferiority of insulin degludec to insulin glargine. With respect to fasting plasma glucose, there were no significant differences between treatment groups in either trial.

Treatment with insulin degludec, however, was associated with lower rates of hypoglycaemia. In type 1 diabetes, rates of overall confirmed hypoglycaemia (i.e. plasma glucose concentration <3.1 mmol/L or severe episodes requiring assistance) were similar in the two treatment groups, but the rate of nocturnal confirmed hypoglycaemia (episodes occurring from 00h01 to 05h59) was significantly lower by 25% with insulin degludec (P = 0.021) (Table 1). In type 2 diabetes, rates of overall confirmed hypoglycaemia were significantly lower by 18% (P = 0.0359) and rates of nocturnal confirmed hypoglycaemia were significantly lower by 25% (P = 0.0399) compared with insulin glargine (Table 1). Similar results were observed for rates of hypoglycaemia during the maintenance phase (week 16, when insulin dose had stabilised for most participants, to end of trial) (Table 1).

In both trials, rates of severe hypoglycaemia were low and seemed similar between groups, and rates of other adverse events did not differ between groups. Mean weight gain was similar between treatments: 1.8 kg versus 1.6 kg in type 1 and 3.6 kg versus 4.0 kg in type 2 diabetes for insulin degludec and insulin glargine, respectively (P = ns in both cases).

### Table 1

Estimated rate ratios for hypoglycaemic episodes with insulin degludec:insulin glargine in two trials of basal–bolus therapy [6,7].

<table>
<thead>
<tr>
<th></th>
<th>Total treatment period</th>
<th>Maintenance period&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated rate ratio</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>for insulin degludec:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>insulin glargine (95%</td>
<td></td>
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<tr>
<td></td>
<td>CI)</td>
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<tr>
<td><strong>Type 1 diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1.38 (0.72–2.64)</td>
<td>0.34</td>
</tr>
<tr>
<td>Overall confirmed</td>
<td>1.07 (0.89–1.28)</td>
<td>0.48</td>
</tr>
<tr>
<td>Nocturnal confirmed</td>
<td>0.75 (0.59–0.96)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Type 2 diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Overall confirmed</td>
<td>0.82 (0.69–0.99)</td>
<td>0.0359</td>
</tr>
<tr>
<td>Nocturnal confirmed</td>
<td>0.75 (0.58–0.99)</td>
<td>0.0399</td>
</tr>
</tbody>
</table>

CI: confidence interval; NR: not reported.

<sup>a</sup> From week 16, when insulin dose had stabilised for most participants, to end of trial.

<sup>b</sup> Insufficient episodes for statistical assessment.
In type 1 diabetes, at the end of the trial mean values for daily basal, bolus and total insulin doses were significantly lower ($P < 0.05$) with insulin degludec. In type 2 diabetes, mean values for bolus and total daily insulin doses did not differ between treatments at 52 weeks, but mean basal dose was slightly higher for insulin degludec ($P = 0.0279$).

To sum up, the recent trials showed a reduced risk of confirmed hypoglycaemia in type 2 diabetes, and nocturnal confirmed hypoglycaemia in type 1 and type 2 diabetes, for insulin degludec compared with insulin glargine in basal–bolus therapy, with the two insulins providing similar glycaemic control.

In interpreting the results of these trials, it is worth noting some aspects of their design. Both were designed as treat-to-target trials, with similar degrees of glycaemic control achieved, as required by the US Food and Drug Administration [11]. This means that between-treatment comparisons of the frequency and severity of hypoglycaemia are interpretable without being confounded by differing levels of glycaemic control.

Furthermore, cross-trial comparisons of different insulins have in the past been hampered due to the use of different definitions of hypoglycaemia. In order to avoid this, in all the phase 3 trials of insulin degludec, including the two under discussion, hypoglycaemic events were only recorded if they were confirmed by a measured plasma glucose concentration of less than 3.1 mmol/L or were severe episodes requiring assistance.

The trials were open-label because it was not feasible to disguise differences in the pen devices used. However, the safety, titration and cardiovascular event adjudication committees were all blinded to treatment group assignment, as were staffs involved in data handling until the dataset was locked for statistical analysis.

How are these results relevant in the context of treatment of diabetes in France? For type 1 diabetes, basal–bolus therapy is the gold standard therapy in France, as elsewhere. The significant reduction in nocturnal confirmed hypoglycaemia with insulin degludec versus insulin glargine in type 1 diabetes suggests that insulin degludec could be useful in this context, as nocturnal hypoglycaemic events are frequently the limiting factor in titrating basal insulin, as well as being stressful for patients.

For type 2 diabetes, guidelines on treatment from the French Health Authority (Haute Autorité de santé) have just been published [12]. These confirm current practice in France, which is to prescribe basal insulin (NPH insulin or an analogue) only when patients have failed to achieve glycaemic control with a two-drug combination, and to progress to basal bolus therapy when basal insulin plus one or more oral therapies fails to achieve glycaemic control. The French recommendations are in line with the recent Position Statement of the American Diabetes Association/European Association for the Study of Diabetes, which recommends an incremental approach, while also stressing the need for individualisation of therapy according to the patient’s needs and comorbidities [13].

The reduced risk of confirmed and nocturnal confirmed hypoglycaemia seen with insulin degludec in type 2 diabetes may help to reduce patients’ and physicians’ fear of hypoglycaemia. This could encourage physicians and patients to initiate insulin earlier in the disease and to titrate it more aggressively and maintain better treatment adherence. This should lead to better glycaemic control and thence, ultimately, to improved long-term outcomes.

A phase 3 trial comparing insulin degludec with insulin glargine for insulin initiation in type 2 diabetes has now also been published [14]. There were significantly fewer episodes of nocturnal confirmed hypoglycaemia with insulin degludec ($P = 0.038$) [14]. Thus, insulin degludec may also have a place when insulin is initiated as basal–oral therapy in type 2 diabetes.

These results represent a further step forward in the improvement of insulin therapy through the development of analogues with profiles that more closely resemble physiological patterns of insulin secretion. These trials suggest that insulin degludec has a place in the French clinical setting in basal–bolus therapy in type 1 and in type 2 diabetes.

Disclosure of interest

Véronique Kerlan has received honoraria as an investigator, consultant or speaker for Boehringer-Ingelheim, Eli Lilly, Novo Nordisk and Sanofi-Aventis. Didier Gouet has participated as an investigator in clinical trials with Novo Nordisk, Lilly, Boehringer-Ingelheim, Medtronic, Johnson & Johnson and Sanofi. Michel Marre has acted as an Advisory Panel member for Novo Nordisk, Sanofi, and Servier, and as an Advisory Board member for Lilly and Merck. Éric Renard discloses consultant activities for the following companies: A. Menarini Diagnostics, Abbott, Cellnovo, DexCom Inc, Eli Lilly, Johnson & Johnson (Animas, LifeScan), Medtronic, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi-Aventis and has received support for research activities from Abbott, DexCom Inc., Insulet Inc.

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