Fighting the Hydra: Optimizing treatment for type 2 diabetes
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The future of basal insulin supplementation

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Abstract

This review presents an overview of the candidates for an improved basal insulin in the pharmaceutical pipeline. The first new basal insulin to enter the market is most likely insulin degludec (IDeg), currently reporting in phase 3 of development, from Novo Nordisk (Bagsvaerd, Denmark). IDeg has a longer duration of action than currently available analogs. Phase 2 studies show comparable efficacy and safety outcomes compared with insulin glargine once daily with less hypoglycemia in type 1 diabetes. The final results of phase 3 studies seem to confirm this, also in type 2 diabetes. Biodel (Danbury, CT) has two long-acting basal insulin formulations in the pipeline, both in the preclinical phase of development: BIOD-Adjustable Basal, a modified formulation of insulin glargine, is available in long-, medium-, and short-acting forms and could be mixed, and BIOD-Smart Basal releases insulin proportional to the subcutaneous glucose concentration. Eli Lilly (Indianapolis, IN) is also developing a basal insulin. Phase 2 trials have been completed, but no results are published yet. Clinical trials with the new patch pump from CeQur (Montreux, Switzerland) have recently started in Europe. This patch pump delivers both basal and bolus doses subcutaneously and is intended for people with type 2 diabetes who need multiple daily injection insulin therapy.
Introduction

Good glycemic control significantly and importantly reduces the risk of long-term complications of type 2 diabetes. Insulin is the most powerful glucose lowering drug [1]. However, action is needed to increase the proportion of individuals achieving recommended glycemic goals [2]. Despite the known benefits of timely initiation and intensification of insulin therapy, both patients and physicians are often reluctant to start or intensify insulin therapy because of perceived fear of painful injections, hypoglycemia, weight gain, impairment of quality of life, complexity of insulin regimens and drug costs [3].

Optimizing basal insulin therapy and addressing these barriers can facilitate timely and more aggressive intervention and therefore more optimal glycemic control in patients with type 2 diabetes. The two currently available long-acting basal insulin analogs show advantages compared to the classical NPH insulin [4-6], yet there are properties of these two insulin analogs that could be improved. The aim of this review is to present an overview of the candidates for an improved basal insulin in the pharmaceutical pipeline.

Which properties of currently available long-acting analogs could be improved?

Flat or near-flat time-action profile
Achieving lower blood glucose levels carries an increased risk for hypoglycemia. Hypoglycemia and fear of hypoglycemia are considered the main barrier to achieving good glycemic control by patients and clinicians [7]. An insulin analog with a really flat or near-flat “peakless” time-action profile could limit peak-induced hypoglycemia.

NPH has a pronounced peak after 6-8 h [8]. Two long-acting insulin analogs (detemir and glargine) were engineered aiming at a longer duration of action, thereby inherently limiting the peak effect [8-11]. Several studies have indeed confirmed that once-daily (OD) insulin glargine (IGlar) or OD or twice-daily insulin detemir gives equivalent glycemic control to OD or twice daily NPH insulin but with significantly less hypoglycemic episodes, particularly nocturnal episodes [4;5;12-14]. Many of these studies were performed in type 2 diabetes patients initiating on OD long-acting. In type 1 diabetes the differences are even more pronounced [12;15], and we would expect the same result in insulin-treated type 2 diabetes patients who require insulin for several years with advancing pancreatic B-cell failure.
At present, the insulin with possibly the smallest peak known so far is IGlar. However, the initial pharmacodynamic studies of IGlar raised some criticism, and it should be concluded that IGlar is not peakless [16]. Nevertheless, when we conclude that the attenuated peak effect of IGlar and detemir induces a substantial clinical benefit in nocturnal hypoglycemic events compared to insulin NPH, a new long-acting insulin analog with a near-flat time-action profile can possibly decrease the number of hypoglycemic events in type 1 and type 2 diabetes patients even more.

**Low or no variability**

Lower within-subject variability of insulin absorption would promote improved glycemic control by allowing patients to titrate their insulin doses more aggressively and thereby achieving glycemic objectives more often.

NPH exhibits considerable variation within an individual patient [17]. This variability in insulin action means that identical doses of subcutaneous insulin injections do not always lead to the same glycemic effect, even if dietary intake and physical activity are controlled. IGlar was found to improve the within-subject variability compared to NPH insulin [9;18]. Insulin detemir, with a different mode of protraction, is associated with even less within-subject variability in the glucose-lowering effect from injection to injection, compared to both NPH and IGlar [9]. It is yet uncertain to what extent a lower variability contributes to the lower amount of nocturnal hypoglycemic events when using insulin detemir compared with insulin NPH [19]. Nevertheless, reducing variability theoretically has other possible advantages, even when it does not translate in lower A1c values. The proposed beneficial effects of lowering glycemic variability independently from lowering mean glucose are uncertain [20]. There is potentially much to gain by reducing within-subject variability of absorption with a new long-acting insulin analog.

**Longer duration of action**

A waning of the effect of long-acting insulins frequently necessitates twice-daily administration. NPH insulin has a duration of action considerably shorter than 24-h. The two long-acting insulin analogs, insulin detemir and IGlar, have a longer mean duration of action compared with NPH insulin [8-10]. Euglycemic clamp studies demonstrated that insulin detemir has a dose-dependent duration of action [10] and a mean time-action profile somewhat intermediate between the profiles of insulin NPH and IGlar [9]. It should be noted that similar dose-effect studies have not been published for IGlar. But, neither OD IGlar nor insulin detemir reliably provides 24-h
basal insulin replacement in all patients with type 1 diabetes. Studies of detemir in the basal–bolus therapy of type 1 diabetes have mostly involved twice-daily basal injection. However, even studies with IGlar in which diurnal glucose profiles are reported clearly show a waning of effect [21], while twice-daily administration of IGlar improves glycemic control and reduces the number of nocturnal hypoglycemic events compared with OD IGlar [22;23].

Consequently, a proportion of patients with type 1 may ideally require twice-daily administration with either of these analogs for the achievement of full basal insulin replacement. This might also apply to type 2 patients with little endogenous insulin reserve or predominant insulin resistance. Therefore, there is a need for a reliable true 24-h long-acting insulin which truly requires once-daily injection only in all patients.

**Soluble to allow mix with rapid-acting analog**

A disadvantage of IGlar is that it cannot be mixed with rapid-acting insulins as this would result in precipitation, unlike isophane insulin. Insulin detemir, on the other hand, is a soluble insulin. However, mixing insulin detemir with a rapid-acting insulin should be avoided because the action profile of insulin detemir can be modified with a lower and delayed maximum effect compared with that provided by separate injections [24]. Consequently, patients with biphasic (mixture) insulins will be required to increase their number of daily injections and/or change to a basal-bolus injection regimen. A new long-acting insulin analog should ideally be usable in mixtures to decrease the number of daily injections.

**Low costs**

The use of long-acting insulin analogs has come under scrutiny because they generally cost a lot more than conventional insulins. When considering the increasing incidence rates for type 2 diabetes, physicians cannot disregard the higher cost of the newer insulin preparations. In the United States, the average retail price of a 10-ml vial of the long-acting insulin analogs is $111.88 (IGlar) and $110.49 (insulin detemir) compared with $66.99 for a vial of NPH insulin [25].

Given the rising costs of healthcare and medication to society, a new long-acting insulin analog with clinical benefits might not be first choice therapy if the costs are considerably higher. Moreover, if “biosimilars” become available at lower costs, pressure to lower the costs of insulin analogs may increase.
Less or no weight gain
Insulin detemir has been associated with a consistent, statistically significant, although relatively small reduction of 1 kg in weight gain compared to NPH and IGlar in both type 1 and type 2 diabetes [26]. When developing a new insulin analog, one has to bear in mind that this property of insulin detemir should be retained if at all possible, with weight gain being a common problem in association with intensive diabetes management [27].

No signal of increased mitogenicity
Concern has been raised regarding potential mitogenic effects of insulin analogs. A heavily criticized observational study suggests that IGlar has a dose-related increased risk of cancer compared to human insulin [28-30]. The importance of cross-talk from insulin to the insulin-like growth factor receptor is unclear in this respect, but, nevertheless, newly developed insulin analogs should not display increased affinity to the insulin-like growth factor receptor, increased “on” time to the insulin receptor, or other potential mitogenic signals in preclinical and clinical testing.

Candidates for an improved basal insulin

Insulin degludec
Insulin degludec (IDeg) (formerly known as soluble basal insulin analog) is a new long-acting basal insulin analog currently in phase 3 of clinical development. Its main property is a longer duration of action as compared with currently available analogs.

The IDeg molecule retains the human insulin amino acid sequence except for the deletion of ThrB30 and the addition of a 16-carbon fatty diacid attached to LysB29 via a glutamic acid spacer [31]. The mode of protraction includes soluble multi-hexamer formation and binding to albumin, resulting in continuous, slow, and stable release of IDeg monomers [32].

In a clinical pharmacology study of Jonassen et al., IDeg was administered to 12 subjects with type 1 diabetes. Following 6 days of OD treatment with IDeg, the steady-state pharmacokinetic profile indicates a smooth and stable exposure over a 24-h period. IDeg was found to be detectable in the circulation for at least 96 h after injection [31], although we can not conclude from this that IDeg would still be biologically active at that time. A randomized euglycemic clamp study, performed on 54 subjects with type 1 diabetes receiving either IDeg OD or IGlar OD for 12 days, reported that IDeg also has a lower within-subject variability [33].
Insulin receptor binding studies and in vitro studies indicated that IDeg has a low affinity for the human insulin-like growth factor-1 receptor, comparable with that of human insulin. In addition, it has a low mitogenic/metabolic potency ratio [34].

IDeg has been tested as a single long-acting insulin and in a co-formulation with the rapid-acting insulin analog insulin Aspart (IAsp); this co-formulation is referred to as IDegAsp or Degludec Plus [35].

Phase 2 studies:
Three phase 2 trials investigating the clinical efficacy and safety of IDeg compared to IGlar have been presented in abstract form [32] or in full [35;36]. All had a duration of 16 weeks and were open-label, randomized, parallel-group and treat-to-target trials.

A trial including type 1 diabetes patients reported no differences in hemoglobin A1c, fasting plasma glucose, and mean total daily dose between IDeg OD and IGlar OD, both combined with IAsp [36]. There was a difference in the rate of confirmed hypoglycemia and especially confirmed nocturnal hypoglycemia between IDeg OD and IGlar OD [36]; the rates of overall and nocturnal hypoglycemia of IDeg and IGlar and the risk reductions compared with glargine were 47.9 and 66.2 events/ patient-year (relative risk 0.72) and 5.1 and 12.3 events/ patient-year (relative risk 0.42), both in favor of IDeg OD.

A trial among diabetes type 2 patients tested IDeg in either a OD regimen or a three-times weekly regimen (3W), again compared against IGlar [32]. All efficacy outcome measures, including the mean weekly insulin dose, were similar compared with each other and compared with IGlar. This study among type 2 diabetes patients, other than among type 1 diabetes patients, found no significant differences in the rate of confirmed hypoglycemic events among IDeg OD, IDeg 3W and IGlar OD. Although hypoglycemic events occurred numerically less with IDeg OD [32], they occurred numerically more in the IDeg 3W treatment arm.

One trial investigated a IDegAsp co-formulation, comprising 70% IDeg and 30% IAsp in type 2 diabetes patients dosed at dinnertime [35]. There was no difference in haemoglobin A1c and fasting plasma glucose compared with IGlar OD. Two efficacy outcome measures were in favor of IDegAsp compared with IGlar: IDegAsp had a 27 mg/dL lower mean 2-h post-dinner plasma glucose increment and a 7 U/kg lower mean daily insulin dose. The rate of confirmed hypoglycemic events and nocturnal hypoglycemic events was low for both IDegAsp and IGlar in type 2 diabetes patients [35], without significant differences between the insulins.
In conclusion, phase 2 trials have shown that IDeg gave comparable glycemic control as IGlar at similar molar and unit doses in subjects with type 1 and type 2 diabetes. There were no differences in hypoglycemic events between the two treatment groups in type 2 diabetes patients; this could be attributable to the expected low number of hypoglycemic events in type 2 diabetes patients in combination with a low number of included patients (n of approximately 60 in each arm). There was a tendency toward a lower rate of confirmed hypoglycemia in the IDeg OD group compared with IGlar OD (0.6 events/patient-year vs. 1.1 events/patient-year). However, a tendency toward a greater rate of confirmed hypoglycemia was found when IDeg was administered 3W. This could possibly be explained by an enhanced peak effect if a higher dose of IDeg is being administered at one injection in a 3W regimen. Mostly, the dose administered at one injection of IDeg 3W was doubled compared with the dose of IDeg OD.

In type 1 diabetes patients, who experience hypoglycemic events more frequently, the rate of confirmed hypoglycemia and nocturnal hypoglycemia was relevantly and statistically significantly lower in the IDeg OD treatment group compared with IGlar OD. This indicates that IDeg has the capacity to reduce the amount of hypoglycemic events. The trend is expected to be similar in type 2 diabetes patients using insulin for several years and who are more prone to experience hypoglycemic events. No conclusions could be drawn for severe hypoglycemic events in type 1 and type 2 diabetes patients, as the rates were very low or nil. The longer duration of action of IDeg may provide real 24-h action with flexibility in dosing at any time of the day.

Phase 3 studies:
There are 12 phase 3 trials registered at www.ClinicalTrials.gov aiming to assess the efficacy and safety of IDeg, including approximately 7,000 participants [37]. All phase 3 trials have been completed.

Three randomized trials, with a duration of either 26 weeks or 52 weeks, aim to investigate the efficacy of IDeg in type 1 diabetes patients. Both IGlar an insulin detemir are used as comparator, mostly in combination with IAsp. Two of these trials are extended with 26-52 weeks to investigate the long-term safety of IDeg.

Eight randomized trials, mainly with a duration of 26 weeks, have investigated the efficacy of IDeg in type 2 diabetes patients. Seven randomized trials use IGlar as a comparator; in one trial both treatment arms are combined with insulin aspart. One randomized trial compares IDeg with sitagliptin. IDeg is tested either in a OD or a 3Wregimen, injected in the morning or in the evening. Two of these trials are extended by 26-52 weeks to investigate the long-term safety of IDeg in type 2 diabetes patients.
Table 1 shows preliminary results of the phase 3 trials with IDeg published at the Novo Nordisk website [38]. There were no differences in A1c between IDeg OD and IGlar, although IDeg was not non-inferior regarding A1c when administered 3W in patients with type 2 diabetes. This is likely to result in discontinuation of this dosing option. When dosed OD a reduction in nocturnal hypoglycemia was seen in a 52-week trial, together with a significantly lower fasting plasma glucose level. In patients with type 1 diabetes, IDeg OD reduced the risk of nocturnal hypoglycemia compared with IGlar OD.

Table 1  Preliminary phase 3 results of trials with insulin degludec

<table>
<thead>
<tr>
<th>Type 1 diabetes</th>
<th>Trial</th>
<th>weeks</th>
<th>HbA1c</th>
<th>FPG</th>
<th>Nocturnal hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDeg OD + IAsp vs. IDet OD + IAsp</td>
<td>NN1250-3585 26</td>
<td>Non-inferior</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>IDegFlex+ IAsp vs. IGlar OD + IAsp</td>
<td>NN1250-3770 Flex 26</td>
<td>Non-inferior</td>
<td>NR</td>
<td>↓ 40%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 2 diabetes</th>
<th>Trial</th>
<th>weeks</th>
<th>HbA1c</th>
<th>FPG</th>
<th>Nocturnal hypoglycemia</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDeg OD vs. IGlar OD</td>
<td>NN1250-3579 52</td>
<td>Non-inferior</td>
<td>↓</td>
<td>↓ 35%</td>
<td>Equal</td>
<td></td>
</tr>
<tr>
<td>IDeg OD vs. IGlar OD</td>
<td>NN1250-3586 Asian 26</td>
<td>Non-inferior</td>
<td>NR</td>
<td>Equal</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>IDeg (U200) OD vs. IGlar OD</td>
<td>NN1250-3672 U200 26</td>
<td>Non-inferior</td>
<td>↓</td>
<td>Equal</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>IDeg 3W vs. IGlar OD</td>
<td>NN1250-3724 Morning dose 26</td>
<td>Not non-inferior</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>IDeg 3W vs. IGlar OD</td>
<td>NN1250-3718 Evening dose 26</td>
<td>Not non-inferior</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

4IDegFlex refers to the flexible dosing arm of IDeg: a regimen with fixed dosing intervals alternating between 8 and 40 hours for the administration of IDeg; patients have to inject insulin (e.g. on Monday morning, Tuesday evening, Wednesday morning, Thursday evening etc.). This flexible dosing arm of IDeg is intended to demonstrate that IDeg can be administered with varying intervals differing between 8 and 40 h.

4U200 formulation of IDeg is twice as concentrated as traditional U100 insulin formulations, allowing less injection volume.

3W, three-times weekly; AE, adverse event; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; NR, not reported; OD, once-daily.

Lilly basal insulin

Eli Lilly is developing two new long-acting basal insulin analogs, registered as LY2605541 and LY2963016, currently in phase 2 of development and expected to enter phase 3 clinical testing in 2011 [39]. LY2605541 is a structurally novel basal insulin analog. The
molecular properties of this new analog and its mode of protraction have not been published or presented. LY2963016 is a new insulin glargine product.

One phase 1 study protocol of LY2605541 is mentioned on www.lillytrials.com website. The aim of this study was to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of LY2605541 in 18 Japanese patients with type 2 diabetes mellitus after multiple, daily subcutaneous doses. This study has been completed, but results have not yet been published or presented.

Phase 2 studies:
There are two phase 2 trials registered at ClinicalTrials.gov [37] investigating the clinical efficacy and safety of LY2605541 OD compared to IGLar OD. One is a 16-week crossover trial in type 1 diabetes patients. The other, a parallel trial with a duration of 12 weeks, is performed in type 2 diabetes patients. In the latter trial two dosing algorithms of LY2605541 will be tested. Both phase 2 trials have been completed at the beginning of 2011.

**Sanofi-aventis new basal insulin**
The development of an improved long-acting insulin by sanofi-aventis (Paris, France), SAR161271, was discontinued according to business analysts.

**Biodel**
Biodel (Danbury, CT) has two long-acting basal insulin formulations in the pipeline, both in the preclinical phase of development[37]. BIOD-Adjustable Basal is a modified and possibly improved formulation of IGLar. The main advantage of this new insulin is its availability in long-, medium- and short-acting forms, which could be mixed. This is achieved by adding Generally Recognized as Safe (GRAS) “reduction” excipients. A graph on the www.biodel.com website indicates that the addition of Biodel’s proprietary GRAS ingredients results in a reduction in the duration of action of IGLar in type 1 diabetes patients[37]. Consequently, the duration of this basal insulin could be adjusted and tailored to the patients’ daily glucose profile, monitored with continuous glucose monitoring or an eight-point glucose profile. This could theoretically reduce the risk of hypoglycemia or hyperglycemia.

The preclinical phase includes tests of the new formulation of IGLar compared with unmodified glargine in swine with diabetes. A pharmacokinetic study shows that this new formulation of IGLar has a longer and flatter profile.
Clamp studies in type 1 diabetes patients to confirm the finding of the longer and flatter profile of this new formulation are planned.

The other long acting basal insulin explores a very different concept, called a “smart basal insulin: BIOD-Smart Basal”. This formulation includes IGLar, glucose oxidase and peroxidase at pH ~ 4. The solubility of IGLar is pH dependent, being more soluble at lower pH and less soluble at neutral pH. The combination of glucose oxidase and peroxidase responds to an increased glucose concentration by producing gluconic acid, lowering the pH and thereby increasing the solubility of insulin.

The currently available basal insulins injected in the evening are titrated according to fasting glucose values, although the insulin requirement can easily change during the day. This formulation releases insulin proportional to subcutaneous glucose concentration; it automatically adjusts to unanticipated changes in patient’s insulin needs. This smart-basal insulin could theoretically reduce hypo- and hyperglycemic events because it maintains a more normal glycemic range (e.g. in case of fever, exercise or after a prandial glucoseload). It could also reduce weight gain due to inappropriately high doses with the currently available long-acting basal insulins.

Preclinical studies have demonstrated proof of concept. In vitro studies demonstrated that the amount of insulin released was dependent upon ambient glucose concentration and that the insulin concentration increased in response to a higher glucose concentration. In vivo studies in swine with diabetes compared the use of BIOD-Basal with IGLar. Six fasted pigs with diabetes received either subcutaneous injection of 0.25U/kg of BIOD-Basal or IGLar. Blood glucose was monitored every 15 minutes via a glucose strip. Six hours after the administration of the insulins, they were fed 500 g of swine food as a glucose challenge. BIOD-basal was able to correct the elevated plasma glucose levels faster than IGLar. Subsequently, upon feeding 6 h later, postmeal hyperglycemia was reduced more rapidly in the BIOD-Basal group than in the IGLar group. This study supports the hypothesis that BIOD-Basal releases insulin in response to changing glucose conditions. Ideal future basal insulin may need to be proactive and thus responding to the rate of change of glucose and anticipated hypoglycemia and hyperglycemia.

Patch pumps to provide basal insulin

CeQur (Monreux, Switzerland) is developing a wearable insulin delivery device that delivers insulin subcutaneously. This patch pump delivers both basal and bolus doses and is intended for people with type 2 diabetes who need multiple daily injection insulin therapy. The device can be applied on the patient’s abdominal area
with an adhesive backing. Once in place, insulin is delivered subcutaneously through a cannula from the reservoir. The device offers seven preset basal rates, and a push on the bolus button will release 2 units of insulin. The patch pump can store 300 IU insulin and provides up to 3 days of basal infusion. The CeQur insulin delivery device is designed to use any brand of rapid-acting insulin for both basal and bolus dosing.

An additional feature of this patch pump is that it has a messenger unit that monitors the insulin flow. This messenger unit can warn the patient if the insulin flow is being disrupted. Also, the user will also be notified once the insulin depot is almost finished, and a new patch pump should be applied. Clinical trials have started in Europe in the beginning of 2011.

**Conclusion**

Novo Nordisk’s IDeg is most likely the first new basal insulin to enter the market. Its pharmacodynamic profile seems to allow administration 3W. Phase 2 studies have shown that injection IDeg 3W is comparable in terms of efficacy and safety outcomes to IGLar OD, but preliminary data from the phase 3 program indicate that the non-inferiority criteria with respect to glycemic control against IGLar OD was not met. Furthermore, IDeg dosed OD is associated with a reduction in hypoglycemic events in type 1 diabetes patients compared with IGLar. The final results of phase 3 studies seem to confirm this also in type 2 diabetes.

The two insulins of Biodel and CeQur’s patch pump seem promising. Yet there are no clinical data available to confirm any of the hypothesized benefits. There is only scarce information on Eli Lilly’s new basal insulin and no data on clinical trials are available so far.

Future studies have to indicate if and to what extent the possible candidates for an improved basal insulin are associated with less weight gain. Finally, studies showing acceptable cost-efficacy are crucial, at least in Europe with its current reimbursement climate.
Reference List


27. Gerstein HC. Does insulin therapy promote, reduce, or have a neutral effect on cancers? JAMA 2010; 303(5):446-447.


