Long-acting basal insulin analogs: latest developments and clinical usefulness

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Abstract: All patients with type 1 diabetes mellitus need insulin treatment permanently, and many patients with type 2 diabetes will require insulin therapy. Basal insulin analogs are increasingly used in the treatment of diabetes, with the aim of offering a better replication of the pattern of basal endogenous secretion of insulin. Their flatter pharmacodynamic profile, with a much lower peak of action, their slow and continuous absorption into the systemic circulation, and prolonged duration, more closely duplicate the endogenous insulin secretion leading to physiological basal glycemic control and affording more flexible treatment with fewer hypoglycemia episodes. The basal analogs represent the most significant advances in 'basal insulin' supplementation, and can be used in different insulin regimens achieving the same clinical effectiveness over conventional insulins, with benefits in terms of hypoglycemia and less weight gain, and may be an option for patients with problematic hypoglycemia despite optimization of conventional insulin therapy. At present, there are no data on micro- or macrovascular endpoints, and indeed it is unlikely that these will become available, at least in the foreseeable future. The evidence for basal insulin analogs affecting the risk of cancer is limited, and overriding diabetes indications rather than putative cancer concerns should remain the principal consideration when selecting therapy in patients with diabetes.

Keywords: basal insulin analogs, cancer, clinical effectiveness, diabetes mellitus, hypoglycemia

Introduction

All patients with type 1 diabetes mellitus (T1DM) need insulin treatment permanently, and many patients with type 2 diabetes mellitus (T2DM) fail to sustain long-term, adequate control through lifestyle modifications, or even combined oral antidiabetic drugs (OADs), and will require insulin therapy. Recently, insulin therapy has been recommended during the early phases of the disease, with basal insulin added to the oral drugs.

Until recently, the addition of insulin to OADs has been started with basal neutral protamine Hagedorn (NPH) insulin. Basal insulin analogs, glargine (IGlar) and detemir (IDet), are increasingly being used in the treatment of diabetes, with the aim of offering a better replication of the pattern of basal endogenous secretion of insulin.

Pharmacokinetics and pharmacodynamics

IGlar has been produced by substituting asparagine with glycine in the A-chain at position 21 and adding two arginine residues to the B chain at

positions 31 and 32. These changes shift the isoelectric point towards a more neutral pH, making it less soluble at physiological pH and promoting precipitation following subcutaneous injection [Niswender, 2011]. IGlar has no appreciable peak and a mean ($\pm$ standard error) duration of action of 22 ± 4 h [Heinemann, 2000]. Variation among subjects in the rates of glucose infusion required to maintain euglycemia after injection is also lower than with NPH.

IDet is unique in the sense that a C14 fatty acid has been covalently bonded to lysine in position B29 and the terminal threonine of human insulin in position B30 has been removed. This fatty acid side chain increases self association into hexamers and di-hexamers [Niswender, 2011]. IDet appears to have a shorter time-action profile than IGlar, which is used once daily, and it may be used once or twice-daily dosing [Heinemann, 2000].

Insulin lispro protamine suspension (ILPS) is a protamine-based, intermediate-acting lispro formulation with a similar 24-h duration of action as

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IDet and IGlarg [Hompesch *et al.* 2009]. It may be suitable for either once- or twice-daily dosing.

The longer duration of action of the basal analogs, relative to protaminated or zinc-retarded human insulin, offers better coverage over the between-meal period. Their flatter pharmacodynamic profile, with a much lower peak of action, their slow and continuous absorption into the systemic circulation, and prolonged duration, more closely duplicate the endogenous insulin secretion leading to physiological basal glycemic control, and affording more flexible treatment, with less hypoglycemia.

Clinical effectiveness

T1DM

In most trials of basal-bolus therapy using IGlarg or IDet [Gough, 2007], there were no differences in reduction in glycosylated hemoglobin (HbA1c) between the analog and the NPH insulin group. Nevertheless, studies of up to 6 months in duration generally showed greater decreases in fasting blood glucose (FBG) with basal analogs than with NPH.

IGlarg and IDet, each compared with NPH, were examined to study glycemic control of twice-daily IDet with once-daily IGlarg in type 1 diabetics [Pieber *et al.* 2007]. After 26 weeks, HbA1c decreased to 8.16% with IDet vs 8.19% with IGlarg, Difference IDet-IGlarg: -0.030, but the risk of severe hypoglycemia and the ratios for severe and nocturnal hypoglycemia were statistically significantly lower in favor of IDet.

A meta-analysis of randomized controlled trials (RCTs), reporting comparisons in patients with T1DM and T2DM treated with insulin analogs *versus* regular human insulin, or one long-acting insulin analog *versus* another, found that differences between long-acting insulin analogs and NPH in terms of HbA1c were marginal [Singh *et al.* 2009].

In a review of RCTs in adult (not pregnant women) and pediatric populations utilizing once-daily IGlarg (in basal-bolus regimen) for a minimum of 12 weeks, it was reported that glycemic control is at least comparable to that with NPH [Garg *et al.* 2010].

In a large number of studies examining basal insulins in subjects with T1DM, the benefits with respect to HbA1c are minimal. It is, however important to remember that many of these

studies were conducted as part of a dose-titration approach to demonstrate noninferiority of the analog insulin. There appear to be benefits in terms of reduced episodes of hypoglycemia, and also reduced inter- and intra-individual variability and small benefits in FPG.

T2DM

In type 2 diabetics there are two main approaches to starting insulin therapy: as a basal supplement with an intermediate- to long-acting preparation plus OADs, or as a premixed insulin regimen [Migdalís, 2011]. The most efficacious way of initiating insulin therapy in type 2 diabetic patients who have failed treatment with OADs remains a subject of study.

For persons with T2DM, basal insulin analogs appear to be as effective as NPH when added to OADs. In trials comparing IGlarg or IDet with NPH insulin as once- or twice-daily basal therapy, usually supplementing OADs, HbA1c was generally similar between regimens, but the analog regimens were superior to NPH, in terms of hypoglycemia, postprandial plasma glucose, or weight gain [Gough, 2007].

When IDet was compared with IGlarg, in type 2 diabetics it was found, that a similar proportion of patients reached the primary outcome, and more IDet-treated patients reached HbA1c < 6.5% [Swinnen *et al.* 2010]. A recent review examined four trials lasting 24–52 weeks involving 2250 people randomized to either IDet or IGlarg [Swinnen *et al.* 2011]. Absolute decrease of HbA1c from baseline, and HbA1c equal to or less than 7%, did not differ significantly between treatment groups.

A trial using IDet in basal-bolus therapy in T2DM did not identify a difference in HbA1c or FPG. However, within-person variation in self-monitored blood glucose was significantly lower with the analog regimen [Haak *et al.* 2005].

The efficacy and safety of ILPS has been compared *versus* IGlarg or IDet in RCTs of patients with T2DM [Fogelfeld *et al.* 2010; Koivisto *et al.* 2011], achieving similar glycemic control, with differences in overall hypoglycemia.

Most large studies of T2DM evaluating IGlarg without prandial insulin were performed with the use of bedtime injections. One large study involving subjects with T2DM reported greater

reductions in HbA1c levels with morning rather than bedtime injections of IGlarg (both groups received glimepiride in the morning) [Fritsche *et al.* 2003]. In subjects with T1DM receiving once-daily IGlarg and prandial insulin lispro, the 24-h glucose profiles were identical, regardless of the timing of the injections [Hamann *et al.* 2003].

The smoother profiles of basal analogs and absence of a pronounced peak has the potential to allow larger doses than NPH insulin, allowing for improved fasting glycemic control, without an increased risk of nocturnal hypoglycemia.

In a review, of all RCTs comparing the use of basal insulins in T2DM in which comparable antihyperglycemic efficacy data was reported, it was found few individual differences (in the profiles relating to the frequency of hypoglycemia, treatment-induced weight gain and the number of insulin units needed to achieve the same level of glycemia) between NPH, IGlarg and IDet [Jensen *et al.* 2010]. Furthermore, estimating the number of units of insulin needed to achieve comparable glycemic control, it was described a need for an increased number of units of IDet to achieve comparable HbA1c responses.

To summarize, the basal analogs compared with human long-acting insulins achieve the same glycemic efficacy. There is no clinically relevant difference in efficacy between insulin analogs for targeting hyperglycemia. However, to achieve the same glycemic control IDet was often injected twice daily in a higher dose, while IGlarg was injected once daily.

Special populations

Children and adolescents

There are far fewer data concerning the use of insulin analogs in children. No pharmacokinetic studies have been conducted, although there has been one report of lower nocturnal free insulin levels in children who received IGlarg than in those who received NPH insulin [Mohn *et al.* 2000].

In a study of children, which evaluated the use of IGlarg and NPH with the administration of NPH prior to the study, no significant difference was reported in HbA1c levels between children receiving IGlarg and those receiving NPH [Chase *et al.* 2003].

In a meta-analysis, Singh and colleagues did not observe significant differences between IGlarg and NPH in children and adolescents with T1DM in terms of HbA1c [Singh *et al.* 2009]. The only trial that compared IDet with NPH in children and adolescents showed no significant differences between treatments in terms of HbA1c. The relative risk of nocturnal hypoglycemia and the rate ratios for nocturnal and overall hypoglycemia demonstrated small, statistically significant benefits in favor of IDet.

Pregnant women

The majority of studies on the use of basal insulin analogs in pregnant women with diabetes are small, retrospective, and uncontrolled. The findings from a prospective clinical trial in pregnancy suggest that insulin analogs during pregnancy are not associated with any particular maternal/neonatal morbidity [Negrato *et al.* 2010].

Animal reproduction studies in rabbits and rats revealed no significant differences between IDet and human insulin for embryotoxicity and teratogenicity [Torlone *et al.* 2009].

A safety consideration for basal insulin analog use in diabetic pregnancy is that of insulin antibodies and the passage of insulin across the placenta. The relevance of insulin antibodies to neonatal outcomes is not entirely clear [Lindsay *et al.* 2004].

Basal insulin analogs and body weight

An increase in body weight is a common issue of insulin therapy. In a recent review of 46 studies [Pontiroli *et al.* 2011], the increase in body weight was quantified as an average annual increase of 4.3 ± 2.74 kg (95% CI 4.32–4.38), and correlated with intensity of treatment.

The effects of basal, biphasic, prandial, and basal-bolus insulin analogs on body weight were meta-analyzed from 16 trials and it was identified that biphasic and prandial insulin both caused more weight gain than basal insulin [Giugliano *et al.* 2011]. However, weight gain was limited, at 1 and 1.94 kg, respectively.

While some studies have shown that patients treated with IGlarg initially gain less weight compared with those treated with NPH, no difference between IGlarg and NPH has been noted in patients treated for 1 year. Patients gained

significantly less weight with IGlarg *versus* NPH in the one study where this outcome was reported [Gough, 2007].

For reasons not yet fully understood, some data indicate that IDet has a weight-sparing effect [Bush, 2007]. Trials in patients with T1DM and T2DM have reported significantly less weight gain in comparison with NPH [Hermansen and Davies, 2007]. Moreover, in a study where patients with T2DM were switched from NPH or IGlarg to IDet in combination with OADs, 14 weeks after the switch mean body weight was significantly reduced in patients previously using both NPH and IGlarg [Dornhorst *et al.* 2008]. Hallschmid and colleagues in comparing acute effects of human insulin and IDet on electroencephalography measures and food intake found an enhanced anorexigenic impact of IDet compared with human insulin on the central nervous networks that control nutrient uptake [Hallschmid *et al.* 2010].

In a recent review, the aim of which was to investigate the impact of IGlarg once daily or IDet once or twice daily on weight gain in relation to reductions in HbA1c [Dailey *et al.* 2010], the pooled analysis presented confirmed that the weight gain with IGlarg does not differ from IDet when adjusted for the reduction in HbA1c. Individuals treated with IDet, however, required a higher daily dose compared with the individuals treated with IGlarg in order to achieve the same HbA1c reduction. Therefore, at equipotent dosage, the weight gain was not significantly different between the two basal insulin preparations.

Basal insulin analogs and hypoglycemia

Hypoglycemia has for the most part been inadequately studied for both IGlarg and IDet. Reporting hypoglycemia in the RCTs comparing basal insulin analogs with NPH has not followed a consistent approach, with absolute values used to define low glucose ranging from < 4.0 mmol/L to < 2.0 mmol/L. Moreover, nearly all adequately powered trials to date have reported hypoglycemia only as a secondary endpoint and have not been designed appropriately to compare rates. The majority of trials to date have actively excluded those patients with previous recurrent severe hypoglycemia, or impaired awareness of hypoglycemia [Pickup and Sutton, 2008]. Trial participants with T1DM have tended to be relatively young with a lower mean duration of diabetes of

usually less than 20 years, whereas those with T2DM have had a relatively short duration of preceding insulin therapy. This, in addition to inconsistencies and inadequacies in collecting/reporting hypoglycemia, means that only limited interpretations of the data can be made for those with long-duration T1DM, and in particular, impaired awareness of hypoglycemia or long-duration, more insulin-deficient T2DM. Further research in this area is ongoing.

In keeping with their flatter pharmacokinetic and pharmacodynamic profiles [Porcellati *et al.* 2011], lower rates of overnight hypoglycemia were to be expected with the long-acting analogs, and the evidence confirms that for the most part, this promise is delivered [Arutchev *et al.* 2009].

Reductions in hypoglycemia, particularly nocturnal hypoglycemia, were found in most of the trials with IGlarg and IDet [Gough, 2007]. Lower rates of overnight hypoglycemia have also been demonstrated in T2DM with both IGlarg and IDet across the full range of HbA1c. A meta-analysis of four of the studies that compared IGlarg with NPH as basal therapy in T2DM showed reductions in the incidence of overall symptomatic, nocturnal, severe and severe nocturnal hypoglycemia [Rosenstock *et al.* 2005].

The safety of ILPS has been studied versus IGlarg or IDet, in addition to OADs, or in a basal-bolus regimen, in RCTs of patients with T2DM [Fogelfeld *et al.* 2010; Koivisto *et al.* 2011]. It was resulted a non-inferior glycemic control with ILPS compared with IGlarg or IDet. A significantly higher incidence of nocturnal hypoglycemia was observed for patients injecting ILPS twice daily versus IGlarg, but not for patients injecting ILPS once daily.

Newer studies should be adequately designed to capture optimally hypoglycemia incidence/severity, including silent nocturnal events, perhaps by more accurate continuous glucose monitoring devices powered to detect hypoglycemia-specific differences.

Basal insulin analogs and cancer

There is a continuing debate concerning the risk of cancer and the association with insulin use. Currently available insulin analogs exhibit an affinity for the type 1 insulin growth factor receptor ranging between 16% and 641% relative to

native human insulin, depending on the specific insulin analog and cell line studied [Kurtzahls *et al.* 2000; Sommerfeld *et al.* 2010; Ciaraldi *et al.* 2001]. The speed of insulin dissociation from the insulin receptor may also contribute to the mitogenic potential of insulin analogs [Kurtzahls *et al.* 2000]. The mitogenic potential of insulin analogs was investigated in studies performed *in vitro* with different cell lines, and the increased mitogenic potency was observed only in the studies with human osteosarcoma cells [Zib and Raskin, 2006; Kurtzahls *et al.* 2000].

In recently published analyses of epidemiological studies investigating the effects of insulin use on cancer risk [Dejgaard *et al.* 2009; Hemkens *et al.* 2009; Jonasson *et al.* 2009; Colhoun *et al.* 2009; Rosenstock *et al.* 2009; Home and Lagarenne, 2009; Currie *et al.* 2009], various results have been reported, and, however, are liable to a number of inherent weaknesses in the study design, the main limitation being the inability to control for confounding factors, which importantly included weight, duration of diabetes, and smoking in some instances. However, as these *post hoc* analyses were based on limited duration trials that were not specifically designed to investigate mitogenic potential, these findings should also be interpreted with caution.

No evidence for increased cancer risk has been reported in newer studies [Rosenstock *et al.* 2009], or meta-analyses, in patients treated with IDet, IGLarg, or NPH insulin [Home and Lagarenne, 2009; Dejgaard *et al.* 2009].

Other pharmacokinetic issues must also be considered. It is not clear whether there is a biologic difference between the exposure of neoplastic cells to fluctuating levels of endogenous insulin observed under normal physiologic conditions compared with the levels of endogenous insulin noted in obesity, T2DM, and/or after administration of exogenous human or synthetic insulins. It is also critical to recognize that cancer cells in patients with T2DM may be exposed to abnormally high levels of endogenous insulin for many years prior to the administration of exogenous insulin.

It is not possible to draw definite conclusions on the risk of cancer promotion of insulin analogs based on the published clinical data from different studies that did not have sufficiently long-term duration and size. The European Association

for the Study of Diabetes, the American Diabetes Association (ADA), and the International Society for Pediatric and Adolescent Diabetes have issued statements that the present data on the link between insulin analogs and cancer are not conclusive and further studies should be conducted [Werner *et al.* 2011].

The recently published consensus guidelines issued by the ADA and American Cancer Society conclude that the evidence for specific diabetes drugs affecting the risk of cancer is limited, and that overriding diabetes indications rather than putative cancer concerns should remain the principal consideration when selecting therapy in patients with type 2 diabetes [Giovannucci *et al.* 2010].

Basal insulin analogs and diabetic complications

It is known that tight glycemic control is associated with significant reductions in diabetic complications. Whether the observed effects are treatment-specific, or related to tight blood glucose control, remains a matter of debate. A retrospective database analysis suggested a reduced risk of acute myocardial infarction in patients treated with IGLarg compared with NPH [Rhoads *et al.* 2009]. In a meta-analysis of RCTs that reported data and comparisons among patients with T1DM and T2DM treated with insulin analogs *versus* regular human insulin or one long-acting insulin analog *versus* another, it was demonstrated that studies of insulin analogs were not sufficiently powered or of adequate duration to measure differences in long-term diabetes-related complications or death [Singh *et al.* 2009].

Basal insulin analogs and quality of life

Few of the studies have reported on patient satisfaction with treatment or quality of life. This suggests that these outcomes are rarely measured or are selectively reported. When data for these outcomes were available, substantial heterogeneity in methods across studies precluded pooling of the results. Some studies reported that insulin analogs are statistically significantly superior to conventional insulins in terms of quality of life [Poon and King, 2010]. However, results were inconsistent and differences often appeared to be small and of uncertain clinical significance.

Novel insulins

Insulin degludec

Insulin degludec (IDeg) is a long-acting basal insulin analog with a longer duration of action (measured beyond 42 h) 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 acid side chain has been connected to the LysB29 by a glutamic acid spacer [Meneghini and Bresta, 2012]. The mode of protraction includes soluble multihexamer formation and binding to albumin, from which monomers gradually separate and are absorbed into the circulation, resulting in a flat and stable pharmacokinetic profile. These features suggest that the risk of hypoglycemia might be reduced, and clinical effectiveness might be achievable with dosing once a day or three times a week.

In phase III comparative studies IDeg appears to have similar glycemic control to IGlarg in patients with both T1DM and T2DM, with consistently lower risk of hypoglycemia, especially nocturnal [Meneghini and Bresta M, 2012].

IDeg represents a new generation of ultralong-acting basal insulin preparations that confer similar efficacy but improved safety for patients with insulin-requiring diabetes.

Lilly basal insulin

Eli Lilly is developing two new long-acting basal insulin analogs, registered as LY2605541 and LY2963016 [Esposito and Giugliano, 2012]. LY2605541 is a structurally novel pegylated basal insulin analog. LY2963016 is a new insulin glargine product.

Cost-effectiveness of insulin analogs

An analysis of the cost-effectiveness of insulin analogs compared with conventional insulins in the management of T1DM or T2DM in adults, found that the cost-effectiveness of insulin analogs depends the type of insulin analog and whether the patients receiving the treatment has T1DM or T2DM [Cameron and Bennett, 2009].

With the exception of rapid-acting insulin analogs in T1DM, routine use of insulin analogs,

especially long-acting analogs in T2DM, is unlikely to represent an efficient use of finite healthcare resources.

Conclusion

Current insulin-replacement therapy in diabetic people is still imperfect. The pharmacodynamic and pharmacokinetic profiles of current insulin analogs offer discrete advantage over human insulins.

The currently available, long-acting insulin analogs represent the most significant advances in 'basal insulin' supplementation and can be used in different insulin regimens. Offering the same clinical effectiveness over conventional insulins with benefits in terms of hypoglycemia and less weight gain, they may be an option for patients with problematic hypoglycemia despite optimization of conventional insulin therapy. At present, there are no data on micro- or macrovascular endpoints, and indeed it is unlikely that these will become available, at least in the foreseeable future.

IDeg, a new generation of ultralong-acting basal insulin preparations, has the potential to broaden further the options for diabetes treatment with a possible thrice-weekly dosing regimen, and may facilitate insulin management for patients and physicians.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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