REVIEW

Analog insulin detemir for patients with type 1 and type 2 diabetes: a review

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Objective: To review insulin detemir for clinical use to better manage patients with type 1 and type 2 diabetes.

Methods: A MEDLINE search, in English, from June 30, 2006 to December 1, 2008, using the terms "insulin analogs," "insulin detemir" and "long-acting insulin analog."

Results: Insulin detemir improves glycemic control, based on HbA_{1C} reduction and fasting glucose levels, without increasing the risk of hypoglycemia and weight gain. Insulin detemir has lower glycemic variability, with less intra-subject variability in blood glucose levels in patients with type 1 and type 2 diabetes, without increasing the risk of hypoglycemia. When added to oral anti-diabetes agents (OADs) in type 2 diabetes, insulin detemir demonstrates superiority to other basal insulin options.

Conclusion: Insulin detemir appears to provide better glycemic control with a lower risk of hypoglycemia and less weight gain in the treatment of patients with type 1 and type 2 diabetes.

Keywords: type 1 diabetes, type 2 diabetes, insulin analogs, insulin detemir

Introduction

This review examines the most recent MEDLINE search, and updates a previous review of insulin detemir compiled through June 30, 2006.[1] This long-acting basal analog has unique properties including a more consistent pharmacodynamic profile, with less glycemic variability, a lower risk of hypoglycemia and less weight gain. Insulin detemir appears to be the most suitable choice of basal insulin for clinicians who treat diabetes.

Normalization of glucose levels is the primary goal of managing patients with diabetes. The Diabetes Control and Complications Trial (DCCT), and the United Kingdom Prospective Diabetes Study (UKPDS), unequivocally demonstrated that tight metabolic control reduces the incidence, and also delays the development, of complications in patients with type 1 and type 2 diabetes, respectively.[2–7] The DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) proved that intensive diabetes therapy had long-term beneficial effects by reducing the risk of cardiovascular disease in patients with type 1 diabetes after 17 years of treatment.[8] Intensive therapy in the DCCT/EDIC trial was defined as basal insulin with pre-prandial short-acting insulin, or continuous insulin infusion. Intensive insulin therapy replicates normal physiology, utilizing a long-acting insulin analog, which provides a basal dose of insulin throughout the day, and adding short-acting insulin analog for mealtime dosing.

In type 1 diabetes, insulin is fundamental, utilizing a long-acting analog (qd/bid), or a continuous, variable, subcutaneous infusion of short-acting analog insulin,

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supplemented with meal time short-acting analog bolus therapy. Insulin should be initiated early in the course of diabetes to attain optimal glucose control. Intensive management of type 2 diabetes, as in the Steno-2 Study, was associated with an average reduction of cardiovascular events by 7.8 years, as well as reduction in nephropathy, retinopathy and autonomic neuropathy by about half compared with a conventional multifactorial treatment.[9]

More recently, three large clinical studies, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease (ADVANCE) trial, and the Veterans' Administration Diabetes Trial (VADT), invoked controversy.[10] In ACCORD, all 10,251 patients were randomly assigned to receive comprehensive intensive therapy targeting a glycated hemoglobin level of less than 6.0% or to receive standard therapy targeting a level of 7.0% to 7.9%. With the use of a double two-by-two factorial design, 4733 patients were randomly assigned to lower their blood pressure by receiving either intensive therapy (systolic blood-pressure target, <120 mmHg) or standard therapy (systolic blood-pressure target, <140 mmHg). In addition, 5518 patients were randomly assigned to receive either fenofibrate or placebo while maintaining good control of low-density lipoprotein cholesterol with simvastatin. The blood-pressure and lipid trials are continuing, and results for these remain masked. Of note, in ACCORD, all oral anti-diabetes agents (OADs), including multiple sulfonylureas, biguanides, alpha glucosidase reductase inhibitors and thiazolidinedione agents, were utilized to provide "intensive glycemic control," and it was this multi-drug treatment group that was terminated early, due to a higher rate of all cause mortality, although lower than predicted. This intensive group had significantly fewer nonfatal myocardial infarctions. The results of ADVANCE and the VADT conflict with ACCORD and beg the question for more uniformity of diabetes management, limiting the number of oral agents and utilizing insulin as basal, bolus or combinations of both when intensifying blood glucose levels.

The rate of hypoglycemic events was significantly more in all of these trials when diabetes management was intensified, irrespective of the use of insulin therapy. Future studies will need to examine insulin therapy in type 2 diabetes with limited use of OADs, quite possibly to metformin as the lone oral agent, since it has already demonstrated cardiovascular risk reduction in UKPDS.[11] Potentially, a basal bolus arm should be considered in type 2 diabetes.

In the future, studies will examine cardiovascular risk reduction in type 1 and type 2 diabetes with a greater intent to define hypoglycemia as a major contributing cause of morbidity and death. Cardiovascular risk reduction trials will focus on glucose variability and targeting near-normal glycemic levels utilizing strategies and therapies which reduce postprandial glucose levels, and lower rates of hypoglycemia as well as technologies to better measure hypoglycemia, like continuous glucose sensing (CGM).[12–15]

Hypoglycemia and weight gain are beguiling issues for patients with type 1 and 2 diabetes, especially with intensive reduction of glucose levels. Theories abound, but there is evidence that basal insulin detemir is a predictable basal insulin with lower glycemic variability. These unique properties have been associated with less weight gain compared to NPH and glargine.

Glycemic variability

Insulin glargine is a modification of the amino acid sequence of human insulin, in that two arginine residues added to the C terminus of the B-chain shift the isoelectric point from pH 5.4 to 6.7[19]. Insulin glargine is injected as a solute in an acidic formulation, forms a microprecipitate in the (neutral pH) subcutaneous tissue, and has a prolonged duration of action due to its slow dissolution of the precipitate. Insulin glargine has a prolonged duration of action and is indicated for once-daily dosing. The precipitate depot represents a potential source of variability.

Insulin detemir's formulation is remarkably different from other basal insulins. The prolonged action of insulin detemir is accomplished by attaching a 14-carbon fatty acid chain (myristic acid) to the lysine residue at position B29 such that each monomer bears a myristic acid side chain. This side chain contributes to enhanced self-association of insulin detemir molecules in the subcutaneous depot and albumin binding in the subcutaneous depot, circulation and the interstitial tissue, resulting in a substantial prolongation of action. Insulin detemir is a clear neutral solution that is 98% albumin bound, with a duration of action of 24 hours, indicated for once- or twice-daily dosing, having an important buffering effect to limit pharmacodynamic variability.

Insulin glargine, on the other hand, is a modification of the amino acid sequence of human insulin, with two arginine residues added to the C terminus of the B-chain shifting the isoelectric point from pH 5.4 to 6.7[19]. Insulin glargine is injected as a solute in an acidic formulation and forms a microprecipitate in the (neutral pH) subcutaneous tissue. The prolonged duration of action of this basal insulin is due to its slow dissolution of the precipitate which represents a potential source of its variability.

Heise reviewed the pharmacodynamics data of both insulin detemir and glargine as derived with the glucose clamp technique. In this review, the common definition for duration of action (time from injection to plasma glucose >8.3 mmol/L) was applied, and study data were recalculated when necessary. Despite differences in methodological details, the results of most clamp studies were very consistent. Both analogs demonstrated a similar "gentle rise and fall in glucose-lowering action" over time. The duration of action with both analogs is dose dependent, ranging from of 0.35 to 0.8 U/kg, and close to 24 hours in patients with type 1 diabetes. The dose range may be higher in type 2 diabetes. While both analogs seem to be very similar with regard to the mean shape of their pharmacodynamics profile and duration of action, detemir demonstrates less within-subject variability in its metabolic effect. These findings in experimental glucose clamp studies are consistent with observations in clinical trials and support routine once daily use with either analog.

Danne et al compared the within-subject variability of insulin detemir and glargine in children and adolescents with type 1 diabetes in a recent, doubled blind, crossover trial.[16] Thirty-two children and adolescents (19 girls and 13 boys; mean $\pm$ SD: age 13 ± 2.5 years and type 1 diabetes duration 6.3 ± 3.0 years) with a hemoglobin A1c (HbA_{1c}) of $7.9\% \pm 1.0\%$, were randomized to a specific treatment sequence in which a dose of 0.4 U/kg of insulin detemir and insulin glargine was injected subcutaneously 24 hours apart at each of two dosing visits. Insulin detemir showed statistically significantly less within-subject variability compared with insulin glargine for children aged 8 to 12 years and adolescents 13 to 17 years. No safety concerns were raised during the trial. In a previous euglycemic clamp study involving patients with type 1 diabetes, by the same authors, the pharmacokinetic/pharmacodynamic properties of insulin detemir did not differ across all age groups including adults, ages 18 to 65 years.[17] However, there appeared to be a greater sensitivity for patients over the age of 65 years, suggesting that slightly lower dosing may be as effective.

Insulin determir: once or twice daily dosing

In the just published ADAPT trial, Le Floch et al showed no difference in efficacy between once-daily and twice-daily dosing of insulin detemir in 520 patients with type 1 diabetes. Of interest is that patients who received detemir once daily had a lower total daily dose than the twice-daily group.[18] In this 7-month trial, HbA_{1c} at 4 months was 8.1 ± 0.9 vs $8.0\% \pm 1.0\%$ with qd and bid detemir, respectively, with an adjusted between-group difference of 0.12% (95% CI -0.01; 0.25%), showing non-inferiority for qd dosing. Similar results were found in the per protocol population. Improvement in HbA_{1c} was similar in both groups (-0.4 ± 0.8 vs $-0.5\% \pm 0.8\%$; $p = 0.09$, NS), but with differences in the 7-point glucose profile. Detemir doses were lower (29 ± 18 vs 39 ± 20 U/d, $p < 0.001$), but aspart doses higher (34 ± 17 vs 26 ± 14 IU/d, $p < 0.001$) with qd detemir. At 7 months, HbA_{1c} decreased slightly in patients switched from qd to bid (8.2 ± 0.8 vs $8.0\% \pm 0.8\%$; $p = 0.34$, NS) in association with increased total insulin doses ($p < 0.05$) but HbA_{1c} increased in those switched from bid to qd (7.2 ± 0.9 vs $7.6\% \pm 0.8\%$; $p < 0.05$) in association with decreased doses ($p < 0.05$).

Efficacy: reduction of HbA_{1c}

Insulin detemir has proven efficacy in type 1 and type 2 diabetes. Prior to 2006 several studies compared the efficacy of insulin detemir in both a once- and twice-daily dosing regimen with NPH insulin.[19–27] All trials were multicenter, randomized, parallel-group and open-labeled. Most studies were conducted in patients with type 1 diabetes, and three large studies were conducted involving patients with type 2 diabetes.

The Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation (PREDICTIVE) Study is a global, multi-center, open-label, observational study in patients with type 1 or type 2 diabetes who were transferred to insulin detemir for the management of their blood glucose. The information obtained from this trial reflects a "real world" experience and involves more than 30000 patients throughout the world. Of note, among the PREDICTIVE trials, the subgroup analysis of the German cohort of patients with type 2 diabetes (n = 6000),[28] and the Predictive 303 study,[29] demonstrated superior HbA_{1c} reduction with insulin detemir, in patients with type 2 diabetes, previously treated with OADs, alone, or in combination with NPH or glargine.

Insulin detemir-treated patients achieved a HbA_{1c} reduction of $1.1\% \pm 0.03\%$ ($p < 0.0001$), achieving a mean HbA_{1c} at the end of study of $7.2\% \pm 0.02\%$. When insulin detemir was added to OADs, HbA_{1c} decreased $1.29\% \pm 0.3\%$ ($p < 0.0001$ from baseline), and those transitioning from NPH or glargine had an additional reduction in HbA_{1c} of $0.6 \pm 0.9\%$, and $0.59\% \pm 0.6\%$ ($p < 0.0001$), respectively. At the end of the study, 42.2% of patients achieved a HbA_{1c} of less than 7%, compared to 10.8% at baseline ($p < 0.0001$). These studies demonstrate the efficacy of insulin detemir as

the initial basal insulin for naïve patients on OADs, as well as more beneficial improvement in glycemic control when patients were switched from NPH or glargine.

The Predictive 303 study (n = 5604) evaluated the effectiveness of insulin detemir, using a simplified patient self-adjusted dosing algorithm (303 Algorithm group) compared with standard-of-care physician-driven adjustments (Standard-of-care group) in a predominantly primary care setting, over a period of 6 months. Insulin detemir was initiated once daily as add-on therapy to OADs, or as a replacement of pre-study basal insulin (NPH or glargine) in patients with type 2 diabetes. The self-adjusted 303 Algorithm group changed their insulin detemir dose every 3 days based on the mean of three "adjusted" fasting plasma glucose (aFPG) values (capillary blood glucose calibrated to equivalent plasma glucose values) using a simple algorithm: when the mean aFPG is <80 mg/dL (4.4 mmol/L), reduce dose by 3 U; when aFPG is between 80 and 110 mg/dL (4.4–6.1 mmol/l), no change; when aFPG is >110 mg/dL (1.1 mmol/L), increase dose by 3 U. The dose of insulin detemir for patients in the standard-of-care group was adjusted by the investigator as they normally would do in their practice. Mean HbA_{1c} levels decreased from 8.5% at baseline to 7.9% at 26 weeks for the 303 Algorithm group and from 8.5% to 8.0% for the Standard-of-care group (p = 0.0106 for difference in HbA_{1c} reduction between the two groups).

Fasting glucose

Fasting plasma glucose (FPG) levels were significantly reduced in the German cohort, with mean FPG levels reduced by 49.8 ± 1 mg/dL (p < 0.0001).

Mean FPG values decreased from 175 mg/dL at baseline to 141 mg/dL for the 303 Algorithm group and decreased from 174 mg/dL to 152 mg/dL for the Standard-of-care group (p < 0.0001 difference in FPG reduction between the two groups).

Lower rate of hypoglycemia

In the German cohort, baseline total, daytime and nocturnal hypoglycemic events (3.3, 2.0 and 1.3 events per patient year, respectively) decreased by 2.7, 1.6 and 1.2, respectively (p < 0.0001) during the study as did the percentage of patients experiencing these events (7.2%, 5.5% and 3.7% at baseline compared to 2.0%, 1.6% and 0.5% at follow up). In Predictive 303, the overall rate of hypoglycemia (events/patient/year) decreased significantly from baseline in both groups (from 9.05 to 6.44 for the 303 Algorithm group (p = 0.0039) and from 9.53 to 4.95 for the Standard-of-care

group p < 0.0001). Major hypoglycemic events were rare in both groups (0.26 events/patient/year for the 303 Algorithm group and 0.20 events/patient/year for the Standard-of-care group; p = 0.2395).

Less weight gain

In Predictive, rather than expected weight gain, with improved glycemic control, overall reduction in glucose levels was accompanied by a 0.9 ± 0.1 kg weight reduction (p < 0.0001). Specifically, when patients were transitioned from the three groups: OADs alone; OADs with NPH, or insulin glargine, weight reductions of 0.9 ± 0.1 kg (p < 0.0001), 0.9 ± 0.3 kg (p = 0.00099) and 0.8 ± 0.2 kg (p < 0.0001) were noted. Strikingly, when glycemic control improved, the rate of hypoglycemia and weight loss was significantly lower than expectations from previous studies with other basal insulins. In the Predictive 303 study, mean body weight remained the same at 26 weeks in both groups (change from baseline 0.1 and −0.2 kg for the 303 Algorithm group and the Standard-of-care groups respectively). At 26 weeks, 91% of the patients in the 303 Algorithm group and 85% of the patients in the Standard-of-care group remained on once-daily insulin detemir administration.

Interestingly, in another 52-week trial, when insulin detemir was titrated based on pre-breakfast and pre-dinner plasma glucose target of 108 mg/dL or less, the patients who were adjusted to twice-daily dosing had less overall weight loss compared to insulin glargine. If glargine had been titrated in the same manner to twice-daily dosing based on the same titration as detemir, glargine would have been dosed twice daily as often as detemir and possibly would have been higher. Nevertheless, insulin detemir had superior HbA_{1c} reduction, less hypoglycemia, and weight gain was lower, 3.0 kg for detemir compared to 3.9 kg for the glargine group.[30]

The most recent Predictive BMI study was the first study to examine the effect of once-daily detemir with weight as the primary endpoint in a large population of overweight type 2 diabetes patients. Use of once-daily detemir for intensification of insulin therapy resulted in less weight gain, less hypoglycemia and equivalent glycemic control compared with NPH.[31] At 26 weeks, weight had increased significantly less with detemir (0.4 kg) than with NPH (1.9 kg; difference 1.5 kg, p < 0.0001). The BMI increase was also less with detemir than with NPH (difference 0.6 kg/m², p < 0.0001). The HbA_{1c} decrease was not significantly different, from 8.9% to 7.8% with detemir and from 8.8% to 7.8% with NPH. The incidence of hypoglycemia was lower with deemed

and relative risks 0.62 (all events) and 0.43 (nocturnal) (p < 0.0001 for both).

Conclusion

Insulin detemir is the most suitable basal analog insulin, with lower within-patient variability, and consistent reductions in FPG levels. The pharmocokinetic/pharmacodynamic properties of insulin detemir have demonstrated lower rates of hypoglycemia and weight gain, making it an ideal choice to manage patients with diabetes.

Trials intended to reduce cardiovascular risk should continue to explore the benefits of intensification and normalization of glucose levels. The management of these patients with type 2 diabetes should be simplified with metformin alone and insulin detemir with the intention of focusing on hypoglycemic events. Another consideration in the future will be to analyze the total daily insulin dose and, specifically, to limit the total basal insulin dose to less than 50% of total, and ideally less than 0.5 U/kg, since this has been associated with superior glycemic control, lower fasting glucose levels and less weight gain.[32] Insulin detemir should be given strong consideration as basal insulin diabetes management. Recent information is compelling to suggest this basal analog insulin as the agent of choice in type 2 diabetes.

Disclosures

The author is a clinical investigator, a paid consultant, and owns common stock (individual investment) in Novo Nordisk, Inc. He is also a paid consultant and clinical investigator for Lilly, Sanofi-Aventis, Pfizer, Merck, Medtronic, Inc., and Johnson and Johnson. The author is also a paid consultant, clinical investigator and owns common stock (individual investment) in Amylin Pharmaceuticals.

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