REVIEW

Treatment of Type 1 and Type 2 Diabetes Mellitus with Insulin Detemir, a Long-Acting Insulin Analog

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Abstract: Insulin detemir is a long-acting basal insulin approved for use in patients with type 1 (T1DM) or type 2 diabetes (T2DM). Insulin detemir has demonstrated equivalent glycemic control and hypoglycemic risk when compared to insulin glargine, and insulin detemir has generally but not consistently demonstrated less weight gain than insulin glargine in T2DM. The benefits of basal insulin analogs relative to NPH insulin are well recognized, including less FBG variability, lower risk of hypoglycemia, and less weight gain specifically with insulin detemir. However, NPH insulin continues to be widely prescribed, which may be due in part to economic considerations. While NPH insulin generally costs less per prescription, insulin detemir has been shown to be cost effective compared to NPH insulin as well as insulin glargine. Therefore, insulin detemir is an effective option from both clinical and economic perspectives for patients with T1DM or T2DM who require basal insulin to achieve glycemic control.

Keywords: diabetes mellitus, basal insulins, insulin detemir

Introduction

Diabetes mellitus (diabetes) is a growing epidemic. In 2000, there were an estimated 171 million people world-wide with diabetes, a number that is expected to more than double to 366 million by 2030.[1] The United States (US) is no exception. In 2007, an estimated 23.6 million people had diabetes including 1.6 million newly diagnosed cases in adults resulting in a prevalence of approximately 7.8%.[2] In addition to the well-known health implications, which include cardiovascular disease, neuropathy, and nephropathy, the economic effects are substantial. The American Diabetes Association estimates that the economic burden of diabetes in the US in 2007 was $174 billion, and that a person diagnosed with diabetes had medical expenditures approximately 2.3 times higher than those without the diagnosis.[3]

The underlying causes of type 1 diabetes (T1DM) and type 2 diabetes (T2DM) are both likely combinations of genetic predisposition and environmental exposures.[4,5] The resulting macro- and micro-vascular complications of the disease include cardiovascular disease, renal disease, retinopathy, and neuropathy. Recent studies have found that diabetes is associated with a two- to four-fold increased risk of cardiovascular disease and events such as heart disease and stroke.[6,7] A second diabetes-related complication with severe consequences for morbidity and mortality is renal disease. As diabetic nephropathy is the most common cause of end-stage renal disease, the five-fold prevalence increase from 1980 to 2001 is due largely to diabetes.[8] This increasing prevalence is significant as chronic kidney disease and end-stage renal disease is associated with neuropathies, increased risk of lower-extremity amputation, cardiac arrhythmias, and increased medical costs which have been estimated at $5,439 per employee per month in the average working population.[8,9]

Lifestyle modification is a first-line approach to prevent or minimize diabetes complications and includes improved diet and regular physical activity. Various studies have found that lifestyle interventions alone can reduce the risk of developing or slow the progression of T2DM.[10–12] Pharmacotherapy options for treating T2DM include insulin, sulfonylureas, biguanides, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists.[11,13,14] Insulin therapy is life-sustaining in the management of T1DM and is often used in T2DM cases as the disease progresses and glycemic control is lost. Recognized as the most effective diabetic medication for treating hyperglycemia, insulin dosages can be increased until the desired therapeutic effect is achieved.[15,16]

A major goal of insulin therapy is to mimic the normal physiologic patterns of insulin secretion. This pattern includes bolus insulin secretions in response to food intake and sustained basal secretions that maintain a minimal level of insulin throughout the day. Basal insulin secretion is essential for controlling blood glucose levels as it regulates hepatic glucose production and uptake by target tissues between meals and at night.[17,18] Basal insulin is essential in patients with T1DM and can provide additional glucose control to help overcome insulin resistance and under-secretion in patients with T2DM. As a result, long acting insulins such as neutral protamine Hagedorn insulin (NPH), insulin glargine, and insulin detemir have been developed. Due to their slow-release formulations, long acting insulins help provide better glycemic control, and can reduce the risk of hypoglycemia.[19,20]

Additional benefits with the long acting insulins may occur through decreased fasting plasma glucose (FPG) variability. An observational study of 1,409 type 2 diabetics (age 56–74) found that patients with moderate and high variation in FPG had approximately a 65% higher risk of all-cause mortality compared to patients with the lowest FBG variation over a 10 year period ($P < 0.001$). Even when mean FPG was accounted for in the analysis, FPG variation had a greater prognostic value.[21] Decreased FPG variability may also be beneficial when intensive glucose-lowering therapy is initiated. When the target FPG is lowered, the combination of the lower FPG goal and inherent variability can increase the risk of severe hypoglycemia. As severe hypoglycemia can result in complications ranging from unconsciousness to myocardial ischemia and death,[22] decreases in FPG variability may lower complications associated with intensive therapy. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found an increase in all cause mortality in patients randomized to the intensive-therapy group (target hemoglobin A1c [HbA1c] less than 6%) compared to the standard therapy group (target HbA1c 7.0%–7.9%) (hazard

ratio of 1.22, 95% CI: 1.01 to 1.46). Although the study was not designed to identify specific causes, the difference in the rates of hypoglycemia was included as a possible contributing factor.[23]

Recognizing the role of basal insulins in treating T1DM and T2DM, this paper specifically reviews the evidence related to the use of insulin detemir. The data reviewed includes randomized clinical trial data and observational trial data, as well as data from database studies and pharmacoeconomic evaluations. The purpose is to present these data and assess insulin detemir's place in diabetes therapy.

Pharmacology

Insulin detemir is a long acting basal insulin analog produced through the use of recombinant DNA technology. Insulin detemir differs from human insulin in two respects. First, the amino acid threonine is removed from position B30. Second, a 14-carbon fatty acid chain is attached to the amino acid lysine at B29.[24,25] These changes allow the detemir molecule to form stable hexamers and dihexamers, which delays and creates a more consistent absorption profile. The fatty acid chain also allows insulin detemir to be soluble in a neutral solution, preventing precipitation during administration. This is significant as both NPH insulin and insulin glargine form a precipitate at some point during the administration process. As precipitation and dissolution are unpredictable, this can lead to variations in absorption and insulin action.[26] Albumin binding at the injection site further delays absorption through the capillary wall and into the blood stream, allowing for a slow release over a long period of time which increases the duration of action.[25] Because approximately 98% of insulin detemir in circulation is bound to albumin, this creates a buffer and minimizes changes in insulin activity associated with insulin detemir.[26] Overall, these changes result in a longer and more consistent duration of action.

While insulin detemir's duration of action is longer than regular human insulin, most of the early studies of insulin detemir involved a twice-daily dosing regimen. However, recent studies have found that a once-daily regimen may be just as effective. Insulin detemir has been shown to have a dose-dependent duration of action. One study found that a dose of 0.4 U/kg had a duration of action of 20 hours,

potentially allowing a once-daily dosing regimen. For lower doses, twice-daily dosing may be required due to a shorter duration of action.[27] Le Floch et al compared the results of once-and twice-daily insulin detemir dosing in patients with T1DM on a basal-bolus regimen over a 7-month period.[28] They found similar HbA1c improvements in the two treatment groups, demonstrating non-inferiority of the once-daily dosing regimen. They also found that daily insulin detemir doses were lower with the once-daily dosing. A study by Fontaine et al comparing the outcomes in both T1DM and T2DM on once-and twice-daily dosing regimens found that once-daily dosing was associated with better glycemic control compared with twice-daily dosing.[29] This study also found lower daily doses with the once-daily regimen. Although these studies had limitations (ie, open label design), they show that there may not be an advantage to twice-daily dosing when starting an insulin detemir regimen. Careful clinical judgment should be used to determine the intensity of the insulin regimen required for a given patient, including the use of twice-daily dosing as needed to maintain adequate glycemic control.

Clinical Studies

There is an abundance of data in the literature from clinical trials on the use of insulin detemir in patients with T1DM or T2DM. These studies have compared insulin detemir to NPH insulin and insulin glargine in both T1DM and T2DM, as well as to oral antidiabetic therapy in T2DM. The clinical differences between insulin detemir and NPH insulin are well established and basal analog insulins are recognized as preferred over NPH insulin in treatment guidelines.[30] However, many patients and clinicians continue to utilize NPH insulin, possibly for economic considerations. Thus, an insulin detemir and NPH insulin comparison is included for comprehensiveness.

Type 1 Diabetes Mellitus
Detemir/Glargine
When compared to insulin glargine in two clinical trials, similar levels of glycemic control and effect on weight were identified in patients with T1DM (Table 1).[31,32] These open label trials found no differences between insulin detemir and insulin glargine with regards to HbA1c improvement or overall risk

Table 1. Clinical studies in of insulin detemir versus NPH or insulin glargine in patients with type 1 diabetes mellitus.

Type 1 diabetes reference	Study design*	N	Treatment regimen
Heller et al[31]	52 week randomized open label parallel group	443	Once daily detemir vs. Once daily glargine
Pieber et al[32]	26 week randomized open label parallel group	332	Twice daily detemir vs. Once daily glargine
Bartley et al[33]	24 month randomized open label parallel group	495	Once daily detemir vs. Once daily NPH
Robertson et al[36]	26 week randomized open label parallel group, Children 6–17 years old	347	Once/twice daily detemir vs. Once/twice daily NPH
Kolendorf et al[40]	32 week randomized open label crossover trial	124	Twice daily detemir vs. Twice daily NPH
De Leeuw et al[42]	12 month randomized open label parallel group	316	Twice daily detemir vs. Twice daily NPH
Pieber et al[37]	16 week randomized open label parallel group (3 arms)	400	Twice daily detemir (morning, pre-dinner/bedtime) vs. Twice daily NPH
Hermansen et al[34]	18 week randomized open label parallel group	595	Twice daily detemir with aspart vs. Twice daily NPH with regular human insulin
Russell-Jones et al[38]	6 month randomized open label prospective parallel group	747	Once daily detemir vs. Once daily NPH
Home et al[35]	16 week randomized open label three-arm parallel group	408	Twice daily detemir (2 groups) vs. Twice daily NPH
Vague et al[41]	26 week randomized open label parallel group	447	Twice daily detemir vs. Twice daily NPH
Hermansen et al[39]	12 week randomized crossover trial	59	Once daily detemir vs. Once daily NPH

of hypoglycemic episodes. One of these studies found insulin glargine to be more effective at lowering FPG (difference of 0.70 mmol/l, $P < 0.001$),[32] while the other showed no difference.[31] There was no overall difference in within-subject plasma glucose variability.[31,32] The risk of nocturnal hypoglycemia was 32% lower with insulin detemir in one of the two studies ($P < 0.05$).[32]

Detemir/NPH

Although the specific treatment regimens varied between studies, insulin detemir has shown similar or better efficacy based on HbA1c measures in patients with T1DM in 9 clinical trials (Table 1). Three of these studies reported a greater reduction in HbA1c over NPH insulin of 0.2% ($P < 0.05$).[33–35] A majority of the studies also found insulin detemir was more effective at lowering FPG levels,[33,35–38] and resulted in less FPG variation than NPH insulin.[36,38–41]

A key benefit of insulin detemir relative to NPH insulin observed in multiple studies was a favorable effect on weight. All of the studies that evaluated weight change found that insulin detemir was associated with less weight gain than NPH

HbA1c difference (95% CI)	Fasting blood glucose difference (mmol/l) (95% CI)	Weight change difference (kg) (95% CI)	Hypoglycemia, relative risk (95% CI)
0.01% (−0.13, 0.16)	−0.23 (−1.04, 0.58)	−0.06 (−0.84, 0.73)	Overall: 0.94 (0.74–1.18) Nocturnal: 1.12 (0.87–1.44)
−0.03% (−0.25, 0.19)	0.70 (0.38, 1.02)	−0.44 (−1.11, 0.23)	All: 0.96 (0.68, 1.35) Nocturnal: 0.68 (0.46, 0.99)
−0.22% (−0.41, −0.03)	−1.08 (−1.98, −0.18)	−0.99 (−1.86, −0.13)	All: 0.74 (0.51, 1.07) Nocturnal: 0.54 (0.40, 0.71)
0.1% (−0.1, 0.3)	−1.1 (−2.1, −0.2)		All: 0.89 (0.69, 1.14) Nocturnal: 0.74 (0.55, 0.99)
0% (−0.106, 0.108)			All: 0.82 (0.73, 0.92) Nocturnal: 0.50 (0.38, 0.65)
−0.08% (not statistically significant)	−0.16 (not statically significant)	−1.34 (−2.12, −0.56)	All: 0.78 (0.56–1.08) Nocturnal: 0.68 ($P = 0.016$)
−0.06%, −0.08% (overall $P = 0.636$)	−1.31, −1.99 (overall $P < 0.001$)	−1.3 kg (dinner detemir, $P < 0.001$), −0.6 kg (bedtime detemir, $P = 0.050$)	Similar between all groups
−0.22% (−0.34, −0.10)	−0.52 (−1.06, 0.01)	−1.01 (−1.37, −0.66)	All: 0.79 (0.63, 0.98) Nocturnal: 0.45 (0.35, 0.58)
−0.12% (−0.25, 0.02)	−1.16 ($P = 0.001$)	−0.52 ($P = 0.024$)	All: 0.94 (0.79–1.13) Nocturnal: 0.74 (0.60–0.90)
−0.2% (−0.34, −0.02)	−1.5 and −2.3 (both groups significant at $P \leq 0.004$)	−0.8 and −0.6 (both groups significant at $P < 0.05$)	Ranged from 0.47–0.75 (although not all groups significant at 0.05 level)
−0.04% (−0.22, 0.13)	−0.76 (−1.65, 0.14)	−0.98 ($P = 0.001$)	All: 0.78 (0.62, 0.97) Nocturnal: 0.66 (0.50, 0.87)
	Decreased coefficient of variation with detemir (35% vs. 43%, $P < 0.001$)		60% (detemir), 77% (NPH), $P = 0.049$

Notes: *Study subjects were 18 years of age or older unless otherwise noted. Bolus regimens not specified here.

insulin.[33–35,37,38,41,42] From a safety standpoint, insulin detemir was associated with a decreased risk of hypoglycemia relative to NPH insulin in many, but not all of the included studies.[34,39–41] This decreased risk was especially pronounced at night with a risk reduction generally ranging from 25%–50% relative to NPH insulin.[33,34,36,38,40–42]

Type 2 Diabetes Mellitus
Detemir/Glargine
Four open label trials have compared insulin detemir to insulin glargine in T2DM. These studies found no significant difference in HbA1C improvement between the treatment groups.[43–46] While insulin glargine showed better efficacy in one study, it did not achieve the difference of 0.4% required to show superiority.[44] There were no differences in FPG change[44–46] or risk of hypoglycemia between these treatments.[44–46] Insulin detemir was associated with less weight gain (range: 0.8 to 1.5 kg, $P < 0.05$ for all studies).[43–46] These studies showed mixed results on the required frequency (once vs. twice daily) and dosing of insulin detemir compared to insulin glargine.[43–46]

Detemir/NPH

When insulin detemir and NPH insulin were compared in four studies of patients with T2DM, HbA1c improvements were similar.[47–49] One of the four studies identified slightly better improvement with NPH insulin than insulin detemir (0.16%, 95% CI 0.003–0.312), but insulin detemir was determined to be non-inferior because the upper confidence limit was less than 0.4%.[50] Improvement in FPG also tended to be similar in these studies.[47–50] The risk of hypoglycemia varied, with two studies showing similar risk,[49,50] and the other two studies showing a decreased risk with insulin detemir.[47,48] Three of the studies showed less weight gain with insulin detemir.[48–50]

Safety/Side Effect Data from Clinical Trials

A source of resistance to initiating insulin therapy is the fear of hypoglycemia, which can cause symptoms including cognitive impairment, seizures, and coma in severe cases. When compared to NPH insulin in patients with T1DM in clinical trials, insulin detemir tended to have a lower risk of hypoglycemia.[34,39,40, 41] This benefit was especially pronounced with the risk of nocturnal hypoglycemia, where the relative risk was decreased to approximately 0.50.[40] The risk of hypoglycemia in T1DM or T2DM is generally similar with insulin glargine and insulin detemir. In patients with T2DM, the risk of hypoglycemia with insulin detemir is similar or less than that of NPH insulin (Tables 1 and 2).

One of the key concerns, especially in T2DM, with starting insulin therapy is weight gain. An unexpected finding in studies of patients with T1DM treated with insulin detemir was decreased weight gain compared to those patients treated with NPH insulin.[19] In head-to-head comparisons of insulin glargine and insulin detemir, weight change was similar in patients with T1DM while insulin detemir tended to have a favorable weight change in patients with T2DM (Tables 1 and 2). Although the exact mechanism leading to this weight benefit has yet to be conclusively determined, a number of theories have been proposed. The first is that the capillary endothelial cells in adipose and muscle tissue limit the amount of insulin detemir that can move from the circulation into the extravascular extracellular space. Simultaneously, the fenestrated epithelial cells found in the liver have large gaps that allow hepatocytes an increased exposure to insulin detemir (free and albumin-bound).[51] Thus, insulin detemir has a greater effect on the hepatocytes as compared to adipose tissue.[19,51] A second theory is that the fatty acid chain on the insulin detemir molecule increases its action in the central nervous system, particularly in the hypothalamus. This can affect the feedback mechanisms involved in regulation of body weight and nutrition.[52] Lastly, the decreased risk of hypoglycemia seen with insulin detemir may result in decreased defensive snacking by patients.[53]

Currently there is debate over the impact of insulin therapy on cancer risk, especially related to the use of insulin glargine. Currie et al found that patients were more likely to develop solid tumors if they were on insulin or insulin secretagogue therapy compared to patients treated with metformin.[54] Jonasson et al found evidence that women treated with insulin glargine experienced increased rates of breast cancer compared to women on other forms of insulin.[55] Conversely, other studies have found no association between insulin glargine and cancer risk.[56] Analysis of these studies revealed that the results might have been impacted by a number of confounding factors, including significant variations in treatment groups and detection bias. Additionally, the rapid progression of cancers that would have been required for the development over the relatively short duration of the studies is not consistent with current clinical experience.[57] *In vitro* studies that specifically compared insulin detemir to human insulin found that insulin detemir does not have increased mitogenic activity due to its balanced affinity for insulin and insulin-like growth factor-1.[19] Thus, the available evidence is inadequate to confirm or refute the association of any specific insulin therapy to cancer development.

Injection site reactions can occur with insulin therapy. These events were reported more frequently in clinical trials with insulin detemir therapy compared to insulin glargine and NPH insulin.[31,36,42,46–48]

Observational Studies

Numerous studies have been published which present the results of observational clinical trials evaluating the use of insulin detemir in a more naturalistic setting than randomized clinical trials. There are also several published studies that evaluated insulin detemir in the

Table 2. Clinical studies in of insulin detemir versus NPH insulin or insulin glargine in patients with type 2 diabetes mellitus.

Type 2 diabetes reference	Study design	N	Treatment regimen*	HbA1c difference (95% CI)	Fasting glucose difference (mmol/l) (95% CI)	Weight change difference (kg) (95% CI)	Hypoglycemia, relative risk (95% CI)
Philis-Tsimikas et al[47]	20 week randomized open label parallel group	498	Once daily detemir (morning or evening) vs. Once daily NPH	Morning: 0.13% (−0.07, 0.32) Evening: 0.10% (−0.08, 0.29)	Morning: 0.88 (0.31, 1.5) Evening: −0.46 (−1.05, 0.13)		All Morning: 0.68 (NS) Evening: 0.47 ($P = 0.019$)
Hermansen et al[48]	24 week randomized open label parallel group	475	Twice daily detemir vs. Twice daily NPH	0.13 (0.00–0.25)	0.32 (−0.02, 0.66)	−1.58 kg (−2.18, −0.98)	All: 0.53 (0.42–0.68) Nocturnal: 0.45 (0.32–0.64)
Haak et al[50]	26 week randomized open label parallel group	505	Once/twice daily detemir vs. Once/twice daily NPH	0.16 (0.003, 0.312)	0.11 (−0.40, 0.63)	−0.79 kg (−1.44, −0.14)	All: 0.84 (0.52, 1.36) Nocturnal: 1.02 (0.55, 1.89)
Raslova et al[49]	22 week randomized open label parallel group	394	Once/twice daily detemir with aspart vs. Once/twice daily NPH with regular human insulin	−0.07 (−0.25, 0.13)	NS	−0.62 kg ($P = 0.038$)	All: 0.89 (0.54, 1.45) Nocturnal: 0.62 (0.32, 1.17)
Swinnen et al[43]	24 week randomized open label parallel group	964	Twice daily detemir vs. Once daily glargine	0.08% ($P = 0.15$)		−0.8 kg ($P < 0.001$)	No significant differences between groups
Raskin et al[44]	26 week randomized open label parallel group	385	Once/twice daily detemir vs. Once daily glargine	0.21% (0.01, 0.40)	−0.25 ($P = 0.397$)	−1.5 kg (−2.19, −0.56)	
Hollander et al[45]	52 week randomized open label parallel group	319	Once/twice daily detemir vs. Once daily glargine	0.17% (−0.07, 0.40)	0.36 (−0.26, 0.99)	−1.04 kg (−2.08, −0.01)	All: 0.75 (NS*) Nocturnal: Once daily—0.63 Twice daily—1.15 (both NS)
Rosenstock et al[46]	52 week randomized open label parallel group	483	Once/twice daily detemir vs. Once daily glargine	0.05 (−0.11, 0.21)	0.16 (−0.26, 0.58)	−0.9 kg ($P = 0.01$)	All: 0.94 (0.71–1.25) Nocturnal: 1.05 (0.69–1.58)

Note: *Bolus insulin or oral antidiabetic therapy, if included, is not specified here.
Abbreviation: NS, Not significant.

usual-practice setting based on secondary database analyses, as well as numerous pharmacoeconomic evaluations. Collectively, these studies help to establish the real-world effectiveness and cost effectiveness of insulin detemir relative to other basal insulins or to oral antidiabetic therapy.

Observational trials

The PREDICTIVE™ trial (Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation) was an open label, multinational, prospective observational study designed to assess the safety and efficacy of insulin detemir in patients with T1DM or T2DM. Inclusion and exclusion criteria were based on insulin detemir labeling with enrollment based on the discretion of the patient's physician. This study included over 30,000 patients in Europe, North and South America, Africa and Asia.[58] The European cohort included over 20,000 patients and the US cohort included over 5,000. The primary endpoint was serious adverse drug reactions including major hypoglycemia, with secondary endpoints including HbA1c, self-monitored fasting glucose, weight change, and hypoglycemic episodes.[59,60] Several examples of PREDICTIVE trial results are summarized in this section.

Data from 14-weeks of follow-up in patients with T1DM (n = 7,420) or T2DM (n = 12,981) who required basal insulin in 11 European countries were reported.[61] Patients were prescribed insulin detemir to replace existing basal insulin or as an add-on to other insulin or oral therapy. A total of 214 (1%) of patients reported a serious adverse drug event of which 53% were major hypoglycemic episodes. There was a significant reduction in the mean number of hypoglycemic events that occurred during the 4-weeks prior to the 14-week follow-up visit versus the four weeks prior to initiating insulin detemir. This included a mean reduction in major hypoglycemic events by 2.2 events/patient-year in T1DM and 0.7 events/patient-year in T2DM ($P < 0.001$ for both). Furthermore, nocturnal hypoglycemic events were reduced by 10 events/patient-year and 2.7 events/patient-year in T1DM and T2DM respectively ($P < 0.001$ for both). After 14 weeks of insulin detemir therapy, mean HbA1c levels were significantly

reduced by 0.5% for patients with T1DM and 0.9% for those with T2DM ($P < 0.001$ for both). Mean FPG was also reduced (1.7 and 2.6 mmol/l for T1DM and T2DM respectively; $P < 0.001$ for both), as was within-patient FPG variability (0.5 and 0.7 mmol/l for T1DM and T2DM respectively; $P < 0.001$ for both.) Insulin detemir was dosed twice daily for 50% of patients with T1DM and 23% of those with T2DM.

A 12-week subgroup analysis of 1,832 T2DM patients from the PREDICTIVE™ German cohort, the largest European subgroup, examined the effects of insulin detemir treatment (with and without oral antidiabetics) in patients previously treated with oral antidiabetics alone or in combination with a basal insulin other than insulin detemir. During treatment with insulin detemir, no major hypoglycemic events occurred. Compared to baseline therapy, the frequency of overall and nocturnal hypoglycemic episodes decreased with insulin detemir (decrease of 2.7 and 1.2 events/patient-year, respectively. $P < 0.0001$).[58] Overall HbA1c (−1.10%), fasting blood glucose at follow up (−49.8 mg/dL), and fasting blood glucose variability (−7.4 mg/dL) decreased during insulin detemir treatment ($P < 0.0001$).

The PREDICTIVE™ 303 study was a 26-week, randomized, open label study of 5,604 T2DM patients in the US comparing a patient-adjusted insulin detemir dosing algorithm (adjusted every three days based on fasting blood glucose measurements) to physician-driven insulin detemir adjustments (according to standard-of-care). Patients in both groups showed significant improvements in HbA1C, fasting plasma glucose, and the overall rate of hypoglycemic events. While patients using the 303 Algorithm saw a slightly greater decrease in HbA1C (−0.09%, 95% CI: −0.17, −0.02) and fasting plasma glucose (−11 mg/dL, 95% CI: −14.4, −7.2), they also experienced more overall hypoglycemic events compared to the standard-of-care group ($P < 0.0001$). There was no significant difference between the groups for nocturnal hypoglycemia. There was no significant weight gain in either group.[62]

Observational studies—secondary analyses

Insulin detemir has also been evaluated in several real-world analyses based on medical and pharmacy claims,[63,64] electronic medical record data (EMR),[65] and a national health data repository.[66] These studies, which range in size from approximately 300 to over 18,000

patients, provide data on glycemic control, weight, and insulin dose outcomes for insulin detemir versus insulin glargine in the usual practice setting (Table 3).

The database analyses found that improvement in glycemic control with therapy is similar between the two analog basal insulins. Three of these observational studies evaluated change in HbA1c and did not identify significant differences between insulin detemir and insulin glargine after 6 to 12 months of therapy (difference in HbA1c change of 0.1% to 0.4%; P = NS for all).[63,65,66]

Three studies also evaluated mean daily doses for insulin detemir versus insulin glargine and similarly found no difference between the two insulins.[63,64,66] The average daily dose for insulin detemir ranged from 27 to 35 units/day, while the mean daily dose for insulin glargine ranged from 27 to 32 units/day. It is important to note that these mean daily insulin dose estimates are based on pharmacy claims data and provide insight into insulin use from a dispensing and reimbursement perspective. They do not adjust for non-adherence and therefore do not provide a precise estimate of daily insulin dose on the days that insulin was administered, and are not able to distinguish once-daily and twice-daily dosing.

As with clinical trials, weight findings were inconsistent in the database studies. One retrospective study found that weight gain was less with insulin detemir (0 kg) than insulin glargine (+0.9 kg; P = 0.04).[65] However, a second study did not identify a significant difference in weight gain between these insulins (+0.2 kg for insulin detemir vs. +1.2 kg for insulin glargine; P = NS).[66]

Pharmacoeconomic analyses

Numerous published pharmacoeconomic analyses have evaluated costs associated with insulin detemir therapy relative to NPH insulin and insulin glargine either alone or a basal bolus combination with a short acting insulin, or compared to oral agents (Table 3). These analyses are segregated for discussion purposes by cost effectiveness models[67–72] or cost analyses based on real-world[63] or clinical trial data.[73,74]

Cost effectiveness models

Insulin detemir cost effectiveness analyses have been published based on healthcare costs in the US, UK and Europe using the Center for Outcomes Research (CORE) diabetes model, a validated, peer-reviewed and published diabetes clinical and economic outcomes model.[67–72,75,76] The CORE diabetes model combines published data on the risk of long-term complications with quality-of-life utilities to simulate the clinical, economic, and humanistic outcomes of diabetes therapies in the intermediate to long-term.

Studies evaluating insulin detemir cost effectiveness have used the CORE model to estimate the cost associated with insulin detemir for each quality adjusted life year (QALY) gained. QALY is a measure of treatment outcomes that adjusts changes in life expectancy with an intervention by the corresponding change in quality of life.[77] The definition of cost effectiveness, or willingness to pay per QALY gained, is subjective and varies by country. In the US, for example, $50,000–$100,000 per QALY is commonly accepted as cost effective, and in the UK, the National Institute for Health and Clinical Excellence (NICE) has historically defined a cost effectiveness threshold of £20,000 to £30,000 per QALY.[78] In the evaluated studies, assumptions of clinical effectiveness were drawn from controlled or observational clinical trials, with cost data obtained from published sources of payer reimbursement amounts.

In cost effectiveness studies focusing on T1DM, insulin detemir has shown to be cost effective relative to NPH insulin when given with a short-acting insulin in a basal/bolus regimen.[67–70,72] Cost per QALY (all reported in US dollars), ranged from $719[67] to $30,664.[68] When compared to insulin glargine (both plus Aspart), one study found that insulin detemir was cost saving.[72]

Cost effectiveness models of patients with T2DM have similarly found that insulin detemir is cost effective relative to NPH insulin or insulin glargine. In one study that evaluated the cost effectiveness of insulin detemir with oral antidiabetic agents, the cost per QALY for insulin detemir with oral agents was $7,412 versus oral agents alone, $6,269 versus NPH insulin plus oral agents, and $3,951 versus insulin glargine plus oral agents.[71] Relative to NPH insulin with or without oral agents, the cost per QALY for insulin detemir was $18,383.[70] For both T1DM and T2DM, the economic benefits of insulin detemir versus NPH insulin or insulin glargine were associated with a reduced risk of complications due to better glycemic control[68,71,72] and reduced rates of hypoglycemia.[67,70]

Table 3. Secondary database and pharmacoeconomics studies.

Reference/country	Study design outcomes period/time horizon	Population	Data source/inputs	Treatment regimen*	Outcomes* (detemir vs. glargine)
Database Studies					
Borah[63] US	Retrospective; matched cohort analysis 6 month	N = 306 T2DM Insulin naïve, insulin added to other antidiabetic therapy	US administrative claims database with supplemental laboratory data	Detemir or glargine basal therapy only	Mean (SD) insulin daily dose: 29.9 (17.8) vs. 29.5 (20.8); P = NS Change in HbA1c: −0.7% vs. −1.1; P = NS
McAdam-Marx[65] US	Retrospective; cohort analysis 1 year	N = 18,763 T2DM Insulin naïve; subset of 3796 matched patients	US administrative claims database	Detemir or glargine basal therapy ± mixed or rapid acting insulin	Overall cohort: Mean (SD) insulin daily dose in units: 35 (49) vs. 32 (27); P = NS Proportion of patients with use of non-insulin antidiabetic significantly lower after initiation of detemir (P < 0.001) and glargine (P < 0.50) than before Matched cohort: Mean (SD) insulin daily dose: 35 (55) vs. 32 (23); P = NS Proportion of patients with use of 2+ other antidiabetics significantly less after initiation of detemir or glargine (P < 0.001 for both) than before
McAdam-Marx[64] US	Retrospective; matched cohort analysis 6 month	N = 6,570 T1DM and T2DM; Insulin naïve	US electronic medical record	Detemir or glargine, no other insulin therapy	Adjusted change in HbA1c: −1.5% vs. −1.4%; P = NS Unadjusted change in weight: 0 (7.8) vs. 0.9 kg (6.2); P = 0.04 Unadjusted change in BMI: −0.1 (1.9) vs. 0.3 (2.4); P = 0.03
Heintjes[66] Netherlands	Retrospective; cohort analysis 1 year	N = 419; T2DM Insulin naive	Netherlands PHARMO data (clinical data)	Detemir or glargine; basal use only	Mean change in HbA1c: −0.9% vs. −1.1% (P-value not reported) Proportion at HbA1c goal (<7.0%) at follow-up: 33.3% vs. 35.7%; P = NS Adjusted odds ratio (95% Confidence Interval) for HbA1c goal attainment of detemir relative to glargine: 0.81 (0.57–1.16); P = NS Median daily dose in units (IQR): 26.8 (17.3–39.8) vs. 27.4 (17.8–39.0); P = NS Mean (SD) weight change: 0.2 (4.7) vs. 1.2 (4.4) kg; P = NS
Economic models					
Palmer[68] UK	Cost effectiveness analysis, CORE diabetes model Patient lifetime	T1DM	Outcomes: clinical trial data Costs: published sources	Detemir vs. NPH (basal/bolus, therapy not specified)	Cost per QALY £19,285 for detemir vs. NPH in a basal/bolus regimen (US$30, 664)

Study	Design	Population	Data sources	Comparison	Results
Valentine[72] US	Cost effectiveness analysis, based on CORE diabetes model 35 Years	T1DM	Outcomes: clinical trial data Costs: per Medicare data	Detemir, glargine, or NPH (basal/bolus + aspart)	Cost per QALY US$14,974 for detemir vs. NPH. Detemir cost-saving vs. glargine
Valentine[71] US	Cost effectiveness analysis, based on CORE diabetes model 35 Years	T2DM	Outcomes: PREDICTIVE German cohort Costs: US third-party payer data	Insulin detemir + oral agent(s) converted from oral agents alone, oral + NPH insulin, or oral + glargine	Incremental cost per QALY with detemir plus oral agents compared to: Oral agents alone: US$7412 Oral agents plus NPH: US$6269 Oral agents plus insulin glargine: US$3951
Palmer[69] UK	Cost effectiveness analysis, based on CORE diabetes model Patient lifetime	T1DM	Outcomes: clinical trial data Cost: UK health system	Insulin detemir+ aspart, or NPH + regular human insulin	Cost per QALY £2500 for detemir+aspart vs. NPH and regular human insulin (US$3,975)
Tunis[70] Canada	Cost effectiveness analysis, based on CORE diabetes model T1DM: 60 years T2DM: 35 years	T1DM and T2DM	Outcomes: clinical trial (T1DM) and observational trial (T2DM) data Costs: published literature	Detemir vs. NPH (basal bolus + Apart T1DM, ± oral agents T2DM)	Cost per QALY Can$24,389 for detemir+aspart vs. NPH+aspart in T1DM (US$24,005) Cost per QALY Can$18,677 for detemir ± oral vs. NPH ± oral in T2DM (US$18,383)
Gschwend[67] Europe	Cost effectiveness analysis, based on CORE diabetes model 50 years	T1DM	Outcomes: clinical trial data Costs: country specific sources	Detemir vs. NPH (basal/bolus with Aspart)	Cost per QALY €519 for detemir+aspart vs. NPH+aspart in France (US$719) Cost per QALY €3256 for detemir+aspart vs. NPH+aspart in Italy (US$4510) Detemir-aspart dominated NPH+aspart in Belgium, Germany and Spain
Borah[63] US	Retrospective; matched cohort analysis 6 month	N = 306 T2DM Insulin naïve, insulin added to other antidiabetic therapy	US administrative claims database with supplemental laboratory data	Detemir or glargine basal therapy only	All-cause costs: Pharmacy: US$3074 vs. US$2899; $P = NS$ Medical:US$2319 and US$3704; $P = NS$ Total: US$6014 and US$7023; $P = NS$ Diabetes-related costs Pharmacy: US$1277 vs. US$1149; $P = NS$ Medical: US$707 vs. US$1510; $P = 0.03$ Total: US$2261 vs. US$3408; $P = 0.03$

(Continued)

Table 3. (Continued)

Reference/country	Study design outcomes period/time horizon	Population	Data source/inputs	Treatment regimen*	Outcomes* (detemir vs. glargine)
Pschercher[73] Germany	Cost analysis of trial data 1 year analysis	T2DM	Clinical trial data, costs from German statutory health insurance	Detemir or glargine	Insulin (including supplies): €3675 vs. €2991; difference €684 (range €331–€1,037) (US$4511 vs. US$414; difference US$948, range US$450–US$1437)
Pschercher[74] Germany	Cost analysis of trial data 1 year analysis	T2DM	Clinical trial data, costs from German statutory health insurance	Detemir+oral agent(s) or glargine+oral agent(s)	Insulin (including supplies): €1334 vs. €849; difference of €486 (range: €429–€608) (US$1848 vs. US$1176; difference US$673, range US$594–US$842)

Notes: *Exchange rates as of October 5, 2010 US$1.00 = £0.629 = €0.722 = Can$1.016.

Retrospective economic analyses

Several studies have evaluated costs associated with insulin detemir treatment in T2DM relative to insulin glargine based on US medical and pharmacy administrative claims[63] or clinical trial data.[73,74] The study using medical and pharmacy claims data evaluated all-cause medical, pharmacy and total healthcare costs and for care delivered specifically to treat T2DM, comparing insulin detemir to insulin glargine. For the most part, patient healthcare costs, reported from the perspective of a private US-based managed care payer, did not differ between the two insulins. However, T2DM-related medical costs and total T2DM-related costs were less for insulin detemir relative to insulin glargine. Medical costs for T2DM were $707 for insulin detemir and $1,510 for insulin glargine while total T2DM healthcare costs were $2,261 and $3,408 for insulin detemir and insulin glargine, respectively ($P = 0.03$ for both).[79]

Two additional cost minimization analyses were conducted based on randomized control trials. One of these studies compared insulin detemir and insulin glargine in a basal/bolus regimen with mealtime aspart, while the second study compared insulin detemir and insulin glargine given with oral agents. Costs were estimated from the German Statutory Health Insurance scheme for insulin and supplies required for monitoring blood glucose and administering insulin.[73,74] Both studies, which considered one-year insulin costs but not health outcomes as outcomes were presumed to be identical, concluded that costs were higher with insulin detemir than with insulin glargine. Total insulin plus administration costs were $948[73] per year higher with insulin detemir (range $450–$1,437) when given with mealtime aspart and $673[74] higher (range $594–$842) when administered with oral agents.

Of note, extrapolation of pharmacoeconomic data to countries other than the country in which the analyses were based should be done with caution as medication, medical costs, and patient demographics, which vary between countries, can impact findings.

Place in Therapy

Since the hyperglycemia seen with T1DM is primarily due to a deficiency of endogenous insulin production,[80] insulin therapy should be started soon

after the initial diagnosis to minimize the risk of complications and maintain appropriate glycemic control. As a result, most patients with T1DM are treated with a combination of basal and bolus insulin to maintain appropriate blood glucose control.[81]

Based upon recent American Diabetes Association recommendations, therapy should be initiated or intensified in T2DM when HbA1c $\geq$ 7.0%. Initially, the first step is lifestyle modification combined with metformin therapy, if metformin is not contraindicated. If the HbA1c goal of <7.0% is not reached with metformin alone, guidelines recommend adding a second oral agent, such as a sulfonylurea, or insulin. The selection of the second medication should be based on the patient's HbA1c level. Specifically, if a patient's HbA1c is >8.5%, a basal insulin should receive additional consideration. If initial basal insulin is not sufficient to reach the HbA1c goal of <7%, then insulin therapy should be intensified by increasing the basal insulin dose or by adding a rapid-acting insulin.[82]

The American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) recently released a consensus statement regarding glycemic control in T2DM.[30] This Statement calls for a more aggressive HbA1c goal of 6.5% with therapy evaluation every 2 to 3 months. Similar to other guidelines, lifestyle improvements are recommended for all diabetic patients. In contrast, insulin therapy is typically reserved until after mono-, dual-, or triple-therapy with other antidiabetic agents fails to meet patient specific goals (please refer to algorithm for specific treatment recommendations). Once the decision has been made to start insulin therapy, one of four possible regimens are recommended: basal insulin once daily, premixed insulin, basal-bolus combination therapy, or a 'prandial' regimen. Insulin detemir is an acceptable choice for a long-acting insulin in these regimens with the AACE/ACE statement recognizing the benefits of insulin detemir of excellent reproducibility of the absorption profile and possibly having less weight gain. The use of regular human insulin and NPH insulin is not recommended.

As with any medical treatment, careful clinical judgment based on agent benefits and risks should be used prior to initiating or escalating insulin therapy. Specifically, a patient's risk of hypoglycemia,

concomitant comorbidities, polypharmacy, and cognitive impairment, especially in older individuals, should be weighed against the potential benefits (cardiovascular, etc) of the improved glycemic control.[16] Based upon these and other patient specific considerations, the clinician should decide if insulin detemir is an appropriate therapy. As insulin detemir is generally as effective as the other basal insulins in providing glycemic control, a number of other considerations should be taken into account when making this decision. Specifically, insulin detemir is recognized as a better option than NPH insulin, particularly in patients with T1DM and those with a history of hypoglycemia or where a patient's comorbidities make a hypoglycemic event especially hazardous. Insulin detemir should also be considered in basal insulin candidates whose weight control has been problematic. While the weight benefit on average is modest and the evidence is mixed in T2DM, weight gain, particularly in T2DM patients, is undesirable and can contribute to increased cardiovascular risk.[83] Lastly, as analog insulins can be more costly per prescription than the human insulin options, the patient's ability to pay should be considered as this can impact compliance and long-term outcomes.

Conclusions

Insulin detemir is a long-acting basal insulin approved for once- or twice-daily use in T1DM and T2DM. Insulin detemir has demonstrated equivalent or improved glycemic control and hypoglycemic risk when compared to insulin glargine, and while data are not consistent, insulin detemir has generally demonstrated less weight gain than insulin glargine in T2DM. While insulin detemir may be dosed twice daily to achieve optimal glycemic response, observational data suggest that the daily average doses dispensed to patients with T2DM are similar between insulin detemir and insulin glargine. The benefits of the analog basal insulins relative to NPH insulin are well recognized, including less FBG variability, lower risk of hypoglycemia, and less weight gain specifically with insulin detemir relative to NPH insulin. However, NPH insulin continues to be widely prescribed. This may be due in part to economic considerations. While NPH insulin may cost less per prescription, insulin detemir has been shown to be cost effective compared to NPH insulin as well

as insulin glargine, with cost effectiveness attributed to glycemic response and reduction in hypoglycemia. Therefore, insulin detemir is an effective option from both clinical and economic perspectives for patients with T1DM or T2DM who require basal insulin to achieve glycemic control.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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