

Letter to the Editors

Dear Drs. Edelman and LeRoith:

In a recent article, Johnson and Shimshi¹ reviewed the cost-effectiveness of insulin detemir* in patients with type 2 diabetes mellitus (DM). From the 7 studies identified in their literature review, the authors concluded that higher mean daily doses of insulin were required with detemir than with other basal insulins, resulting in higher daily insulin costs with detemir. On review, I am concerned that several methodologic limitations of the analysis were not discussed or acknowledged. These limitations challenge the validity of the results and conclusions and warrant discussion.

The 7 studies combined for analysis were very different in terms of treatment regimen, duration of study, trial design, and patient demographics. Furthermore, both across and within the individual studies, dosing regimens and titration algorithms were not equivalent. Therefore, combining data across these studies to calculate mean daily basal, bolus, and total insulin doses and the resulting mean daily costs, without adjusting for differences across and within studies, could easily lead to incorrect conclusions. For example, insulin detemir is indicated for once- or twice-daily dosing and has been studied as such; insulin glargine[†] is only indicated for once-daily dosing. It is well established that twice-daily dosing of basal insulin elevates the dose.²⁻⁵ Consequently, calculation of a mean total daily insulin dose for detemir and glargine without accounting for differences in dosing frequency and titration strategies is an unfair comparison. Of note, when once-daily detemir was compared with once-daily insulin glargine and neutral protamine Hagedorn (NPH) insulin,^{‡6,7} similar doses were used.

In addition to relevant differences across and within studies not being adjusted for, inappropriate studies were included in the analysis. For example, Liebl et al⁸ compared 2 different insulin analogue regimens (ie, basal-bolus vs premixed) against a background of no oral antidiabetes drugs. Umpierrez et al⁹ compared a human-versus-analogue basal-bolus insulin regimen in a hospital setting over a 6-day period. These studies, which were very different from the others in terms of treatment regimens, patient populations, and duration of treatment, should have been excluded from the analysis.

Furthermore, the cost of an NPH insulin 10-mL vial is compared with the costs of detemir and glargine pens and is incorrectly cited as the cost of an NPH pen. The price difference between vials and pens inflates the cost difference between human and analogue basal insulins. There are also more accepted and commonly cited pricing sources than Drugstore.com, such as MediSpan.com and FirstDataBank.com.

The cost of diabetes treatment encompasses much more than the direct cost of the drug therapy itself. Despite the authors' acknowledgment that insulin detemir causes less hypoglycemia and less weight gain relative to other basal insulins, these benefits and other factors that affect the cost of therapy, such as quality of life and longer-term outcomes, were not factored into the analysis.

Beyond the methodologic limitations, the authors do not acknowledge other relevant, published clinical and health economics data that challenge the results presented. Numerous studies have reported that the glucose-lowering effect of insulin detemir is comparable to that of insulin glargine and NPH insulin at similar doses.¹⁰⁻¹² Furthermore, the efficacy and safety profile of insulin detemir administered once-daily are well established.¹³⁻¹⁶

In a recently published study conducted by Blonde et al,¹³ the majority of insulin-naive patients with type 2 DM achieved a glycosylated hemoglobin level of <7.0% with moderate doses of insulin detemir used once-daily according to a patient-directed titration algorithm. In addition, in a managed care population of insulin-naive patients who initiated therapy with insulin detemir or insulin glargine, Borah et al¹⁷ found that the daily dose of insulin and glycemic control did not differ significantly between the 2 insulins. However, patients who received insulin detemir incurred lower diabetes-related medical and total health care costs than did those who received insulin glargine.

At the 69th Scientific Sessions of the American Diabetes Association (June 5-9, 2009; New Orleans, Louisiana), Luo et al¹⁸ reported that no statistically significant difference in insulin daily average consumption (DACON) was found between insulin detemir and insulin glargine among patients switched from NPH insulin. At the 14th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research (May 16-20, 2009; Orlando, Florida), McAdam-Marx et al¹⁹ compared the DACON of insulin detemir, insulin glargine, and NPH insulin in patients with type 2 DM in a real-world setting; the DACON was highest with NPH and did not vary significantly between detemir and glargine. Other studies have shown similar results.²⁰⁻²²

In summary, although patient care should remain the focus when making clinical decisions, the cost of therapy is nonetheless a consideration for both the patient and the physician. Insulin dose is a key determinant of cost of therapy for patients

*Trademark: Levemir[®] (Novo Nordisk, Inc., Princeton, New Jersey).

†Trademark: Lantus[®] (sanofi-aventis U.S. LLC, Bridgewater, New Jersey).

‡Trademark: Humulin[®] N (Eli Lilly and Company, Indianapolis, Indiana).

with type 2 DM. However, simple comparisons of insulin dose across studies can yield misleading results and should be interpreted with caution. Differences across and within studies related to study design, patient populations, and therapy regimens should be considered, and results should be interpreted within the context of other relevant published data. When evaluating potential differences in dosing between 2 insulins, such as insulin detemir and insulin glargine, observational or real-life data may provide the fairest comparison, assuming proper adjustments for the data are made. However, in this particular case, the need for a randomized, controlled study comparing insulin detemir and insulin glargine in identical once-daily dosing regimens in patients with type 2 DM is apparent. The EFFICACY trial, initiated by Novo Nordisk, Inc., will provide greater insight into the similarities and differences between these 2 basal insulin analogues.

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The authors respond:

Personal observations pertaining to the use of insulin detemir initiated our interest in this particular basal insulin. When attempting to switch patients who had type 2 diabetes mellitus (DM) for many years, we continued to titrate the dose of detemir upward, first as a single daily dose of basal insulin, then as twice-daily doses of basal insulin. We initially tried detemir in a lean patient (body mass index [BMI], 23 kg/m²) with insulin-requiring DM who had considerable experience in self-titration of insulin. The patient became increasingly frustrated and asked to be switched back to glargine. Later, we initiated detemir in several patients who had type 2 DM and a BMI of 35 to 40 kg/m². All patients became frustrated and insisted on being switched back to their previous basal insulin (glargine).

This prompted us to investigate the original studies of detemir that were submitted to the US Food and Drug Administration. We found that the insulin was indeed much less potent on a mole-to-mole basis and had to be reconstituted in a formulation 4 times more concentrated (2400 vs 600 nmol/mL) than that used for other available insulins.¹ This initiated our research of the articles that had been published at the time, in which detemir was compared with NPH and glargine as basal insulin. We acknowledge that there are indeed major methodologic differences in the studies referenced in our paper, as well as in those mentioned by Dr. Meneghini. However, we do not believe that this invalidates the results of the studies that we quoted.

In the study by Klein et al,² which examined albumin-bound basal insulin analogues, the investigators acknowledged that there may be a diminished metabolic effect in patients with higher amounts of visceral fat (hence, increased insulin resistance), as well as in patients with more subcutaneous fat-layer thickness. They also suggested that because there are many more patients with type 2 DM than with type 1 DM, more studies are needed in this target population.

One of the possible differences in detemir dosing in patients with type 2 DM is most likely related to the degree of obesity in the study population (the average BMI was 29–30 kg/m², and very few studies allowed patients with a BMI >35 or 40 kg/m²).³ In addition, it is well known that in different ethnic groups, different BMIs are associated with different degrees of insulin resistance. Therefore, unless one can clearly determine the doses that were used, by quartiles of BMI, it is inappropriate to discount studies that do exhibit significantly higher dose requirements for detemir than for glargine. In addition, by specifically selecting insulin-naive patients or those with recent-onset DM for enrollment in studies, it is very likely that these patients' own endogenous insulin production was able to compensate for the possibly higher dose requirement with detemir.

We did not refer to the studies by Valentine et al,^{4–6} which used a theoretical model of the cost of detemir and reported a reduction in cost of ≥15%. Without consideration for the fact that glargine will be off patent years before the patent for detemir expires (which will markedly reduce the cost of the medication), we believe this questions the validity of the results of these studies.

We do agree that it is important to acknowledge methodologic differences in studies. It is equally important to recognize studies that are based on theoretical projected costs rather than currently known costs of insulins. The true clinical effects and costs of medications often do not become available until they have been used by hundreds of thousands of patients, long after they received approval for marketing.

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