

## Question: Is Insulin Glargine More Effective?

Agnieszka Kitowicz, MD (PGY-3); Dan F. Criswell, MD

**Question:** In patients with diabetes mellitus type 2 who have failed oral agents, is insulin glargine more effective than intermediate plus short acting combinations for controlling blood sugar levels?

**Answer:** Probably not.

**Date answer was determined:** January 6, 2006

**The level of evidence for the answer:** B

**Resident:** Agnieszka Kitowicz, MD (PGY-3)

**Faculty:** Dan F Criswell, MD

**Program name:** Southwest Oklahoma Family Medicine Residency Program

### Summary of the issues:

Sooner or later many patients with type 2 diabetes will require insulin, providing they live long enough. With a decline in  $\beta$ -cell function, oral hypoglycemic medications are no longer sufficient to maintain HbA1C level below 7% as recommended by the American Diabetes Association (ADA). Theoretically, insulin glargine with its once-daily dosing and fewer hypoglycemic events seems to be a more attractive option to patients. However, its cost can be a limiting factor compared to the premixed insulin. Insulin glargine cost is approximately double of insulin regular 70/30 but is similar to insulin aspart 70/30 and insulin lispro 75/25. Three recent RCTs were designed to address that issue in type 2 diabetics who are not controlled with oral medications. This population is most often encountered in our clinic when it comes to insulin initiation therapy.

### Summary of the evidence:

In the first multi-national RCT supported by Aventis Pharma, 371 insulin naive patients on oral medications with HbA1C 7.5 to 10.5% were randomized to a group taking once-daily insulin glargine in the morning plus glimiperide and metformin and to the second group on twice-

daily 30% regular/ 70% NPH insulin without oral medications. A weekly titration algorithm was used to target FBG  $\leq$  100mg/dL for both groups and predinner BG  $\leq$  100 mg/dL for the insulin 70/30 group. A significant decrease in HbA1C was noted in the glargine group -1.64 [CI 95% -1.5 to -1.78] versus -1.31% [CI 95% -1.17 to -1.44] in the 70/30 group (P = 0.0003). More patients also reached a target HbA1C  $\leq$  7% in the glargine group (45.5 % vs. 28.6%, P = 0.0013).<sup>1</sup>

In the second RCT sponsored by Novo Nordisk, 233 insulin naive patients with HbA1C  $\geq$  8% went through a 4-week run-in period during which sulfonylureas and  $\alpha$ -glucosidase inhibitors were stopped, Metformin dose was optimized to 1500-2550 mg/day and pioglitazone was continued at a dose up to 30mg if the patient was on TZD prior to the study. The patients were then randomized to take either insulin glargine at bedtime or biphasic insulin aspart 70/30 (BIAsp) twice daily before breakfast and supper. Algorithm-directed titration was used to target blood glucose 80-110mg/dL. The HbA1C reduction was greater in the BIAsp 70/30 group versus glargine group (-2.79 vs -2.36, P < 0.01). The difference was even more pronounced in the patients with baseline HbA1C above 8.5% (-3.13 vs -2.60, respectively; P < 0.05). More patients from the BIAsp group reached the target HbA1C as well (HbA1C  $\leq$  7%: 66 vs 40%, P < 0.001).<sup>2</sup>

As expected, both RCTs found more hypoglycemic events in their premixed insulin arms. An interesting point was noted regarding weight gain in Raskin et al. study. The weight gain was similar in both groups for patients taking pioglitazone (5.1 vs 4.5kg; BIAsp 70/30 vs glargine, respectively; P > 0.05). In patients not taking TZD weight gain was significantly greater in the BIAsp 70/30 group (5.6 vs 3kg; BIAsp 70/30 vs glargine, respectively; P < 0.01).

Direct correspondence to: OUHSC, Dept. Family & Preventative Medicine, 900 NE 10th St., OKC, OK 73104

The third study from Spain and France supported by the Lilly Research Laboratories enrolled a bit different population – patients inadequately controlled while taking insulin NPH once or twice daily alone or with oral agents, or once-daily human insulin mixture with oral agents. After a 6-week lead-in period 97 patients were randomized to be either treated with insulin lispro mixture (25% lispro and 75% NPH) before breakfast and dinner plus metformin (1550-2500mg/day) or with insulin glargine at bedtime plus metformin. At endpoint, HbA1C was lower in the lispro mixture group versus glargine group ( $7.54\% \pm 0.87\%$  vs.  $8.14\% \pm 1.03\%$ ,  $P < 0.001$ ). The reduction in HbA1C from baseline to endpoint was greater in the lispro mixture group as well ( $-1.00\% \pm 0.85\%$  vs.  $-0.42\% \pm 0/92\%$ ,  $P < 0.001$ ). A higher percentage of patients treated with insulin lispro mixture plus metformin achieved HbA1c at or below 7% (30% vs 12%,  $P = 0.002$ ).<sup>3</sup>

#### **Comment**

The benefit of HbA1C reduction with more intensive insulin regimen most likely outweighs the risk of hypoglycemia and weight gain when initiating insulin therapy. Further larger trials are needed to address not only efficacy of the treatment but also cost effectiveness and patient compliance.

#### **Search terms**

Glargine, Lantus, DM type 2, glycemic control, premixed insulin, initiation therapy

#### **Inclusion criteria**

Studies that involved type 2 diabetics not controlled with oral medications who were initiating insulin therapy

#### **List of articles reviewed:**

1. Janka HU, Plewe G et al: Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial therapy for Type 2 diabetes. *Diabetes Care* 2005;28(2):254-9.
2. Raskin P, Allen E et al: Initiating insulin therapy in Type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005;28(2):260-5.
3. Malone JK, Bai S et al: Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. *Diabetic Med* 2005;22(4):374-81.

# OSMA Board Awards

## **Nominations Due Friday, February 16, 2007.**

The following awards will be presented at the Awards Luncheon during OSMA's Annual Meeting on Saturday, April 21, 2007.

**Don J. Blair – Friend of Medicine Award** is presented to an outstanding layperson whose work positively impacts the practice of medicine, the delivery of health care, or the prevention of negative health consequences in their community.

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**Ed Calhoon, MD, Leadership in Medicine Award** This award was established by the Board of Trustees in 2001, and is presented to an OSMA member physician in recognition of his or her distinguished leadership and service to organized medicine at the county, state or national level.

Please submit your nominations in writing to the OSMA no later than Friday, February 16, 2007 to Donna Bartlett, OSMA, 601 NW Grand Boulevard, Oklahoma City, OK 73118; fax to 405-842-1834 or e-mail to Bartlett@osmaonline.org.