Improved Treatment of Type 2 Diabetes: Results From the 4B Trial

Written by Brian Hoyle

Bruce Wolffenbuttel, MD, University of Groningen, Groningen, The Netherlands, presented results from a randomized trial that prospectively compared the glycemic control achieved using basal insulin glargine, exenatide, and metformin therapy (BET) with basal insulin glargine, bolus insulin lispro, and metformin therapy (BBT) in subjects with type 2 diabetes mellitus (T2DM). The results support BET as an alternative to BBT in some patients with T2DM [Wolffenbuttel BHR et al. EASD 2013 (abstr 1); NCT00960661].

Current treatment for T2DM with elevated HbA1C is basal insulin supplemented with prandial insulin. This regimen produces weight gain and increased episodes of hypoglycemia. Exclusion of prandial insulin and the inclusion of exenatide BID coincident with the largest meals may improve glycemic control with reduced risk of hypoglycemia. Presently, the BET and BBT regimens were evaluated in T2DM patients whose hyperglycemia was uncontrolled after 12 weeks of intensified insulin glargine treatment.

Patients (n=1036) were screened for 2 weeks. Of these, 917 patients (Table 1) entered the basal phase designed to titrate the insulin glucose dose to achieve the lowest fasting blood glucose level (target level 5.6 mmol/L) without hypoglycemia.

Table 1. Characteristics of Patients in the Basal Insulin Optimization Phase

Mean age, years	60
Body mass index, kg/m^2	32
Duration of T2DM, years	12.6
HbA1C, % (mmol/mol)	8.5 (69)
Serum fasting glucose, mmol/L	8.3
Insulin glargine dose, IU/kg/day	0.45
Metformin dose, mg/day	1993

Peer-Reviewed Highlights From

49 EASD BARCELONA 2013

Six hundred thirty-seven patients unable to achieve HbA1C ≤7% (53 mmol/mol) were randomized 1:1 to the BET arm (n=316, per-protocol population [PP] n=247) and the BBT arm (n=321, PP n=263) for the 30-week treatments. The BET regimen was titrated basal insulin glargine prior to bedtime plus exenatide (5 µg BID for 4 weeks, then 10 µg BID). The BBT regimen was titrated basal insulin glargine at bedtime plus bolus insulin lispro TID titrated based on 4-point self-monitored blood glucose (premeal glucose <6.1 mmol/L, no hypoglycemia). The primary outcome was noninferiority in HbA1C change from baseline to 30 weeks for PP. Secondary outcomes were comparisons of the BET and BBT arms with respect to levels of fasting glucose, postprandial glucose, and self-monitored blood glucose, and hypoglycemia for PP.

The mean reduction in HbA1C through 30 weeks for BET was noninferior to BBT. The weight change in the BET arm (–2.4±0.3 kg) was significantly different from the BBT arm (+2.1±0.2 kg) (difference between BET and BBT –4.6 kg; 95% CI, –5.2 to –3.9; p<0.0001). The insulin lispro dose at 30 weeks in the BBT arm was 0.5±0.4 IU/kg/day. Other findings are summarized in Table 2.

The incidence of transient gastrointestinal events was higher for the BET arm versus BBT arm and included nausea (32% vs 2%), vomiting (12% vs 1%), and diarrhea (11% vs 5%). Overall, hypoglycemia, expressed as events per 100 years, was less in the BET arm than the BBT arm (minor, 206 vs 522; major, 2 vs 7; non-nocturnal, 64 vs 350), except for nocturnal events.

The data support the use of insulin glargine plus twice-daily exenatide as an alternative to a regimen involving basal insulin glargine and insulin lispro in T2DM patients with uncontrolled hyperglycemia after a regimen of intensified basal insulin glargine.

Table 2. Comparison of BET and BBT Arms

Measure	BET	BBT	BET vs BBT	95% CI
IG at randomization, IU/kg/day	0.7 (0.3)	0.7 (0.3)	—	—
IG at 30 weeks	0.6 (0.3)	0.6 (0.3)	—	—
HbA1C at randomization, %	8.3 (1.0)	8.2 (0.9)	—	—
HbA1C at 30 weeks, %	7.2 (0.9)	7.1 (0.8)	0.03 (0.07)	–0.11, 0.18
Change (Δ) in HbA1C	–1.1 (0.05)[a]	–1.1 (0.05)[a]	–0.04 (0.07)[a]	–0.18, 0.11
Fasting glucose at randomization, mmol/L	7.1 (2.3)	7.0 (2.5)	—	—
Fasting glucose at 30 weeks	6.5 (2.0)	7.2 (2.8)	—	—
Δ Fasting glucose	–0.46 (0.16)[a]	0.18 (0.15)[a]	–0.64 (0.20)[a*]	–1.05, –0.24
Δ Postprandial glucose, mmol/L				
Δ Morning 2 hours post meal[b]	–2.6 (0.14)[a]	–2.3 (0.14)[a]	–0.27 (0.18)[a]	–0.63, 0.09
Δ Mid-day 2 hours post meal[b]	–2.2 (0.16)[a]	–3.1 (0.16)[a]	0.93 (0.21)[a**]	0.52, 1.34
Δ Evening 2 hours post meal[b]	–2.9 (0.17)[a]	–3.2 (0.17)[a]	0.28 (0.22)[a]	–0.16, 0.72

BBT=basal insulin glargine and bolus insulin lispro therapy; BET=basal insulin glargine and exenatide therapy; IG=insulin glargine. Values are mean (standard deviation) except as indicated. Shaded: Least squares mean change by mixed-effect model repeated measure. [a](SE) *p=0.002 for BET versus BBT; **p<0.0001 for BET versus BBT. [b]From self-monitored blood glucose profiles. Endpoint data is 30 weeks, per-protocol population.

Wolfenbuttel BHR et al. EASD 2013 (abstr 1).

Once-Weekly Exenatide Allows Sustained HbA1C Control

Written by Brian Hoyle

Jaret Malloy, PhD, Bristol-Myers Squibb, San Diego, California, USA, reported on the 3-year results of the Efficacy of Exenatide Once-Weekly and Once-Daily Insulin Glargine in Patients With Type 2 Diabetes Treated With Metformin Alone or in Combination With Sulfonylurea [DURATION-3; NCT00641056] open-label, randomized, controlled trial. Sustained HbA1C, greater weight reduction, and less frequent hypoglycemia were evident up to 3 years in subjects with type 2 diabetes mellitus (T2DM) compared with insulin glargine [Malloy J et al. EASD 2013 (abstr 2)].

Sustained control of glucose levels becomes increasingly difficult in T2DM because of the temporally progressive decline in insulin secretion. Typically, more intensive therapy is needed. The present study compared the abilities of the glucagon-like peptide-1 receptor agonist exenatide and insulin glargine to sustain HbA1C control, defined as achieving and maintaining HbA1C ≤7% (53 mmol/L) after 26 weeks of treatment. Loss of HbA1C control, or failure to achieve control, was evident as HbA1C >7% at two consecutive visits 10 to 12 weeks apart or HbA1C >9% at a single visit after 26 weeks of treatment. Insulin glargine dose was established using the Initiate Insulin by Aggressive Titration and Education (INITIATE) algorithm.

Patients in the intention-to-treat (ITT) group (n=466) who received exenatide (n=233) or insulin glargine (n=223) were followed through a 26-week core phase with an option for continued treatment for up to 156 weeks. At baseline, the exenatide and insulin glargine arms were similar in mean age (57 and 58 years), proportion of males (52% and 55%), mean duration of diabetes (both ~8 years), and mean HbA1C (both 8.3%). Metformin alone and metformin along with a sulfonylurea was taken by 70% and 30% of patients, respectively, in both study arms. Of the ITT group, 140 exenatide patients and 147 insulin glargine patients continued treatment for the full 3 years.

HbA1C control was achieved and sustained at the last visit by 50% of exenatide patients and 43% of insulin glargine patients in the ITT population. Of the patients treated with exenatide and insulin glargine for 3 years, the rate of HbA1C control was 43% and 33%, respectively. HbA1C control was maintained longer for those receiving exenatide (median 25.0 months) than for insulin glargine patients (median 16.7 months). Of those who displayed HbA1C control until the last visit, a more pronounced reduction of the level of HbA1C was evident in patients receiving exenatide (least squares [LS] mean –1.32%) than in insulin glargine patients (LS mean –1.17%; 95% CI difference, –0.34 to 0.04; p=0.12). Exenatide patients displayed less reduction in fasting serum glucose and greater weight loss (LS mean –2.28 mmol/L and –3.44 kg, respectively) than insulin glargine patients (LS mean –3.07; 95% CI difference, 0.03 to 1.54; p=0.04; and LS mean +0.70 kg; 95% CI difference, 5.71 to –2.56; p<0.0001, respectively). Exenatide patients displayed less hypoglycemia than insulin glargine patients (event rate per year 1.1 vs 3.1), but the rates of nausea (16% and 2%) and diarrhea (14% and 7%) were more common in exenatide patients than insulin glargine patients.

Despite continued uptitration of insulin, patients with T2DM treated with exenatide displayed better HbA1C control, greater weight reduction, and less frequent hypoglycemia than patients treated with insulin glargine.

Liraglutide Is a Safe and Beneficial Adjunct to Insulin in Glycemic Control in Type 1 Diabetes

Written by Brian Hoyle

Simon Heller, University of Sheffield Medical School, Sheffield, United Kingdom, reported on the short-term findings of a randomized, double-blind, placebo-controlled crossover trial that demonstrated the prowess of the glucagon-like peptide-1 analogue liraglutide, used